Design and synthesis of glycomimetics: recent advances

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Abstract:

In the past few decades, our understanding of glycans' information encoding power has notably increased, thus leading to a significant growth also in the design and synthesis of glycomimetic probes. Combining data from multiple analytical sources, such as crystallography, NMR spectroscopy and other biophysical methods (e.g. SPR and carbohydrate microarrays) has allowed to shed light on the key interaction events between carbohydrates and their protein-targets. However, the low metabolic stability of carbohydrates and their high hydrophilicity, which translates in low bioavailability, undermine their development as drugs. In this framework, the design of chemically modified analogues (called *carbohydrate mimics* or *glycomimetics*) appears as a valid alternative for the development of therapeutic agents. Glycomimetics, as structural and functional mimics of carbohydrates, can replace the native ligands in the interaction with target proteins, but are designed to show enhanced enzymatic stability and bioavailability and, possibly, an improved affinity and selectivity towards the target. In the present account, we specifically focus on the most recent advances in the design and synthesis of glycomimetics. In particular, we highlight the efforts of the scientific community in the development of straightforward synthetic procedures for the preparation of sugar mimics and in their preliminary biological evaluation.

CONTENTS

1. Introduction

An increased understanding of glycan ability to encode a large number of biochemical information, particularly in the initial stages of inflammation, infection and cancer proliferation, has inspired numerous efforts towards the development of glycobiology.[1] In this context, glycosidic and pseudo-glycosidic molecules have been increasingly involved in drug discovery programs, with the aim of developing both new therapeutics and diagnostic tools.[2] The insufficient metabolic stability, the poor permeation properties and the rapid clearance of carbohydrate-based drugs often compromises both their bioavailability and potency. To overcome this issue, chemically modified analogues of carbohydrates, referred to as glycomimetics, have been designed as a potential alternative with the aim of mimicking the structural and functional aspects of the corresponding natural carbohydrates.[3] One of the main goals in the field of glycomimetics is the manipulation of the chemical information encoded by sugars, by tuning (controlling and altering) the information they direct.[4] Glycomimetics are meant to show improved drug-like character, enhanced chemical and enzymatic stability in comparison to their corresponding natural counterpart and the same, or possibly better, affinity and selectivity towards the desired protein targets.

The design and synthesis of glycomimetics remain a very challenging task. The main mediators of sugar encoded information are a class of proteins, called lectins, which have rarely been exploited in drug discovery programs. Their binding sites are large, flat and solvent exposed, which makes recognition of oligosaccharides an intrinsically low-affinity process.[5] However, recent successful clinical trials for galectin modulator TD139 and for selectin antagonists, such as Rivipansel (GMI-1070) and uproleselan (GMI-1271), are attracting increasing attention from pharmaceutical companies and investors alike. Progresses in the development of glycomimetics targeted against lectins have been reviewed recently.[6-8] The most successful lectin antagonists reported so far generally contain a natural glycan fragment, often a monosaccharide, meant to act as an anchor, which directs the ligand to the lectin carbohydrate recognition domain (CRD). This element is then connected, possibly using non-glycosidic bonds, to scaffolds or supplementary fragments, capable of establishing additional interactions with the target in the vicinity of the sugar binding site. Although these molecules still remain challenging from a synthetic point of view, the recent remarkable developments of carbohydrate chemistry have led to a wide variety of structural modifications, resulting in improved drug-like characteristics and *in vivo* stability. Often, the structural modifications selected in this approach are also designed to reduce the ligand polarity, which, besides increasing ligand affinity, also results in improvement of passive permeation and other pharmacokinetic parameters for glycomimetics over the polyhydroxylated structures of native

carbohydrates. Strategies that have been used to improve the pharmacokinetics properties in glycomimetics design have been reviewed very recently.[8]

Of remarkable interest is also the development of glycomimetics as transition-state analogues for enzyme inhibitions.[9-10] Glycoside hydrolases (GHs) and glycosyl transferases (GTs) are involved in the biosynthesis of glycoconjugates associated with intercellular recognition, immune response, inflammation and metastasis.[11] The role of altered glycosylation, in particular sialylation, has been found of crucial importance in various disorders and cancer.[12] GHs and GTs are classified into over 150 distinct families in the carbohydrate active enzymes database (CAZy),[13,14] based on the amino acid sequence similarity. Many different kinds of glycosidase[15-16] and glycosyltransferase[17-18] inhibitors have been reported and found use as mechanistic probes, chemical biology tools and therapeutics. Typically, the design of these successful cases has been based on mimicry of the transition state formed during glycoside hydrolysis, which possesses substantial oxocarbenium character. This was achieved either by "flattening" the pyranose ring, to imitate the shape (conformation) of an oxocarbenium ion, or by including ionizable groups to mimic its positive charge. This idea has led to the neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza), that have both found clinical application for the treatment of influenza, as well as the iminosugars miglustat (inhibitor of glucosylceramide synthase, treatment of type I Gaucher disease) and miglitol (inhibitor of α-glucosidases in the intestinal tract, treatment of diabetes).

In this review, we mainly focus on recent progresses concerning two major groups of sugar mimics, which have been devised by replacement of either the *endo*-or *exo*-cyclic oxygen atom with another atom, *e.g.* carbon, sulphur, phosphorous and nitrogen (**Fig. 1**). Additionally, we cover recent reports on the development of fluorosugars and fluorinated glycomimetics.

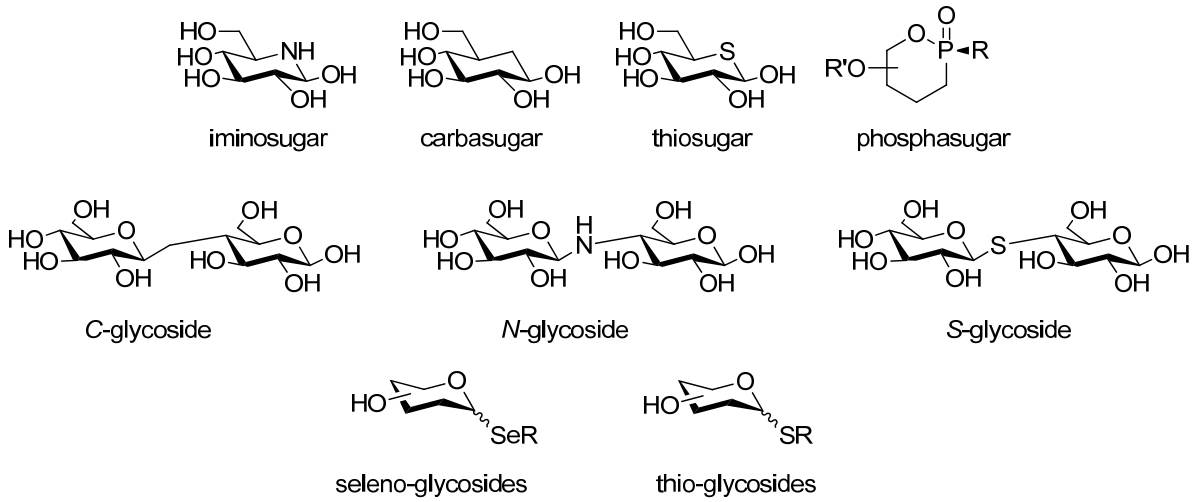


Fig. 1 Examples of glycomimetics described in this manuscript

All the above mentioned modifications induce a change in the chemical and enzymatic stability, polarity, charge, conformation, ring flexibility, and hydrogen-bonding pattern of the molecules, influencing at the same time their affinity for the target protein.[19] Some recent advances in the design of this kind of glycomimetics will be discussed, mainly from a synthetic point of view, taking also into account the investigation of their physico-chemical and biological properties.

2. Endocyclic oxygen replacement

2.1 Iminosugars

Iminosugars are glycomimetics obtained through the substitution of the endocyclic oxygen atom with a nitrogen.[20] They represent the largest and best-developed class of monosaccharide mimics reported so far. Naturally occurring iminosugars and related compounds have found important application as candidates for the treatment of various diseases, including cancer, diabetes, viral infections and lysosomal storage disorders, such as Gaucher and Fabry diseases.[21] Iminosugars can be classified into two major groups: monocyclic (pyrrolidines, piperidines or seven membered azepanes) and bicylic iminosugars (pyrrolizidines, indolizidines or nortropanes). Both classes have been recently exstensively reviewed.[22-23]

Iminosugars behave as potent competitive inhibitors of carbohydrate processing enzymes, such as glycoside hydrolases, glycosyltransferases or glycogen phosphorylases.[22-24] Their inhibitory potency against glycosidases is believed to depend on the structural and electronic similarity at physiological pH to the oxocarbenium transition state of the natural substrate.[23] It has also been shown that sub-inhibitory concentrations of iminosugars can work as pharmacological chaperone of defective

glycosidases. In this role, iminosugars bind to the enzyme and stabilize its conformation enough to prevent premature degradation and to rescue its catalytic activity. This effect has been exploited for the treatment of lysosomal storage disorders, a set of diseases that depend on defects of lysosomal proteins and lead to accumulation of a wide-range of possible substrates, most notably glycosphingolipids. Iminosugars can act as pharmacological chaperone candidates on the basis of pH-dependent affinity for the target lysosomal enzyme. The chaperone should display high affinity in the endoplasmic reticulum (pH 7) and lower affinity in lysosomal compartments (pH 4.5). Ligand binding in the ER helps the protein to fold correctly and to be routed to the lysosome. Upon entering the hydrolytic compartment, the chaperone dissociates, which allows the enzyme to bind its native substrates and preserves the activity of the protein. In this context, an inhibitor of α-galactosidase, Migalastat® (**Fig. 2a**) has been successfully developed for the treatment of Fabry disease.[25] More recently, iminosugars based on modifications of 1-deoxynojirimycin (DNJ, **Fig 2a**) a known β-glucocerebrosidase inhibitor, have been developed for the treatment of Gaucher disease, which results from a β-glucocerebrosidase deficiency.[26-28] In particular, the isothiourea-iminosugar **1** (**Fig 2a**), derived from the hydrochloride salt of DNJ (**2**) through thiourea **3**, is one of the most active compounds reported so far. This area represents one of the major successes in the glycomimetic field and various iminosugars have been introduced in clinical use as an alternative to enzyme replacement therapy with some success.[29] Some recent examples also include multivalent iminosugars,[30-31] obtained through the conjugation of multiple units to a variety of scaffolds with multiple arms. These constructs allowed a significant enhancement of inhibitory activity per ligand unit and a remarkable selectivity against a panel of glycosidases when compared to the monovalent derivatives.[32] The results of these studies strongly suggested that multivalent interactions, which have been mostly exploited to antagonize multivalent protein receptors, can also be relevant for the inhibition of enzymes.

In 2014, the Crich's laboratory reported on a set of polyhydroxylated *N*-alkoxypiperidines, synthetized as mimics of β-(1→3)-glucans (**Fig. 2b**).[33]

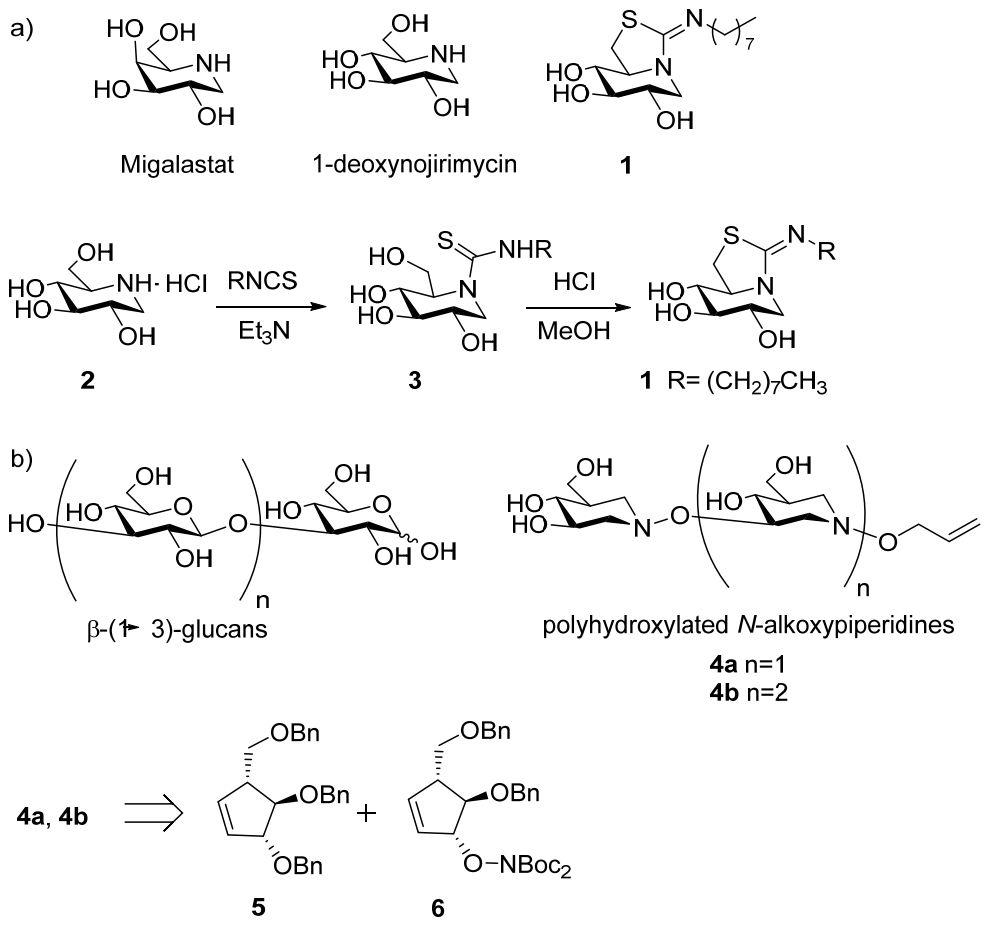


Fig. 2 a) Iminosugars as pharmacological chaperones used for the treatment of lysosomal storage diseases. b) Polyhydroxylated *N*-alkoxypiperidines as mimics of β-(1->3)-glucans.

β-(1→3)-glucans are known immunomodulating agents, thanks to their affinity for dectin-1[34] and for the CRD of complement receptor 3 (CR3)[35]. Binding of β-glucans to dectin-1 can stimulate a cascade of cellular responses *via* the Syk/CARD9 signalling pathway, including phagocytosis, that promotes inflammation and immunity.[36] The difficulties in the isolation of pure oligomers of β-glucans have stimulated considerable interest in their chemical synthesis and have prompted the synthesis and evaluation of possible glycomimetic alternatives. Di- and tri-meric structures of polyhydroxypiperidines connected through an *N*-alkoxy bond (compounds **4a** and **4b** in **Fig. 2b**) have been synthesised from **5** and **6**.[33] Interestingly, the conformation of these molecules is strongly influenced by the low inversion barrier of the *N*-alkoxypiperidine moiety:[37] at room temperature, the N atom is not a stereogenic center, which should confer to these molecules the ability to adapt to lectin binding sites, including possibly those recognising either α- or β-linked oligosaccharides. The ability of compounds **4a** and **4b** to inhibit

binding of anti-CR3 and anti-dectin-1 antibodies and to stimulate phagocytosis provided proof of principle that they represent promising glucan mimics.

Fluoro–containing iminosugar *C*-glycosides have recently gained particular attention for their promising inhibitory activity against glycosidases. Of note, the impact of fluorine atoms on the glycosidase inhibition potency still remains not predictable, because fluorination might deeply influence the hydrophobicity or the electron density of iminosugars, as well as the pKa of the amine function. Behr et al.[38-39] have recently reported the synthesis of iminosugars that bear a perfluoroalkyl chain at the pseudo-anomeric position, where the key synthetic step is the stereoselective nucleophilic addition of fluorinated Grignard reagents onto cyclic nitrone **7** (**Fig. 3**).

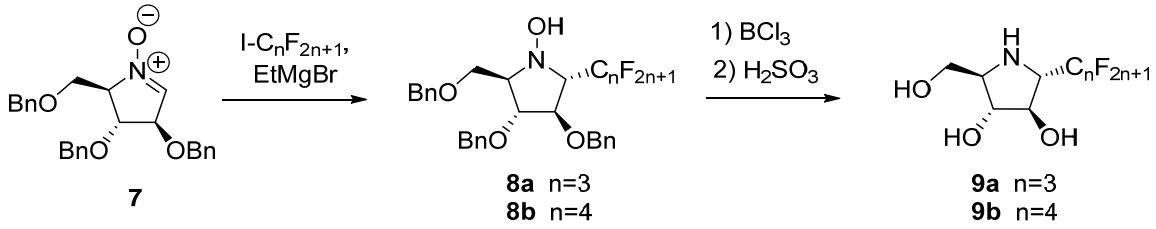


Fig. 3 Synthesis of iminosugars **9a** and **9b**, bearing a perfluoroalkyl chain at the pseudo-anomeric position.

Two fluorinated iminosugars with a perfluoropropyl (**Fig. 3**, compound **9a**) or a perfluorobutyl chain (**Fig. 3**, compound **9b**) were tested against a panel of glycosidases: while the introduction of a C_4F_9 group (compound **9b**) resulted in an inactive compound for enzyme binding, the presence of a C_3F_7 chain (compound **9a**) afforded potent and selective inhibition of bovine liver α-fucosidase, yeast α-glucosidase from *S. cerevisiae* and almond β-glucosidase.[39]

A facile access to complex iminosugars and imino-*C*-nucleoside analogues was recently provided in excellent yield, diastereoselectivity and enantioselectivity *via* proline catalyzed one-pot reaction of aliphatic aldheydes **10** with *N*-chlorosuccinimide (NCS) and dioxanone **12** (**Fig. 4**).[40] Under these reaction conditions **10** is α-chlorinated and the *S*-proline catalyzed aldol condensation with **12** occurs with dynamic kinetic resolution (DKR) of the chloro-aldheyde **11**, resulting in the aldol **13** as a single isomer. Reductive amination of the ketone, followed by intramolecular S_N2 displacement of the halogen atom provides the iminosugar **14**.

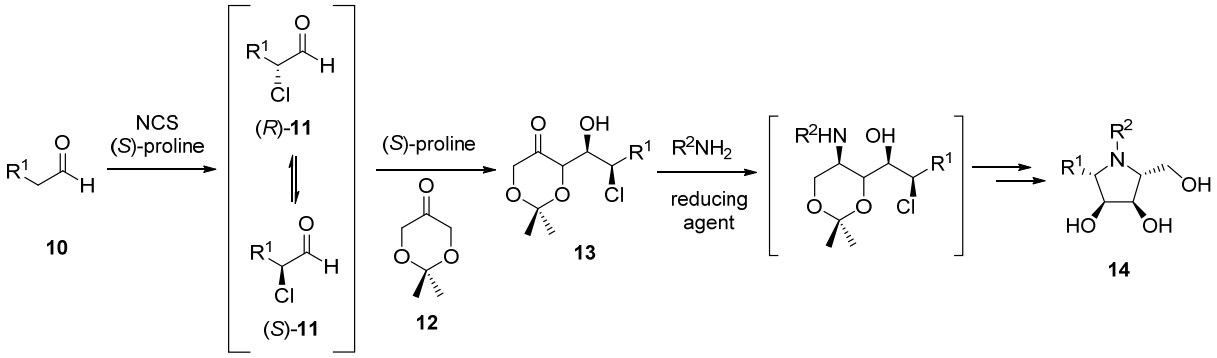


Fig. 4 Synthesis of polyhydroxypyrrolidine iminosugars: organocatalytic tandem α-chlorination-DKR aldol reaction coupled with a reductive amination/annulation sequence

This approach was used to synthesize a group of iminocyclitol inhibitors of *O*-GlcNAcase (OGA) that were found to be orally available and to permeate into rodent brain to increase *O*-GlcNAc levels.[41]. The increase of *O*-GlcNAc levels has been shown to reduce both the formation of tau aggregates and the loss of neuronal cells,[42] thus these compounds have the potential of blocking the progression of Alzheimer's disease.

Although iminosugars have been extensively studied and have already found clinical use, recent efforts in their chemical synthesis coupled with an increased understanding of their affinity and target selectivity [27-28] have notably improved their advancement as drug candidates. Efficient syntheses and new methods that allow to master the chemical and stereochemical complexity required are under continuous improvement.[40, 43-46]

2.2 Carbasugars

The substitution of the ring oxygen in monosaccharides by a methylene group leads to carbasugars. Carbasugars have been extensively studied since the 1960s and some of the synthetized compounds were later found in Nature, such as *myo*-inositol, validamycin (antibiotic) and acarbose (commercialized to treat obesity and Type 2 diabetes mellitus).[47] In these glycomimetics, the lack of anomeric reactivity implies an increased metabolic stability towards glycosidases and glycosyltransferases. Replacement of the endocyclic oxygen with carbon also abolishes the anomeric effects, modifies the intramolecular hydrogen-bond pattern, modulates the amphiphilicity of the sugar ring and results in changes of the flexibility and conformation population distributions.[48] This leads to potential pitfalls, since it can result in molecules that, despite the formal similarity, adopt a 3D shape which differs significantly from the native sugar. In 2014 a seminal work by the groups of Jiménez Barbero and Sollogoub showed that stereoelectronic effects similar to the anomeric effects can be re-engineered in carbasugars, as well as in *C*-glycosides (see below), using fluorinated derivatives.[49]

The synthetic methodologies, as well as the conformational and biological aspects of carbasugars have been extensively reviewed.[50-51] One of the most used synthetic procedures to generate carbasugars is based on Ferrier rearrangement (**Fig. 5**), a Hg^{2+} promoted process that proceeds *via* the hydroxymercuriation of a terminal olefin (**15** in **Fig. 5**), yielding **16**, which rearranges forming an aldehyde and a mercury enolate (**17** in **Fig. 5**). Intramolecular aldol condensation ensues, affording the carbacycle **18**.[52] The method has been strongly improved replacing $HgCl_2$ with $AlBu_3$ (TIBAL) or $Ti(OiPr)Cl_3$ which, upon coordination of the anomeric and the C-2 oxygens, allows the rearrangement to proceed while maintaining the glycosidic bond.[53]

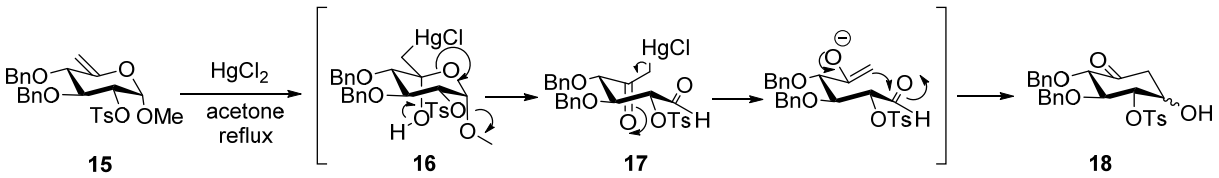


Fig. 5 General mechanism of Ferrier rearrangement for the synthesis of cyclitols

In a recent example, Ferrier rearrangement was used for the synthesis of fluoro-carba analogues of glucosamine-6-phosphate (GlcN6P) (**19a, Fig. 6a**), the natural glmS ribozyme ligand.[54] GlmS ribozyme is a gene-regulating riboswitch that controls cell wall synthesis and is present in several human pathogenic bacteria. [55-56] It uses GlcN6P as a cofactor to induce catalytic self-cleavage with a unique mechanism, not shared by other riboswitches. Activation of the *glmS* riboswitch results in a loss of the GlmS enzyme, which is essential for the synthesis of bacterial cell wall, and thus can lead to antibacterial drugs. The carba-analogue of GlcN6P, compound **19b**, was described to act as a *glmS* riboswitch activator and represents a lead structure for the development of antibiotics with a novel mode of action. The fluorinated carbocyclic mimic bearing a fluorine atom at the carba-position (compound **20** in **Fig. 6a**) was synthesized *via* the Ferrier intermediate (**21** in **Fig. 6b**), which was resolved in the two epimers upon chromatographic separation of the corresponding silylethers. Isolated **22** was fluorinated using LDA and *N*-fluoro-benzenesulfonimide (NFSI) to afford **23**(**Fig. 6b**).

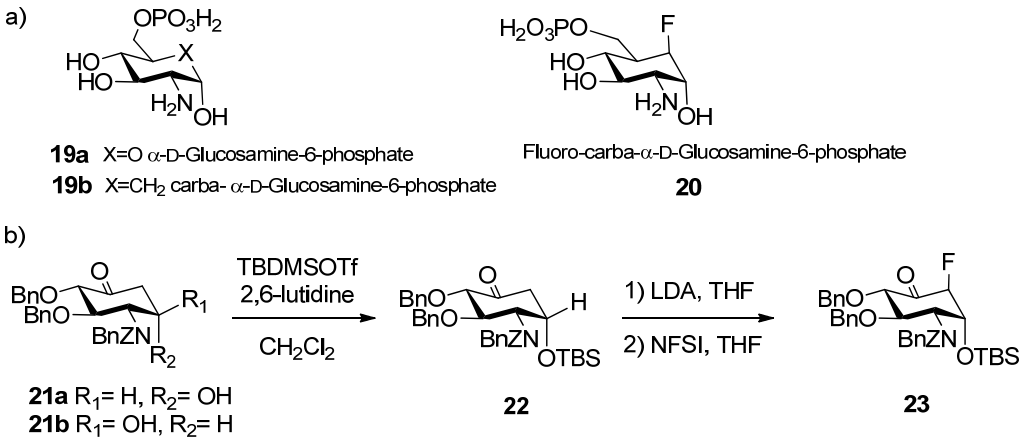


Fig. 6 a) The natural glmS cofactor, α-D-glucosamine-6-phosphate **19a** , the carbocyclic mimics **19b** and **20** (fluoro-carba analogue); b) key steps in the synthesis of intermediate **22** leading to the fluoro-carbacyclic mimic **20.**

Ensuing multistep transformations afforded the monofluorinated analogue **20** (**Fig. 6a**) that was analysed to test its capability to induce glmS ribozyme self-cleavage in vitro. The fluorinated carba-GlcN6P **20** was found to be active in *glmS* ribozyme cleavage assays, but the EC_{50} values evaluated for two bacterial strains were found to be significantly higher than the respective values for carba-GlcN6P **19b**, which remains the most active artificial cofactor of the *glmS* ribozyme described so far.

Alternatively, the Claisen rearrangement has been used for the synthesis of carbasugars. In a recent example, the Claisen rearrangement was used to synthesize carbocyclic analogues of *N. meningitides* serogroup A (MenA) capsular polysaccharide **24-26** (**Fig. 7**).[57] The natural polysaccharide suffers from poor stability in water, due to the chemical lability of the phosphodiester linkages on the anomeric position and this issue has stimulated the design of carba-analogues **24**-**26** (**Fig. 8**), bearing the phosphodiester linkages on the pseudo-anomeric position. The trimer **26** was able to induce specific anti-MenA IgG antibodies with detectable bactericidal activity in vitro, suggesting that carba-analogues can be used for the development of synthetic vaccines.[58] Interestingly, the conformational behavior of these analogues was also investigated,[59-60] showing that the carbasugar mimics preserved the $^4C_1$ geometry of the corresponding natural fragments.

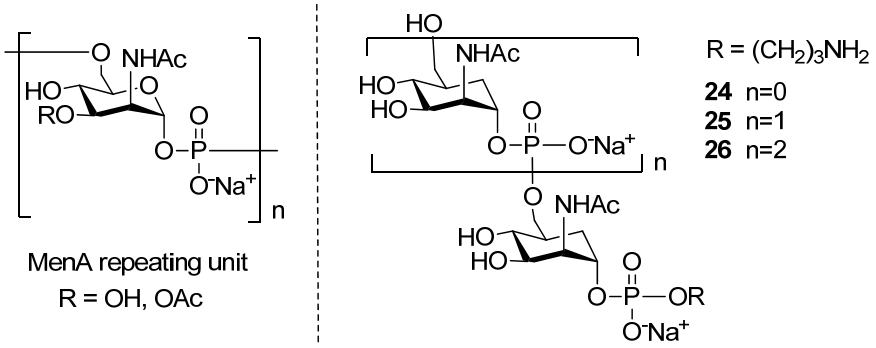


Fig. 7 Men A capsular polysaccharide carbocyclic analogues reported in ref[57]

The Claisen rearrangement was also a key step in the construction of the carbocyclic system of pseudo-disaccharides designed to mimic the minimal natural epitope Manα(1,2)Man **27** of DC-SIGN (**Fig. 8**).[61] DC-SIGN is a tetrameric transmembrane protein expressed by immature dendritic cells that binds to pathogens (HIV, Ebola and Dengue viruses) by specifically recognizing highly glycosylated structures displayed at their surface.[62] The natural ligand of DC-SIGN on HIV envelope is the high-mannose glycan, $(Man)_9(GlcNAc)_2$, which interacts mostly *via* its non-reducing end Manα(1,2)Man disaccharide fragment. Mannose-based glycomimetic antagonists of DC-SIGN have been designed to mimic the natural epitope by connecting a terminal mannose residue to a conformationally locked cyclohexanediol moiety which can both mimic the 3D shape of the natural ligand **27** and improve the metabolic stability (compound **28**, **Fig. 8**).[63-66] In 2016, the analogue **29** was described, whereby the cyclohexane scaffold of **28** is replaced by carbamannose. The stereoselective synthesis of the pseudo-disaccharide **29** (**Fig. 9**) was based on glycosylation of the carbamannose glycosyl acceptor **30** with tetrabenzoyl mannose trichloroacetimidate **31** (**Fig. 8**). The DC-SIGN affinity of **29**, determined by SPR competition assay, was found to be in the low millimolar range, similar to the natural ligand **27** and the mimic **28**.

A further elaboration of the pseudodisaccharide **28**, the 6-amino derivative **32**, was recently designed[67] to select for DC-SIGN and against Langerin, a mannose-binding C-lectin of Langheran cells that binds to HIV envelope glycoprotein gp120 with protective effects. The design of **32** was based on comparative analysis of the two lectin structures in the vicinity of the sugar-binding sites, which revealed the presence and functional significance of a lysine residue in Langerin (Lys313), which is absent in DC-SIGN. Thus the amino group in **32** does not substantially modify the ligand affinity for DC-SIGN, but impairs binding to Langerin, presumably by electrostatic repulsion with Lys313. Indeed, the selectivity of compound **32** was such that neither the interaction nor the selectivity factor with Langerin were any longer measurable by SPR competition assay against Man-BSA. This approach, which the authors dubbed “rational differential design”, exploits structural differences between lectins binding

sites revealed by X-ray analysis and it is likely applicable to other cases. Selectivity among lectins of similar specificity is an important issue that has rarely been addressed in the field of glycomimetic discovery and characterization (for selected examples see:[68, 69, 70]).

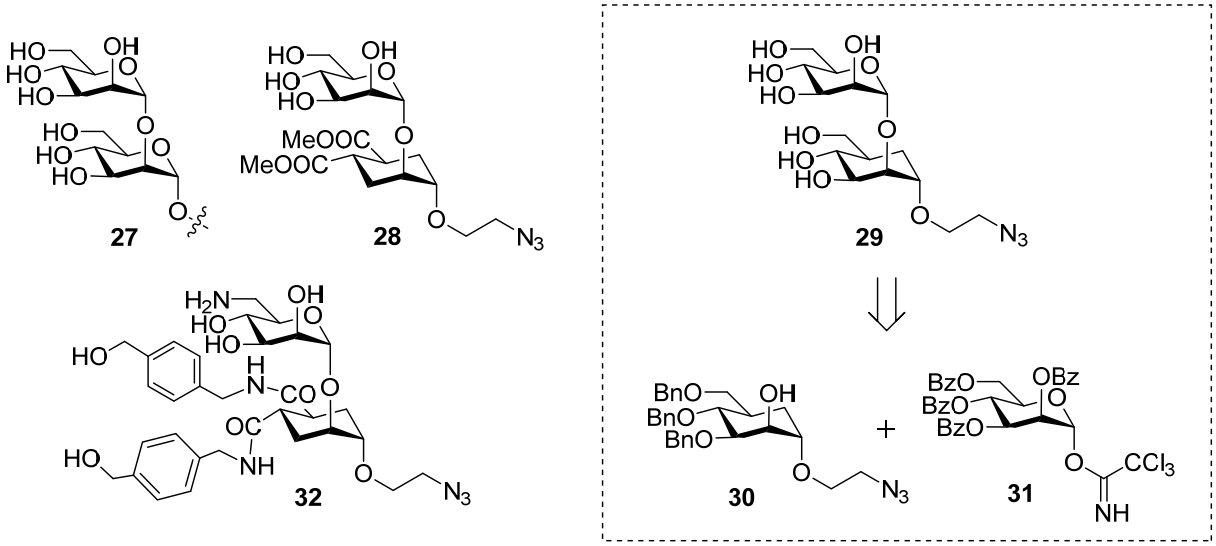


Fig.8 Chemical structures of pseudo-disaccharides **28** and **29** as carba-analogues of epitope **27**. Glycosylation reaction between acceptor **30** and donor **31** to obtain **29**. The 6-amino pseudo-disaccharide **32** is a mimic of **27** which binds selectively to DC-SIGN and not to Langerin.

Among recently reported carbasugars, a new protocol for the synthesis of aminocyclitols was proposed by Harit et al. in 2016,[71] based on a McMurry pinacol coupling reaction, as shown in the retrosynthetic scheme reported in **Fig. 9**. The amino-carbasugar structural motif of aminocyclitols is particularly important since it is found in a variety of biologically active compounds like aminoglycoside antibiotics and alkaloids.[72] In addition, aminocyclitol derivatives have been reported as inhibitors of glycosidases.[73] Aminocyclitols **33** were obtained by McMurry coupling from the fully protected aldehyde **34**, obtained in turn by oxidation of diol **35** generated *via* reductive ring opening of **36** with $LiAlH_4$. Compound **36** was synthesised in few steps from tri-*O*-benzyl-D-glucal **37**, following a modified procedure of the Danishefsky reaction. Under optimized conditions, the pinacol coupling step is partially stereoselective, leading to a mixture of two readily separable isomers (out of four possible ones).

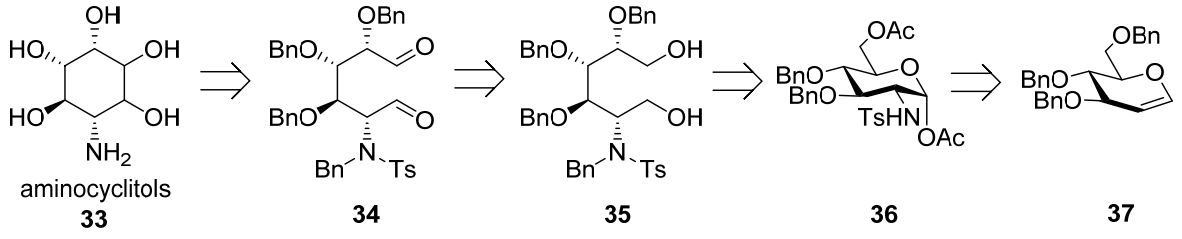


Fig. 9 Synthesis of aminocyclitols

In recent years, due to an increased understanding of transition state analogy in the context of glycosyl hydrolases (GH) enzymes,[74] carbasugars have seen an application as mechanism-based covalent inhibitors of GHs. A mechanism-based covalent inhibitor is a compound that, bearing a structural similarity to an enzymatic substrate and also a reactive functionality, results in direct covalent binding to the enzyme and thus to its inactivation. Cyclopropyl rings have been explored in this context, because their strained σ-bonds[75] can stabilize discrete cationic species generated under catalysis of glycosyl hydrolases, yielding cationic intermediates which covalently trap catalytically relevant nucleophiles in the ezyme active site. Chakladar et al.[76] designed two bicyclo[4.1.0]heptyl analogues of galactose (**38** and **39**, **Fig. 10a**) containing the cyclopropyl moiety and targeted against retaining α-galactosidases.

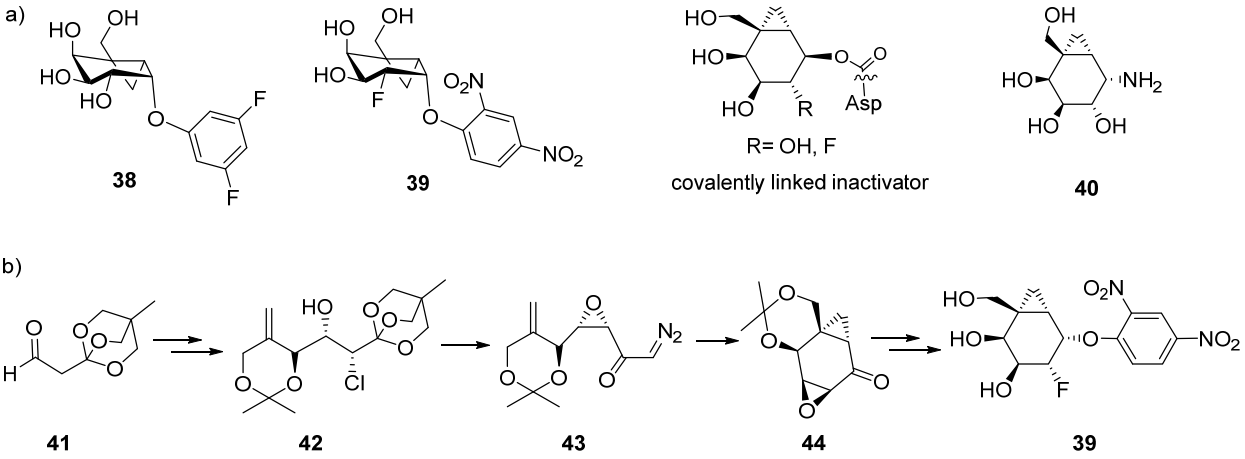


Fig. 10 a) Structures of the cyclopropyl-containing covalent inhibitors **38** and **39**, the competitive α-galactosidase inhibitor **40**; b) synthesis of carbasugar **39**, as reported in ref [77].

The bicyclo[4.1.0]heptyl carbohydrate analogue **38** was found to be an inactivator of coffee bean α-galactosidase, with a rate of inactivation decreasing in the presence of the known competitive inhibitor **40**, thus indicating that inactivation occurred at the active site of the enzyme. This was confirmed by isolation of a single alkylated peptide upon digestion and mass analysis of the inactivated enzyme. The alkylation event occurs on the enzymatic nucleophile, an aspartic acid residue in this case. To further

investigate the mechanism of inactivation, a second generation inactivator (compound **39**, **Fig. 10a**), bearing both a better leaving group (2,4-dinitrophenol) in the pseudo-anomeric position and a fluorine atom in place of the pseudo-C2 hydroxyl group, was designed and synthetized (**Fig. 10b**). Improving the leaving-group ability of the pseudo-aglycone favors rapid formation of the covalent enzyme–inhibitor complex, while replacing the C2 hydroxy group with a fluorine atom slows down the subsequent hydrolysis of the covalent intermediate.[78-80] Fluorocarbasugar **39**[77] was synthetized starting from orthoester **41**. The key step of the sequence, leading to compound **42**, involves a one-pot organocatalytic α-chlorination/DKR asymmetric aldol reaction in the presence of (*R*)-proline, followed by a Julia–Kocienski olefination. Three additional steps lead to diazoketone **43**, which undergoes intramolecular Rh-carbenoid cyclopropanation to yield the bicyclo[4.1.0]heptane scaffold (**44**) in the desired D-*galacto*-configuration. Epoxide opening with fluoride, protecting group manipulations and nucleophilic aromatic substitution with dinitrofluorobenzene finally afforded fluorocarbasugar **39**. The crystal structure of α-galactosidase from *Thermotoga maritima* (TmGalA, GH36 family) alkylated by **39** was obtained [77] and showed clearly the trapped carbasugar intermediate within the enzyme binding site.

Recently, functionalized carba "cyclopropyl" analogue of cyclophellitol (compounds **45-47**, **Fig. 11**) have been designed as β-glucosidase inhibitors, based on the conformational requirement of retaining β-glucosidase inhibitors, supposed to react *via* a $^4H_3$ transition-state.[81]

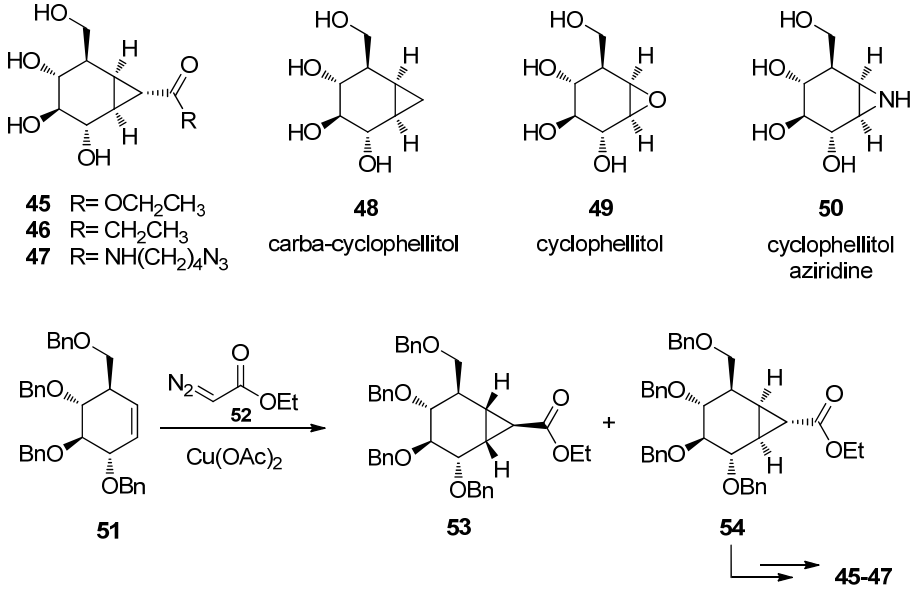


Fig. 11 Gluco-pyranose-configured cyclophellitol cyclopropanes (**45-47**); carba-cyclophellitol **48**, cyclophellitol **49** and cyclophellitol aziridine **50** proposed as carbohydrate mimics by Overkleeft et al. [82]

Carba-cyclophellitols **48** were originally reported by Hashimoto and co-workers[83], as analogues of cyclophellitol (**49**; **Fig. 12**),[84] a 7-oxa-bicyclo[4.1.0]heptane isolated from *Phellinus sp. fungus* as a potent inhibitor of retaining β-glucosidases. In particular, cyclophellitol **49** and its aziridine derivative **50**[85] are configurational analogues of β-glucopyranosides, the substrates of retaining β-glucosidases. However, their conformation was found to be different from β-glucopyranoses that preferentially adopt a $^4C_1$ chair conformation, since both the epoxide and the aziridine force the 6-membered ring into a $^4H_3$ half-chair conformation.[81] Cyclophellitol **49** and its aziridine derivative **50** are thus potential conformational analogue of the oxocarbenium ion transition-state during enzymatic hydrolysis of a β-glucosidic linkage. By replacing the cyclophellitol epoxide oxygen with carbon (**45-47**), new competitive inhibitors of retaining β-glucosidases were designed, based on quantum mechanical analysis of their favored conformation.[81] The carba-cyclophellitol derivatives also adopt the $^4H_3$ conformation, but the cyclopropane motif provides stability toward the nucleophiles within the enzyme active site (compared to cyclophellitol **49** and its aziridine derivative **50**), thus offering the opportunity to study the ligand-enzyme complex.

The synthesis of compounds **47-50** was achieved *via* cyclopronation of *O*-perbenzylated cyclohexene **51** [86-87], using ethyl diazoacetate **52** [88-89] and $Cu(acac)_2$ as catalyst. Inhibition potency towards *Thermotoga maritima* GH *(*TmGH1) in comparison with deoxynojirimycin, a known competitive TmGH1 inhibitor, showed micromolar inhibition for compounds **45** and **46** and low nanomolar inhibition for compound **47**. Compound **47**, in particular, bearing a hydrophobic moiety at the terminal cyclopropyl carbon in a psuedoaxial position, was indeed a potent inhibitor of the β-glucosidase. The crystal structure of TmGH1 containing carba-cyclophellitol **47** was compared with that of an unreacted cyclophellitol derivative and it was shown that they both bind in $^4H_3$ conformation, as predicted. An optimized synthetic pathway allowed the synthesis of gluco- and galacto-pyranose-configured cyclophellitol cyclopropanes.[82]

With a similar approach, a bicyclo[3.1.0]hexane scaffold, with general structure **55** (**Fig. 12a**) was designed as a carbocyclic analogue of sialic acid (NeuAc) with the aim of mimicking the conformation adopted during its enzymatic cleavage within the active site of influenza A neuraminidase.[90-91] Desialylation of host membrane oligosaccharides is a key step for the spread of viral infection after budding of new flu virus particle from host cells. Competitive inhibitors of flu virus neuraminidase A, such as Zanamivir and the orally available Oseltamivir (**Fig. 12a**), were developed by design in the late 90s and marketed for treatment of influenza. In a recent study, the bicyclo[3.1.0]hexane scaffold was functionalized with a carboxylic acid group on the cyclopropane ring and with additional functionalities on the five membered ring, comprising the 3-pentyl side chain of Oseltamivir,[92] amine carrying lipophilic

groups (like in compound **56**, **Fig. 12a**), a guanidium moiety, as in Zanamivir,[93] different ether side chains other than the 3-pentyl ether side chain (compounds of general formula **55**, **Fig. 12a**), which is known as a major cause for resistance, resulting in the diffusion of mutated neuraminidases such as the H274Y mutant.[94]

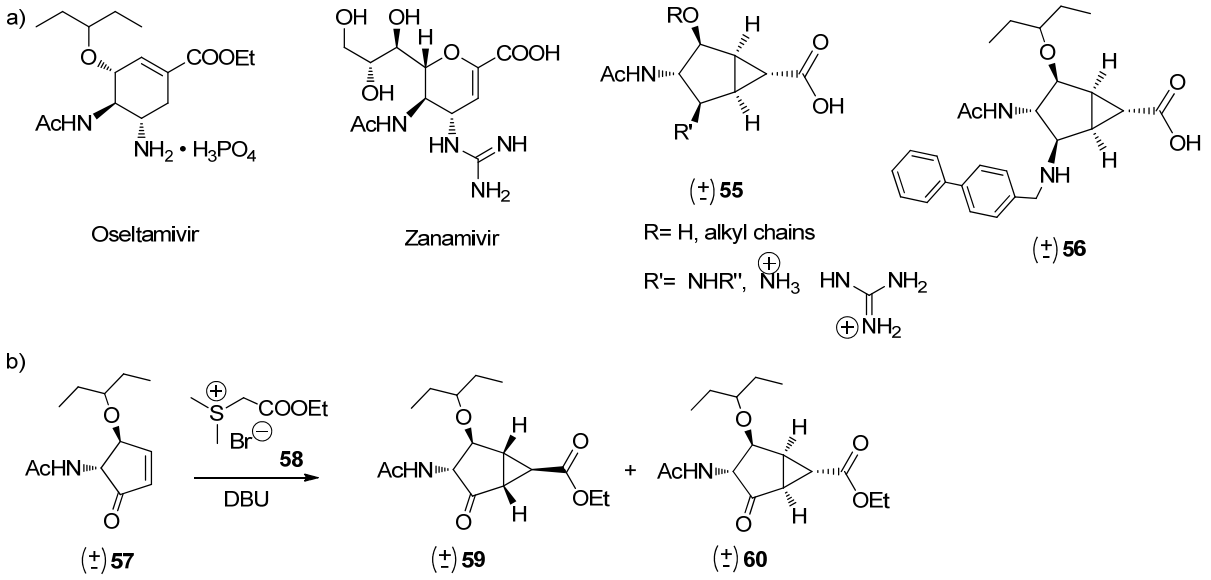


Fig. 12 a) Structure of Oseltamivir, Zanamivir and the bicyclo[3.1.0]hexane derivatives **58** and **59**; b) general synthetic strategy for the installation of a functionalized cyclopropane.

The key synthetic step, involving the installation of the cyclopropane ring, was performed on an α,β unsaturated ketone (**57**, **Fig. 12b**) *via* a Michael-initiated ring closure reaction (MIRC) reaction, using a sulfur ylide, generated *in situ* from the corresponding sulfonium bromide **58** and DBU.[95] Interestingly, compounds of the first series, bearing the 3-pentyl side chain (like compounds **59** and **60**), displayed micromolar affinity for N1 and N2 sialidases (4 orders of magnitude less active than oseltamivir) and no affinity toward the oseltamivir resistant strain (H274Y mutant), as expected. The low activity of these molecules was ascribed to flattening of the bicyclic ring system, which twists it out from the distorted boat that sialic acid adopts during enzymatic cleavage. In addition, the functionalizations of a second set of compounds (different alkyl chains and free ammonium and guanidinium groups) did not result in productive interactions with neuraminidases, suggesting the importance of hydrophobic groups on the bicyclic scaffold for productive binding. Although recent progresses have been made towards the synthesis of compounds less susceptible to drug resistance,[96-97] current drugs against influenza still elicit the emergence of resistant viral strains,[98-99] which likely results from these analogues not being good transition state analogues inhibitors.[100]

In conclusion, carbasugars have been increasingly used to replace carbohydrates with non-carbohydrate-based scaffolds, able to mimic either pyranoses or their hydrolytic transition states and to provide advantages in terms of stability and reduced hydrophilicity (drug-like properties). We showed that well-known synthetic methodologies like the Claisen rearrangement, Ferrier rearrangement, McMurry pinacol coupling reaction, etc are successfully used for the synthesis of carbasugars. The most challenging aspect of carbasugars is the rational design of the scaffolds, that should display the essential functional groups and retain their spatial orientation to match the binding mode of the native ligands and substrates.

1.4 Thio sugars

Thio-sugars are carbohydrate mimics obtained by replacement of the endocyclic oxygen atom with a sulphur atom, in both furanose and pyranose structures.[101-102] Due to the unique conformational and electronic properties imparted by the sulphur atom, these compounds have found widespread applications in medicinal chemistry and in particular as glycosidase inhibitors.[103] Salacinol, with its thiosugar sulfonium sulfate structure (**Fig. 13**), was isolated from the antidiabetic herbal extracts of various *Salacia* species[104] and is a potent inhibitor of the mammalian intestinal α-glucosidases. Other sulfonium-ion glucosidase inhibitors isolated so far included Salaprinol, Ponkoranol, Kotalanol, and related analogues.[105] These thiosugars strongly inhibit human intestinal α-glucosidases (maltase, sucrase and other disaccharide hydrolases that degrade disaccharides to monosaccharides) and could serve as therapeutics for treatment of type-2 diabetes.[106] Some other synthetic compounds have been recently reported,[107-109] like 3'-O-alkylated Salacinol analogues[110] with the introduction of hydrophobic substituents on Salacinol or its analogues (compounds **61** and **62**, **Fig. 13**). These derivatives showed increased α-glucosidases inhibition compared to Salacinol.[108]

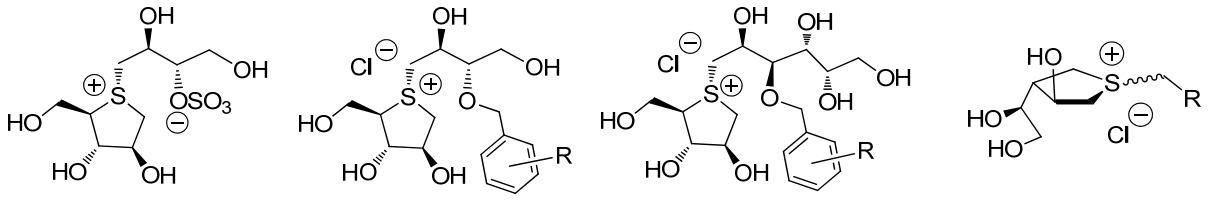


Fig. 13 Sulfonium-ion glycosidase inhibitors.

Sulfonium ions have also been recently reported as inhibitors of glycosyltransferases, in particular of the mycobacterial galactofuranosyltransferase GlfT2, one of the two essential enzymes for mycobacterial cell wall biosynthesis.[111] A set of compounds with the general structure **63** (**Fig. 13**) have been designed

as mimics of the postulated transition state of GlfT2 glycosylation reaction,[111] that has significant oxocarbenium-ion character. Evaluation of their ability to inhibit GlfT2 showed some of the compounds to be weak inhibitors of the enzyme.

Several methodologies have been developed for the preparation of thiosugars.[112-115] Among the most recent examples, a general one-pot synthesis of thiosugars **64** by double nucleophilic displacement from various alditol precursors **65** (with *xylo*, *ribo*, *manno*, *gluco*, *galacto*, and *fuco*-configurations) was reported by Zhang et al. (**Fig. 14a**).[116] The introduction of sulfur on furanose and pyranose sugar analogues was also described *via* an intramolecular double displacement of tosylate in α,ω-di-*O*-tosyl aldonolactones (compound of general formula **66**, **Fig. 14b**) mediated by the "sulfur transfer" reagent benzyltriethylammonium tetrathiomolybdate $[BnEt_3N]_2MoS_4$.[117] The subsequent reduction of thiosugar lactones with borohydride exchange resin afforded thiosugars of general formula **67** in good overall yield.

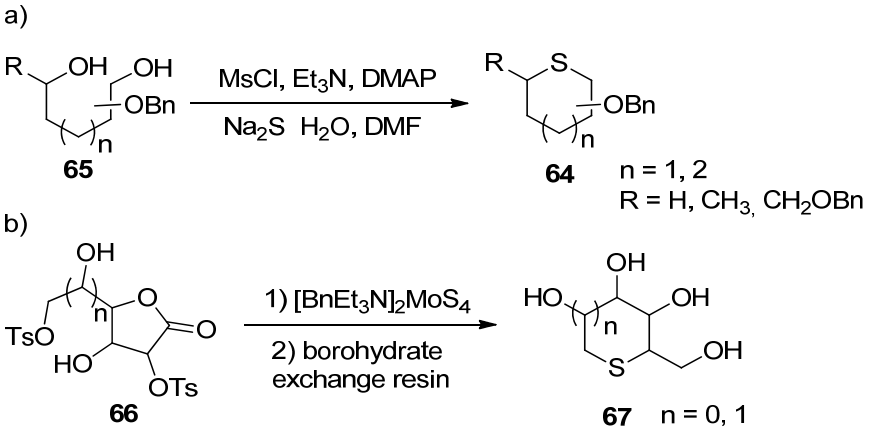


Fig. 14 Recent methods for the preparation of thiosugars

One of the main strategies for the synthesis of thiosugars, relies on the intramolecular thiol-ene reaction, where thiyl radicals, generated by interaction of a thiol with a radical species, undergo intramolecular thiol-ene "click" reaction with alkenes to give sulphur containing heterocycles.[118-119] In general, the regioselectivity of the cyclisation is dependent on the substitution pattern on the alkene,[120] although mixtures of isomers are often observed, due to the ability of the reaction to proceed *via* both *exo* and *endo* cyclisation modes. Recently, Scanlan et al.[121-122] have reported an optimised intramolecular thiol-ene "click" reaction where the 6-*endo* product **68** was formed in 72% isolated yield and the 5-*exo* product **69** in 12% as a mixture of diastereoisomers. Thiol **70**, prepared in four steps from commercially available 2,3,5-tri-*O*-benzylarabinose **71** (**Fig. 15**), was irradiated in the presence of 10 mol % of 2,2-

dimethoxy-2-phenylacetophenone (DPAP) as a radical initiator and 10 mol % of 4-methoxyacetophenone (MAP) as a photosensitizer.

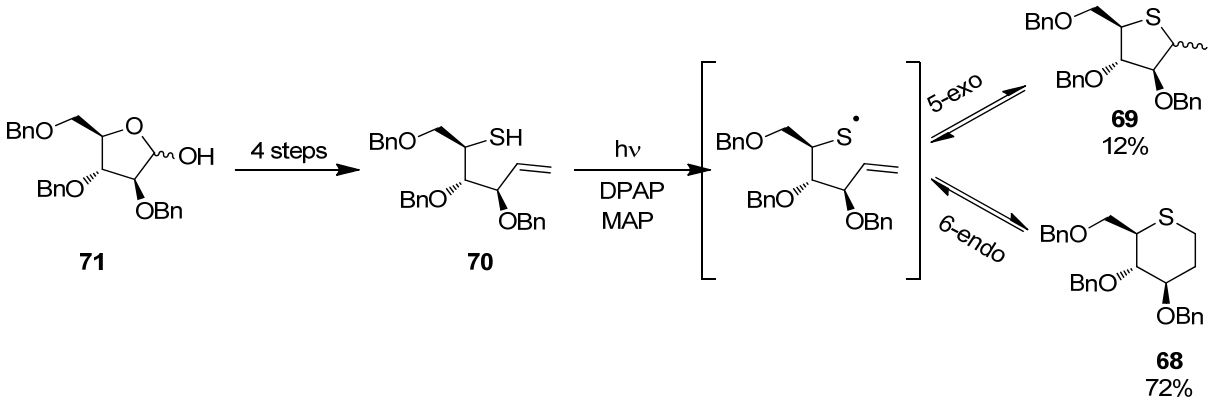


Fig. 15 Intramolecular thiol-ene cyclisation reaction for the preparation of thiosugars

Furthermore, Scanlan et al.[123] also reported that introduction of the endocyclic sulphur atom can be achieved *via* a thiol-yne radical mediated cyclization (**Fig. 16**), favouring the 5-*exo* or the 6-*endo* glycal depending on the configuration of the sulfur-bearing stereocenter. Indeed, the free-radical mediated process provides access to the 5-*exo* product **72** (**Fig. 16a**) exclusively when the configuration of this carbon is *R*, like in **73** (and in D-sugars). None of the corresponding 6-*endo* product **74** was observed. On the other hand, with the opposite configuration at this center, as in **75**, a mixture of both the 5-*exo* and 6-*endo* products **76** and **77** (**Fig. 16b**, in a combined yield of 55 % and in a ratio of 3:2 in favour of the *exo*-product) was observed. These results demonstrate that the stereochemistry of the substituents on the carbohydrate backbone has a significant influence over the regioselectivity of the reaction, similarly to the thiol–ene reactions.[118]

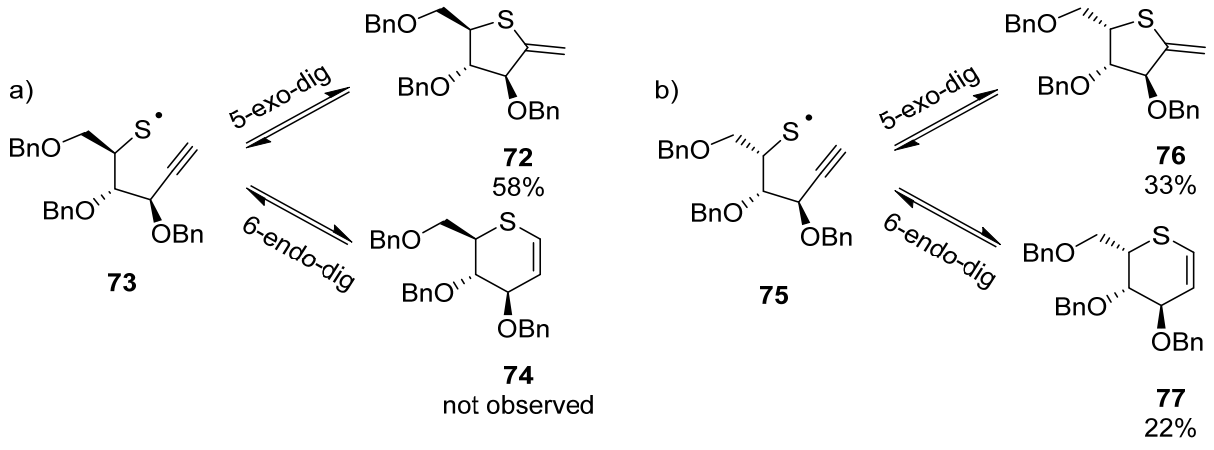


Fig. 16 The free-radical version of the intramolecular thiol-yne cyclisation reaction proposed by Scanlan et al. for preparation of a) D-thioglycals[123] and b) L-thioglycals.

Of note, 5-*exo*-glycal products are by far the favoured product of ionic cyclization pathways (**Fig. 17**). In a recent example, thioester **78** was obtained by treatment of alcohol **79** with triflic anhydride followed by nucleophilic displacement with KSAc. Treatment of **78** with MeONa promoted spontaneous formation of the 5-*exo*-glycal product **80** in high yields. Similarly, the 5-*exo* epimer **76** was obtained exclusively upon ionic cyclization of thioacetate **81**, deriving from alcohl **82** (**Fig. 17**).

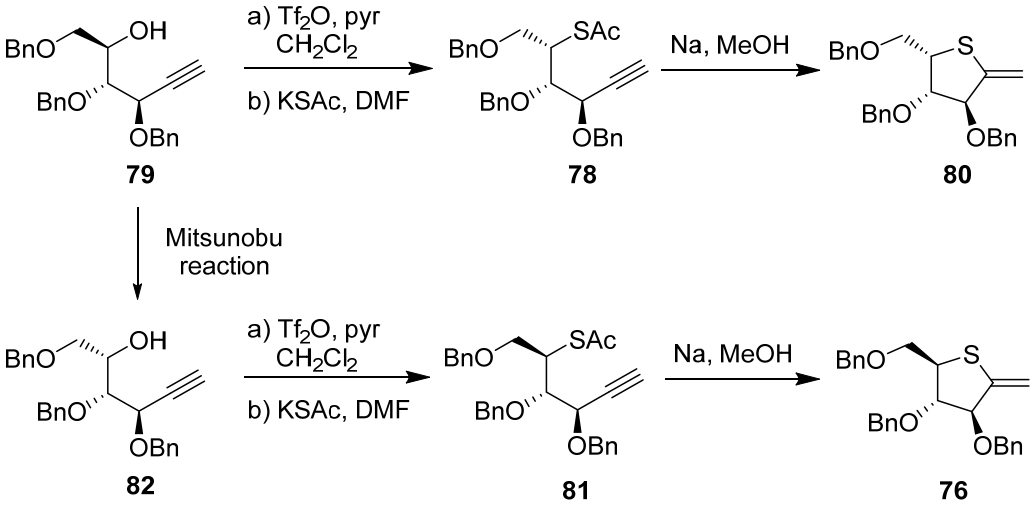


Fig. 17 Ionic version of the intramolecular thiol-yne cyclisation reaction for preparation of 5-*exo*-thioglycals in the L-(**80**) and D-(**76**) series

Thiosugars bearing a sulfonyl moiety at the anomeric center (**Fig. 18**) have been studied as glycosyltransferase inhibitors and anticancer agents. Recently, Kashyap and coworkers[124] have developed a method for the synthesis of C(2)–C(3)-unsaturated glycosyl sulfones **83** and mannosyl sulfones **84**. Starting from glycal **85**, the synthetic procedure involves a sequential Ru-catalyzed stereoselective glycosylation to afford **86**, chemoselective oxidation of **86** to give **83**, and regioselective dihydroxylation to **84** in one-pot.

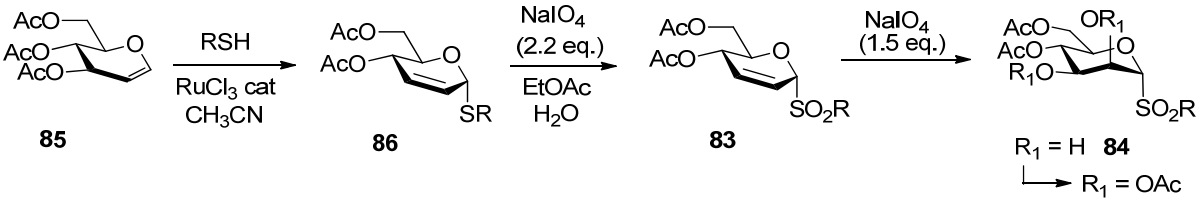


Fig. 18 One-pot synthesis of C(2)–C(3)-unsaturated glycosyl sulfones **83** and mannosyl sulfones **84**.

In a recent screening of various classes of sugars (thio-, anhydro-, and sulfamido-sugars and myo-inositol oxide), synthesized and studied for cytotoxicity against human cancer cell lines, some sulfur-containing compounds were found to be promising for future developments due to antineoplastic activity.[125] In particular, compound **87-90** (Fig 19) were assessed for cytotoxicity and apoptosis against human cancer

cell lines (A549, LoVo, MCF-7 and HeLa).[126] Compound **87** was more active against MCF-7 cells (an estrogen-dependent breast cancer line), while the other thiodisaccharides showed strongest activity against A549 cells (a lung adenocarcinoma line).

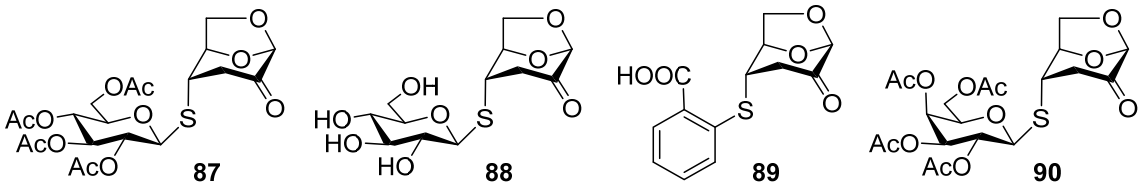


Fig. 19 (1-4)-*S*-thiodisaccharides **87-90**

Indeed, in addition to thiosugars, where sulfur is used to replace the endocyclic oxygen, another class of sulfur-containing compounds, thioglycosides, has been developed, where sulfur is used to substitute the glycosidic linkage. These compounds are further described in section 4.4.

2.4 Phosphorus-based sugars

Phosphorus-based sugars and phosphorous containing glycomimetics are cyclic molecules that present a phosphorus atom in place of the anomeric carbon or alternatively in place or linked to the endocyclic oxygen. Depending on how the phosphorous atom is inserted into the cycle, three main classes of compounds can be obtained: phospha-sugars, phosphono-sugars (or phostones) and phosphino-sugars (phostines, or 1,2-oxaphosphinanes), schematically reported below (**Fig. 20**).[127] Some phosphorus heterocycles that are being referred to as phospha-sugars do not contain hydroxyl substituents on the cyclic skeleton and thus are not really carbohydrate analogues in a strict sense. In recent years, however, some of these phosphorus heterocycles have been synthesized and reported for applications as anti-cancer agents.[128-130]

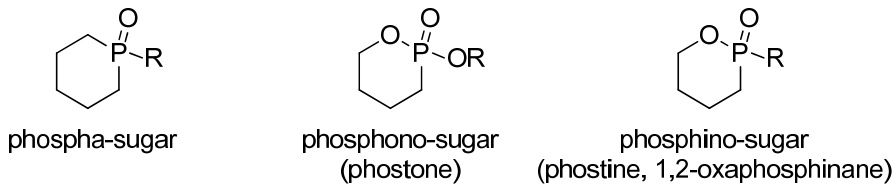


Fig. 20 General classification of phosphorous containing ring systems used as glycomimetics.

Generally, the compounds containing a phosphoryl bond show high Lewis/Brønsted basicity. In addition, phosphorus six-membered rings show also stereoelectronic-dependent interactions with phosphorus atoms similar to the anomeric effect.[131] Compared to glycopyranosides, however, oxaphosphinanes are

considerably more resistant to the ring-opening/closure processes occurring between the open forms and the cyclic pyranose forms.[132-133]

Hanaya with his team have dedicated an intense activity to the development of new methods to introduce of a phosphinyl group into the sugar skeleton, especially for the preparation of D-mannopyranose phosphasugar analogues **91** and **92** (**Fig. 21**).[134]

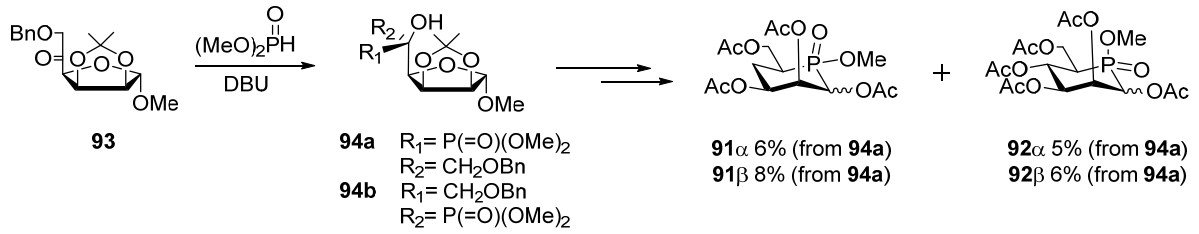


Fig. 21 Synthetic pathway of phospha-sugars proposed by Hanaya et al.[134]

The phosphonyl group was introduced as dimethyl-phosphonate, in the presence of DBU, on the key intermediate **93** (**Fig. 21**) [134]. After a few standard manipulations, compounds **94a-b** were converted into the corresponding penta-acetates **91** and **92**. In particular, after chromatographic purification, 1,2,3,4,6-penta-*O*-acetyl-5- deoxy-5-[(*R*)-methoxyphosphinyl]-α-D-mannopyranose (**91α**; 6%), its β-anomer **91β** (8%), the 5-[(*S*)-methoxyphosphinyl]-α-isomer **92α** (5%), and its β isomer **92β** (6%) were obtained from compound **94a**. The same strategy was then employed and optimized for the synthesis of other phospha-sugars.[135-136]

Phosphino-sugars (or phostines) are those compounds that present an 1,2-oxaphosphinane heterocyclic core. The phosphinolactone group of phostines is an isoster of the corresponding lactols. These compounds are different from the phostone family because of the exocyclic P−C bond, which confers to the molecules a higher stability compared to the P-O bond in phostones. In some respect, thus, phostines can be considered analogues of *C*-glycosides. Pirat and his group [137] reported the first synthesis of 2-phenyl-1,2-oxaphosphinane under base-catalyzed transesterification conditions. Oxaphosphinanes were prepared using ethylphenylphosphinate **95** under basic conditions (**Fig. 22**).[138-139] Compound **95** reacted with tri-*O*-bezylarabinofuranose **71** or the protected mannofuranoses **96** and treatment with potassium tert-butoxide allowed spontaneous transesterification to afford *P*-phenyl-phopshinosugars (**97** or **98** in **Fig. 22**).[139]

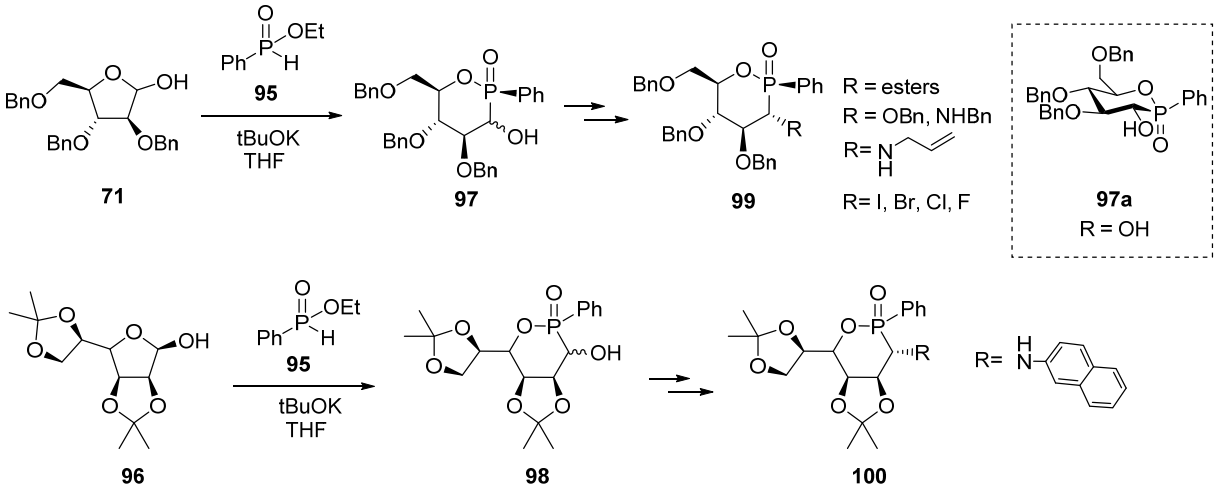


Fig. 22 Synthesis of phosphinosugars proposed by Pirat and co-workers[137]

In vitro screening against 11 cancer cell types revealed potent activities of several derivatives of general formula **99**,[139-140] that opened therapeutic perspectives against glioblastoma. Compound **100** (**Fig. 22**) was identified as a hit compound, since it inhibited invasion and migration of both GBM stem cells and GBM cancer cell lines on fibronectin, vitronectin, and laminin.[140] The glucose-like phostine **97a** (**Fig. 22**) was selected for its ability to inhibit the Mannoside acetyl GlucosAminylTransferase-5 (MGAT5), an enzyme that regulates tumoral development by remodelling of *N*-glycans on cell surface. MGAT5 overexpression is associated to malignancies and correlates with cell migration, invasion, and epithelial–mesenchymal transition.[141-142] In addition, α-halogenated oxaphosphinanes were synthesised and tested for cancer anti-proliferation and anti-migration activity on a panel of six cancer cell lines and were found to be active against melanoma, epidermoid carcinoma, hepatocarcinoma, prostatic carcinoma and breast adenocarcinoma cell lines.[143].

Pseudo-disaccharides containing the oxaphosphinane core (**Fig. 23**) have been also synthesised in order to create more stable pseudoglycans.[144] The synthetic pathway for these structures, starting from oxaphosphinanes **97a** (**Fig. 23**) introduced a glycosidic bond at the free hydroxyl group in position 2, using glycosyl donors **101**. The phostine, used as glycosyl acceptors, becomes more acidic (pKa≈ 13.5) than a typical sugar alcohol (pKa usually between 16 and 19),[145] due to proximity of the phosphoryl group with the hydroxy group, thus improving the glycosidation results and affording the pseudo-disaccharides **102** in high yields.[146]

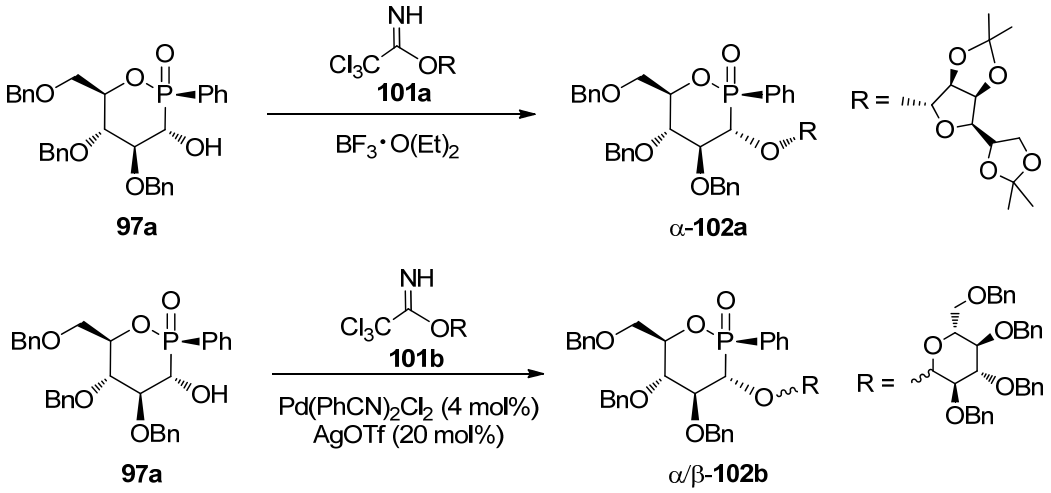


Fig. 23 Coupling reaction between α-mannosyl donor **101a-b** and oxaphosphinane **97a**

Crich and coworkers[147] have recently described the stereoselective synthesis of phostone-mimetics of disaccharides (**Fig. 24**), using six-membered cyclic *P*-chiral ammonium phosphonite–borane **103** and per-*O*-benzyl protected mannosyl donor **104**. Activation of **103** with BOPCl followed by treatment with DMAP and **104** afforded the α-disaccharide mimic **105**. When DMAP is replaced by the 3-nitro-1,2,4-triazole, the β-isomer **106** is obtained. Oxidative deborylation by means of *m*-CPBA gives the corresponding phosphonite **107** and **108** with full retention of configuration.

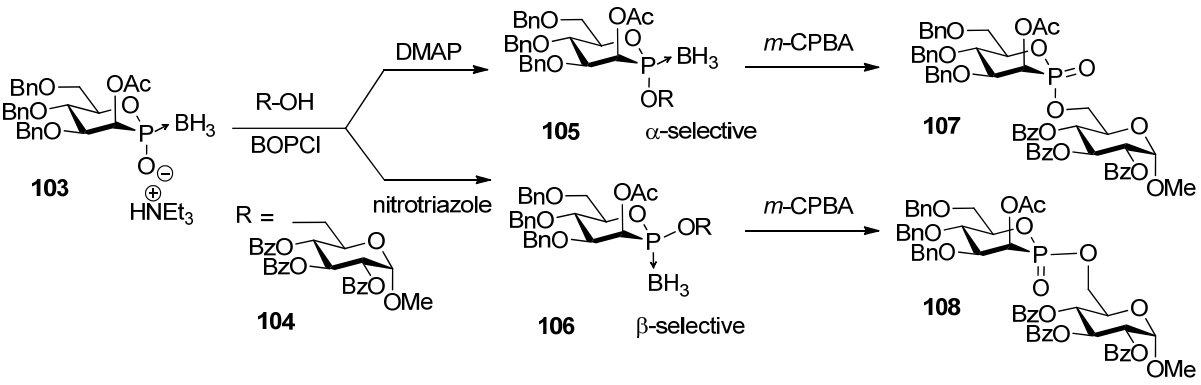


Fig. 24 Synthesis of phostone-mimetics of disaccharides.

In conclusion, although phosphorus-based sugars have recently shown some success as potential therapeutic agents with anticancer activities, the relevant synthetic procedures are still not fully developed. This leaves room for a renewed synthetic effort, in particular using the phostone linkage as a suitable replacement of glycosidic bonds for the synthesis of oligosaccharide mimetics.

3. Fluorosugars

The incorporation of fluorine atoms into bioactive molecules is a general strategy in medicinal chemistry to improve their pharmacokinetics and to modulate their biological properties.[148] From the perspective of steric effects, fluorine is the smallest substituent that can be used as replacement of the H atom, with a van der Waals radius of 1.47 Å, close to the 1.20 Å value for hydrogen. However, the high electronegativity of fluorine (3.98 on the Pauling electronegativity scale compared to 2.20 for H, 3.44 for O, and 2.55 for C) results in a highly polarized C–F bond, which presents a strong dipole moment. Depending on the substituted position, fluorine substituents can have remarkable effects upon the physical and chemical properties of the molecule. A fluorine atom can induce increase of lipophilicity, decrease in pKa values of certain groups by OH–F electrostatic interaction, can modulate the hydrogen-bond acceptor/donor ability or foster the presence of a particular ring conformation.[149] This feature has been exploited in many ways for the development of enzyme inhibitors, as seen before in section 1.2, or to make the molecule resistant to chemical degradation.

The strategic fluorination of antigenic glycans has emerged as an interesting approach for glycoconjugate vaccines development: selectively fluorinated carbohydrate antigens have shown improved metabolic stability, as well as comparable or even enhanced immunogenicity.[150] Some other examples of fluoro-containing carbohydrate mimetics are reported in **Fig. 25**. Among them, Gemcitabine (**109**) is a fluorinated nucleoside analogue, marketed as an anticancer drug. It acts as a prodrug that undergoes intracellular phosphorylation to yield the active form that inhibits DNA synthesis, leading to apoptosis. The synthesis of gemcitabine has been recently reviewed[151] and provides a compendium of all the different strategies for CF_2-introduction in a sugar moiety.

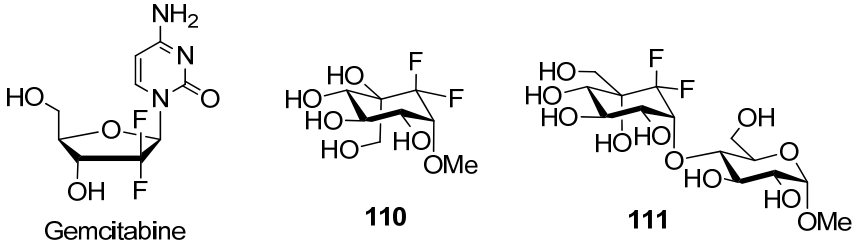
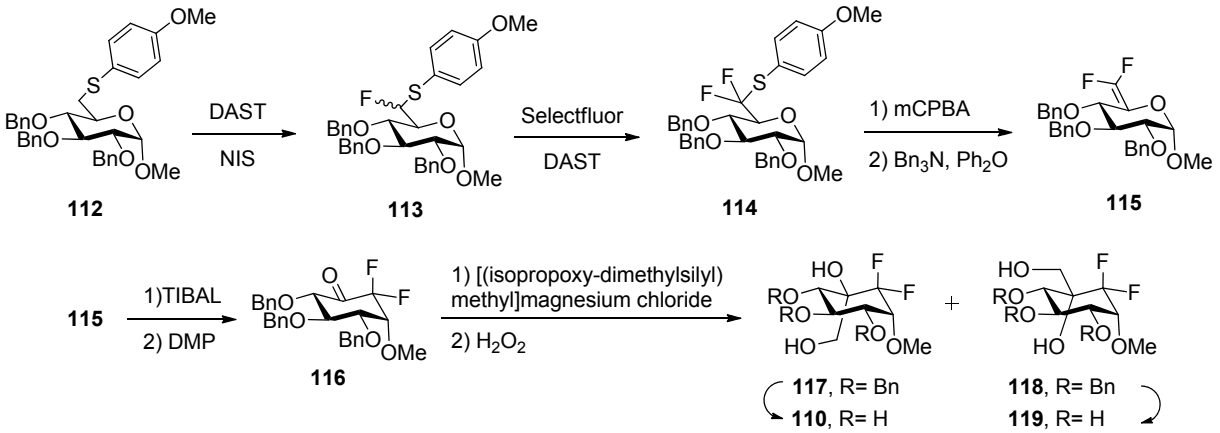


Fig. 25 The nucleoside analogue and anticancer drug Gemcitabine (**109**) and examples of *gem*-difluorocarbasugar analogues: **110** (β-L-idose like) and *gem*-difluorocarbadisaccharide **111**

As mentioned above (see 1.2), Jiménez-Barbero and Sollogoub have shown that replacing one of the oxygen atoms of the acetal moiety of a sugar with a CF_2 group can emulate the anomeric effects,[49] which allows a closer mimicry of the natural sugar conformation than using non-fluorinated analogues. Recently, the same authors have examined the specially compelling case of mimics of monosaccharides

641 of *ido* configuration[152]. The iduronic acid moiety of heparin is one of the classic cases of conformational
642 dynamic behaviour in carbohydrate chemistry. It has been shown that different conformation of the *ido*
643 ring are recognized by different heparin receptors, such as the antithrombin receptor AT-III or the
644 fibroblast growth factor FGF-I. The authors analyzed the behaviour of the *gem*-difluorocarbasugar
645 analogue of β-L-idose (**110**, **Fig. 25**) and of the *gem*-difluorocarbadisaccharide (**111**, **Fig. 25**), which
646 contains the β-L-*ido* ring of **110** at the non-reducing end. A conformational bias similar to the exo
647 anomeric effect was observed for **111** and conformational flexibility similar to the natural idose ring was
648 seen for the *gem*-difluorocarbasugar analogue **110**. None of these effects is observed in the
649 corresponding CH_2-carba derivatives. The presence of fluorine atoms emulates, to a certain degree, the
650 properties of the endocyclic oxygen, which are lost in regular CH_2-carbasugars.[152] The synthesis of **110**
651 (**Fig. 26**) involved a modified Pummerer reaction on intermediate **112**, using diethylaminosulphur
652 trifluoride (DAST) as fluoride source in combination with *N*-iodosuccinimide (NIS). The reaction proceeds
653 through a selective iodination of the sulphur atom, followed by HI elimination triggered by succinimide
654 to give the sulfonium ion, which is then attacked by fluoride to give α-fluoro-sulphide derivative **113**.
655 The second fluorination process was performed using Selectfluor in the presence of DAST to afford **114**,
656 which in turn, treated with *m*-CPBA, followed by thermolysis, afforded the difluorovinyl compound **115**.
657 Ferrier rearrangement of **115** (with TIBAL), followed by Dess-Martin periodinane (DMP) oxidation of the
658 carbacycle, gave ketone **116**. Treatment of the ketone with Tamao's reagent provided β-hydroxysilanes,
659 which were subjected to oxidative cleavage of the Si-C bond by basic hydrogen peroxide giving diols **117**
660 and **118**, subsequently separated by flash chromatography. Removal of the protecting groups led to the
661 target *gem*-difluorocarbasugars **110** and **119**, respectively.



662
663 *Fig. 26* Synthesis of *gem*-difluorocarbasugars **103**

The potential of fluorine substitution has been widely recognized and fluorinated glyco-analogues have found applications in medicine and diagnostics (^{18}F-2-deoxy-2-fluoro-D-glucose as a radiotracer for positron emission tomography scans is an example).[153] There is indeed a growing interest in the synthesis of fluorinated analogues[154] and the investigation of their properties, aiming at generating glycomimetics with improved pharmacokinetics properties that are still recognized by their native receptors.[155] Indeed, the fluorine atom is a bioisoster of the hydroxyl group and has been used to reduce the polar surface area of the molecule, reducing the overall hydrophilicity and thus facilitating passive permeation.[156] The fluorination of sugars and glycomimetics has been also used to destabilize the oxocarbenium intermediate required for glycoside hydrolysis,[77] as described in section 2.2. This property can be exploited to reduce the rate of metabolic degradation of glycomimetics.

4. Exocyclic oxygen replacement

Another class of sugar mimics has been created by replacement of the exocyclic oxygen atom. The conformational behaviour of these mimetics can drastically change compared to their natural counterparts. This usually depends on an increased flexibility around the interglycosidic linkages as well as on the presence of ring conformations that are not populated in the native compound.[49] These modifications can be detrimental to target interaction when the native ligand is recognized in the most populated solution conformation, but it becomes very effective when the bound conformation of the natural ligand differs from the most abundant one in water solution.[157]

4.1 *C*-glycosides

Replacement of the exocyclic anomeric C–O bond with a C–C bond is a good strategy to provide hydrolytically stable derivatives, called *C*-glycosides. These carbohydrate mimics have received considerable attention due to their diverse and valuable properties.[158] There are many examples in the literature describing the efforts made to generate an anomeric nucleophile (typically a carbanion or an organometallic species) that, through the reaction with an electrophilic carbon atom or an anomeric radical, can generate the *C*-glycoside. The most recent synthetic advances for the preparation of *C*-glycosides have been reviewed by Yu and Yang.[159]

Various strategies have also been devised to introduce acyl groups at the anomeric carbon in glycosides. Besides being obvious synthetic intermediates, *C*-acyl glycosides display interesting biological activity, such as irreversible inhibition of glycosidases[160] and inhibition of reactive oxygen species (ROS, involved

in oxidative stress cell-signaling) and glutamate-induced cell death.[161] Indeed, some carbonyl *C*-glycosides isolated from *Scleropyrum pentandrum* displayed better radical scavenging activity and oxygen radical absorbance capacity (ORAC) than well-known antioxidants, such as ascorbic acid and Trolox.[162] *C*-acyl glycosides have been prepared by nucleophilic addition of organometallic reagents to *C*-glycosyl aldehydes followed by oxidation.[163] As an alternative, addition of aldehydes[164] or electrophilic acylating agents[165] to glycosyl-based lithium, tin or samarium reagents **120** has been used to achieve anomeric acylation and thus compounds of general formula **121** (**Fig. 27a**). The addition of Grignard reagents to glycosyl nitriles **122**[166] (**Fig. 27b**) or glycosyl benzothiazoles[167] is an additional route leading to compounds of general formula **123**. Recently, Gong et al.[168] have proposed a nickel-catalyzed reductive coupling of aliphatic carboxylic acids with glycosyl bromides **124** that takes place under mild conditions and leads to *C*-acyl glycosides **125** with retention of configuration in good-to-moderate stereoselectivity (**Fig. 27c**).

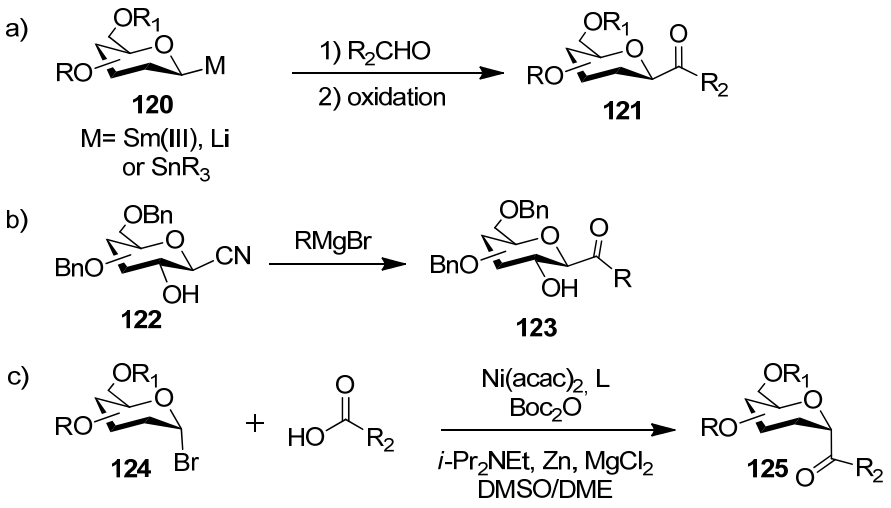


Fig. 27 Synthesis of *C*-acyl glycosides: a) addition of aldehydes or acylating agents to C1 glycosyl nucleophiles; b) addition of Grignard reagents to glycosyl nitriles[166]; c)Ni-catalysed reductive coupling of aliphatic acids with glycosyl bromides proposed by Gong et al.[168]

Another method recently introduced by Walczak and co-workers[169] employed a stereoretentive palladium-catalyzed acylation reaction of anomeric stannanes **126** and **127** (**Fig. 28**) with thio- and selenoesters, affording the corresponing *C*-acyl glycosides **128** and **129** with retention of configuration. Anomeric stannanes are configurationally stable nucleophiles that can be stored and manipulated under ambient conditions without loss of stereochemical integrity, even after extended periods of time (six months at room temperature or one year at -20°C). They can be easily prepared starting from the corresponding glycal **130**, affording either 1,2-*cis* or 1,2-*trans* glycosides, thus allowing formation of both C(1) anomers.[170-172]

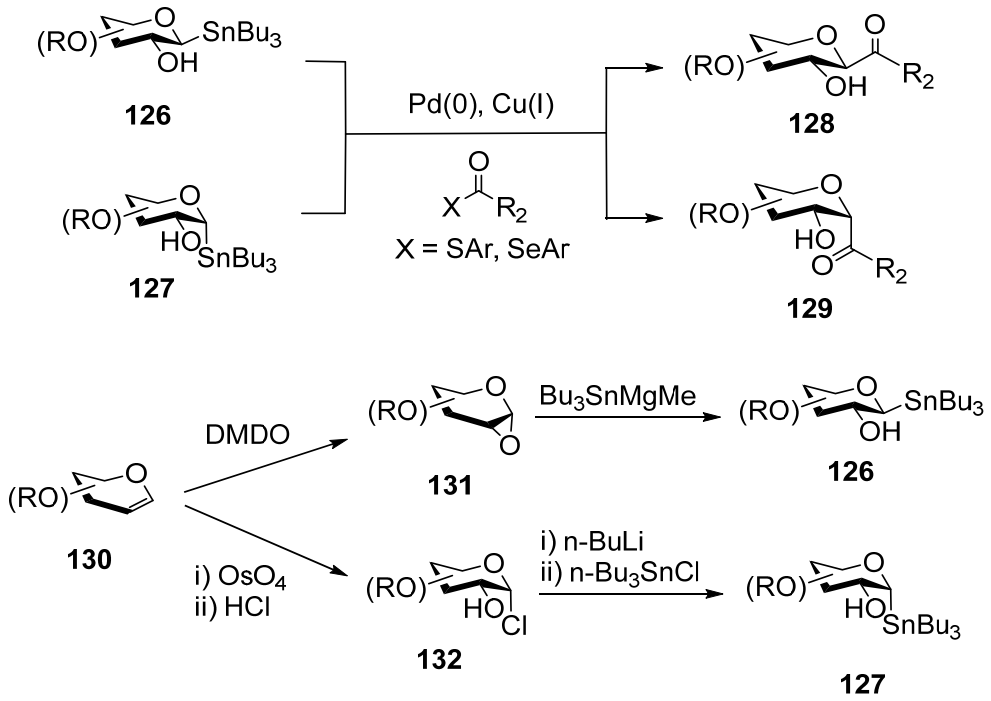
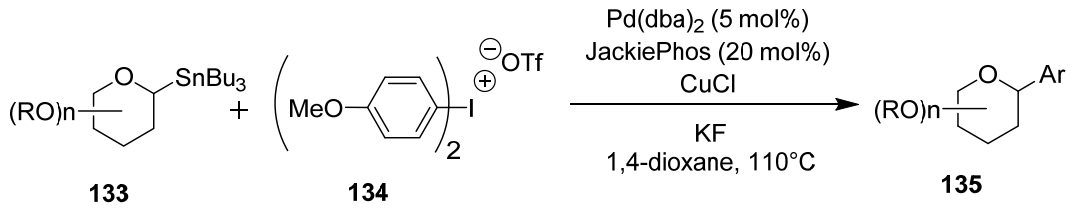


Fig. 28 Synthesis of *C*-acyl glycoside using anomeric stannanes.

The preparation of the 1,2-*trans* anomer **126** (**Fig. 28**) starts from dimethyldioxirane (DMDO) epoxidation of glycal **130,** followed by ring opening of epoxide **131** by $Bu_3SnMgMe$. For the synthesis of the 1,2-*cis* stannane **127**, glycal **130** has to be converted into the α-chloride **132**, using HCl, and then exposed to n-BuLi or lithium naphthalenide at -100°C. The resulting lithium carbanion is finally quenched with Bu_3SnCl. This procedure allows transfer of the configurational information from α-chloride **132** to the corresponding anomeric stannane **127**. Of note, late-stage manipulation of C1 ketones can lead to glycomimetic diversification to access C(sp^3)-linked and fluorinated glycomimetics.[169] With a similar method, Walczak and co-workers proposed a stereospecific cross-coupling reaction of glycosyl stannanes **133** and diaryliodonium triflate **134** (**Fig. 29**)[172] to synthesise aryl *C*-glycosides **135**, a common structural motif in many bioactive natural products and imaging agents.[173-175] The most noticeable commercial application of aryl *C*-glycosides is Gliflozins, a class of sodium-glucose cotransporter (SGLT2) inhibitors used as a treatment for diabetes mellitus type 2.[175]

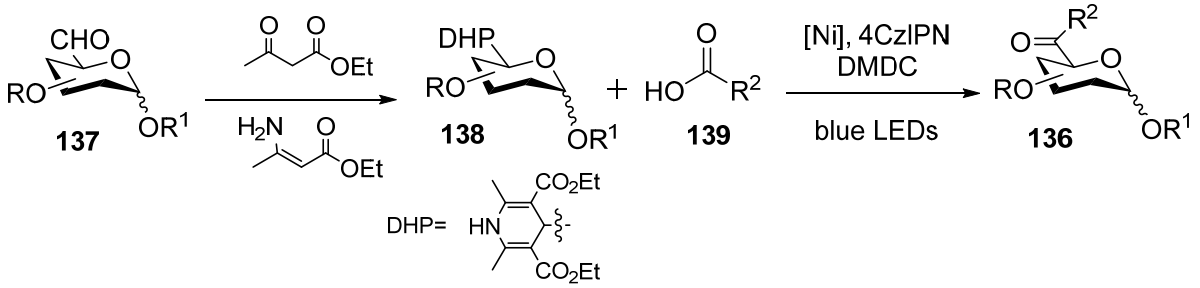


734

735 *Fig. 29* The stereospecific cross-coupling reaction using a diaryliodonium triflate with glycosyl stannanes.[172]

736 This process, promoted by a palladium catalyst in the presence of a bulky phosphine ligand (JackiePhos),
737 proceeds with exclusive transfer of the anomeric configuration from the substrate to the product,
738 thanks to the configurationally stable C1 stannanes that promote a stereoretentive reaction.

739 Recently, Molander and co-workers[176] have proposed the synthesis of "reversed" *C*-acyl glycosides, *i.e.*
740 compounds of general formula **136,** using a dual-catalytic Ni/photoredox system that is moderately
741 stereoselective and highly compatible with a vast array of functional groups (**Fig. 30**). The starting
742 formylglycosides **137** are easily converted in one step to the 1,4-dihydropyridines (DHP) **138**, bench-
743 stable radical precursors that can be used for cross coupling reactions with carboxylic acids **139**
744 activated *in situ* by dimethyldicarbonate (DMDC). An organic dye (4CzIPN) was used as the photocatalyst
745 in the presence of blue light to achieve oxidative cleavage of the DHP group, thus generating the alkyl
746 radical that enters the Ni-catalyzed cross coupling process. By replacing the activated acid with
747 arylhalogenides, similar conditions lead to the synthesis of 5-arylmonosaccharides.[177] The mild
748 conditions required for the process and the high tolerance for functional groups are attractive for late
749 stage functionalization of complex bioactive molecules.



750

751 *Fig 30.* Dual-catalytic Ni/photoredox system [176], leading to the synthesis of "reversed" *C*-acyl glycosides **136**.

752 Of note, these recent examples of *C*-glycoside synthesis demonstrate that the interest in the application
753 of new catalytic and photocatalytic methods to the synthesis of glycomimetics is steadily increasing,
754 together with the efforts towards the application of novel organic reactions in the carbohydrate field.

4.2 *N*-glycosides

N-glycosides are a class of carbohydrate mimics where the anomeric oxygen is replaced by a nitrogen atom. Many compounds of high pharmaceutical interest, for example anti-cancer agents,[178-179] belong to this class. Additionally, glycosylation is actively employed as a mean of improving the physicochemical properties and the membrane permeability of peptide drugs.[180] *N*-glycosidic linkages created between a sugar and an aglycon (often a peptide) are well described in the literature,[181-184] while synthetic methods for the synthesis of *N*-glycosidic bonds between two sugar units remain rare.[185] In Nature, *N*-linked glycosylation of peptides occurs through the amine group of an asparagine residue, resulting in the formation of an amide bond with a β-linkage to the sugar moiety. Synthetically, glycosyl azides have been used for the synthesis of *N*-glycosyl amides[186-187] and *N*-glycosyl triazoles.[188-189] Anomeric azides are configurationally and chemically more stable than glycosyl amines, thus they represent excellent starting materials for the synthesis of other *N*-glycosides in either configurations. Recently, a direct glycosylation of carboxyamides has been described using a catalytic methodology.[190-191] Glycosyl thioacetimidates **140** and **141** are activated using a catalytic amount of the halogenated azolium salt **142**·TFA (**Fig.31**) and treated with primary amides **143,** to yield *N*- glycosylamides **144** and **145** in good yields. The methods features a wide tolerance of functional groups and may be of interest for late stage modification of pharmaceuticals.

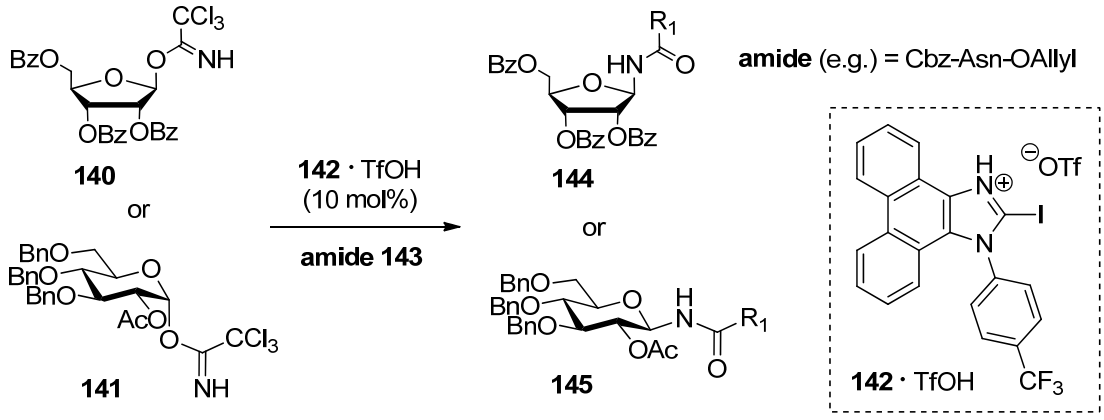
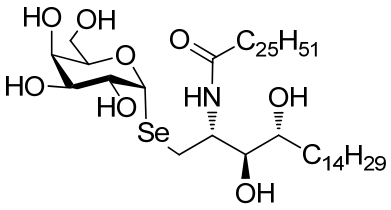


Fig. 31 Direct *N*-glycofunctionalization of amides with glycosyl trichloroacetimidate

4.3 Selenoglycosides

Selenoglycosides are known to possess various useful biological activities and thus they have been employed in the development of new carbohydrate-based drugs for anti-metastatic, anti-tumor[192-193] and immunostimulatory[194] therapeutic treatments (compound **146** as an example in **Fig. 32**).



146
α-Se-GalCer immunostimulant

Fig. 32 An example of selenoglycomimetic used as immunostimulant

Selenoglycosides can also be used as tools for the investigation of sugar-protein interactions.[195-197] From a synthetic point of view, they show a unique reactivity as glycosyl donors:[198] indeed, the C-Se bond can be readily ionized under photo-[199-201] and electro-chemical[202] conditions, generating very reactive cationic and radical-cationic species. However, the preparation of selenoglycosides involves major limitations: generally, only one anomer is accessible, the synthesis is not trivial and the substrate scope narrow (for instance, unprotected sugars are not tolerated under the reaction conditions).

Walczak and co-workers in 2018 proposed a stereoretentive preparation of *Se*-glycomimetics, through a Cu-catalyzed, stereospecific cross coupling process between anomeric stannanes **147** and symmetrical diselenides **148** that allows to obtain either anomeric product (**Fig. 33**), similarly to the method already described in section 4.1.[203]

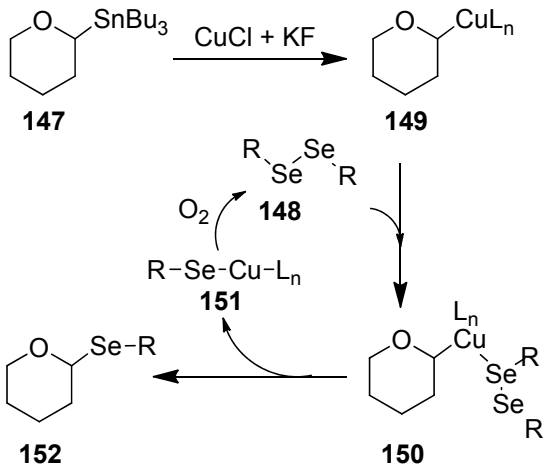


Fig. 33. Proposed mechanism for the stereoretentive glycosyl cross-coupling for the synthesis of *Se*-glycosides.[203]

The proposed mechanism (**Fig. 33**) involves replacement of the Sn-substituent by Cu, generating the intermediate **149** that is configurationally stable at C(1); the intermediate undergoes nucleophilic reaction with the diselenide **148**, giving **150** and the seleno-copper by-product **151**. Under oxidative conditions, **151** can be converted into the original diselenide **148** which can enter the cycle again, to finally afford compound **152**. Interestingly, the cross-coupling reaction with anomeric stannanes **153** and

symmetric diselenides bearing two sugar units **154** generates an 1,1-selenodisaccharide **155** (**Fig. 34a**). In particular, the retention of anomeric configuration along all the process allows a perfect stereocontrol of the final product by the proper selection of the corresponding coupling partners. Finally, the authors applied the same method to the synthesis of selenium-containing glycopeptides. The cross-coupling between protected glycosyl stannanes **156** and seleno-L-cysteine **157** produced the corresponding selenocysteine glyconjugates **158** in good yields (**Fig. 34b**).

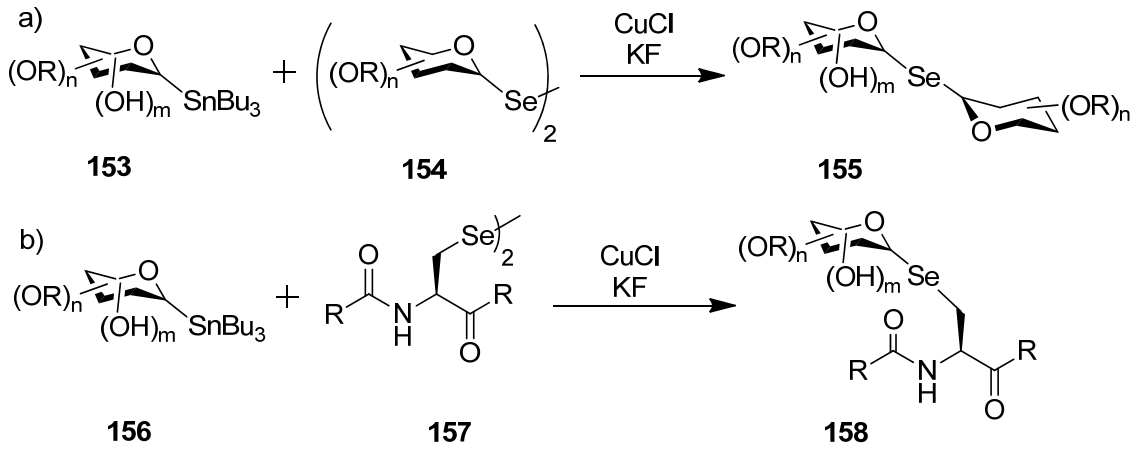


Fig. 34 a) Cross-coupling reaction between symmetric diselenides and anomeric stannanes to generate 1,1-selenosaccharides; b) stereospecific synthesis of selenoglycopeptides

4.4 Thioglycosides

Since sulphur is less basic than oxygen, the *S*-glycosidic linkage is typically more resistant toward both acid-catalyzed and enzymatic hydrolysis. So thioglycosides have been developed as more stable versions of the natural counterparts. As such, thioglycosides have often been found to perform as competitive inhibitors of glycosidases and promising molecules for the development of new therapeutics.[204] Synthetically, thioglycosides have been used successfully in the synthesis of oligosaccharides as glycosyl donors with unique activation conditions.[205] In recent years, glycosyl thiols have become key building blocks for the construction of thio-oligosaccharides and thio-glycoconjugates. Indeed anomeric thiols, once formed, often retain their anomeric configuration in subsequent reactions[206] and do not mutarotate easily, unless they are exposed to harsh conditions. It was however demonstrated that 1-thio-aldopyranoses undergo mutarotation in aqueous media in a pH dependent way.[207] Various methods are available in the literature for the preparation of glycosyl thiols.[208-214]

In 2015, a series of thio-α or β-D-mannose derivatives (**Fig. 35**) were synthesized by Wu and his team in order to investigate the role of the thiol group in different positions of the mannopyranose ring in binding affinity towards the lectin Concavalin A (Con A).[215] These compounds were obtained using the

strategy of protection/deprotection pattern and inversion. An example is reported below (**Fig. 35**) for the synthesis of β-thio-mannopyranose **159**).

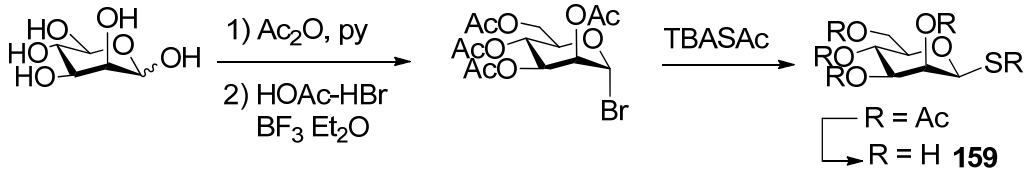


Fig. 35 Synthesis of 1-thio-α/β-D-mannopyranose **159**.

Recently, a selective *S*-deacetylation reaction has been proposed by Shu and co-workers as a practical strategy toward the synthesis of glycosyl thiols **160** (**Fig. 36**).[216] The method, inspired by Native Chemical Ligation (NCL), allows to selectively deacetylate anomeric thioacetates **161** with control of the anomeric configuration.

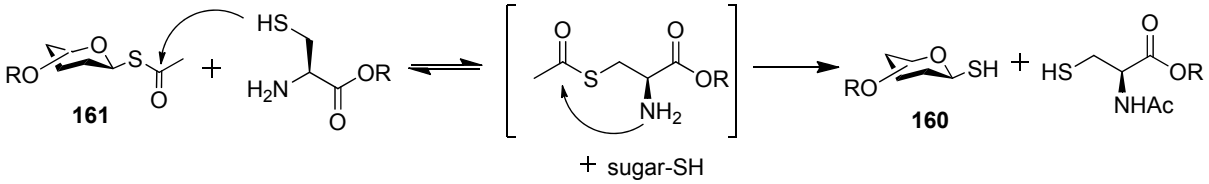


Fig. 36 Selective *S*-deacetylation reaction inspired by NCL proposed by Shu et al.

The procedure was optimized on the peracetylated thio-glucoside **162** (**Fig. 37**). In the presence of the cysteine methyl ester hydrochloride **163** (quenched by $NaHCO_3$), the reaction proceeded fast and the desired product (**164**) was isolated in 95% yield, together with *N*-acetyl cysteine.

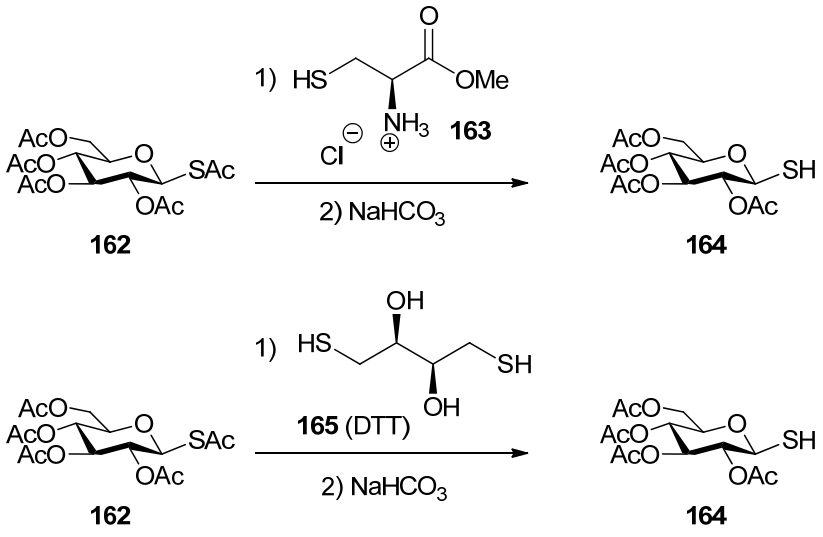


Fig. 37 Optimization of selective thio-deacetylation reaction conditions

When 1,4-dithiothreitol **165** (DTT) was used in stoichiometric amount in combination with $NaHCO_3$, the reaction still proceeded smoothly giving the desired deacetylated compound in 90% yield. Since the *trans*-thio-esterification step is reversible, in the optimized procedure DTT was used in excess.

This method[216] was finally employed for the preparation of the *S*-linked-trisaccharide **166** (**Fig. 38**).

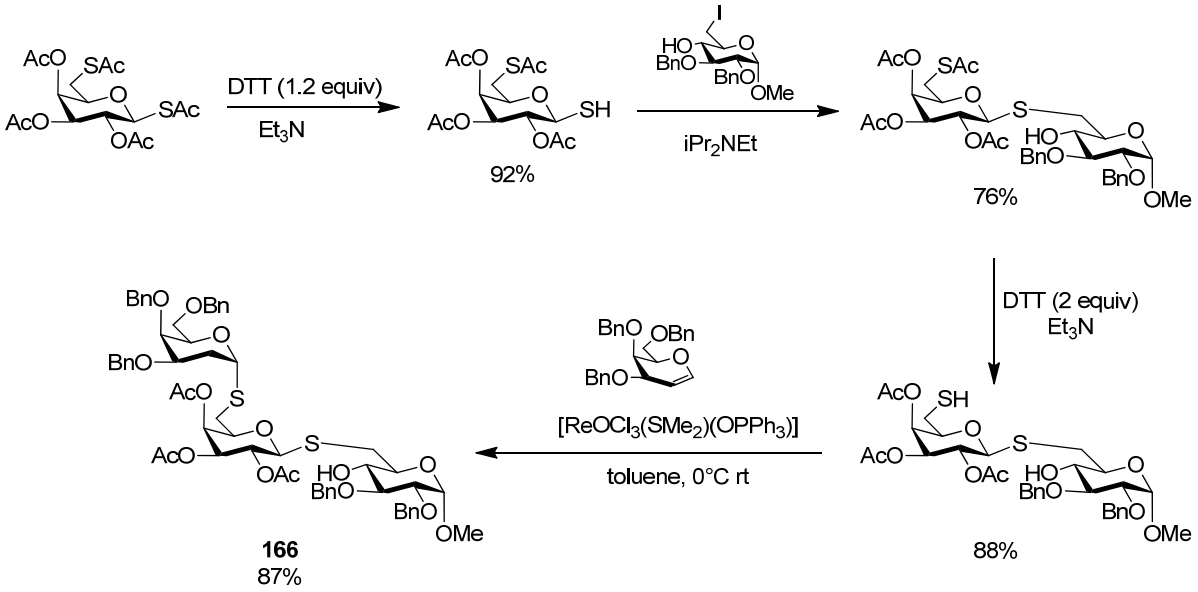


Fig. 38 Preparation of the *S*-linked-trisaccharide **157**

Thioglycosides have been used as nucleophiles in the presence of transition metal-catalysts for the preparation of (hetero)arylthioglycosides (compounds of general formula **167**, **Fig. 39**), an approach that has been recently reviewed.[217] Among different examples reported, the Pd catalysed approach of Messaoudi and co-workers stands out as an efficient and stereoselective coupling of various unprotected and protected glycosyl thiols **168** with aglycon halides **169** in mild conditions, achieved employing G3-XantPhos as the precatalyst (**Fig. 39**).[218]

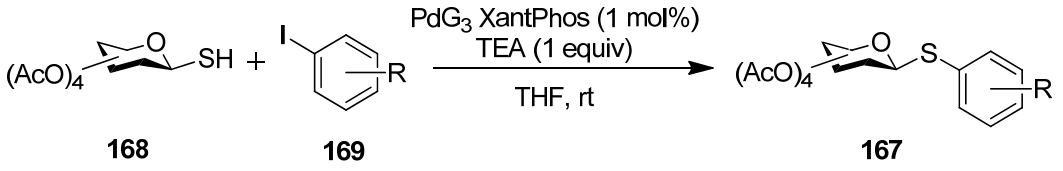


Fig. 39 Coupling of glycosyl thiols with aglycon halides by using G3-XantPhos as precatalyst

The reaction is versatile (various aryl, akenyl and alkynyl halides can be used), tolerates several functional groups (e.g. –Br, -OTs, -OH, -CN, $-CO_2Me$, $-CONR_2$, C(Me)=NNHTs) and it is reproducible up to a multigram-scale. The scope was then expanded to (1→2)-*S*-linked saccharides and *S*-linked glycoconjugates.[219] The same method was also applied to heteroaryl bis-glycosides, where *N*-glycosyl

quinolin-2-ones (general structure **170** reported in **Fig. 40**) where a glycosyl unit is attached to a quinolin-2-one core (one of the most important heterocycle in medicinal chemistry).[220]

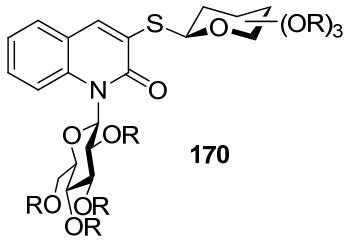


Fig. 40 General structure of *N*-glycosyl *S*-galactosyl quinoli-2-ones

The first use of PdG3-WantPhos in a tandem process for the synthesis of unsymmetrical biaryles thioglycosides **171** was recently described by the group of Messaoudi (**Fig. 41**).[221] The procedure involves a single Pd-catalyst which promotes the catalysis of two individual steps: the first one is the selective coupling reaction between β-thiosugars (**172**) and di-halogeno-arenes (iodo-bromoarenes, **173**); the second step is the C-C bond formation between the mono-halogenated thioglycoside intermediate and various aryl boronic acids (**174**, **Fig. 41**).

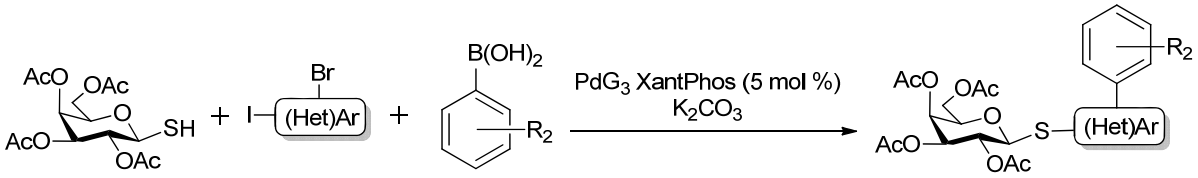


Fig. 41 First use of PdG3-WantPhos for the synthesis of unsymmetrical biaryles thioglycosides

In 2012, Marra and Dondoni exploited thiol-ene coupling reactions for the synthesis of *S*-disaccharides (**Fig. 42**).[222] These transformations can be regarded as "click" reactions, since they occur at room temperature under UV irradiation at λ_{max} 365 nm, using 2,2-dimethoxy-2-phenylacetophenone (DPAP) as initiator. As an example, reaction of the glucosylthiol **175** with alkene **176** was described to afford the thio-1,6-disaccharide **177** in 89% yield at room temperature in 15 min (**Fig. 42**).

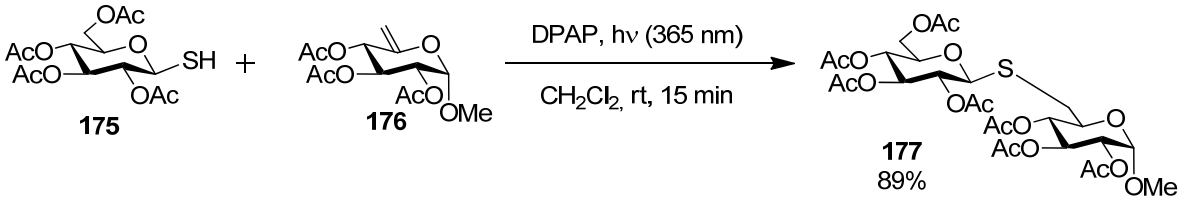


Fig. 42 Examples of thiol-ene coupling between sugar thiols and sugar alkenes

The same method was then applied for the construction of *S*-linked glycopeptides **178** and **179** (**Fig. 43**).

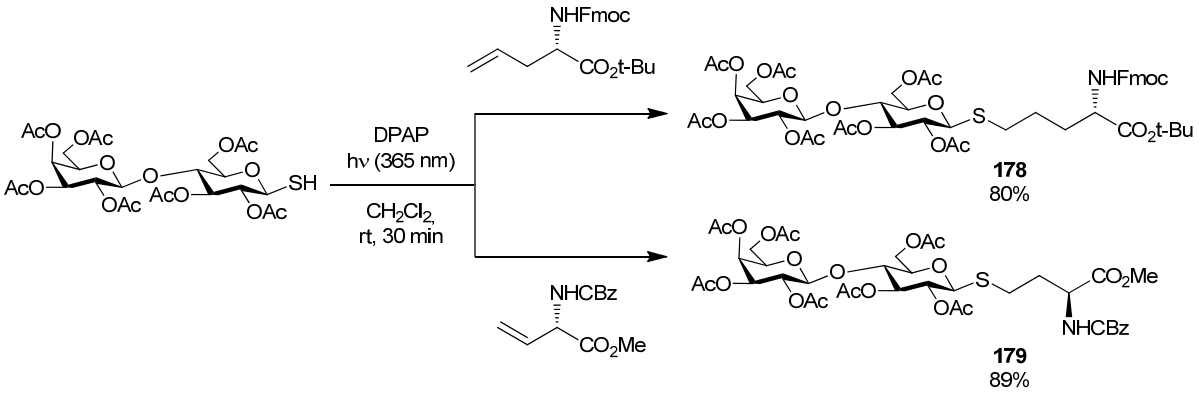


Fig. 43 Synthesis of alkyl-tethered *S*-lactosyl glycosides

In 2016 Belz and co-workers proposed a practical synthesis of *S*-linked glycosides achieved through S_N2 displacement of sugar halides by sugar thiolates generated *in situ* from thioacetates.[223] This procedure allowed to avoid isolation of the free thiol compound, which is often unstable and prone to dimerization. In particular, two different approaches were proposed: the first one requires an initial insertion of the mercapto group into the glycosyl acceptor, with the leaving group on the glycosyl donor (or viceversa) and it is the most convenient for the synthesis of β-linked compounds (as α-glycosyl halides can be readily prepared). The second approach is based on the configurational stability of anomeric thiolates. This strategy is applied for α-linked *S*-glycosides, installing the sulphur atom into the glycosyl donor with stereochemical control at the building block stage. Belz's work focused in particular on the preparation of *S*-linked α-1,6-oligomannosides. As an example, **180** is obtained by coupling iodide **181** and thioacetate **182** (**Fig. 44**) in the presence of diethylamine in dimethylformamide.

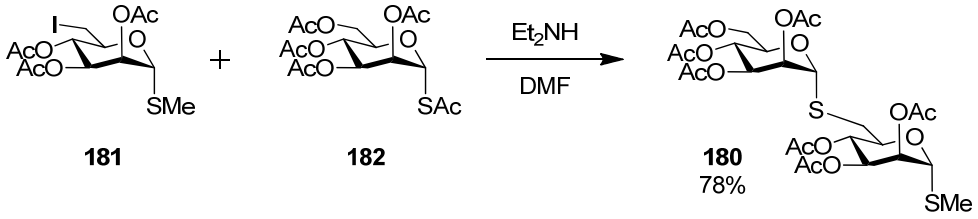


Fig. 44 Preparation of *S*-linked α-1,6-oligomannoside **180**

In a recent application, this method was exploited for the synthesis of Manα(1,2)Man disaccharide mimics, using the one-pot opening reaction of epoxide **183** by the glycosyl thiol **184a** generated *in situ* from **184** (**Fig. 45**). Compound **185** was obtained as a single isomer from *trans*-diaxial opening of **183**, owing to the conformational stability imparted to the cyclohexane ring by the two carbomethoxy substituents.[224]

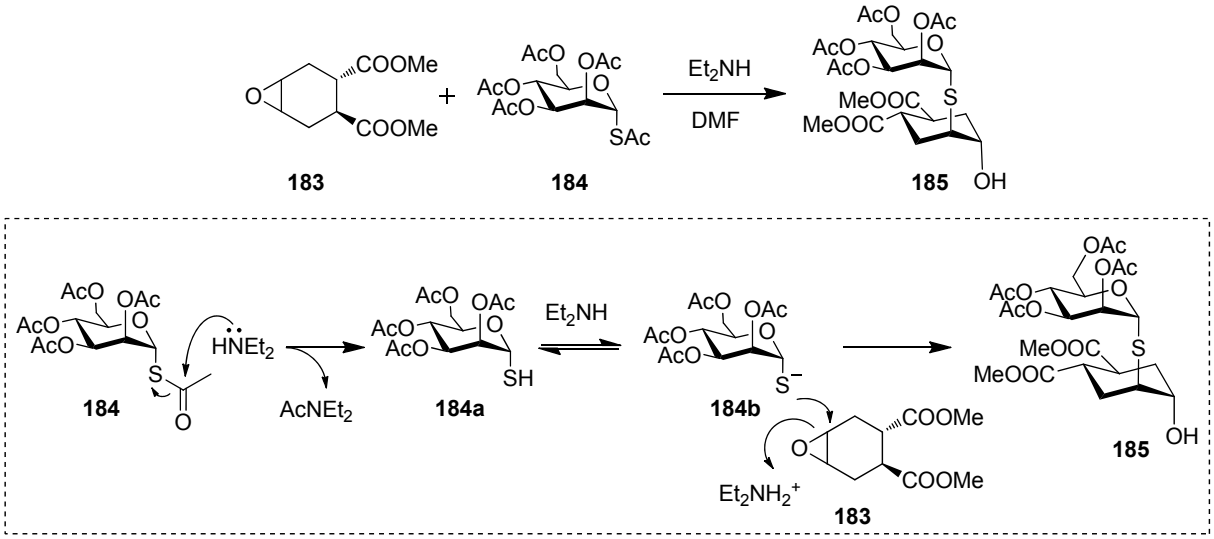


Fig. 45 Synthesis of Manα(1,2)Man disaccharide mimic **185**

5. Conclusions

The recent advances in glycobiology are bringing to the fore the multiple roles played by carbohydrate-protein interactions and by sugar-modifying enzymes in physiological and pathological events, particularly in the immune system. Modulation and control of the proteins involved is attracting increasing attention in the medicinal chemistry world. Only very recently, the identification of multiple secondary sites on lectins that can be targeted with drug-like small molecules/fragments has been reported.[225-226] In the case study reported by Aretz et al.,[225] the small molecules discovered do not bind to the sugar site in the carbohydrate recognition domain, but to a vicinal site that apparently allosterically controls the glycan binding site. The consequences of this novel binding mode to the downstream signalling events controlled by the glycan-lectin interaction are so-far unknown. For the time being, the use of a monosaccharide anchor modified into a glycomimetic structure is still affording maximal likelihood of discovering ligands that can target sugar-binding proteins. The optimization of these structures will depend critically on the ability not only to enhance their binding affinities, but, crucially, to overcome the inherently poor pharmacokinetic properties of carbohydrates. Strategies applied to this end in glycomimetics design have recently been reviewed and relevant examples highlighted.[8] The present overview about the state of the art of glycomimetic synthesis highlights the strong interest that these structures have raised in the past few years. It clearly appears that even new methods still under development in synthetic organic chemistry, such as organocatalytic and photocatalytic methods, are rapidly being applied to carbohydrates, generating a bounty of new

opportunities for glycomimetic design. It is our expectations that new developments of therapeutic and diagnostic tools should be fast to follow.

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