Carbohydrates in diversity-oriented synthesis: challenges and opportunities

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Organic & Biomolecular Chemistry

REVIEW

Carbohydrates in diversity-oriented synthesis: challenges and opportunities

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Over the last decade, Diversity-Oriented Synthesis (DOS) has become a new paradigm for developing large collections of structurally diverse small molecules as probes to investigate biological pathways, and to provide a larger array of the chemical space. Drug discovery and chemical biology are taking advantage of DOS approaches to exploit highly-diverse and complex molecular platforms, producing advances in both target and ligand discovery. In this view, carbohydrates are attractive building blocks for DOS libraries, due to their stereochemical diversity and the high density of polar functional groups, thus offering many possibilities for chemical manipulation and scaffold decoration. This review will discuss research contributions and perspectives on the application of carbohydrate chemistry to explore the accessible chemical space through appendage, stereochemical and scaffold diversity.

Introduction

The screening of small molecule libraries represent a relevant and powerful approach in early-stage drug discovery, with aim of identifying hit candidates for the development of new drugs. Several approaches have been proposed to improve the quality and quantity of small molecules representing a library, in order to populate the medicinally relevant chemical space broadly.[1] In this context, Diversity-Oriented Synthesis (DOS)[2] has proven to be very effective since Schreiber's seminal paper in 2000.[3] Opposed to traditional Target-Oriented Synthesis (TOS), DOS operates in the way to generate the maximum diversity and complexity from simple starting materials, using divergent synthetic strategies, such as the use of complexity-generating reactions and the build/couple/pair approach.[4]

In recent years, natural product structures have received increasing interest for the construction of small molecules libraries, thanks to the intrinsic chemical and structural diversity,[5] the selectivity towards a wide number of targets, and the capability of following Lipinski's rules for drug-like properties.[6] In these years, several diversity-oriented small molecules collections were developed using amino acids,[7] terpenes[8] and alkaloid compounds.[9] Despite their availability and abundance in Nature, carbohydrates remain quite underdeveloped and unexplored among the groups of chiral compounds exploited in diversity-generating synthetic strategies. In fact, they are generally used as starting material for chiral auxiliaries, reagents, ligands and organocatalysts.[10]

Even though carbohydrates play a relevant role in many pathophysiological events, only a limited area in the world of pharmacopeia is covered by sugar-derived compounds. In fact, many important carbohydrate-protein interactions have yet to be discovered, and some issues connected to their oral availability and plasma stability have still to be solved. However, remarkable examples of carbohydrate-derived drugs, where the oral bioavailability is not required, are represented by Voglibose (Glustat), a α-glycosidases inhibitor for the treatment of diabetes,[11] the anticonvulsant Topiramate (Topamax),[12] and Miglustat (Zavesca) for the treatment of type 1 Gaucher disease[13] (Figure 1a). A noteworthy example of the development of glycomimetic drugs is illustrated by the Oseltamivir phosphate (Tamiflu)[14] for the inhibition of neuraminidases related to H_1N_1 and H_5N_1 influenza viruses. Starting from the intermediate sialosyl cation involved in the reaction mechanism of the target enzyme, an orally available drug was achieved by removing the polar groups without losing the groups required for the biological affinity (Figure 1b).[15] In addition to their interest as drugs, carbohydrates are attractive building blocks for the generation of high-quality small molecule collections, taking advantage of their structural bias and the high density of polar functional groups, which offer many possibilities for derivatization, scaffold decoration and additional reactions. Furthermore, their intrinsic stereochemical diversity allows to obtain chemical libraries with high variability in their tridimensional structure, thus increasing the chance of finding complementary interactions with protein targets. Just to give a picture of the diversity potential of carbohydrates, when considering a simple monosaccharide, up to four different interconverting forms consisting of five- or six-membered rings and two possible anomeric configurations can be obtained. These features have been exploited since the Nineties in traditional combinatorial chemistry.[16]

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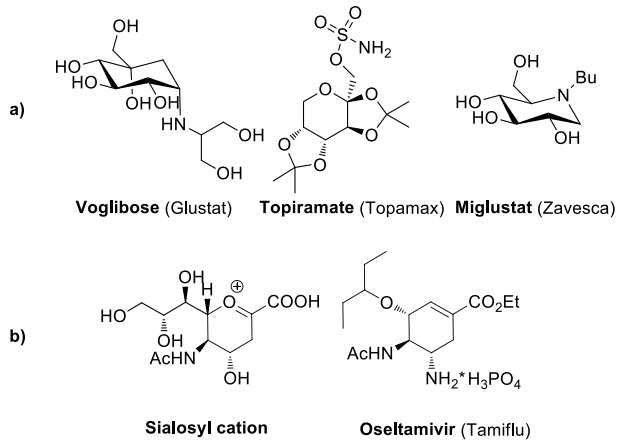


FIGURE 1. Carbohydrate-derived drugs. (a) Structure of anti-diabetes Voglibose (Glustat),[11] the anticonvulsant Topiramate (Topamax)[12] and of Miglustat (Zavesca)[13] for the treatment of type 1 Gaucher disease; (b) structure of the sialosyl cation, intermediate of the reaction mechanism of neuraminidase enzyme, and of Oseltamivir (Tamiflu)[14] for the treatment of H_1N_1 and H_5N_1 influenza viruses.

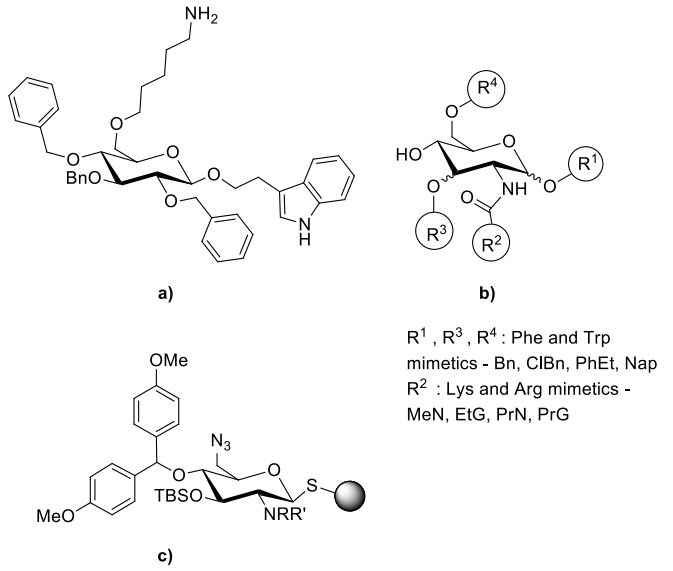
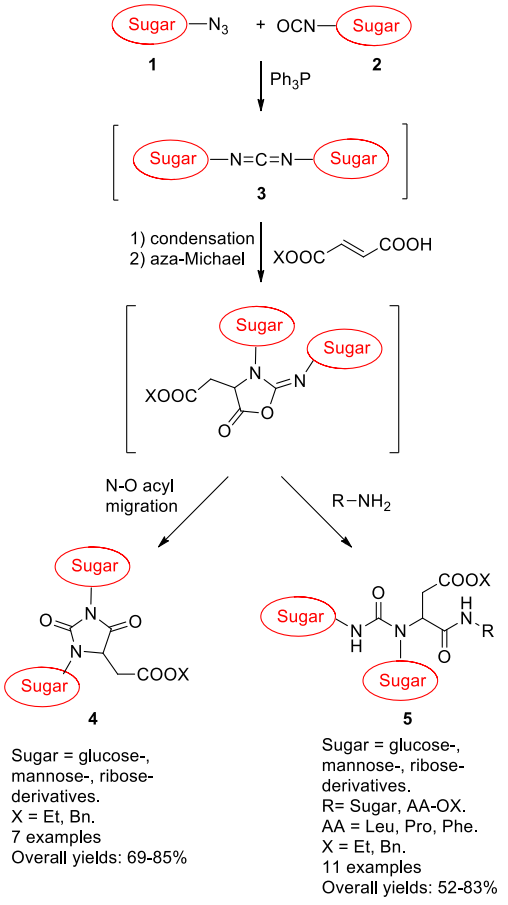


FIGURE 2. (a) Hirschmann's glucose-based somatotropin release inhibiting factor (SRIF) mimetics; (b) Meuterman's pyranose-based peptidomimetic library; (c) Kunz's orthogonally protected 2,6-diaminoglucose scaffold for solid-phase combinatorial synthesis.

Carbohydrate-derived compounds can be used, in fact, as molecular templates to display pharmacophoric groups in well-defined spatial orientations, and they have become very attractive for the development of peptidomimetics due to enhanced conformational constraints. Since Hirschmann's seminal paper based on D-glucose somatotropin release inhibiting factor (SRIF) mimetics (Figure 2a),[17] several improvements were reported. Meutermans and co-workers developed a library of 490 pyranose-based scaffolds containing one positively charged and two aromatic amino acids (Figure 2b).[18] The *in vitro* screening of this chemical library allowed for the discovery of five hit compounds capable to interact with somatostatin and melanin-concentrating hormone (MCH) receptors, thus revealing the versatility of this approach in protein receptor drug discovery. Kunz and co-workers developed orthogonally protected pyranose scaffolds that allowed for the selective deprotection at four different positions (Figure 2c).[19] This 2,6-diaminoglucose scaffold was further exploited for the synthesis of RNA ligands libraries, leading to the discovery of novel inhibitors of the HIV-1 infection in HeLa cells.[20] In all these strategies, the chemical diversity was achieved by the strategic substitution of the hydroxyl functional groups. Although decorating monosaccharides with additional functional groups for subsequent chemical manipulation result in the achievement of high-quality chemical libraries, the combinatorial libraries developed in such approaches contained quite similar structures, thus limiting the chemical diversity required for finding new drug candidates towards novel disease targets. This account aims to give an overview of recent examples of the application of monosaccharides in diversity-oriented synthesis. Most relevant works in this field have been divided into the three main DOS approaches for molecular diversity: appendage, stereochemical and skeletal diversity.

Such typologies of chemical diversity can be directly correlated to the diversity potential of carbohydrates, as appendage, stereochemical and skeletal diversity benefit of the presence of several functional groups, high density of stereogenic centers, and high diversity of monosaccharide scaffolds, respectively.

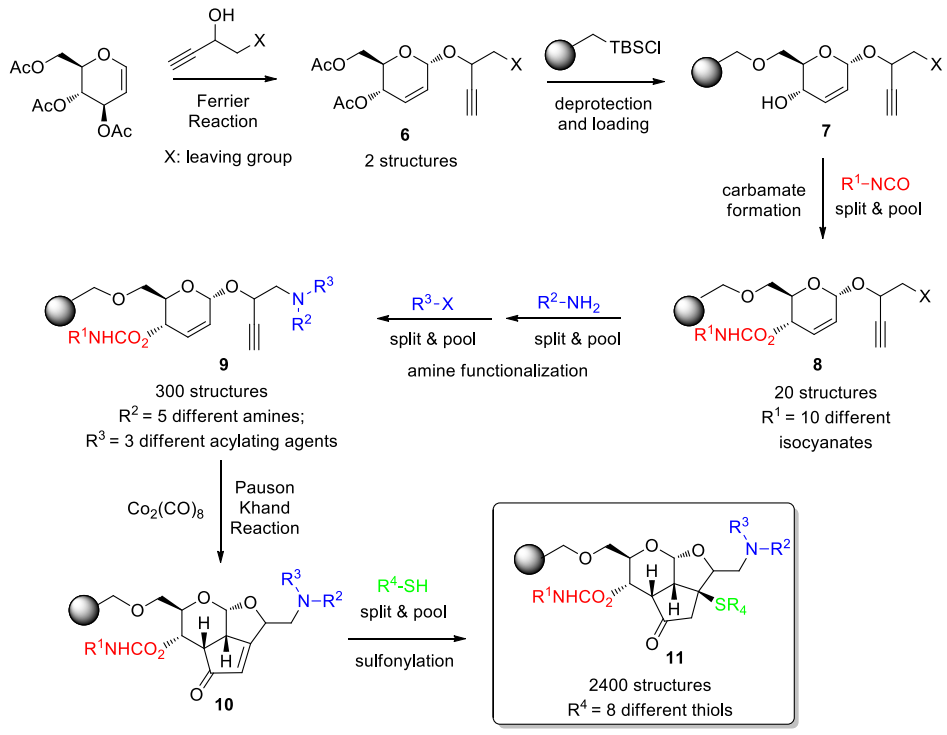
The synthetic strategies leading to multivalent glycomimetics will not be taken into account in this review,[21] although this is an important issue in medicinal chemistry, indeed. From a drug design perspective, we have to consider that carbohydrates on cell surfaces are displayed in multivalent arrays and interact with biological targets in a multivalent fashion. Because of the chemical complexity of these biomolecules, the combinatorial and diversity-oriented synthesis of oligosaccharides is still unlikely achievable. However, the need to populate the medicinally relevant chemical space broadly, together with the demand to obtain different molecular frameworks, is pushing the researchers to increase the efforts in this field. For example, in recent years, Volonterio et al.[22] applied DOS principles for the synthesis of different hetero di- and trivalent glycomimetic scaffolds, using a multicomponent, high-yielding and efficient process. As shown in Scheme 1, the highly reactive carbodiimide **3**, resulting from the coupling between glycosylazides **1** and isothiocyanates **2**, reacted with fumaric acid monoesters generating the corresponding cyclic intermediate through a domino condensation/aza-Michael reaction. Then, a N→O acyl migration led to the glycol-hydantoin divalent scaffold **4**, whereas the nucleophilic addition of an external amine allowed to achieve linear di- or trivalent glycopeptide conjugate **5**. [23]



SCHEME 1. Multicomponent domino process for the diversity oriented combinatorial synthesis of di- and trivalent glycomimetics from glycosylazides and isothiocyanates.

Appendage Diversity

A simple way to generate diversity consists of decorating reactive centres of the molecules with a variety of different appendages. This approach, which can generate up to millions of different products, was exploited from the very beginning of diversity-oriented synthesis, as it is similar to combinatorial chemistry. In a remarkable work Schreiber and co-workers[24] reported a *split-and-pool* library synthesis of 2400 tricyclic compounds (Scheme 2). Although some difficulties in the purification process, the solid-phase *split-and-pool* technique is a powerful strategy to produce a great number of small molecules.[25] Specifically, this technique combined with *in vitro* chemical genetics studies[26] allowed for the discovery of several *hit* compounds.[27] As shown in Scheme 2, in Schreiber's synthesis, the α-anomer products **6**, obtained by a $BF_3{\cdot}Et_2O$-catalyzed Ferrier reaction between 3,4,6-tri-*O*-acetyl-D-glucal and *R*- or *S*- phenyl propargylic alcohol, was carried on polystyrene macrobeads and split into ten different reaction vessels. The first solid-phase diversity step was obtained by functionalizing the 4-hydroxy group of the glucal templates **7** with ten different aromatic and aliphatic isocyanates. Then, a double diversity position was introduced by reacting the propargylic alcoholic group of compounds **8** with five different primary amines and three different acylating reagents. Finally, after the Pauson-Khand reaction of 2,3-unsaturated enynes **9**, the resulting tricyclic α,β-unsaturated ketones **10** were further functionalized by the treatment with eight different thiols, thus providing up to 2400 tricyclic sulphides **11**. Unfortunately, *R*- and *S*- diastereomeric products **7** exhibited different reactivity.



Scheme 2. Split and pool library synthesis of 2400 tricyclic compounds starting from 3,4,6-tri-*O*-acetyl-D-glucal.[24]

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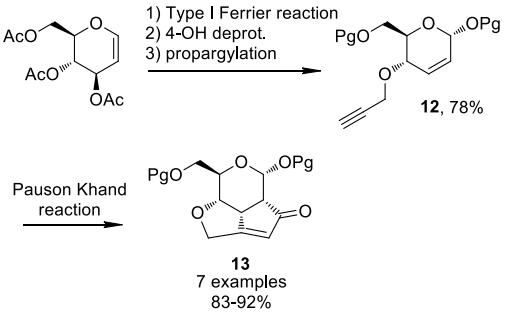
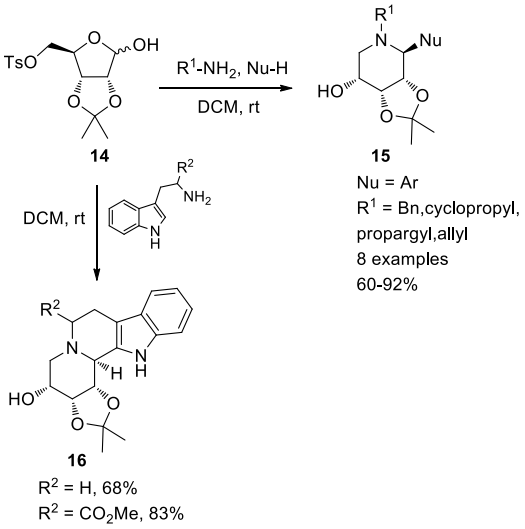


Scheme 3. Tricyclic scaffold obtained by Hotha e Tripathi starting from 3,4,6-tri-*O*-acetyl-D-glucal.

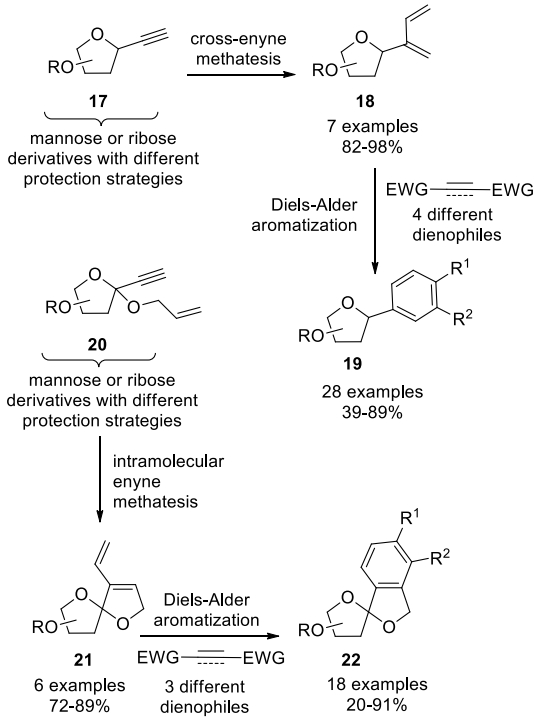
When *S*-propargylic alcohol was used, compounds **9** failed to undergo Pauson-Khand reactions, probably because of repulsive steric interactions between R^2 and R^3 groups and the hydrogen atom at C-5 position of the glucal template. This problem was solved by Hotha and Tripathi three years later.[28] Starting from the glucal template **12** having the propargylic moiety at the C-4 position instead of C-1, the Pauson-Khand reaction was performed efficiently in both the diastereomeric series, giving the skeletally different tricyclic enones **13** (Scheme 3), thus fulfilling the versatility required in the *split-and-pool* synthesis.



Scheme 4. One-pot synthesis of different iminosugar *C*-glycosides from D-ribose tosylate **14**.

An important application of appendage diversity-oriented synthesis is the development of efficient reactions applicable to a wide variety of starting materials. In this context, Baskaran and co-workers reported an efficient one-pot method for the stereoselective synthesis of iminosugars β-*C*-aryl glycosides **15** starting from D-ribose tosylate **14** (Scheme 4).[29] The generality of this methodology was further explored using tryptamine and similar compounds, which consisted of the cyclic iminium ion intermediate undergoing a domino Pictet-Spengler reaction,[30] thus furnishing the polyhydroxy indolo[2,3-a]quinolizidine scaffold **16**.

With the same purpose, Kaliappan and co-workers reported an efficient approach for the synthesis of a variety of *C*-aryl and spiro-*C*-aryl glycosides (compound **19** and **22** respectively, Scheme 5).[31] In this work, seven different *C*-alkynyl glycosydes **17** and six sugar-derived enynes **20** were subjected to a sequential enyne metathesis/Diels-Alder aromatisation reaction, where the possibilities of using different sugar derived dienes and different dienophiles allowed to obtain high quality chemical libraries.



Scheme 5. Synthesis of *C*-aryl glycosides **19** and spiro-*C*-aryl-glycosides **22** starting from *C*-alkynyl glycosides **17** and sugar-derived enynes **20**.

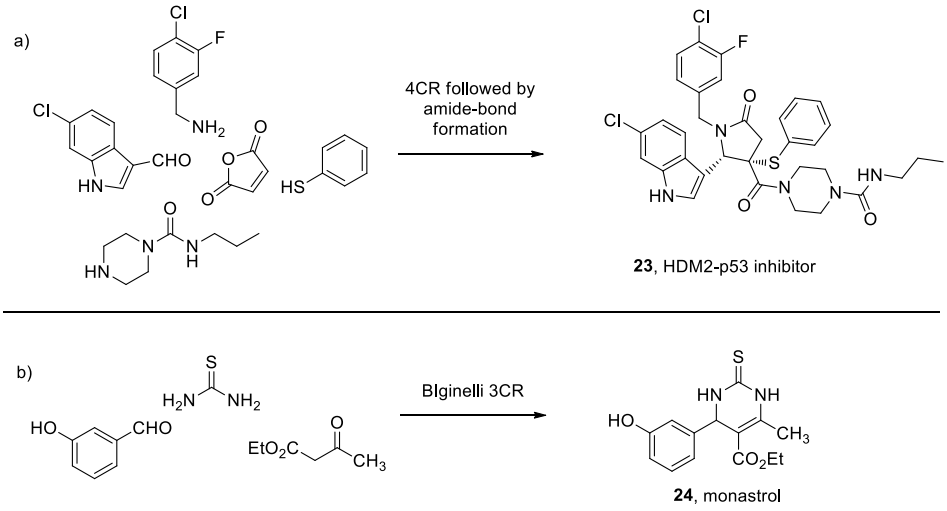
In the search of efficient and easily accessible protocols for the construction of versatile heterocyclic scaffolds, multicomponent reaction (MCRs)[32] played a significant role. Multicomponent reactions, where three or more chemical entities react selectively to form a single product in a unique process, are attractive transformation in diversity-oriented

synthesis. Furthermore, MCR products can be used directly for High-Troughput Screening (HTS) campaigns. The strength of this strategy is demonstrated by the great number of approved drugs discovered through the application of MCR libraries in drug discovery issues. Just to name a few, the company Priaxon identified the MDM2-p53 inhibitor **23** from a 4CR chemical library,[33] and the mitotic spindle kinesin (Eg5) inhibitor monastrol **24** was obtained by the Biginelli 3C reaction (Scheme 6).[34]

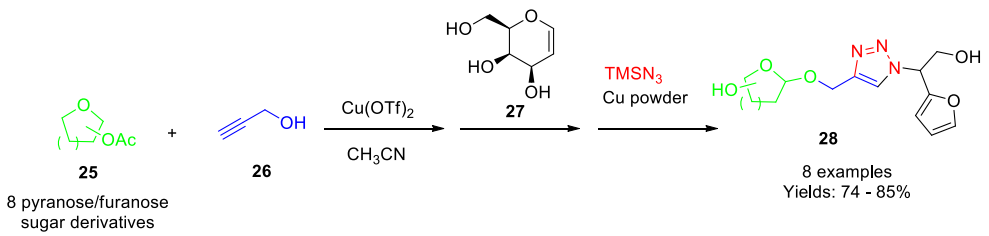
Despite the great number of MCRs applied in DOS strategy starting from complex materials, such as α-hydroxyaldehyde,[35] imines,[36] and heterocyclic diene containing aldehydes,[37] to our knowledge the use of pentose and hexose carbohydrates in diversity-oriented synthesis using MCRs is still a largely underexplored area.[38] Neverthless, a remarkable example was reported by Mukherjee and co-workers.[39] They developed a one-pot 4-component synthesis of furan-based glycoconjugates **28** starting from D-glucal **27** and a glycosyl donor **25.** As shown in Scheme 7, the furyl azide resulting from glucal **27** and $TMSN_3$, reacted in a copper-mediated Huisgen cycloaddition with the glycosyl alkyne derived from sugars **25** and propargylic alcohol, leading to the achievement of carbohydrate-derived highly functionalized motifs with high yields and an high degree of atom economy.

The combination of diversity-oriented synthesis and *in situ* biological screening performed without the need of purification steps is a very interesting feature in drug discovery. In this context, the Cu-catalyzed Azide-Alkyne Cycloaddition (CuAAC) reaction between alkynes and azides, generally as referred to 'click-chemistry', has become a widely used strategy in medicinal chemistry.[40] The chemoselectivity of this reaction does not require the use of protecting group strategies and can be carried out in aqueous systems, thus allowing to perform biological activity assays without isolating the products. As a remarkable example about this approach, Delgado and co-workers reported the synthesis of an aminocyclitol library by using a CuAAC reaction between the *N*-propargylaminocyclitol **29** and 25 different azides selected by a collection of 343 compounds through *in silico* calculations (Scheme 8).[41] After a preliminary screening of library members of general structure **30** against glucocerebrosidase (GCase), the hit compounds with interesting activity were resynthesized and characterized for further biological tests.

Generally, the approach to appendage diversity using carbohydrates was achieved by decorating the hydroxyl groups of the sugar scaffold. Recently, López and co-workers focused on a novel approach, which consists on modifying the carbohydrate moiety with appropriate functionalities in order to perform further synthetic elaborations.[42-45] They reported an efficient one-pot method for the achievement of the furanose epoxy *exo*-glycal **32** from *C*-glycals **31** (Scheme 9). Compound **32** is a powerful scaffold for carbohydrate-based diversity-oriented synthesis, as the presence of the oxirane moiety and of the exocyclic enol-ether olefin allows performing a variety of diversity generating reactions beyond the usual exploitation of the anomeric carbon reactivity.



Scheme 6. (a) Achievement of Priaxon's MDM2-p53 inhibitor **23**;[33] (b) Achievement of Eg5 inhibitor **24**, monastrol.[34]



Scheme 7. Four-component copper-mediated synthesis of furan-based glycocongugates **28**.

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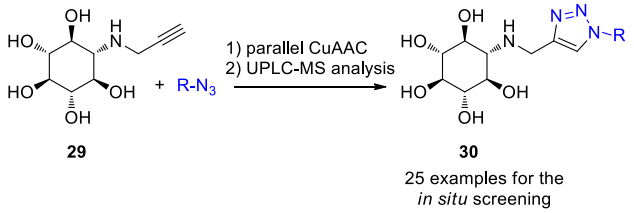
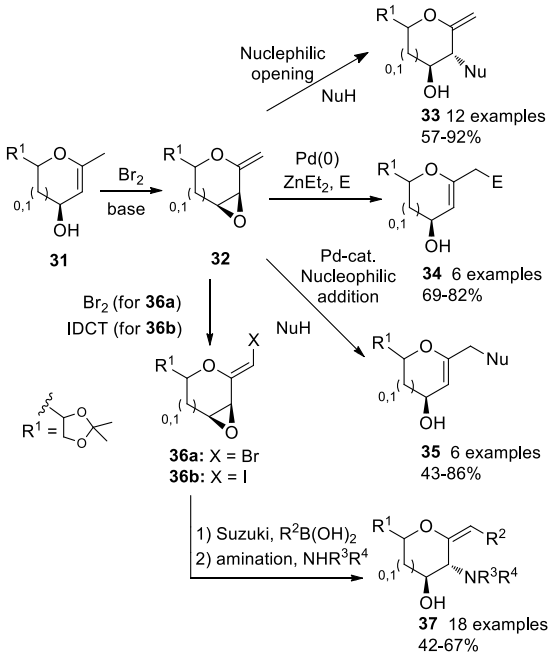


Scheme 8. Application of 'click-chemistry' to the synthesis of *N*-substituted aminocyclitols and the *in situ* screening for glucocerebrosidase Inhibitors.

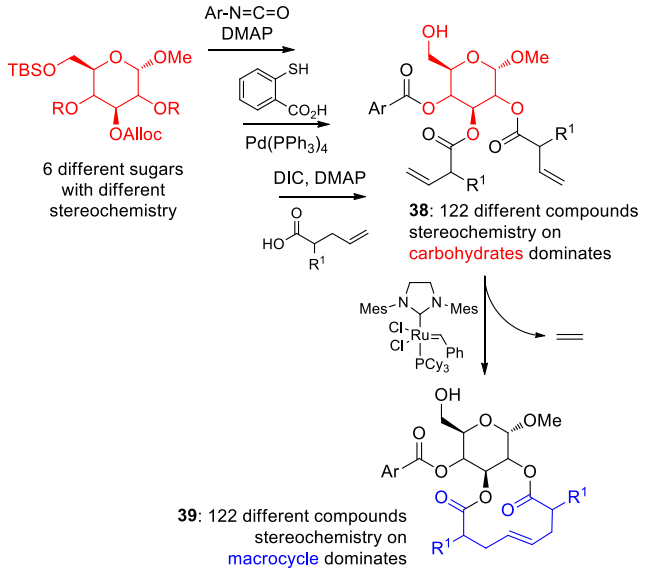
As shown in Scheme 9, the oxirane moiety was opened regioselectively by several nucleophiles to give C-2 derivatives **33**, whereas the exocyclic olefin was exploited to obtain derivatives **36** by a stereocontrolled electrophilic addition.[43] The whole allyl-epoxide moiety was opened by palladium-catalyzed Tsuji-Trost reaction to give functionalized *C*-glycals **35**.[43] The same reaction was performed under Pd(0) catalysis employing diethylzinc and a suitable electrophile giving analogue derivatives **34**.[44] The presence of an additional halogen atom in the olefin moiety (see compound **36**) allowed to obtain a variety of furanosidic and pyranosidic alkenes (**37**) as useful carbohydrate-derived synthetic intermediates for the application of cross-coupling reactions.[42-45]



Scheme 9. Appendage diversity form epoxy exo-glycals **32** and **36**.

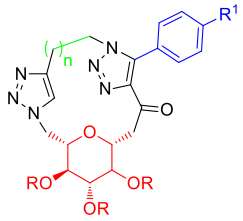
Stereochemical Diversity

Considering that different three-dimensional arrangements result in different biological interactions, an increase in stereochemical complexity enhances the chance of modulating challenging targets, such as protein-protein interactions and protein-DNA interactions.[46] In this context, in a pioneering work Schreiber and co-workers described a systematic and quantitative method to measure the role of stereochemistry and conformational constraints in modulating protein interactions.[47] They reported the synthesis of a collection of 122 carbohydrate-derived monocyclic precursors **38** (Scheme 10), having different stereochemistry and different alkene-based appendages, in order to provide a variety of 12-membered macrocyclic compounds **39** through a ring-closing metathesis reaction.[48] The influence of carbohydrate- and appendage-stereochemistry was assessed in both ring-closing reaction efficiency and biological activity. Specifically, the authors demonstrated that when the two ester functionalities are in *cis,* the reaction proceeds rapidly, giving selectively a bent bicyclic product, whereas if these two groups are in *trans,* two different planar bicyclic products are obtained. Also, the effects of the stereochemistry of both monocyclic and bicyclic compounds towards bioactivity were assessed in a multidimensional chemical genetics approach,[49] using 40 parallel cell-based assays to study the perturbation of four protein-specific cellular events, namely DNA synthesis, esterase activity, mitochondrial membrane potential and the intracellular reducing activity. Statistical data analysis revealed that the stereochemistry of the macrocyclic appendages was the most important feature for the activity of the bicyclic compounds, whereas the stereochemistry within the carbohydrate ring played a dominant role on the global activity pattern of monocyclic compounds **38**.



Scheme 10. Synthesis of test library of monocyclic **38** and bicyclic compounds **39**, highlighting the role of the stereochemistry towards biological activity.

Sugar-derived macrocycles are often used as key molecules to address challenging biological interactions. In fact, these structures have important pharmacological properties, such as increased structural complexity, stereogenicity and rigidity,[50] together with the ability to form stable hydrogen-bonds in solution.[51] Thus, carbohydrate-derived macrocycles play a significant role in medicinal chemistry. In recent years, several reports on the synthesis of carbohydrate-derived macrocycles appeared in the literature.[52] In this framework, some elegant examples combined the chemistry of carbohydrate-derived macrocycles with diversity-oriented synthesis approaches.[53] Tripathi and co-workers reported the synthesis of a library of 14-, 15- and 16-membered pyran-based macrocyclic glycoconjugates starting from D-glucose and D-mannose.[54] As shown in Figure 3, these molecules offer many options for molecular diversity, such as the opportunity of decorating the pyran skeleton and the aromatic ring, the possibility of varying the length of the bridge between the two triazoles, and the intrinsic variety of the five stereogenic centers of the sugar template.



R = H, $COCH_3$
R^1 = H, OMe, Cl
n = 0, 1, 2

Figure 3. Pyran-based macrocyclic glycoconjugates developed by Tripathi and co-workers.

The importance of developing stereochemical diversity-oriented synthesis is also demonstrated by the efforts in the search of stereodivergent routes through a common starting material.[55] Although this approach appears being quite challenging in the field of carbohydrate chemistry,[56] Casiraghi and co-workers described the synthesis of a variety of sterochemically different carbafuranoses (**47**, **49**, **55** and **57**) and carbafuranosylthiols (**48**, **50**, **56** and **58**) by exploiting a short, selective and divergent protocol.[57] As shown in Scheme 11, this strategy consisted of a highly stereoselective vinylogous cross aldolization coupling reaction between a dienoxy silane donor (**40**) and the aldehyde **41**. Further double bond hydrogenation on **42** and side chain oxidative cleavage of compound **43** led to the aldehyde **44**, which was subjected to a direct intramolecular cycloaldolization to access the cyclitol frame of lactone/thiolactone **45**/**46** diastereoselectively. These compounds were further exploited through a reductive ring opening process to give carbafuranoses **47**/**49** and carbafuranosylthiols **48**/**50**, respectively. In order to achieve carbasugars of the corresponding L-series (**55**-**58**) the 4,5-*erythro*-configured butenolide **51** was easily obtained via Et_3N-promoted C-4 epimerization of the intermediate **42**.

In most of carbohydrate-based DOS strategies the stereochemical, skeletal and appendage diversities are generally obtained by reactions involving the anomeric carbon atom. In 2013 Manna and Pathak reported for the first time the use of non-anomeric parts of the sugar moiety to exploit the reactivity of a vinyl sulfone-modified hex-2-enofuranoside at C-2 and C-3 positions with a β-dicarbonyl compound.[58]

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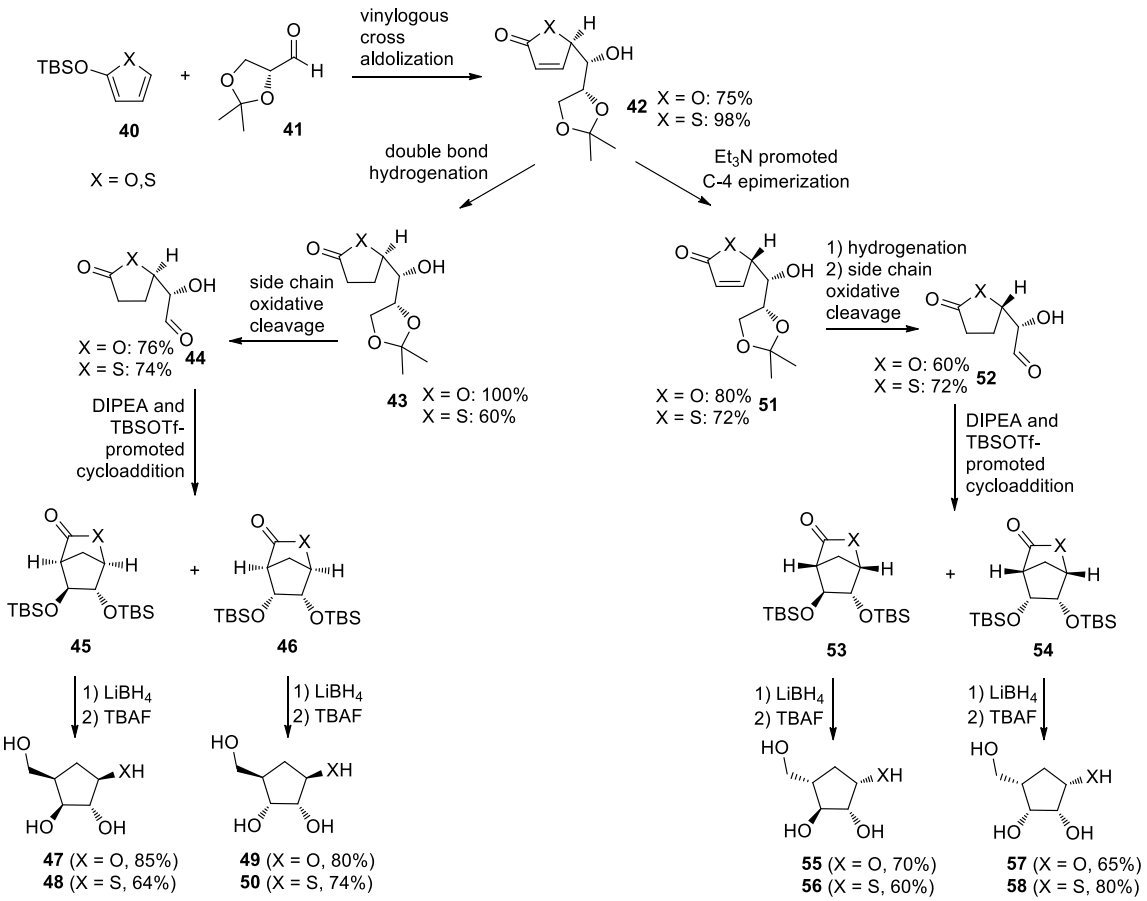
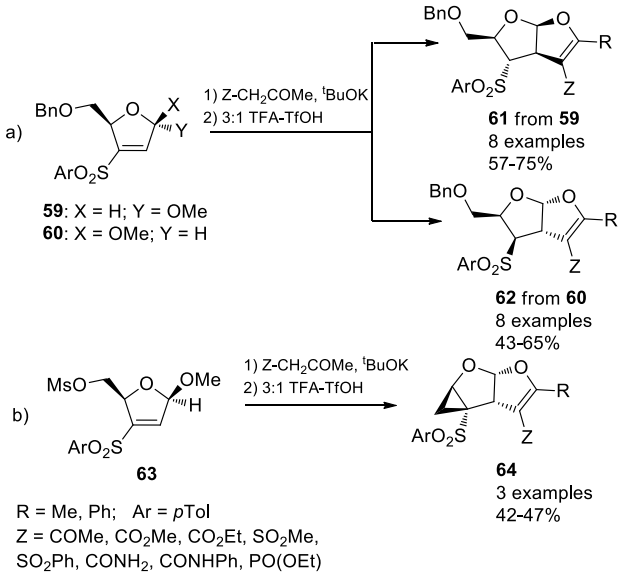


Scheme 11. Stereochemical diversity-oriented synthesis of carbafuranoses (**47**, **49**, **55** and **57**) and carbafuranosylthiols (**48**, **50**, **56** and **58**) developed by Casiraghi and coworkers.

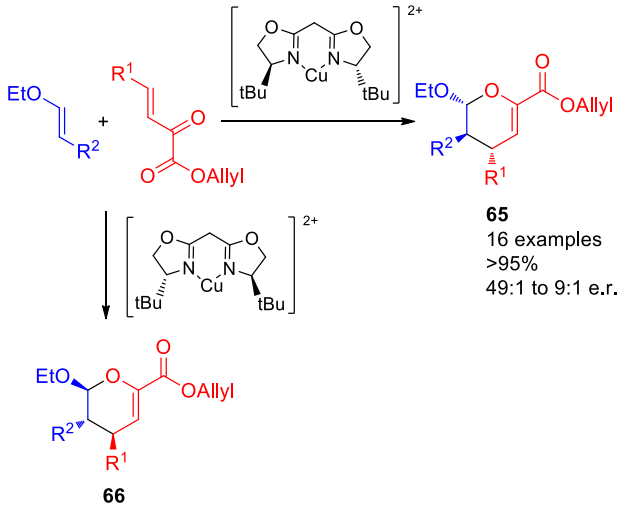
In particular, the three different functionalities of this molecule, namely the aldehyde, the Michael acceptor and the leaving group, were used to achieve novel furofurans in one-pot processes. They consisted of a Michael addition and an intramolecular nucleophilic attack on the double bond to create three new stereocenters with complete stereocontrol (Scheme 12a). A range of furofurans **61** were obtained from the reaction of α-furanoside **59**, whereas the stereoisomers **62** were obtained from β-furanoside **60** with comparable yield. Interestingly, when the benzyl protecting group of **60** was replaced by a good leaving group (as for the mesyl-derivative **63**), this strategy gave the cyclopropanated tricyclic furofurans **64** resulting from a second intramolecular nucleophilic attack on the C-5 position (Scheme 12b).

Pathak and co-workers exploited the potential of these vinyl sulfone-modified sugars also in previous works. In detail, they reported the diversity-oriented synthesis of C-5 branched sugars through the diastereoselective Michael addition of a variety of different nucleophiles to vinyl sulfone-modified hex-5-enofuranosides, achieving many highly functionalized sugar-derived carbocyclic compounds.[59]

In planning stereochemical DOS, the use of enantioselective catalysis plays a central role, even though this aspect is still underexplored. The development of asymmetric steps in DOS is more demanding and challenging when compared to those in total synthesis, because the synthetic method has to work with a variety of substrates, thus requiring generality, reliability and efficiency for controlling the stereochemistry in branching pathways. Nevertheless, some remarkable examples appeared in literature in recent years.[60] As an example applied to carbohydrate chemistry, Schreiber and Stavaner reported the enantioselective heterocycloaddition of vinyl ethers and unsaturated ketoesters to achieve 4320 stereochemically and structurally different dihydropyrancarboxamides **65** and **66** by using the catalysis of bis(oxazoline)metal Lewis acid complexes in a solid-phase technology platform (Scheme 13).[61]

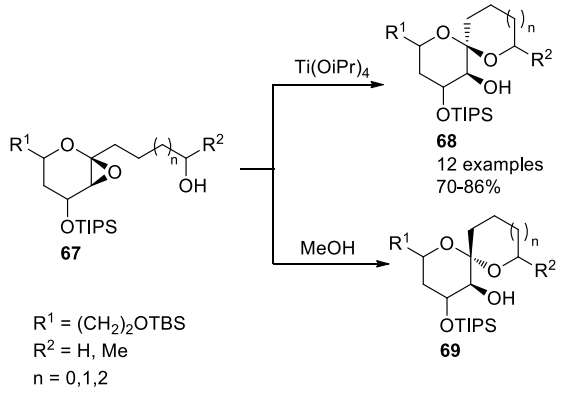


Scheme 12. (a) One-pot synthesis of stereomeric furofurans **61** and **62** from the reaction between 1,3-dicarbonyl reagents and vinyl sulfone modified furanoside **59** and **60** and (b) one-pot synthesis of cylcopropanated furofuran **64** from vinyl sulfone modified furanoside **63**.



Scheme 13. Enantioselective heterocycloaddition of vinyl ethers and β,γ-unsaturated ketoesters for the synthesis of stereochemically different dihydropyrancarboxamides.

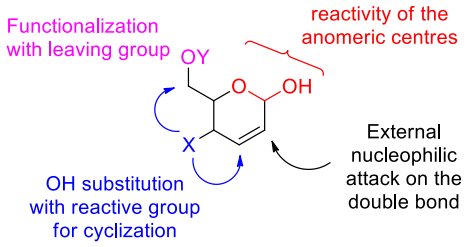
Finally, Tan and co-workers developed a stereoselective synthetic strategy for the generation of anomeric spiroketals **68** and **69** (Scheme 14) through the selective epoxide ring-opening of alkylpyran **67** via different reaction conditions.[62] Methanol-mediated spirocyclization gave the spiroketal **69**, where the configuration of the anomeric carbon was found inverted. To obtain the thermodynamically less favored spiroketals **68**, titanium(IV)-isopropoxide was exploited as a 'noncovalent tethering' Lewis acid able to promote the formation of an oxonium intermediate and to direct the side-chain nucleophile on the β-face of the anomeric carbon. Such reaction conditions worked well with both *erythro*- and *threo*-substrates, thus demonstrating the versatility of this stereochemically divergent synthesis.



Scheme 14. Stereochemically divergent synthesis of spiroketals **68** and **69**.

Skeletal Diversity

In the panorama of diversity-oriented synthesis, the achievement of skeletal diversity has received increasing interest in recent years.[63] This kind of diversity has been developed in order to obtain several distinct molecular frameworks able to explore more widely the chemical space. In fact, though this is the most difficult type of chemical diversity to achieve,[64] it is the most attractive one, considering that the scaffold complexity is a tight requisite for the interactions with target biomacromolecules.[65] There are a lot of remarkable examples of skeletal diversity-oriented synthesis based on natural products, such as steroids,[66] amino acids,[7,67] benzopyrans,[68] tetrahydroquinoline,[69] and other oxygen- and nitrogen-containing heterocycles. Nevertheless, synthetic processes involving structural rearrangements of carbohydrate-based compounds are still underdeveloped. A lot of efforts have been directed to the exploitation of different sugar moieties, such as double bonds of glycals and their derivatives, the reactivity at the anomeric carbon, and functionalization/substitution of the hydroxyls for the achievement of carbohydrate-derived scaffold having enhanced structural complexity (Scheme 15), although still retaining the high-valued sugar functionalities characterized by the stereocentres, the polyhydroxylated chains and the conformational constraints.



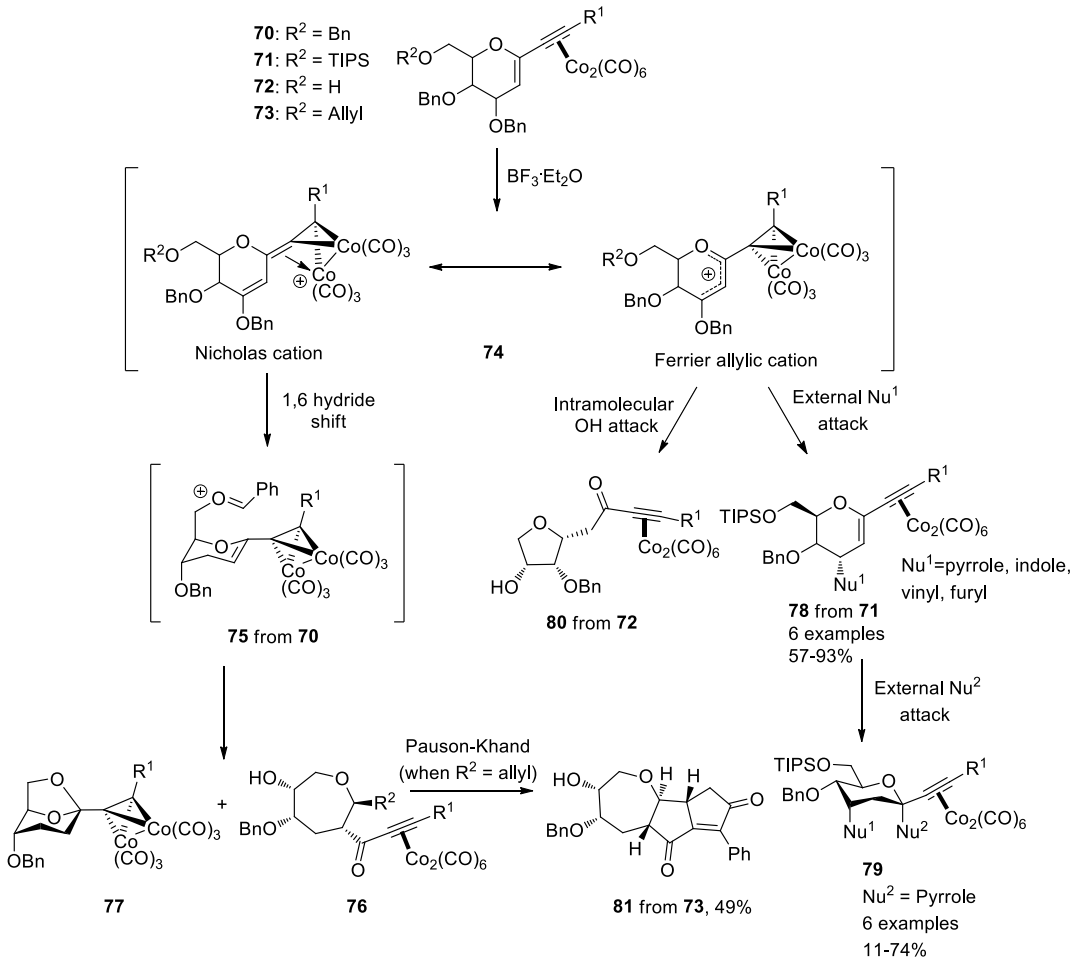
Scheme 15. Strategic exploitation of different sugar moieties, for the achievement of carbohydrate-derived scaffold.

Diverse and complex skeletons according to DOS approach are generally achieved in two ways: (a) using different reagents on the same substrate (reagent-based approach) or (b) pre-encoding the transformation in different starting materials and

subjecting them to a common set of reaction conditions (substrate-based approach).[63a]

A remarkable example of a substrate-based approach to address this issue was reported by López and co-workers, using glycal dicobalt hexacarbonyl derivatives **70**-**73** (Scheme 16).[70] Starting from these compounds and using the same reaction conditions ($BF_3{\cdot}Et_2O$ in CH_2Cl_2) different products were achieved taking advantage of the properties of C-6 substituents. As shown in Scheme 16, a mixture of oxepane scaffold **76** and 1,6-anhydro derivatives **77** was obtained from 6-*O*-benzyl derivatives **70**. The oxepane formation was optimized using unsubstituted terminal alkyne and aromatic rings with electron-withdrawing groups, probably due to the higher electrophilicity character of the oxocarbenium ion **75**, that underwent more easily the Prins cyclization necessary for the ring expansion. On the other hand, the loss of benzaldehyde and subsequent cyclization led to the 1,6-anhydro compound **77**. When the initial 1,6-hydride transfer step was avoided, as in the 6-*O*-TIPS derivative **71**, the Ferrier-Nicholas cation **74** reacted with external nucleophiles generating C-3 branched glycal pyranosides **78** in a complete regio- and stereo-selective fashion. Such compounds still possess a reactive glycal double bond, thus allowing to obtain bis-*C*-*C*-glycosides **79** by a further nucleophilic addition. Interestingly, this reaction showed high stereoselectivity, too, leading only to the *cis* adducts. Starting from 6-hydroxy derivatives **72**, ring contracted tetrahydrofuran derivatives **80** were obtained, thanks to the intramolecular Nicholas addition of the internal nucleophilic OH group. In addition to the decobaltation, these products proved to be very useful in tandem processes. Indeed, by the combination of Ferrier-Nicholas rearrangement with the Pauson-Khand cyclization, 6-*O*-allyl derivatives **73** were selectively transformed in an efficient one-pot process into the tricyclic compounds **81**.

1,2-Unsaturated carbohydrate derivatives, also called glycals, proved to be very useful intermediates for expanding the skeletal diversity in DOS approaches. Tan and co-workers[71] exploited *erythro*-4-deoxyglycals **82** to obtain six differently functionalized monosaccharides (compounds **83**-**88** in Scheme 17). In fact, a $Sc(OTf)_3$-catalyzed condensation with salicylaldehyde allowed to obtain the tricyclic scaffold **83**.[72] Also, the highly reactive 1,2-double bond was exploited to obtain the β-epoxide **84**, which was further transformed into α-D-*arabino*-4-deoxy-*C*-glycoside derivatives **85**. Compound **82** was also converted stereoselectively into the β-C-2 alcohol **86** by means of a hydroboration–oxidation treatment, and into C-1 substituted glycals **87** by a lithiation-alkylation protocol,[73] which allowed to achieve the doubly-substituted product **88**.



Scheme 16. Substrate-based diversity-oriented synthesis for the achievement of skeletally different scaffold starting from differently-(*O*-6)-substituted dicobalt hexacarbonyl alkynyl glycals **70**-**73**.

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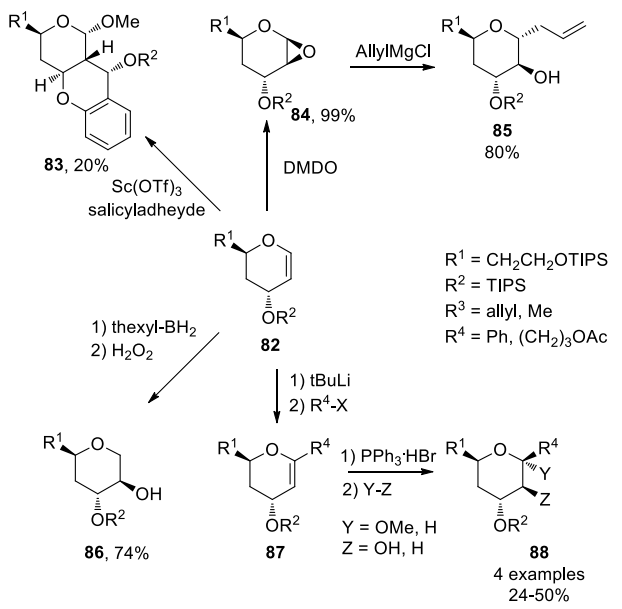
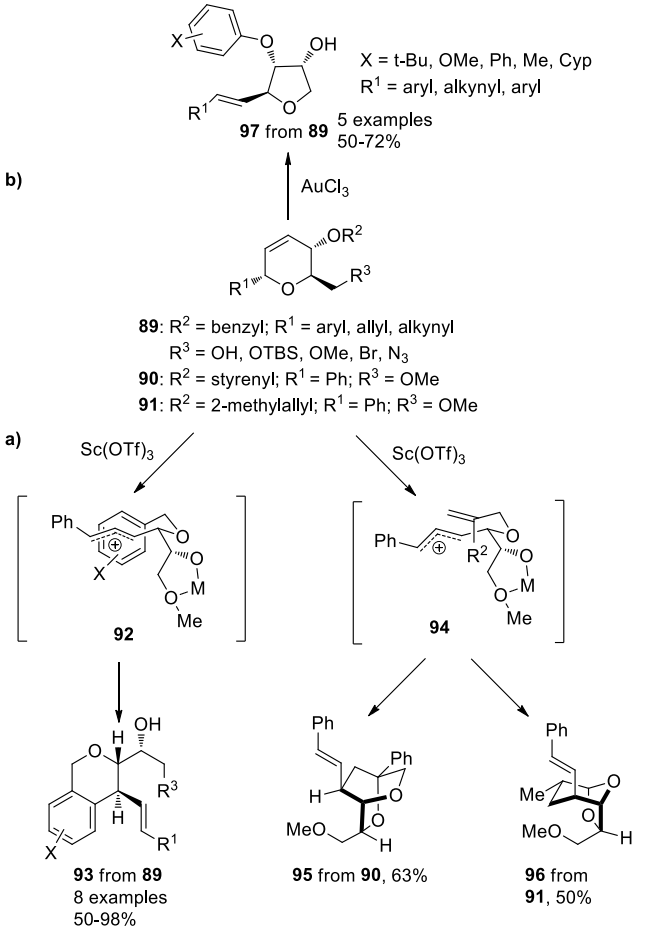


Scheme 17. Diversity oriented synthesis from *erythro*-4-deoxyglycal **82**.

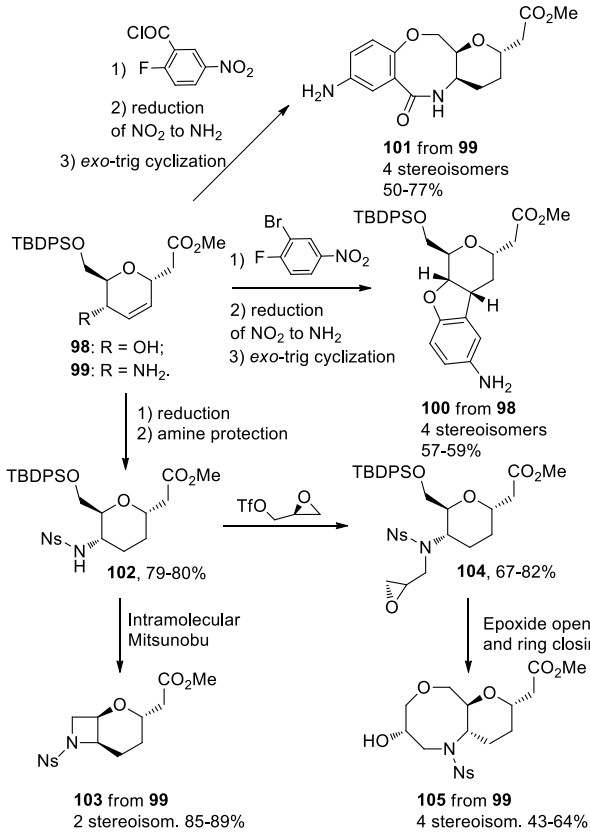
Glycal-derived compounds were exploited by Porco and co-workers to access skeletal diversity in both substrate-based and reagent-based approaches.[74] As shown in Scheme 18a, starting from glycal-derived dihydropyrans **89**-**91**, easily obtained from tri-*O*-acetyl-D-glucal, four skeletally different scaffolds were achieved simply by changing the nature of C-1 and C-6 substituents or by changing the reaction conditions. In fact, C-4 benzyl ether dihydropyrans **89** were converted to isochroman-like compounds **93**, by a Friedel Crafts alkylation on the allylic cation **92** generated by $Sc(OTf_3)$-promoted ionization of the anomeric C-O bond. On the other hand, the allylic cation **94**, arising from the cation-olefin cyclization of C-4 allyl ether dihydropirans **90** and **91**, underwent two different additional transformations. In particular, α-styrenyl ether **90**, afforded the dioxabyciclo[2.2.2]octane **95** by the attack of the metal-alkoxide to the carbocation. Interestingly, when the allyl moiety was methylated, as in compound **91**, the skeletally different dioxabyciclo[3.2.1]octane **96** was obtained, probably because of an internal 1,2-hydride shift of the intermediate cation **94**. In addition, by changing the reaction conditions, the Au-mediated ring contraction of aryl ether *C*-glycosides **89** allowed to obtain the highly substituted tetrahydrofuran **97** (Scheme 18b).

Glycal-derived compounds **98** and **99** were exploited also by Marcaurelle and co-workers to develop skeletally different bi- and tricyclic pyran-fused products using short, selective, and high-yielding processes (Scheme 19).[75]



Scheme 18. (a) Substrate-based and (b) reagent-based approach divergent strategies for the achievement of skeletally different compounds from substituted dihydropyrans **89**-**91**.

Specifically, [6,5,6]-benzofuran scaffold **100** was obtained by a three step process consisting of a nucleophilic substitution with bromo-benzene and a 5-*exo*-trig radical cyclization. A similar process applied to the amine-derivative **99** allowed to obtain, after amine protection with nitrobenzoyl chloride, the [6,8,6]-tricyclic scaffold **101** characterized by a 8-membered lactam. On the other hand, the azetidine-containing compound **103** was achieved by an intramolecular Mitsunobu reaction on the reduced compound **102**, whereas the epoxide insertion on the starting compound **99** and the subsequent epoxide-opening/ring-closing reaction led to the achievement of the 8-membered oxazacane scaffold **105**. The same processes were repeated on four different stereoisomers of the starting compounds **98** and **99**, thus achieving a large collection of pyranose-fused small molecules.



Scheme 19. Skeletal diversity oriented synthesis of fused bi- and tricyclic ring systems from glycal-derived compounds **98** and **99**.

The Principal Moments of Inertia (PMI) analysis employs normalized shape based descriptors to position minimum energy conformation of each library member in a triangular graph plot, describing the chemical space with respect to the molecular shape of chemical library members.[76] The PMI analysis of library members by Marcaurelle and coworkers showed that pyran-containing fused-ring compounds access a different chemical space as compared to analogue libraries obtained by the same authors using aldol-[77] or azetidine-based[78] pathways (Figure 4).

An elegant example of skeletal diversity within the panorama of natural product synthesis was reported by Chattopadhyay and co-workers.[79] Starting from the versatile intermediate azido-alkyne sugar-derived homoallylic alcohol **106**, the furanopiperidine derivative **108** was obtained in two high yielding steps, consisting of the olefin ozonolysis and a one-pot Staudinger reaction/reductive amination cyclization. The versatility of compound **108** was demonstrated by the achievement of 4-*epi*-fagomine (**109**), 4,5-dihydroxypipecolic acid (**110**) and bicyclic dihydroxyindolizidine skeleton **111** under few standard reactions conducted upon the intermediate aldehyde (Scheme 20).

The exploitation of microwave irradiation in diversity-oriented synthesis is quite useful for the development of inexpensive, accessible in ton-scale and efficient synthetic protocol.

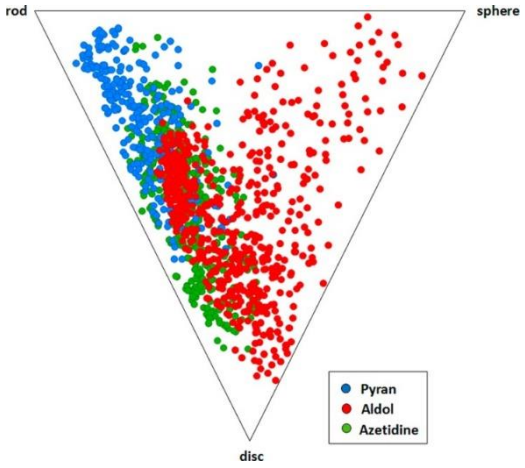
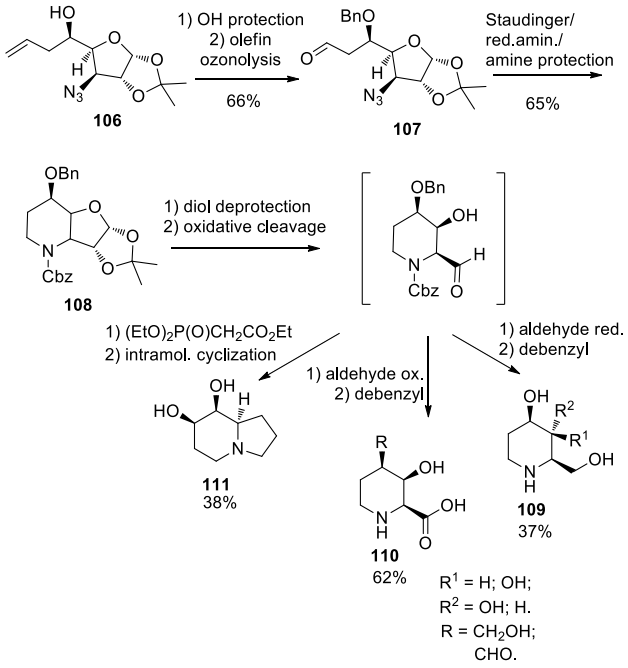


Figure 4. PMI Analysis of piran-based collection (blue) obtained by Marcaurelle and coworkers, compared to the previously reported aldol- (red) and azetidine- (green) libraries.[75] Reprinted with permission from ref. 75. Copyright (2013) American Chemical Society.



Scheme 20. Divergent synthesis of 4-*epi*-fagomine **109**, 3,4-dihydroxypipecolic acid **110** and dihydroxyindolizidine **111** from D-glucal derived aldehyde **107**.

Accordingly, Patel and co-workers,[80] reported an efficient microwave-enhanced diversity oriented synthesis (MEDOS) of a variety of interesting heterocyclic compounds, starting from 1,3-oxazine-2-ones(thiones) **112** and **113**, obtained by D-xylose and D-glucose, respectively, using a domino cycloisomerization/dehydration process, promoted by microwave irradiation and Clay catalysis (Scheme 21). Specifically, furo- and pyran- oxazin-2-ones(thiones) **114** and **115** were obtained by a simple cyclodehydration of compounds **112** and **113**, respectively.

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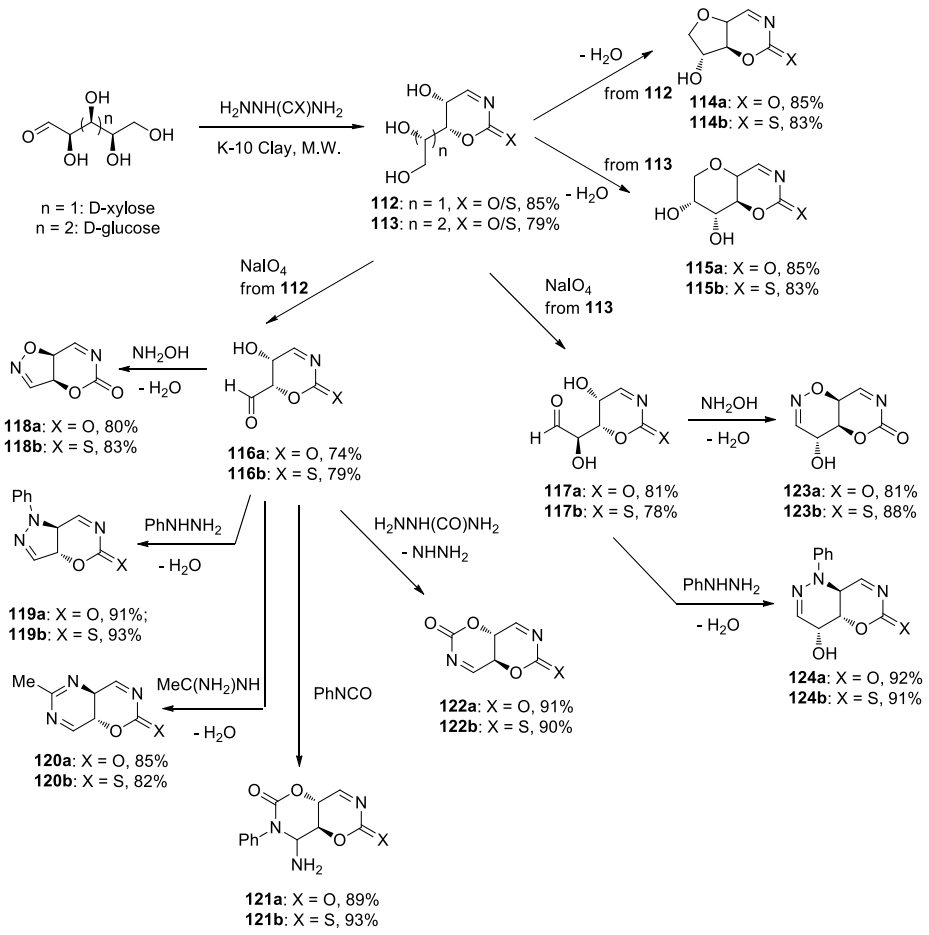
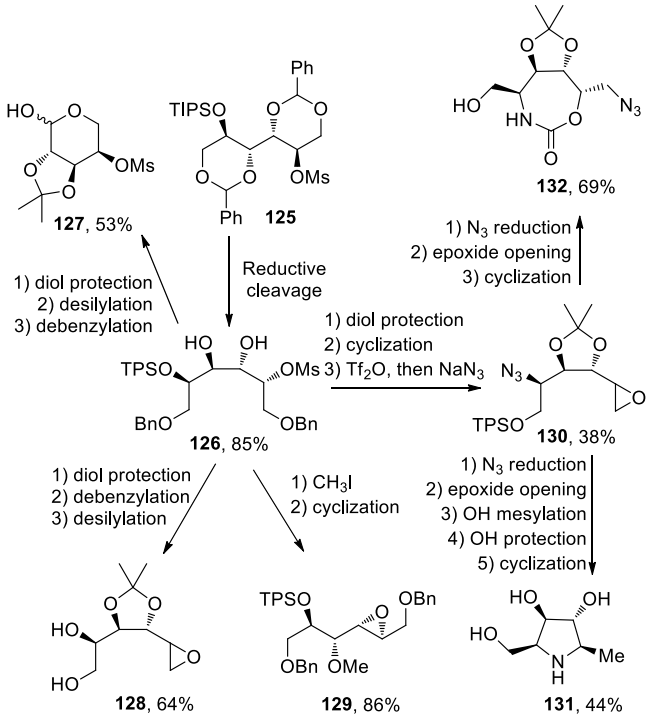


Scheme 21. Microwave-enhanced diversity oriented synthesis (MEDOS) of fused-ring 1,3-oxazin-2-ones(thiones) from D-glucose and D-xylose.

In addition from aldehyde **116**, obtained by the oxidative cleavage of **112**, isoxazoles **118**, pyrazoles **119,** pyrimidines **120**, and oxazinoxazin-2,6-ones(thiones) **121** and **122** were achieved in high yield by the simple condensation of the appropriate reagent. In a similar fashion, aldehyde **117**, obtained in the same way from the glucose-derived building block **113**, led to the achievement of bicyclic compounds **123** and **124**.

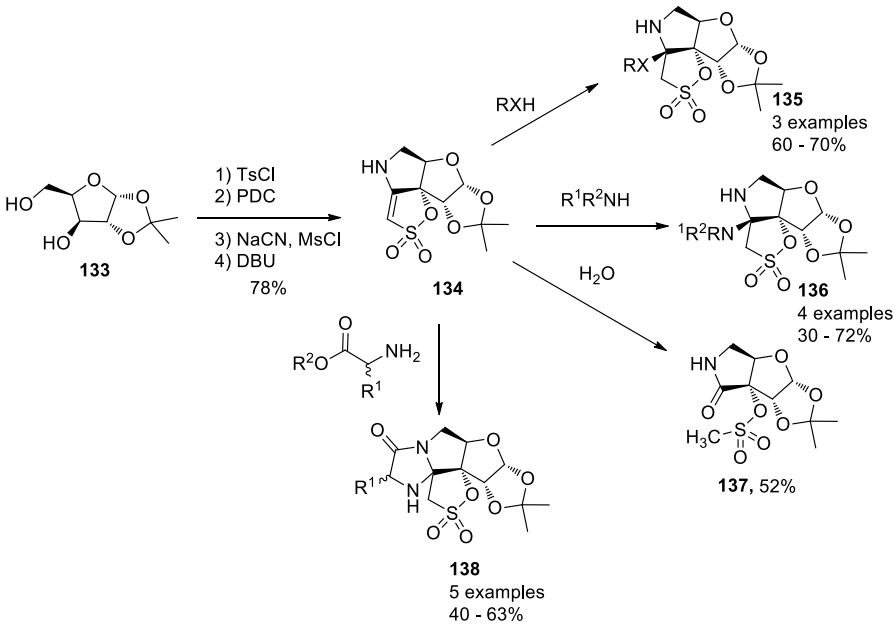
The facile synthesis of densely functionalized chiral building blocks was reported by Baskaran and co-workers, who described the synthesis of a variety of useful drug-relevant synthetic intermediates simply by changing the order of functional group deprotection of diol **126**, obtained by the reductive cleavage of mannitol-derived acetal **125** (Scheme 22).[81] Lactol **127** is an important intermediate in the synthesis of pharmaceutically important codonopsinol, 1,4-dideoxy-1,4-imino-L-arabinitol and 3-hydroxy-γ-butyrrolactone.[82] Epoxy-diol **128** is useful for the synthesis of 3,4,5-trihydroxypiperidines and microsclerodermin E,[83] whereas the epoxide **129** is necessary to obtain tetrahydrofurans and virgutasin.[84] Furthermore, the synthetic potential of azido-epoxy derivative **130** was demonstrated also by the complete synthesis of the fucosidase inhibitor **131** and the cyclic carbamate **132** (with structure similarity of some HIV-protease inhibitors).[85]

In the panorama of sugar-derived synthetic intermediate, San-Felix and co-workers described the synthesis of the high-added value cyclic enamine **134** starting from 1,2-*O*-isopropylidene-*R*-D-xylofuranose **133**, which allowed to obtain several unusual by- and tricyclic products by regio- and stereoselective addition of *O*-, *N*-, *S*- and *C*-nucleophiles (Scheme 23).[86] In particular the addition of amino acids afforded a tetracyclic derivatives **138**, which possess an highly constrained and very complex skeleton.



Scheme 22. Diversity-oriented synthesis of useful chiral building blocks from mannitol-derived diol **126** and synthetic applications of azido-epoxy derivative **130**.

As discussed above, build/couple/pair (B/C/P) strategy is a powerful approach for developing large collection of skeletally different scaffolds, as it works with the aim of assembling building blocks in polyfunctional intermediates able to undergo different intramolecular cyclizations. As a result, we recently reported a B/C/P approach starting from D-mannose and glycine derivatives, which allowed to obtain six skeletally different polyhydroxylated heterocyclic scaffolds.[87] As shown in Scheme 24, the reductive amination between dimethoxy dimethyl acetal and mannose-derived building blocks **139** and **140**, under different reaction conditions, led to the achievement of three different intermediates (**141**, **142** and **143**). Successively, the amine protection and acid-mediated *trans*-acetalization pairing reactions allowed to obtain straightforward the bicyclic oxazine scaffolds **152** and **157**/**158** from the coupling intermediates **141** and **143**, respectively, and polyhydroxylated morpholine **155**[88] and 6,8-dioxa-3-azabicyclo[3.2.1]octane **154**,[89] both from compound **145** by tuning carefully the reaction time. Furthermore, Cbz-deprotection and reductive amination on the oxidized derivative resulting from **146** gave pyrrolidine **150**, whereas the intramolecular nucleophilic substitution on the reactive α-bromoacetyl species of the intermediate **147** led to the corresponding eight-membered ring lactam **151** and bicyclic scaffold **156**, the latter resulting from subsequent *trans*-acetalization reaction over compound **151**. The potential of combining carbohydrate-derived building blocks to amino acid derivatives gives great opportunities to expand the area of chemical diversity in terms of appendage, stereochemical and skeletal diversity, taking advantage of the wealth of stereocenters and chemical handles from the chiral pool.



Scheme 23. Skeletal diversity and synthetic applications of xylose-derived cyclic enamine **134**.

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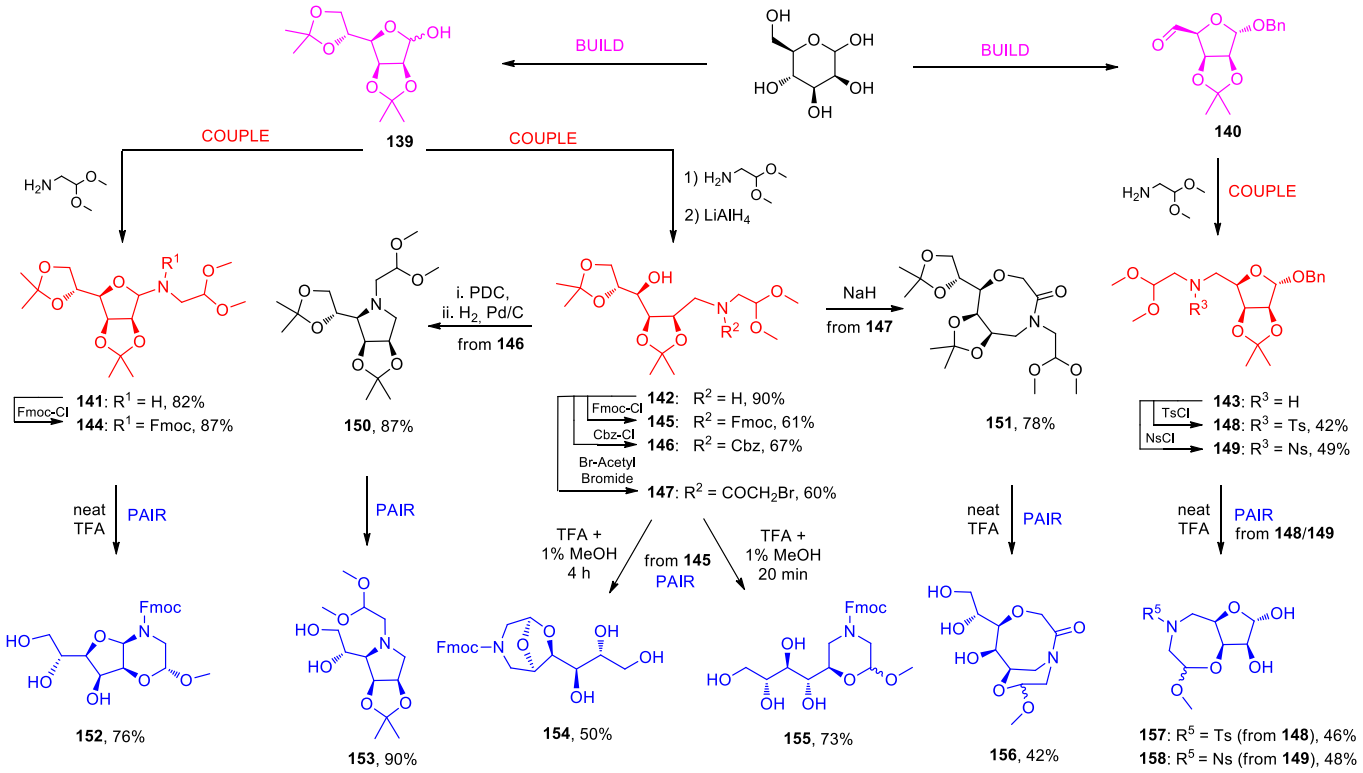

Scheme 24. Diversity-oriented synthesis around D-mannose: build/couple/pair strategy for the achievement of skeletally different scaffolds **152**-**158**.

Conclusions

In conclusion, carbohydrates are attractive building blocks for DOS libraries, due to their stereochemical diversity and the high density of polar functional groups, thus offering many possibilities for chemical manipulation and scaffold decoration. Appendage diversity is the simplest way to generate diversity, consisting of decorating reactive centres of the molecules with a variety of different appendages, which may result in the generation of up to millions of different products. Both glycals and glycosides from the pool of carbohydrates have been generally exploited for this purpose.

Although stereochemical diversity-oriented synthesis is quite challenging in the field of carbohydrate chemistry, the importance of this approach has been studied through the search of stereodivergent routes using a common starting material. Finally, skeletal diversity, which is the most attractive type of diversity for its potential in exploring more widely the chemical space, has been developed through structural rearrangements of carbohydrate-based compounds. Different sugar moieties, such as glycal double bonds, anomeric carbon reactivity and OH-functionalization/substitution have been exploited in order to achieve carbohydrate-derived scaffold having enhanced structural complexity, and still retaining the high-value sugar functionalities, such as stereocentres, polyhydroxylated chains and conformational constraints. We expect that in the future carbohydrates are being taken into account as suitable building blocks for the generation of complex molecules in terms of high density of stereocenters and appendages. More efforts are needed in exploiting sugar-derived building blocks for the generation of complex cyclic molecules according to skeletal diversity principles, as this approach is the most rewarding in giving high degree of chemical novelty in terms of complexity and diversity.

Acknowledgements

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