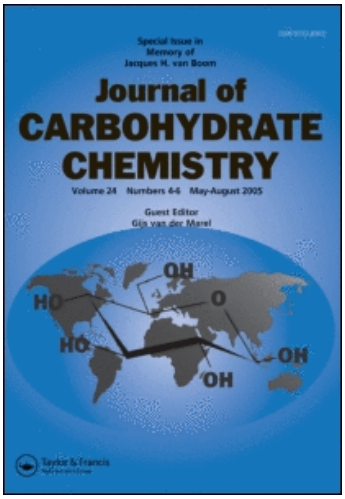

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Carbohydrate-Based Molecular Scaffolding

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Carbohydrate-Based Molecular Scaffolding

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The use of modified carbohydrates, such as sugar amino acids (SAA), iminosugars and policyclic derivatives, as scaffolds for the generation of bioactive compounds, and the use of carbohydrates as building blocks or ligands for the production of polymers for biomedical applications, is reviewed.

Keywords Scaffolds, Iminosugars, Sugar amino acids, Chemical libraries Glycomimetics, Peptidomimetics, Biomaterials

INTRODUCTION

Monosaccharides are one of the relevant classes of natural compounds that, like amino acids, constitute the building blocks for the generation of the polymers of life. It is well known that, through the variation of the anomeric configuration and the position of the hydroxyl group involved as acceptor in glycosidic linkages, carbohydrates exploit their great diversity potential, exerting an impressive role in biological recognition phenomena.

As a matter of fact, carbohydrates present unique features widely exploited by nature: (1) their cyclic structure guarantees an adequate conformational rigidity, (2) the presence of multiple hydroxyl groups provides different positions for linkages, and (3) the chirality provides different orientations of the hydroxyl groups and therefore different directions for the substituents linked to them. In other words, nature exploits carbohydrates as "scaffolds" to build up natural molecular architectures.

Taking advantage of this concept, recently synthetic chemists started to exploit carbohydrates as scaffolds for the generation of a variety of non-natural potentially bioactive compounds.

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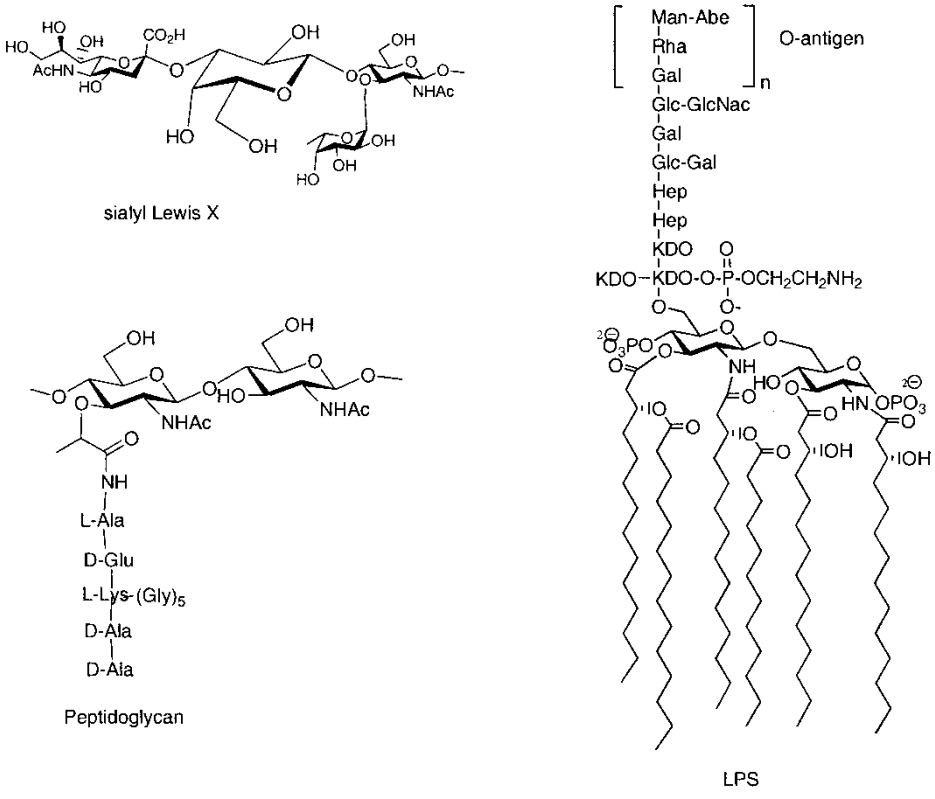

Figure 1: Examples of how nature exploits carbohydrates as scaffolds that link other sugars, lipids, peptides, and phosphates in well-defined positions and orientations.

Using carbohydrates as scaffolds, nature is very heterogeneous: other sugars, but also lipids, peptides, phosphates, and sulphates, are linked to the different hydroxyl groups providing the required diversity as exemplified in Figure 1.

In sialyl Lewis X, a monomer such as galactose, highlighted in the figure, links sugar residues in two different positions. In peptidoglycan, *N*-acetylmuramic acid links a sugar (GlcNAc) and a peptide. In lipopolysaccharide (LPS), a glucosamine scaffold links in different positions not only another glucosamine and a complex saccharidic chain, but also lipidic chains and a phosphate.

Also, synthetic chemists exploited their fantasy, using natural and modified monosaccharides, oligosaccharides, and glycomimetics as scaffolds for the generation of libraries of compounds for pharmacological screening, as well as for the production of biomaterials for tissue engineering and as molecular tools for the generation of nanostructures. This review will provide an overview of the products of this fantasy. It does not have the ambition to be exhaustive.

SCAFFOLDS DERIVED FROM NATURAL MONOSACCHARIDES AND THEIR USE FOR THE GENERATION OF LIBRARIES OF BIOACTIVE COMPOUNDS

The use of carbohydrates as building blocks for the generation of libraries of biologically active compounds is relatively recent, Hirschmann, et al. using for the first time in 1992 a β-D-glucoside scaffold as a peptidomimetic targeting the somatostatin receptors.[1] The field has known a rapid and diverse development, partially covered in some reviews.[2]

There are a number of factors that make sugars, monosaccharides in particular, attractive molecular scaffolds: availability, high functionalization, chirality, and structural rigidity. Schematically, in an hexopyranosidic scaffold (Fig. 2), diversity can be generated by the five functional groups present at carbon atoms C(1)–C(4) and C(6) as well as by the five contiguous stereocenters at carbon atoms C(1)–C(5).

These characteristics have been exploited in the construction of bioactive compounds following two different (we would say opposite) philosophies. For one side, well-defined mimics of known bioactive compounds have been built up, properly exploiting the structure of the sugar scaffold; from the other side, libraries of diverse compounds bearing various pharmacophores in a combinatorial approach have been produced, exploiting the points of diversity intrinsic in the sugar structure.

Target Oriented Synthesis of Bioactive Compounds using Natural Monosaccharide Scaffolds

Examples of application of the first "philosophy," which can be defined as target oriented synthesis of bioactive compounds using carbohydrate scaffolds, have been described in the field of peptidomimetics.

There are a large number of peptides with potential therapeutic interest that display limited biostability (due to proteases hydrolysis) and poor oral

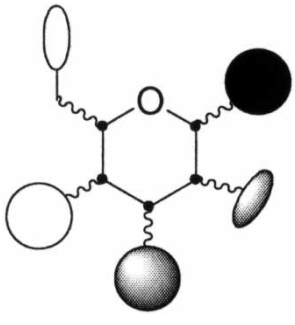

Figure 2: Structural diversity points on a hexopyranose.

activity, limiting thus the application of peptide drugs.[3] One solution to this problem is the design of peptidomimetics in which the amide backbone is substituted with a different skeleton while maintaining the proper orientation of the amino acidic substituents.[4] While the design of nonpeptide peptidomimetics using novel scaffolds was anticipated by Farmer in 1980,[5] when he proposed the attachment of side chains to a cyclohexane ring, the first to synthesize a non peptide peptidomimetic (**1**, Fig. 3) were Belanger and DuFresne.[6]

Compound **1** featured a bicyclooctane core with novel scaffolding, being recognized by the opiate receptor for which it was designed.

Papageorgiou[7] and Hirschmann et al.[1,8] first introduced peptidomimetics that possessed a carbohydrate backbone. In both cases it was desired to create mimics of the hormone somatostatin (SRIF), a cyclic tetradecapeptide with a wide variety of biological activity, most of it inhibitory in nature,[9] but that displays a very short biological half-life.[10]

Papageorgiou et al. utilized the tetrasubstituted xylofuranose **2** (Fig. 4) as scaffold for mimicking somatostatin,[7] while Hirschmann et al. attached the amino acid side chains of somatostatin and its analogs to a glucose scaffold, compounds **3** and **4,** that would maintain the functional groups in the bioactive conformation.[8]

Since these original exploitations of carbohydrates as templates for peptidomimetics, the sugar skeleton, mostly in its pyranosidic form, has been largely utilized as scaffold for the design of various bioactive compounds. Glucose-based mimics of the depsipeptide hapalosin, such as **6** and **7**, were also synthesized.[11] Glucose and allose scaffolds were used for the design and synthesis of mimics of the cyclic peptide endothelin antagonist BQ123 (**5**, Fig. 4).[12] Other examples are reported by Murphy et al.,[13] Locardi et al.,[14] Le Diguarher,[12] Wessel et al.,[15] and Hanessian et al., [16] who synthesized mimics of other pharmacologically relevant peptides, taking advantage of the multifunctionality of a sugar.

Another example of target oriented synthesis of bioactive molecules based on a carbohydrate scaffold is that reported by Nicolaou et al.,[17] who designed carbohydrate mimics of the cyclic peptide cRGD*F*V (Fig. 5), an antagonist of vitronectins, $\alpha_v\beta_3$, natural ligands to integrins, which are a class of extracellular proteins that facilitate cell-cell recognition.

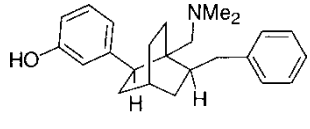

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Figure 3: Nonpeptide peptidomimetic.

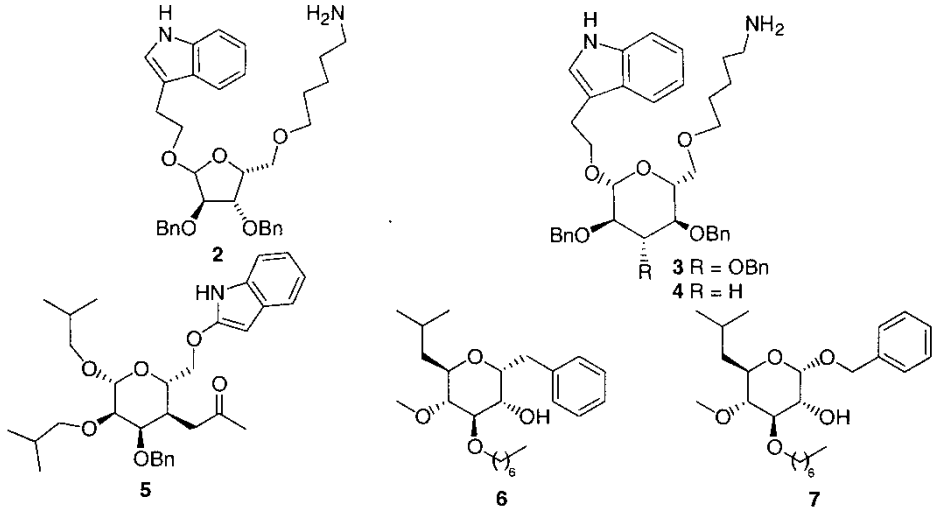


Figure 4: Carbohydrate-based peptidomimetics.

Target Oriented Synthesis of Bioactive Compounds using Sugar Amino Acids

A different approach to the generation of peptidomimetics emerged, in which various synthetic strategies were used to attach the amino acid functionalities directly to the carbohydrate skeleton and to generate thus synthetic sugar amino acids (SAAs).[18,19] SAAs are well spread in nature,[20] and a well-known example is the sialic acid family widely found peripherically on glycoproteins.

SAAs have been synthesized since the 1950s,[21] but were utilized as biopolymer building blocks to mimic oligo- and polysaccharide structures. A great variety of these examples have been reported[22] and reviewed[23], which take

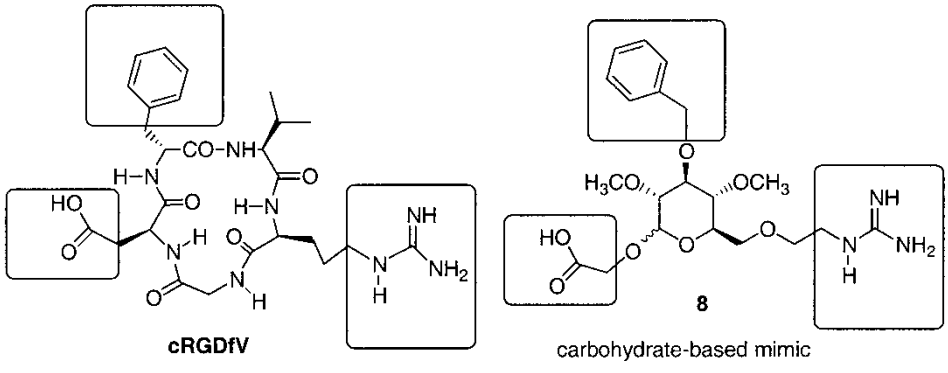


Figure 5: Cyclic peptide cRGD*f*V and its mimic.

advantage of the fact that well-established peptide synthesis methodologies both in solid phase and in solution can be exploited for the synthesis of carbopeptoids oligomers. Furthermore, the folding properties of those oligomeric carbopeptoids have attracted interest.[24]

The first example of a sugar amino acid synthesized to be used as a peptidomimetic comes from the work of von Roedern and Kessler.[25] Glucosyluronic acid **9**, (Fig. 6) was incorporated into a cyclic peptide with the β-turn motif of the somatostatin containing tetrapeptide Phe-D-Trp-Lys-Thr.

Starting from sugar β-amino acids, in which the β-carbon is the anomeric center of a furanoid sugar,[26] Taillefumier et al. recently reported the first synthesis of anomeric spiroannelated glycodiazepines,[27] compounds discussed in "Diversity in spirocyclic systems," as potential new templates for biological tools and peptidomimetic scaffolds.

Libraries Generated from Carbohydrate Scaffolds

The generation of a library of compounds can follow two different approaches: it can be constructed through a parallel synthesis of individual targets or adopt a combinatorial approach. Initial efforts in this area were dedicated mostly to designing and synthesizing building blocks that would be then incorporated in cyclic peptides; the possibility of molecular scaffolding (i.e., construction of libraries from the structural variety present in the building block) being somewhat less explored. An example of the first type of approach is that reported by Nicolaou et al. [28] for the generation of carbohydrate mimetics of the cyclic peptide cRGD*F*V. Using molecular calculations (Insight-Discover, CV-Force Field), several structures of carbohydrate-based mimics were minimized, and as a result, a small library of nine compounds emerged. Each of the components of the library was then subjected to synthesis, and an example is outlined in Scheme 1. Starting with methyl α-D-mannopyranoside, compound **10** was prepared in a sequence of selective protection/deprotection reactions. Methyl mannoside **10** was selectively *O*-benzylated at C(3) and then exposed to diethylaminosulfur trifluoride (DAST), to provide **11** after

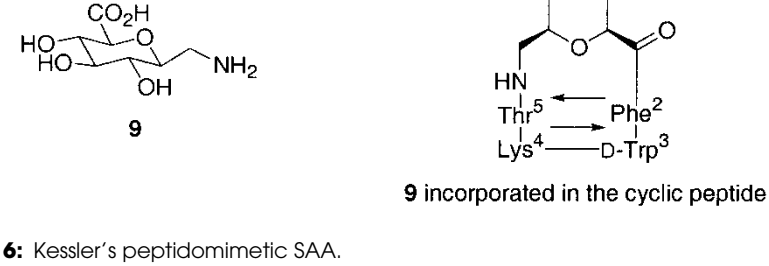
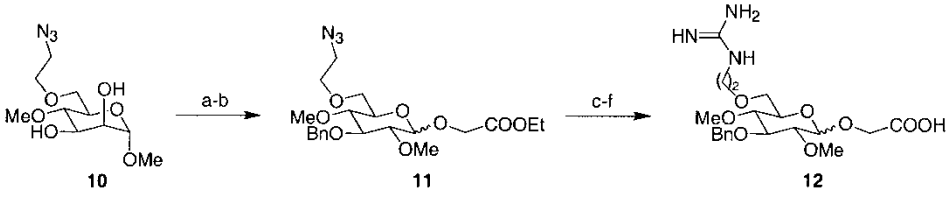


Figure 6: Kessler's peptidomimetic SAA.



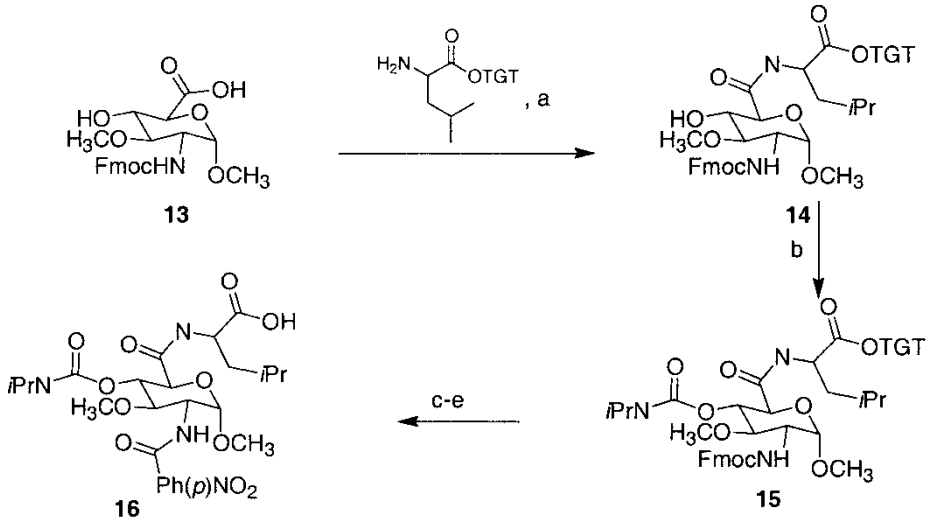
Scheme 1: *Reagents and conditions*: a) i. *n*-Bu_2SnO, MeOH, Δ; ii. BnBr, CsF, DMF, 25°C, 14 h, 93%; b) DAST, CH_2Cl_2, 40°C, 4 h, 63% (α/β, 2:3); c) Cp_2ZrCl_2, $AgClO_4$, $HOCH_2CO_2Et$, 4 Å mol. sieves, PhH, 25°C, 4 h, 55% (α/β, 2:3); d) Ph_3P, THF, H_2O, 65°C, 4 h, 85%; e) LiOH, THF/H_2O (8:1), 25°C, 4 h; f) 1*H*-pyrazole-1-carboxamidine · HCl, *i*-Pr_2NEt, DMF, 25°C, 16 h, 80% over two steps.

treatment with $HOCH_2CO_2Et$. During the latter process, the C(1) methoxide migrated to C(2), with simultaneous inversion of configuration, and a 2:3 mixture of α- and β-anomeric fluorides was formed. When this mixture was subjected to excess of 2-hydroxyethyl acetate, in the presence of Cp_2ZrCl and $AgClO_4$, glycosides **11** were obtained, precursors to the targeted mimetics. Further manipulations of the azide and ethyl ester moieties provided scaffolds **12**, which contained on the side chains the necessary guanidine and carboxylic acid functionalities.

The previously described results open the way to the second "philosophy" concerning the use of carbohydrate scaffolds, which takes advantage of the sugar diversity and multifunctionality to generate libraries of compounds for high throughput screening in drug research. By manipulations of the diversity points present in a monosaccharide, through both a careful choice of orthogonal protecting groups and configurational interconversions, libraries of structurally related compounds (same molecular weight, same pharmacophoric groups, comparable solubility, different spacial orientation, hence different biological properties) can be achieved. [2c,29,30] Since the diversity at the chiral centers is readily available from nature, most of the studies to date explored the diversity offered by the selective functional group of protection/deprotection, at three,[31,32] four, and all five positions.[33,34]

The preferred way of introducing three pharmacophores on a sugar monomer is by having two functionalities orthogonally protected, while the third functionality (usually at C(1) or at C(6)) is linked to a solid support and is removed last.[32] An example in which the C(6)-functionality of a glucoside-based scaffold is linked to a polymer comes from Sofia et al.'s work.[31] Amino glucoside **13** (Sch. 2), containing three points of diversity, at C(2), C(4) and C(6), was prepared from glucose in seven steps and an overall 22% yield.

Coupling of **13** with eight amino acid-functionalized trityl-Tentagel resins, using *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) as coupling agent, in the presence of diisopropylethyl amine, generated new scaffolds of type **14**, featuring two points of diversity, at C(2) and at C(4). Treatment of **14** with isopropyl isocyanate introduced the



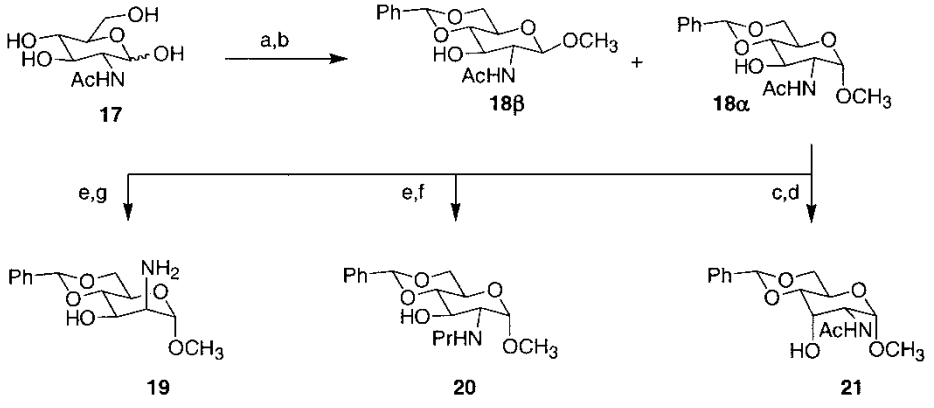
Scheme 2: *Reagents and conditions:* a) HATU, DIPEA, DMF, rt 100%; b) 0.5 M *i*-PrNCO/DMF, Cu(I)Cl, rt 100%; c) 20% piperidine/DMF, rt d) 4-$NO_2C_6H_4COOH$, HATU, DIPEA, DMF, rt e) 10% TFA/1,2-dichloroethane, rt 100%.

carbamate pharmacophore at C(4); subsequent deprotection of the fluorenylmethoxy carbonyl group using piperidine and condensation of the resulting free amine moiety with *p*-nitrobenzoic acid introduced the last pharmacophore at C(2). Final cleavage from the solid support generated compound **16**. In this manner, a 1,648-member sublibrary of biologically active compounds was created.

A different perspective on creating molecular diversity is given by Emmerson et al.,[35] who rather than manipulating only the functional diversity present in monosaccharides, chose to exploit diversification through chirality interconversion as well. They prepared 4,6-*O*-benzylidene derivative **18** from readily available *N*-acetyl-D-glucosamine **17** (Sch. 3). Manipulation of the stereochemistry at C(1)–C(3), and of the protecting groups at the amine moiety, generated 24 related compounds, out of which only three are depicted in Scheme 3. Compounds **19**–**21** were then used as chiral ligands for the asymmetric reduction of aldehydes with dialkyl zinc.

From the combinatorial chemistry point of view, compound **18** is a molecular scaffold with diversification of three sites. Stereochemical manipulations of **18** generate new scaffolds **19**, **20**, and **21**, containing now two points of diversity, at C(2), and C(3), which could be further exploited through selective protection/deprotection strategies.

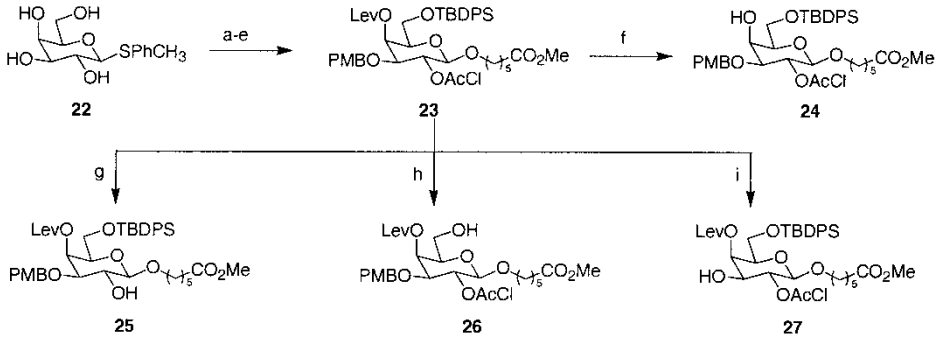
While linking one of the functionalities present in a sugar scaffold to a polymer support is a method mostly used when creating diversification at four sites of the scaffold,[9a,33] other approaches were also exploited, due to



Scheme 3: *Reagents and conditions:* a) MeOH, AcCl, 100%; b) $PhCH(OMe)_2$, *p*-TsOH, DMF, 70°C, 69%; c) DMSO, $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, −78°C, 75%; d) *L*-selectride, THF, −78°C, 60%; e) N_2H_4, 130°C, 88%; f) 1.1 eq. PrI, K_2CO_3, MeCN, reflux, 63%; g) H_2O_2, Na_2WO_4, MeOH, H_2O, 46% then $LiAlH_4$, THF, 0–50 °C, 28%.

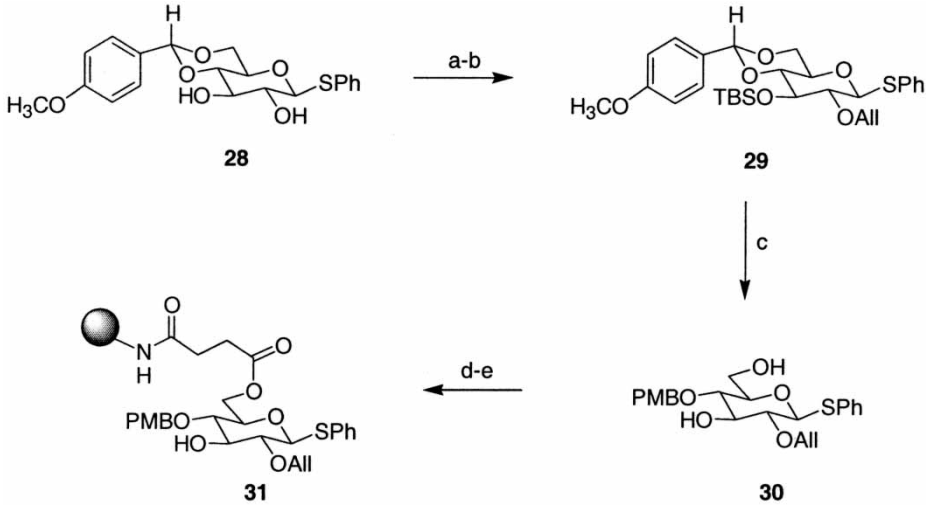
inconveniences of working in solid phase. Limitations in choice of the functional groups due to (a) sensitivity of linkers and pharmacophores to the deprotection conditions, (b) need of Williamson etherification as means of functionalization of free hydroxyl groups, and hence the stability to strong bases, are examples of such inconveniences, apart from the usual difficulties of solid phase (solubility, linker lability). In particular, orthogonality of protecting groups is particularly problematic when the points of diversity are expanded; acidic and/or basic conditions, oxidations, catalytic hydrogenations, use of fluoride ions to deprotect silyl ethers, isomerizations of double bonds, and photolysis can be exploited for deprotection, but very often protecting groups are labile to more than one of these treatments. Furthermore, after deprotection, a derivatization must be effected in experimental conditions, not interfering with the remaining protecting groups and with the linkages of the already introduced substituents. An approach coming from Wong et al.'s work[36] avoids the use of polymer support and exploits the different reactivity of the four hydroxyl groups of a thiol glycoside in the solution phase chemistry. For instance, orthogonally protected galactoside **23** (Sch. 4) was rapidly synthesized by introducing the four orthogonal protecting groups, *t*-butyldiphenylsilyl at C(6), followed by *p*-methoxybenzyl at C(3), chloroacetyl at C(2), and finally, levulinyl at C(4). Final glycosylation with methyl 6-hydroxyhexanoate gave the desired scaffold, which upon selective deprotection and subsequent glycosylation with seven donors generated a library of 45 protected oligosaccharides.

In our group, a glucoside scaffold presenting four points of diversity was efficiently prepared after linking the C(6) functionality to a polymer support.[32c] Thus, treatment of the easily available benzylidene acetal **28** with



Scheme 4: *Reagents and conditions:* a) TBPSCl, imidazole, DMF, 100%; b) i. Bu_2SnO, toluene, benzene, reflux; ii. PMBCl, Bu_4NI, DMF, 60°C, 49%; c) $ClCH_2COCl$, Et_3N, CH_2Cl_2, −20°C to rt 52%; d) levulinic acid, DCC, DMAP, CH_2Cl_2, 83%, e) i. $HO(CH_2)_5CO_2Me$, NIS, TMSOTf, 4 Å molecular sieves, CH_3CN, −20°C to rt; ii. $HgBr_2$, toluene, CH_3NO_2, 60°C, 85%; f) NH_2-NH_2 AcOH, THF/MeOH, 10:1, 90%; g) $NaHCO_3$, MeOH/H_2O, 5:1, 60°C, 99%; h) HF-pyridine, AcOH/THF, 1:4, 98%; i) CF_3COOH, CH_2Cl_2, −20°C, 97%.

t-butyldimethylsilyl chloride in the presence of imidazole selectively provided the silyl ether at C(3) (Sch. 5). Subsequent allylation gave compound **29**, which was then exposed to a $LiAlH_4$-$AlCl_3$-reducing system to afford reductive opening of the acetal with simultaneous hydrolysis of the silyl ether. Due to the low reactivity of the carboxy-polystyrene resin toward compound **30**, the latter was functionalized at C(6) with a succinate linker and then linked to an amino-polystyrene resin, finally providing **31** with an acceptable loading value



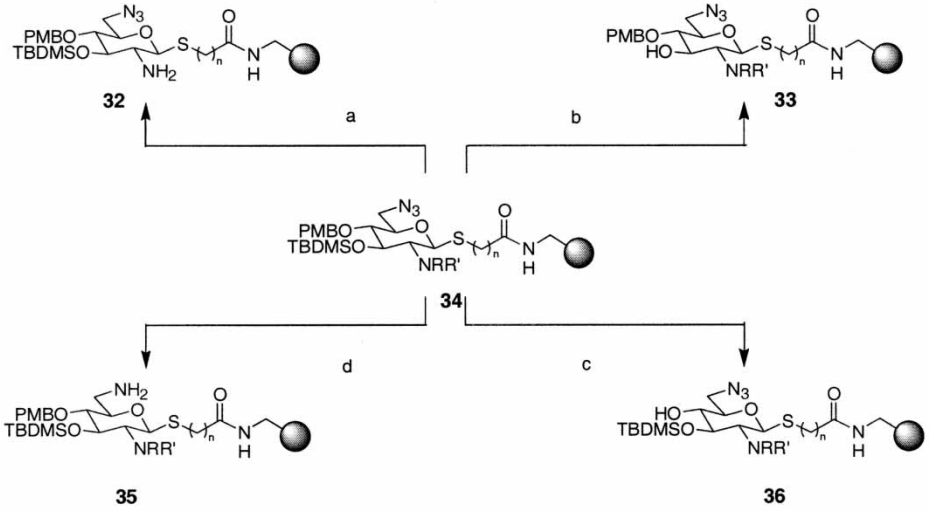
Scheme 5: *Reagents and conditions:* a) TBDMSCl, Imidazole, CH_2Cl_2, 94%; b) AllBr, NaH, DMF, 70%; c) $LiAlH_4$-$AlCl_3$, CH_2Cl_2, Et_2O, 82%; d) succinic anhydride, pyridine, DMAP; e) NH_2-PS/DV, HOBt, HBTU, DIPEA, DMF.

(0.9 mmol/g). In compound **31** the four diversity sites were generated by the thiol moiety at C(1), the allyl ether at C(2), the secondary unprotected hydroxyl group at C(3), and the *p*-methoxybenzyl ether at C(4).

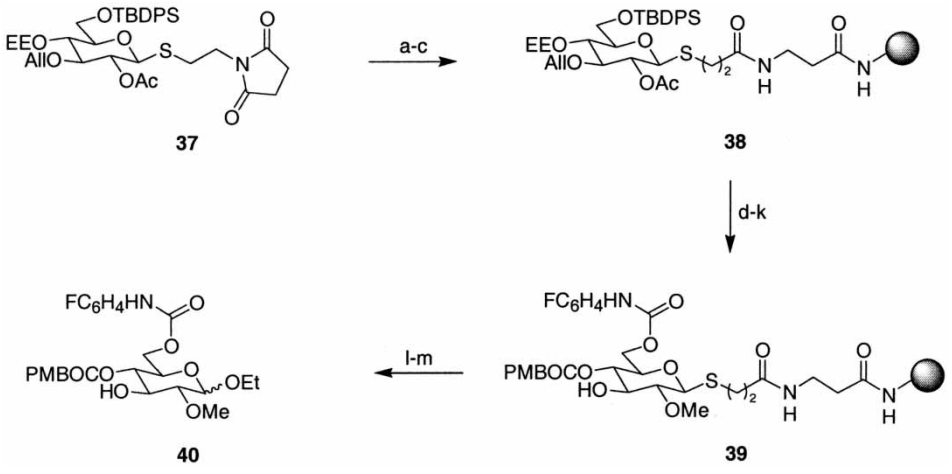
Most recently, Hunger et al. employed 6-azido-6-deoxyglucosamine to generate diversity at four sites of the building block.[37] In scaffold **34** (Sch. 6), the anomeric center was linked to a polymeric support through a thioglycoside anchor and was not used as a source of diversity. Any of the protecting groups present in the molecule, an Alloc group at C(2), a *tert*-butyldimethylsilyl ether at C(3), a *p*-methoxybenzyl ether at C(4), and an azide at C(6), were selectively removed in the presence of the others, independently of the deprotection sequence and in quantitative yields.

The novelty brought by this approach is that a second generation of scaffolds could be created by replacing any of the protecting groups with a molecule containing a functionality corresponding to that of the replaced protecting group. This approach limits the request of orthogonalities as for each point of diversity, and protecting group and substituents are labile and stabile to the same experimental conditions.

An example of a glucoside scaffold in which all five hydroxyl groups were used to create diversity comes from the work of Opatz et al.[33c] The previously synthesized thioglycoside **37** was converted into building block **38** in three steps (Sch. 7), involving hydrolysis of the succinimide ring, linkage of the resulting carboxylic acid to polymer support, and a final acetylation of the aminofunctions present on the polymer. In this manner, scaffold **38** presents an anomeric center anchored to polymer support, easily convertible into a *O*-, *N*-,



Scheme 6: *Reagents and conditions:* a) TBAF, THF; b) DDQ, CH_2Cl_2, H_2O (10 vol%); c) i. Bu_3P, DMF; ii. Et_3N, DMF, H_2O; d) ($Pd_2(dba)_3$), *p*TsOH, DMF; all yields are quantitative.



Scheme 7: *Reagents and conditions:* a) LiOH, THF, H_2O, quant.; b) TOTU, HOBt, DIPEA, DMF, aminomethylpolystyrene; c) Ac_2O, pyridine, dioxane, 98%; d) NH_2-NH_2 H_2O, DMF, e) KOtBu, DMF; f) MeBr, DMF; g) TBAF, THF; h) FC_6H_4NCO, DMAP, dioxane; i) PPTS, MeOH, dioxane; j) Steglich esterification at position 4; k) *p*-TsOH, $(Pd(PPh_3))_4$, DME, dioxane; l) NBS, EtOH, DTBP, CH_2Cl_2; m) Et_4NBr, cyclohexene, CH_2Cl_2, 79% yield.

or *S*-glycoside and four orthogonal protecting groups, a *t*-butyldiphenyl silyl ether at C(6), a 1-ethoxyethyl group at C(4), an allyl ether at C(3), and an acetate at C(2). Using the sequence of deprotections depicted in Scheme 7, a library of 36 compounds type **40** was generated.

Moitessier et al. constructed stereodiverse libraries based on a glycodic scaffold in which an amino group is linked through an appendage at the anomeric carbon, whereas a carboxylic function decorates one of the other hydroxyl groups of the sugar.[38] Compounds **41** (Fig. 7), based on a xylopyranosidic backbone, are mimetics of the RGD sequence, aiming to reproduce the RGD loop both in fibronectin ($\alpha_{\Pi b}\beta_3$ integrin receptors) and vitronectin ($\alpha_v\beta_3$ integrin receptor).

The scaffold used for the construction of the library was D-xylose, which possesses three equatorial hydroxyl groups with the same type of reactivity, and hence one source of diversity. The anomeric hydroxyl, the second diversity point, was selectively transformed into an allyl ether, and then the free hydroxyl groups of the resulting xyloside were subjected to alkylation with different stoichiometries of benzyl bromide.

Libraries Generated from Modified Sugar Amino Acid Scaffolds

We have already mentioned that the presence of a carboxylic and an amino function in a sugar molecule (SAA) is employed in the synthesis of pseudopeptides mimicking well-defined bioactive peptides. SAAs have also found

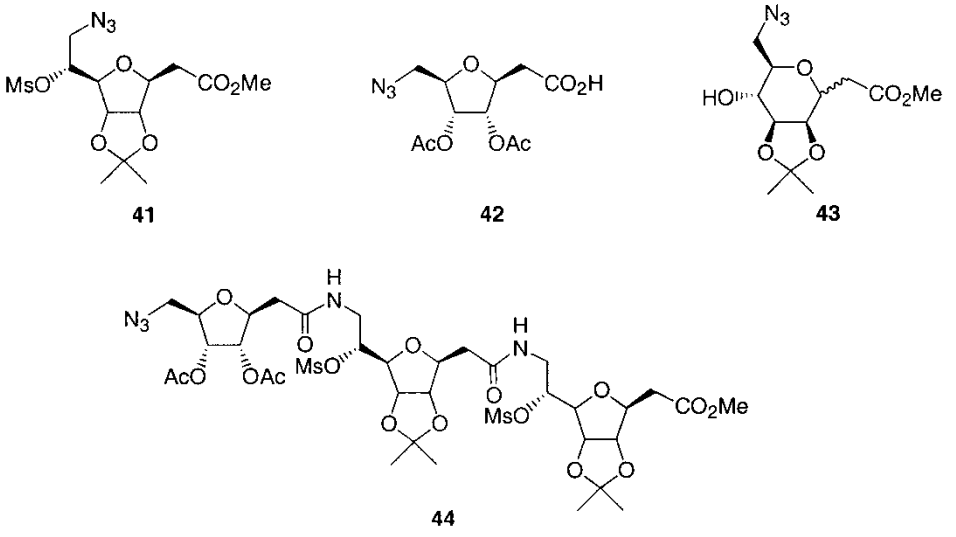


Figure 7: Lansbury's SAA's building blocks.

application in the synthesis of both small and big libraries of potentially bioactive compounds, exploiting not only the amino and acidic function in peptide synthesis, but also the diversity derived from chirality and derivatization of the different hydroxyl groups.

The earliest example of the potential of SAAS as building blocks for the creation of libraries comes from the work of McDevitt and Lansbury.[39] Twelve sugar amino acids were synthesized, from which **45**–**48** are depicted in Figure 8 and Scheme 8, and were then used to generate a small library of oligomers (such as **48**) via oligomerization.

Both furanosidic and pyranosidic forms of sugars were used, and the library was created by manipulations of the azide and carboxylic acid moieties. The advantage of these types of compounds is that they may not be susceptible to proteases cleavage, due to altered backbone relative to natural peptides.

Edwards et al.[40] recently synthesized a library of 99 compounds from 3-deoxy L-lyxose scaffold **51** (Sch. 9), which was in turn prepared from the L-gulonolactone monoacetonide derivative **49**. Compound **51** contained three points of diversity generated by the azide moiety at C(4), the ester group at C(2), and the primary alcohol at C(5). Since the diversification at the primary hydroxyl group through alkylation was found to be problematic for a parallel synthetic approach, the alkyl group was introduced prior to diversification at the remaining functionalities.

Thus, compound **51** was first methylated, and then the azide converted into urea, after hydrogenation, and finally the ester into an amide. Variation of the alkyl groups on the urea and on the ester generated the library. This work

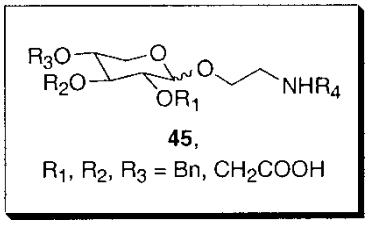


Figure 8: Sugar amino acids library.

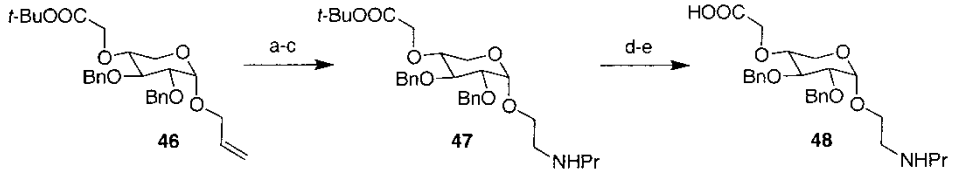
stresses again the value of furanose sugar amino acids as stereodiverse building blocks.

SCAFFOLDS FROM POLYCYCLIC CARBOHYDRATE DERIVATIVES

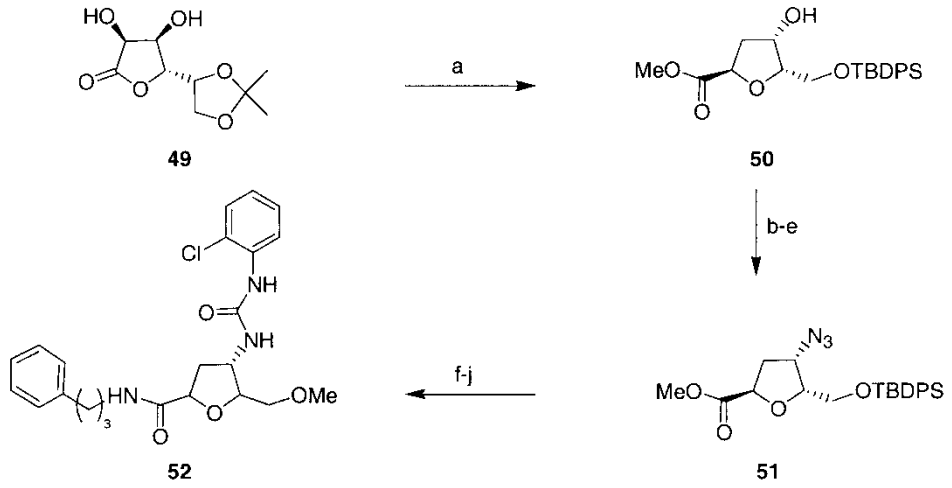
As outlined before, the conformational rigidity of carbohydrates represents one of the attractive features for using them as scaffolds for the design of bioactive molecules. By increasing the conformational rigidity of the parent carbohydrates, the generation of new classes of compounds with better scaffolding qualities is possible. Furthermore, the structural originality obtained by proper manipulations of the natural sugars allows patenting the obtained scaffold, which is of fundamental importance for using it in drug research. One intensively investigated way of reducing the molecular flexibility and generating original structures is the introduction of a second and even a third ring on the sugar backbone, generating a fused or a spirocyclic system.[41–43] Molecular diversity, and thus creation of libraries of such compounds, is obtained in most cases by exploitation of the functionalities originally present in the parent sugar, through generation of new functionalities during the construction of the polycycle, or both.

Diversity in Fused Polycyclic Systems

Timmer et al. recently synthesized a small library of pyranofurans from a mannitol-derived scaffold (**54**, Sch. 10) containing two points of diversity,



Scheme 8: *Reagents and conditions*: a) i. O_3, MeOH, THF, −70°C; ii. $NaBH_4$; b) PPh_3, NBS, DMF, 50°C, c) $C_3H_7NH_2$, DMF, 70°C, d) $(Boc)_2O$, NEt_3, CH_2Cl_2, e) TFA/H_2O, 3:1.

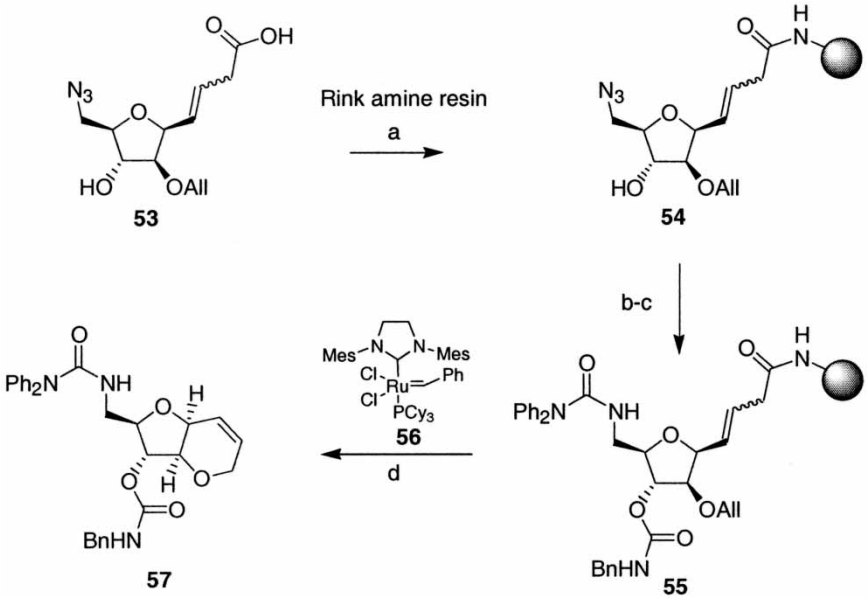


Scheme 9: *Reagents and conditions*: a) 5 steps, 32%; b) Tf_2O, Py, DCM; c) CsO_2CCF_3, butanone; d) MsCl, DMAP, pyridine, 100%; e) NaN_3, DMF, 70%; HCl, MeOH, 78%; f) HCl, MeOH, rt, 73%; g) MeI/CH_3CN (1:1), Ag_2O, 80°C, 99%; h) H_2, Pd/C 10%, EtOAc, i) i. ClC_6H_4NCO, CH_2Cl_2, rt, 16 h; ii. AMP's, rt, 16 h; j) $PhC_3H_6NH_2$, MeOH, 60°C, 24 h, 83%.

originally present in the parent sugar.[44] The *cis*-fused pyranofuran systems were prepared using a solid-phase ring-closing metathesis (RCM) strategy. Thus, diene **53**, prepared in 12 steps from D-(+)-mannitol, was bound to a Rink amine resin, in the presence of BOP and diisopropyl amine. At this point, the molecular diversity present in **54** was exploited by first condensing the free secondary hydroxyl group with various isocyanates to the corresponding carbamates. Subsequent Staudinger reduction of the azide moiety followed by condensation with various acyl chlorides generated fully functionalized resins type **55**. Exposure of **55** to 5 mol% of Grubbs catalyst (**56**) triggered not only the RCM, but also the cleavage of the products from the polymer. A small library of nine *cis*-fused pyranofuranes of type **57** was created in this manner.

In our group, molecular diversity was introduced during the construction of the polycyclic system.[45] Bi- and tricyclic azido acids scaffolds were synthesized in liquid phase, starting from fructose. Thus, *C*-allyl fructose derivative **58** (Sch. 11), prepared in 98% yield and 60% *de* upon treatment of methyl *O*-tetrabenzyl fructoside with allyltrimethylsilane in the presence of borontrifluoride etherate, was submitted to iodocyclization conditions, by treatment with iodine in tetrahydrofurane, at low temperatures.

Compound **59** was then obtained as a mixture of diastereomers, which was further exposed to Zn in acetic acid, to generate the derivative **60** by reductive elimination. The oxidation of the free hydroxyl group in **60** to the corresponding aldehyde was followed by stereoselective addition of vinylmagnesium bromide, to generate the *R* allylic alcohol **61** in good yield and excellent

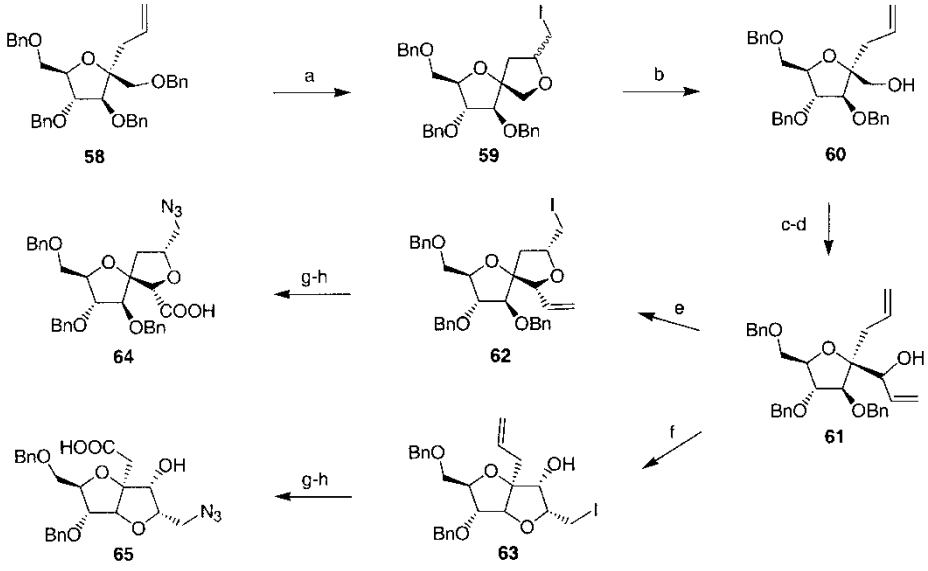


Scheme 10: *Reagents and conditions:* a) BOP, DIPEA, 16 h; b) Bn-N=C=O, Et_3N, 16 h; c) i. Me_3P, THF, 1 h, then H_2O/dioxane 2 h; ii. Ph_2NCOCl, DIPEA, 16 h; d) **56** (5 mol%), CH_2Cl_2, reflux, 16 h, 98% overall yield.

diastereoselectivity. Compound **61** represented the key intermediate for the generation of both spiro (**64**) and fused (**65**) bicyclic scaffolds. Notably, when the 5-exo-trig cyclization was carried out in tetrahydrofuran, it involved the free hydroxyl group of **61** and generated the spirane **62**, whereas in dichloromethane the iodocyclization afforded the fused compound **63**. Manipulations of the iodine and olefin moieties in compounds **62** and **63** afforded finally bicyclic derivatives **64** and **65**. Molecular diversity was generated in scaffolds **64** and **65** by the different spatial arrangement of the azido groups with respect to the carboxyl terminus, allowing thus the possible introduction of various pseudopeptide secondary structures.

Using a similar approach, the fused bicyclic azido acid **66** (Fig. 9) was obtained from D-(+)-arabinofuranose.[46] In compound **66**, the secondary benzyl ether, the azide, and the carboxylic acid moieties create three points of molecular diversity in a conformationally constrained structure.

Once more the presence of the carboxylic and azido functions allowed the use of compound **66** in the synthesis of conformational constrained pseudopeptides. It has been calculated that the distance between these functions in compounds **66** (6 Å) corresponds to that of a β-turn peptide structure; therefore, the synthesis of pseudopeptide **70** with the biologically relevant RGD sequence constrained in a clinked structure has been affected, exploiting the carbohydrate scaffold **66** as a peptide building block, as reported in Scheme 12.



Scheme 11: *Reagents and conditions:* a) I_2, THF; b) Zn, AcOH, EtOH/Et_2O, 1:1; c) DMSO/Ac_2O, 2:1; d) CH_2=$CHCH_2MgBr$, THF; e) I_2, THF, 0°C; f) I_2, CH_2Cl_2, rt; g) NaN_3, Bu_4NI, DMF; h) $NaClO_2$, NaH_2PO_4, CH_3CN.

Diversity in Spirocyclic Systems

Taillefumier et al. recently reported the first synthesis of anomeric spiroannelated glycodiazepines,[47] of the general structure **71** (Fig. 10), as potential new templates for biological tools and peptidomimetic scaffolds. These compounds belong to the class of spironucleosides, which includes the naturally occurring (+)-hydantocidin **72**[48] and the spirodiketopiperazine glucopyranose **73**[49] as depicted in Figure 10.

The preparation of structures like **71** is exemplified by the synthesis of glycodiazepine **77.** The exo-glycal **74** (Sch. 13), upon treatment with benzyl amine and then exposure to an atmosphere of hydrogen, provided the β-amino acid **75**. Coupling of the free amine in **75** with a range of *N*-benzyloxycarbonyl (*Z*) α-amino acids (in the example shown in Sch. 1, with α-alanine) provided dipeptide **76**, which was then converted to the target spirane following a sequence of reactions that included saponification of the methyl ester, hydrogenolysis of the *Z* group, and diphenylphosphoryl azide (DPPA) base cyclization.

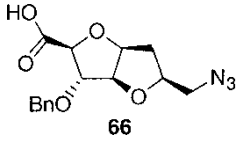
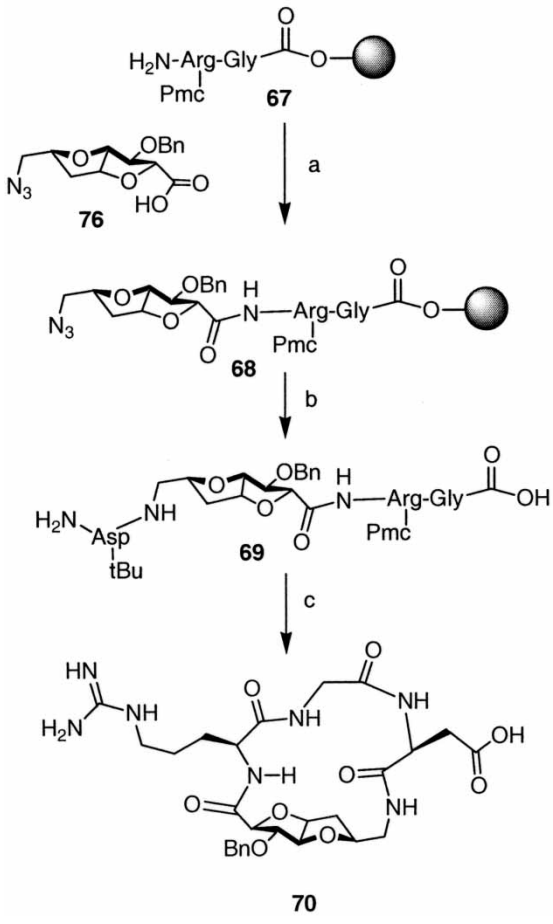


Figure 9: A bicyclic sugar amino acid.



Scheme 12: *Reagents and conditions:* a) HOBT, HBTU, DIPEA, DMF; b) i. Bu_3P, DIC, Fmoc-Asp(OtBu)-OH; ii. piperidine 20% in DMF; iii. 1% TFA in CH_2Cl_2; c) i. 0.5 mM in DMF, HBTU, HOBt, DIPEA; ii. 95% TFA, 2.5% TIS 2.5% H_2O.

A different class of spiroheterocyclic compounds was obtained with good stereoselectivity and yields upon [3 + 2] cycloaddition of *exo*-glycals with nitrones and nitrile oxides.[50] For instance, microwave-activated cycloaddition of compound **78** (Sch. 14) with nitrone **79** provided a spiro-isoxazolidines **80** (ratio at C(3), S/R, 2:1). The formation of the new C(4) chiral center occurred with complete stereo control, the absolute (S) configuration at this center being determined by the (Z) geometry of the starting olefin.

The most used methods for the generation of spiro-carbohydrate derivatives seem to be the ring-closing metathesis and the Pauson-Khand reaction.[51] In these cases, the spirane ring was created at the anomeric center of the sugar.

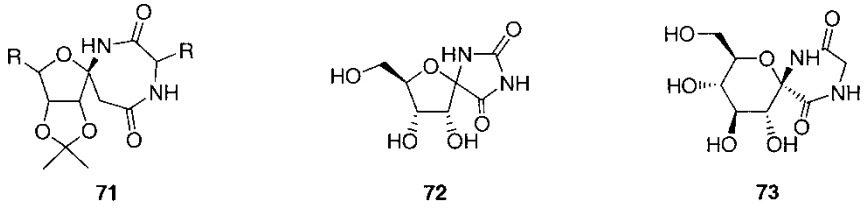


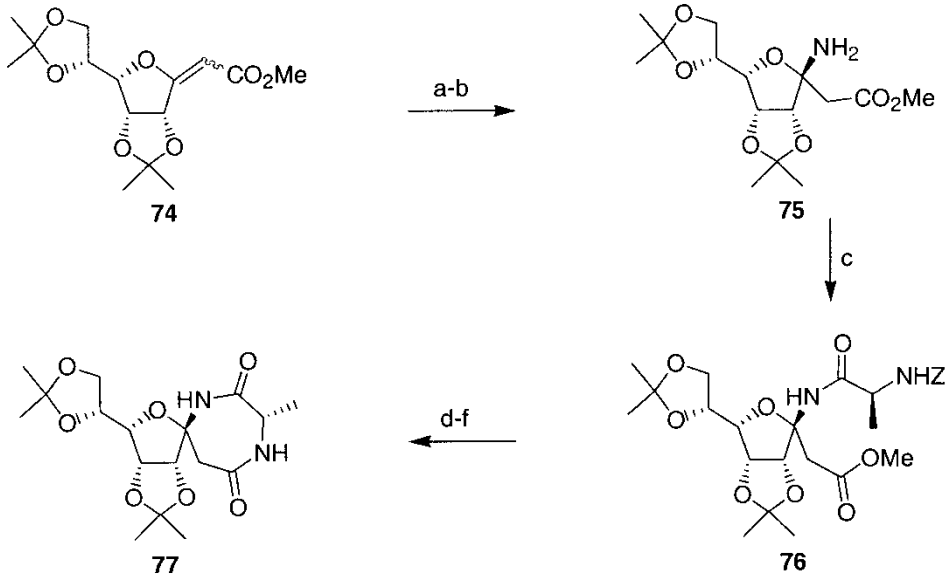
Figure 10: Spironucleosides.

An illustrative example in which of spirosugar building blocks were generated via both ring-closing metathesis and Pauson-Khand reaction comes from the work of Leeuwenburgh et al.[52] Starting from tetra-*O*-benzyl gluconolactone, the synthesized ketoglycosidic enynes **82** and **84** (Sch. 15[53]) are common starting materials for the generation of two different types of oxacyclic scaffolds. On one hand, treatment of **82** and **84** with 5 to 7 mol% of Grubbs catalyst, in toluene, at 60°C, generated spiroacetals **85** and **86**.

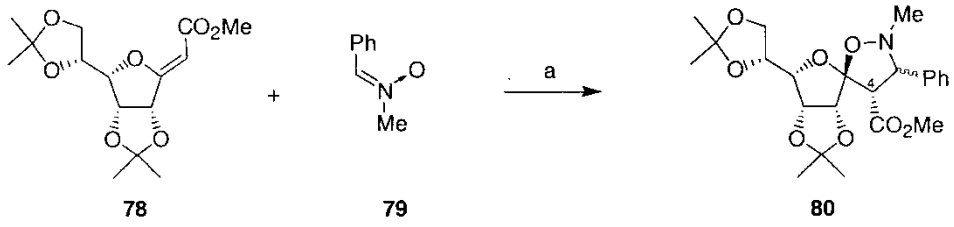
Exposing compounds **82** and **84** to the Co(IV) complex and NMO, the more complex spiroacetals **87** and **88** were synthesized (Sch. 16).

Further exploitation of compounds **85–88** could lead to more complex spiroacetals by manipulation of the functionalities present in these molecules.

In our group, the spirane moiety was introduced at the anomeric center using the iodocyclization approach earlier described.[54] Starting from



Scheme 13: *Reagents and conditions*: a) $BnNH_2$ (neat), 48 h; b) H_2, 10% Pd/C, EtOAc; c) Z-NHCH(CH_3)CO_2H, PyBOP, Et_3N, DMF, rt, 14 h, 92% from **74**; d) K_2CO_3, MeOH/H_2O (10:1), rt, 48 h; e) H_2, 10% Pd/C, EtOH/EtOAc (1.5:1); f) DPPA, Et_3N, DMF, 0°C to rt, 14 h.



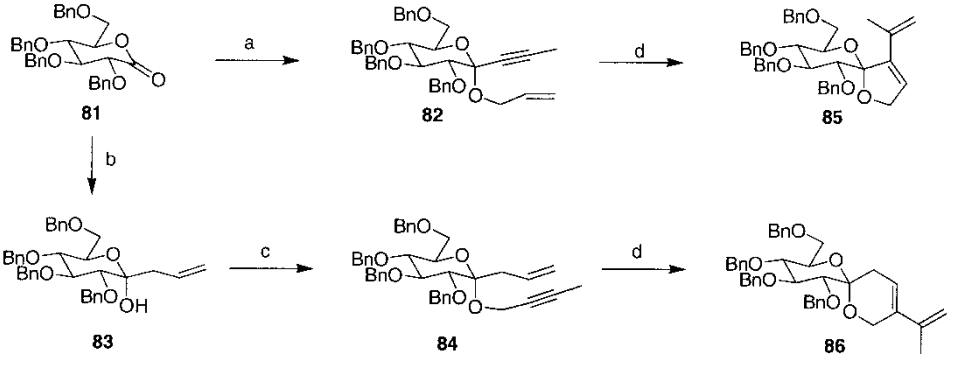
Scheme 14: *Reagents and conditions*: a) toluene, 150°C, 25 min MW activation, 80%.

aldehyde **89** (Sch. 17), a sequence of reactions involved its conversion to the protected amine derivative **90**, and iodocyclization of the latter provided the spirane **91**. Hydrolysis of the fluorenyl ester generated spontaneously oxazolidinone **92**, which, after ring opening upon Fmoc protection and Jones oxidation, afforded the spiro-annulated D-proline mimetic **93**.

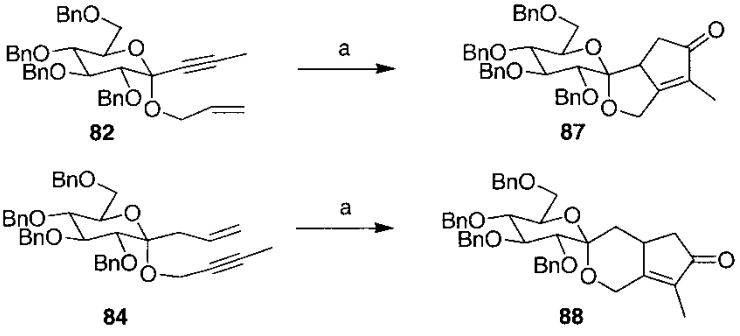
Shibuta et al. reported the preparation of two diastereomeric 1,1-linked galactosyl mannosides possessing a spiro-thiazine ring, which act as sialyl Lewis mimetics.[55] For example, when the unprotected ulo-disaccharide **94** was coupled with *S*-cysteine (Sch. 18), in the absence of an acid catalyst, diastereomer **95** was obtained in good yield.

SCAFFOLDS FROM IMINOSUGARS

Along with structurally modified carbohydrates, bioactive glycomimetics such as iminosugars, which are known to be potent inhibitors of carbohydrate-processing enzymes, have been synthesized and used as scaffolds for the generation of libraries in search of improved selectivity and activity. These compounds are relatively laborious to synthesize, so the creation of a library



Scheme 15: *Reagents and conditions:* a) i. $BrHC{=}CHCH_3$, *n*-BuLi, THF, −78°C; ii. AllBr, HMPA, −78°C to rt; b) ref. (51); c) 2-butyn-1-ol, K-10, mol. sieves, CH_2Cl_2; d) Ru-catalyst (5–7 mol%), toluene, 60°C.



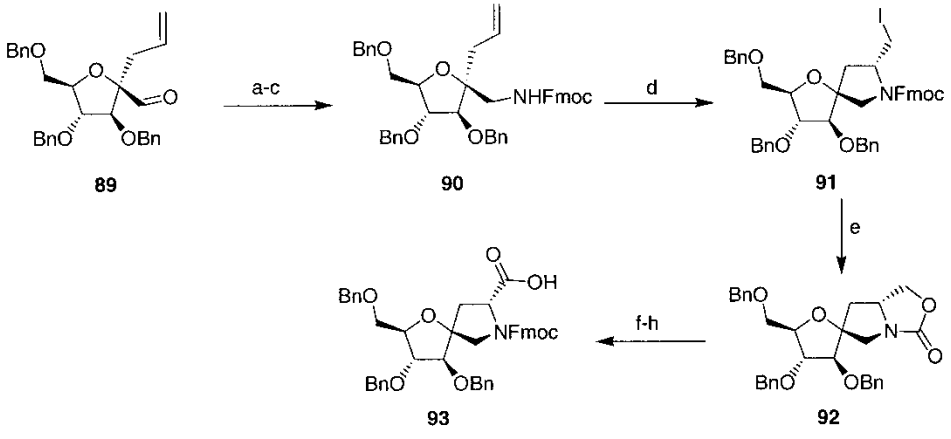
Scheme 16: *Reagents and conditions:* a) i. $Co_2(CO)_8$, CH_2Cl_2; ii. NMO excess, rt.

based on iminosugars, rather than a parallel synthesis of individual structures, could facilitate the search for compounds with improved activity.

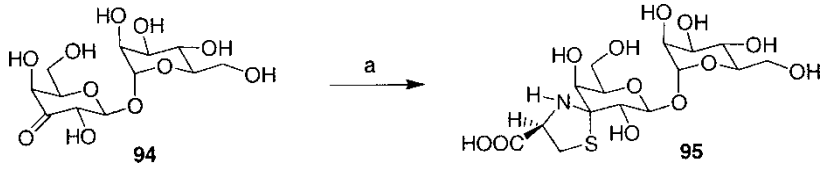
The first example of a library built on an iminosugar is the one reported by Lohse et al.[56] (Fig. 11). An analog of 1-azafagomine, a potent glycosidase inhibitor, is linked to tripeptides obtained from five aminoacids using a combinatorial approach.

A library of 125 compounds was synthesized and investigated toward β-glycosidase inhibition. One of the members of the library, compound **97** (Fig. 12), showed to be an inhibitor having a K_i value of 20 μM.

Chapman et al. realized a pyrrolidine derived library[57] by reacting different Grignard reagents with two cyclic imines **98** and **99** that can be considered sugar-derived scaffolds. The diastereoisomeric iminosugars **100** and **101** were obtained (Sch. 19).



Scheme 17: *Reagents and conditions:* a) NH_2OMe, THF, EtOH; b) $LiAlH_4$, THF; c) FmocCl, DIPEA, CH_3CN; d) I_2, DME; e) NaOH 1 M, CH_3CN; f) NaOH 3 M, EtOH reflux; g) FmocCl, DIPEA, CH_3CN; h) Jones oxidation.



Scheme 18: *Reagents and conditions:* a) L-cysteine, DMF, 72%

The Grignard addition allowed the introduction of a hydrophobic substituent, which in some cases proved to increase enzyme inhibition and bioavailability.

Wu et al.[58] realized a fuconojirimycin-based library in search of fucosidase inhibitors. They obtained 60 compounds by condensing the amino group of fuconojirimycin derivative **102** with different carboxylic acids (Sch. 20). The reaction was carried out in the presence of HBTU (1 equiv.) DIEA (2 equiv.) in DMF, and the products were screened after dilution with H_2O without further purification.

Within the library two compounds (**104** and **105,** Fig. 13) showed the most potent inhibitor properties toward fucosidase known so far.

A very original "dynamic" library was that produced by Gerber-Lemair et al.,[59] which is based on an equilibration between an iminosugar scaffold **106** and different aldehydes **107** to form the corresponding imines **108** (Sch. 21). The originality stays in the fact that all members of a library of aldehydes are reacted simultaneously with amine **106**, generating a dynamic library of imines, which are incubated with the enzyme. The imine that is the best inhibitor is expected to bind preferentially to the enzyme, thus making possible a rapid assay of a large number of imines.

The library was tested as inhibitors towards α-mannosidase, and the highest activities were found for aromatic aldehydes and in particular benzaldehyde and its substituted derivatives.

In these examples the iminosugar was first synthesized and subsequently derivatized in one position; more recently we[60] reported the synthesis of a

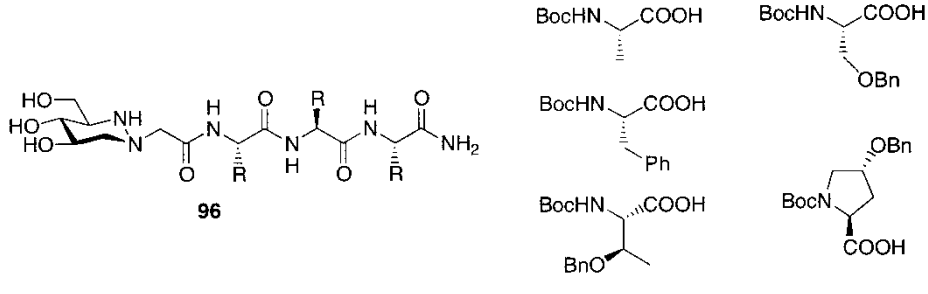
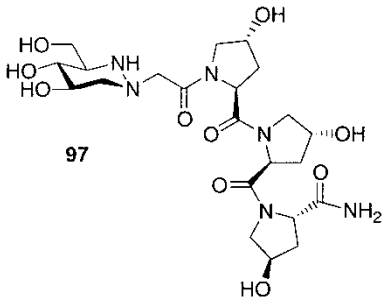


Figure 11: 1-Azafagomine-based library.



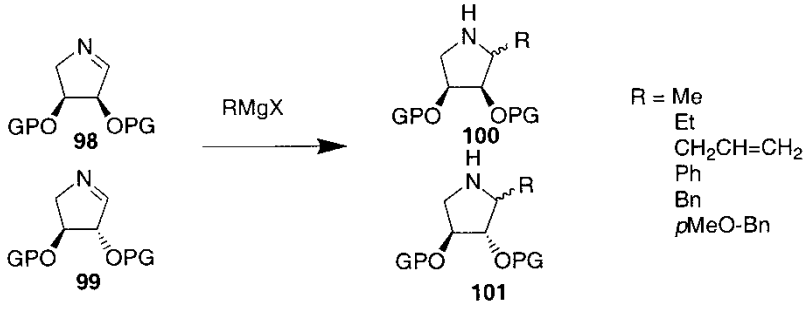
97

Figure 12: A glucosidase inhibitor.

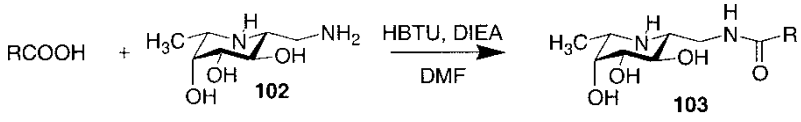
small library of iminosugar scaffolds having various points of diversity: variable stereochemistry on ring substituents and on the nitrogen atom, a carboxymethyl functional group and orthogonal protections on the hydroxyl groups (Fig. 14).

With this approach a library based on eight scaffolds was obtained. Each member could then be selectively derivatized on the primary hydroxyl group, on the carboxylic function, and on the nitrogen, for the scaffolds bearing an *N*-Bn or *N*-allyl group after removal of the *N*-substituents. Examples of scaffold derivatization are reported in Scheme 22; an azido group was introduced exploiting the primary hydroxyl affording derivatives **110**. The ester group was hydrolyzed and the carboxylic acid so obtained was condensed with different aminoacids affording derivatives **114**.

An iminosugar has been also used by Chery et al.[61] as scaffold in the synthesis of a peptidomimetic analog of a known HIV-1 protease inhibitor. A β-D-glucopyranoside-based scaffold (**115**, Fig. 15) reported previously showed an activity that was hypothesized by the authors being related to a competitive binding in the enzyme active site. On this basis the authors designed and synthesized the 1-deoxymannonojirimycin-based analog (**116,** Fig. 15) where the ring nitrogen, which is believed to be protonated at physiological pH,



Scheme 19: Pyrrolidine library by Grignard addition.



Scheme 20: Fuconojirimycin library.

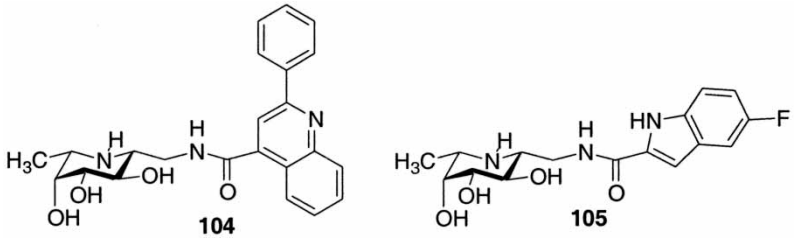


Figure 13: Fucosidase inhibitors.

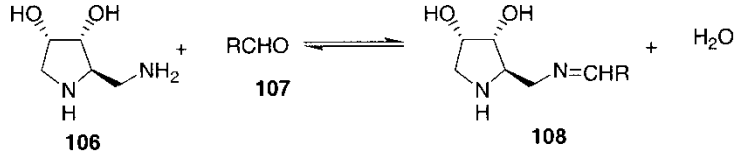
becomes a hydrogen bond donor that, from molecular modeling indications, could bind with a carbonyl group of HIV-protease amide backbone.

CARBOHYDRATE SCAFFOLDS IN POLYMERS

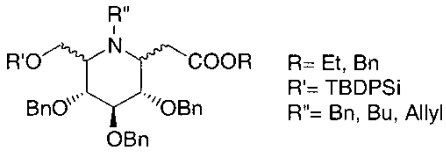
Synthetic polymers based on carbohydrate scaffolds have recently gained interest not only for their mechanic properties combined with the biodegradability, but also as biomaterials for biomedical applications.

Polymer Scaffolds for Tissue Engineering

Carbohydrate-based polymer scaffolds have been and are extensively used in the field of tissue engineering. Every year millions of patients suffer the loss or failure of an organ or tissue as a result of accident or disease, and a revolutionary strategy to treat these patients is engineering a manmade organ or tissue. Polymer scaffolds, in this kind of strategy, are used to repair and regenerate tissue as they serve to support, reinforce, and organize regenerating tissue, and in some cases they also serve to release bioactive substances. For these applications it's fundamental that these polymer scaffolds display



Scheme 21: Dynamic library.



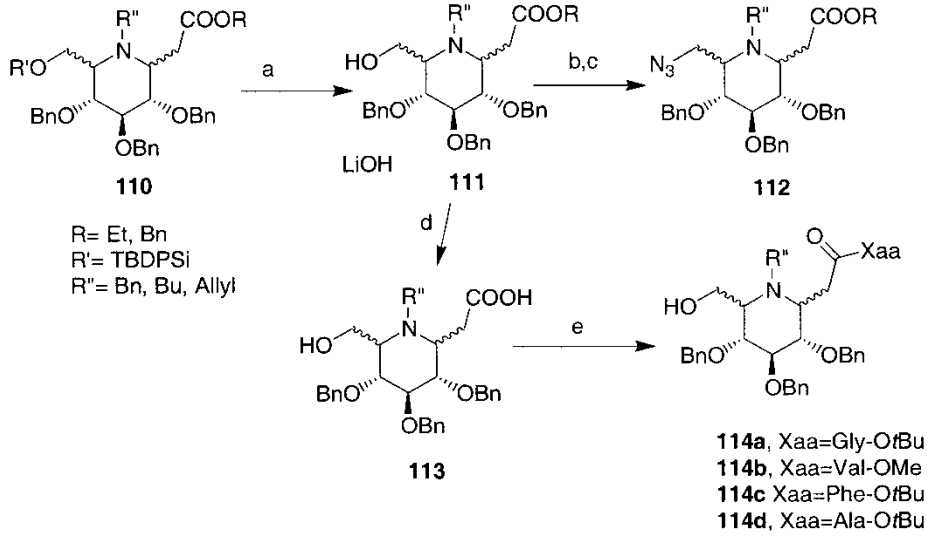
109

Figure 14: Piperidine library.

certain characteristics such as biocompatibility, low toxicity, a precise three-dimensional microstructure, certain mechanical and physical properties, and biodegradability.

Among the great number of natural and synthetic polymers studied and developed for tissue engineering, carbohydrate-based scaffolds, especially chitosan, hyaluronate, alginate, and agarose, find extensive application due to the fact that they frequently show adequate biocompatibility, are often biodegradable matrices, and can be derivatized to modulate their mechanical and physical properties for specific purpose.

Hyaluronate **117** is one of the glycosaminoglycan components of extracellular matrix and has shown excellent potential for tissue-engineering applications. Its structure (Fig. 16) can be modeled through cross-linking with various kind of hydrazide derivatives[62,63] **118–120** to form hydrogels useful as artificial skin,[64] wound healing,[65] facial dermal implants,[66] etc. Hyaluronate gels typically possess low mechanical properties, which have in part limited



110 **111** **112** **113**

114a, Xaa=Gly-O*t*Bu
114b, Xaa=Val-OMe
114c Xaa=Phe-O*t*Bu
114d, Xaa=Ala-O*t*Bu

Scheme 22: *Reagents and conditions:* a) TBAF, THF; b) MsCl, Py, CH_2Cl_2; c) NaN_3, DMF; d) LiOH, $MeOH/H_2O/THF$; e) HBTU, HOBT, DIPEA, DMF, Xaa.

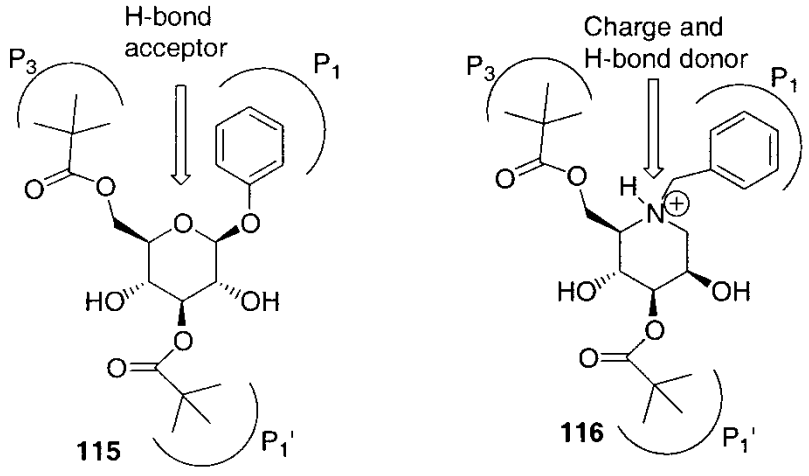


Figure 15: HIV-1 protease inhibitors.

their application, but they can be manipulated in order to improve their properties. A very significant example is an esterified form of hyaluronan, Hyaff-11®.

This biomaterial was obtained from the total esterification of hyaluronate with benzyl alcohol, and it consists of a linear polymer with

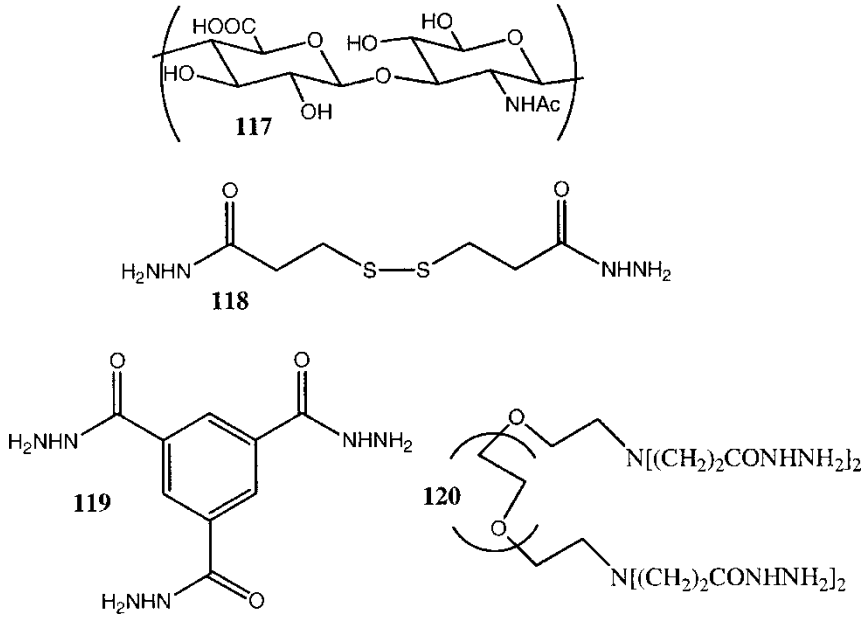


Figure 16: 117, Hyaluronic acid; **118**, 3,3′-dithiobis(propanoic dihydrazide); **119**, 1,3,5-benzene(tricarboxylic trihydrazide); **120**, poly(ethylen glycol)-diamine tetrapropanoic tetrahydrazide.

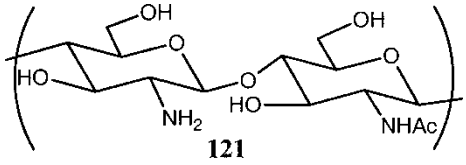
high-molecular-weight distribution. It is insoluble in aqueous solution and ideal for cell growth. Its degradation time is around 40 days, and upon degradation it gives a gel similar to the native hyaluronan found in extracellular matrix. This scaffold has already proved to be an effective scaffold for skin and cartilage tissue engineering,[67–71] and seems to be a promising vascular scaffold.[72]

Chitosan (**121**, Fig. 17), an amino polysaccharide (poly (1,4)-D-glucosamine), is a broadly applicable biomaterial. It is prepared by *N*-deacetylation of chitin and usually contains less than 40% of *N*-acetyl-D-glucosamine residues. Like hyaluronate, chitosan displays a good biocompatibility and low toxicity, structural similarity to natural glycosaminoglycans, and biodegradability operated by chitosanase and lysozyme. Many derivatives have also been developed to enhance solubility and processability of the polymer, such as cross-linkage with glutaraldehyde[73] (**122**, Fig. 17) and derivatization with azide,[14] or to enhance biological functions such as cellular interaction; this is the case of fructose-or galactose-modified chitosan for culture of hepatocytes.[75] In addition, a methylpyrrolidone-derivatized chitosan has been reported to promote bone formation.[76]

Alginate and agarose are both marine algae polysaccharides also widely used in the field. Alginate (Fig. 18) has found use to date in many applications, but, despite its advantageous features of biocompatibility, low toxicity, and low cost, as such it is a poor biomaterial since it degrades easily by losing its cations in the surrounding medium and subsequent dissolution. To overcome the problem it has been covalently cross-linked with various molecules.[77] Another limitation of alginate is its poor cellular interaction; therefore, it has been modified with lectins to enhance ligand-specific binding properties.[78] Cell adhesion peptides, such as CDPGYIGSR, have been covalently coupled to agarose to enhance, like for alginate, the interaction with cells.[79]

Polymeric Materials from Sugar-Based Monomers

The preparation of synthetic polymers containing carbohydrate-derived monomers has been a topic of interest since the 1970s, but has gained



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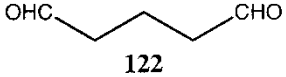


122

Figure 17: 121, Chitosan; **122**, glutaraldehyde.

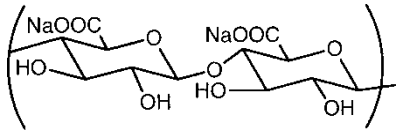


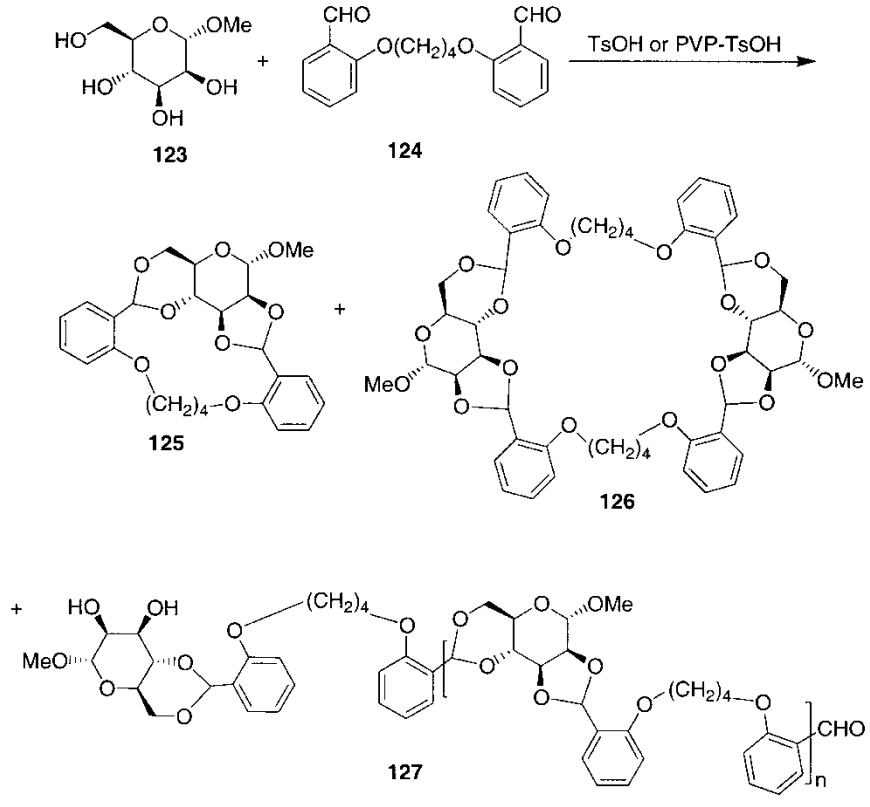
Figure 18: Alginate.

particular attention in the last decade due to the characteristics these monomers are able to confer to classical polyamide and polyester polymers. Synthetic polymers containing a sugar residue in the main chain have been obtained from the polycondensation of different saccharide monomers with several dicarboxylic derivatives.[80] For example 1,4:3,6-dianhydro-D-glucitol and 1,4:3,6-dianhydro-D-mannitol have been used in the preparation of polyesters.[81] Also, the polycondensation of D-glucosamine derivatives has been explored.[82] More recently the polycondensation of α-D-mannopyranoside (**123**, Sch. 23) with different dialdehydes has been investigated,[83] and afforded interesting polymeric compounds such as **127** or macromolecules such as **126**.

Quite recently a great effort has been devoted to modifying polyamides and polyesters to extend their applications to new fields demanding materials with lower environmental impact, that are more biodegradable, and water-soluble, and that display biocompatible properties. Linear polyamides, also known as polyhydroxypolyamides (PHPAs), and poly(ester amide)s are among the carbohydrate-derived polymers that have encountered major interest in the field as analogous of industrial nylons.[84] Esterified aldaric acids, D-glutaric, D-galactaric, D-mannaric, *meso*-xylaric, or the corresponding alkyl-aldaric-1,4-lactones, have been polymerized with different chain length alkylidenediamines to investigate and determine the differences in polymer properties, expecially intramolecular attractive forces and hydrophilicity/hydrophobicity (Sch. 24).[84c,85]

Not only aldaric acids but many other carbohydrate-derived monomers have been used. Among them are the diamine derivatives such as the 1,6-diamino derivatives of D-mannitol (**142**, Sch. 25) and L-iditol (**143**), which have been condensed with different diacyl chlorides affording, once again, polyamides with novel characteristics.[86]

Both the described monomers, aldaric acid esters and diamino derivatives, have also been used in combination for the synthesis of regular polyamides analogous to Nylon 66.[87] Carbohydrate units have also been employed in the synthesis of copoly(ester amide)s (Sch. 26), abbreviated as PVGAn, where *n* indicates the percentage of carbohydrate monomer incorporated in the copoly(ester amide) chain, VG indicates the 5-aminopentyl glutarate unit (**155**), and A the 5-aminoarabinitol succinate unit (**154**).



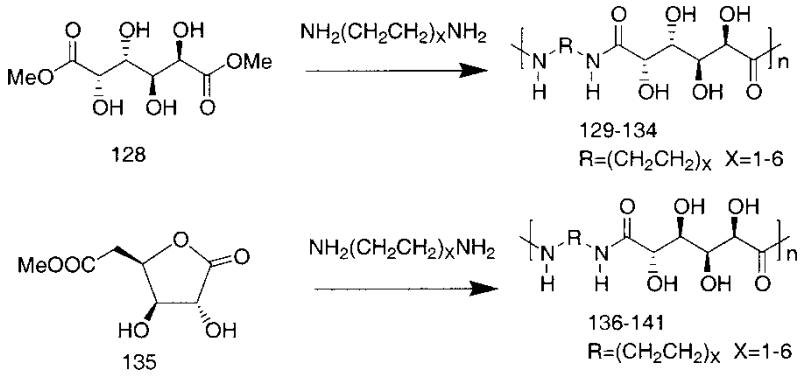
Scheme 23: Polyacetylation of methyl α-D-mannopyranoside (**123**) with 1,4-bis(2-formylphenoxy)butane (**124**).

For the preparation of these polymers, a nonsymmetrical carbohydrate monomer, like **154**, must be previously prepared; these copolymers are expected to improve properties such as biodegradability and biocompatibility.

Polymers with Glycidic Appendages

Cell-surface oligosaccharides perform fundamental functions in biological recognition processes, which are based mainly on carbohydrate-protein interaction.[88] Glycopolymers consisting of sugar residues attached to a polymer backbone emerged recently as important tools for the investigation of sugar-protein interactions.[89] An array of synthetic methods for the polymerization of sugar-based monomers was developed, including ionic polymerization, controlled radical polymerization, and atom transfer radical polymerization (ATRP).

An illustrative example for the preparation of controlled-structure sugar polymers comes from the work of Yamada et al.[90] The block copolymer **158**,



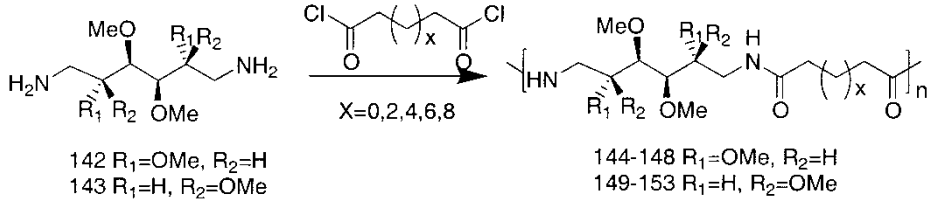
Scheme 24: Examples of PHPAs form the polymerization of dimethyl galactarate (**128**) and D-glucarate 1,4-lactone (**135**) with diamines.

containing an *N*-acetyl-D-glucosamine residue, was synthesized via living cationic polymerization starting from vinyl ether building block **156** (Sch. 27). Treatment of **156** with isobutyl vinyl ether in the presence of trifluoroacetic acid/ethylaluminum dichloride and 1,4-dioxane, in toluene, at 0°C, initiated the living cationic polymerization and afforded the block copolymer **157**. Removal of the acetyl protecting groups in **157**, using hydrazine monoacetate, and subsequent acetylation of the resulting aminogroup at C(2) provided the target molecule.

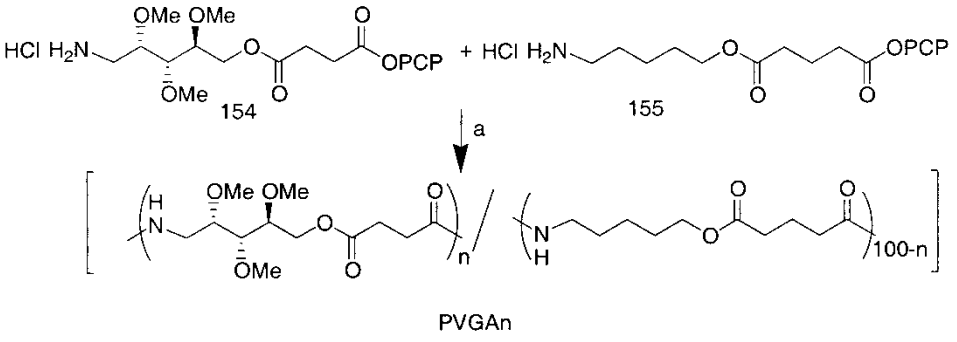
The GlcNAc carrying polymer **158** was investigated in its binding properties toward wheat germ agglutinin (WGA) lectin, and showed a much increased recognition ability compared to monovalent GlcNAc itself and its β-1,4-linked oligomers.

Notably, Narain and Armes recently synthesized low-dispersity, sugar-based polymers starting from unprotected carbohydrate-based building blocks.[91] The starting unit, 2-gluconamidoethyl methacrylate (GAMA), was synthesized by condensation of 2-aminoethylmethacrylate with D-gluconolactone in methanol and in the presence of triethylamine (Sch. 28).

Monofunctional GAMA was then polymerized using atom transfer radical polymerization (ATRP), at 20°C and in protic media, to generate a series of



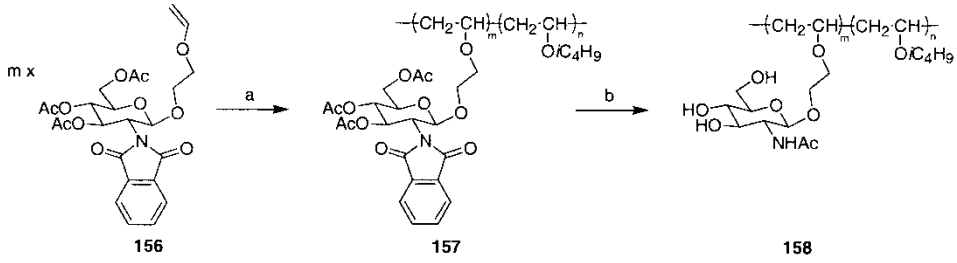
Scheme 25: Condensation of 1,6-diamino derivatives with diacylchlorides.



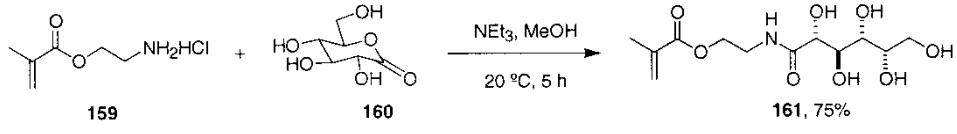
Scheme 26: *Reagents and conditions:* a) *N*-methyl-2-pyrrolidinone, ethyldiisopropylamine, 15 days, 25°C.

controlled-structure sugar polymers. Various biomedical applications (drug delivery, cell targeting, adhesion, etc.) have been suggested for these sugar polymers[89,90,92] thanks to the characteristics conferred by the carbohydrate residue.

Most of the glycopolymers prepared are made up of simple mono-and disaccharides, even if glycopolymers carrying cell surface oligosaccharides such as sialyl Lewis^x (sLe^x)[93] and globosyl oligosaccharides[94] have potentially greater biological significance. The synthesis of the latter is seriously restricted by the difficulty in preparing the oligosaccharide in sufficient amount. Sasaki et al.[95] found that acrylamide copolymers carrying only α-L-fucoside and 3-sulfo-β-D-galactoside residues showed strong activity in



Scheme 27: *Reagents and conditions:* a) CF_3COOH, n x CH_2=CHO*i*C_4H_9, $EtAlCl_2$, 1,4-dioxane, 0°C; b) i. NH_2-NH_2 H_2O, 1,4-dioxane, 60°C, 4 h; ii. Ac_2O, MeOH, rt, 1.5 h, 65%.



Scheme 28.

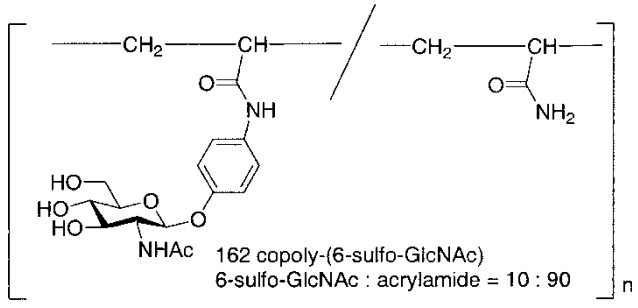


Figure 19: Structure of polyvalent 6-sulfo-GlcNAc.

blocking the L-selectin/sLe^x tetrasaccharide adhesion, which was ascribed to a cooperative binding to L-selectin. This finding suggested the development of a "carbohydrate module method," which involves the segmentation of a targeted oligosaccharide into smaller sugars, synthesis of the glycosylated monomers ("carbohydrate modules"), and their reassembly by copolymerization. This approach was employed for sLe^x, and different glycopolymers carrying different modules have been prepared and analyzed. Glycopolymer **162** (Fig. 19) carrying a 6-sulfo-GlcNAc cluster was found to serve as one of the most promising agents for its potent activity in blocking the L-selectin/sLe^x binding.

CONCLUSIONS

This review clearly shows how, emulating and even overcoming nature, chemists have used carbohydrates as fundamental scaffolds for a variety of purposes. Carbohydrates have so unique and precious features, such as chirality, conformational rigidity, polyfunctionality, and biocompatibility, that there is no limit to the fantasy in their use, in the natural form or after proper modifications, as scaffolds for original and useful molecular architectures that can find application in quite different fields.

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