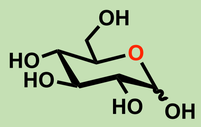
SYNTHESIS OF MONO- AND MULTI-VALENT IMINOSUGARS BY ELECTROCHEMICAL C-H ACTIVATION

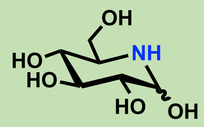
Alberto Marra

Glycochemistry & Molecular Recognition **team of the IBMM, Pôle Chimie Balard, Montpellier**

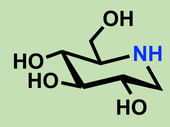
Iminosugars, polyhydroxylated mono- and bicyclic nitrogenated heterocycles, are naturally occurring analogues of carbohydrates bearing a basic nitrogen instead of the endocyclic oxygen atom (e.g. D-glucose vs. Nojirimycin). These products are strong yet poorly selective inhibitors of both glycosidases and glycosyltransferases, the enzymes that catalyze the hydrolysis or the synthesis, respectively, of oligo-saccharides and glycoconjugates.



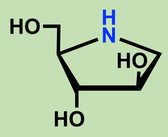
D-glucose



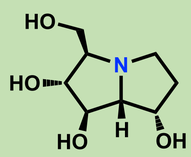
Nojirimycin



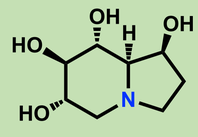
1-Deoxynojirimycin



DAB

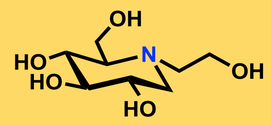


Australine

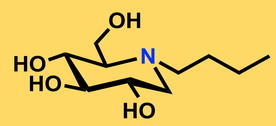


Castanospermine

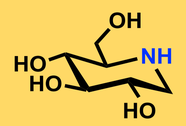
Although hundreds of monosaccharidic iminosugars have been prepared over the last four decades, only three simple iminosugars are on the market, the Miglitol, to treat type 2 diabetes, the Miglustat and Migalastat, to treat lysosomal storage disorders.



Miglitol (Glyset)
(type 2 diabetes)

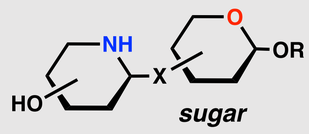


Miglustat (Zavesca)
(Gaucher disease)



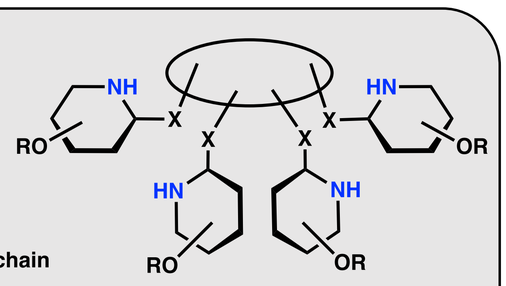
Migalastat
(Fabry disease)

Also synthetized by us and others were less conventional derivatives such as the *imino-disaccharides* and the *iminosugar clusters*. The interest in disaccharidic iminosugars, compounds constituted of an iminosugar moiety linked to a sugar unit, resides in their expected stronger and more selective glycosidases inhibition. Indeed, many glycosidases are endowed with some aglycon specificity, i.e. they selectively recognize the sugar linked to the monosaccharide to be hydrolysed.
The iminosugar clusters are other interesting glycosidase inhibitors. Works performed a few years ago by our team as well as other researchers indicated that the clustering of monovalent inhibitors leads to a significant enhancement of both their activity per iminosugar unit and the selectivity towards different glycosidases.



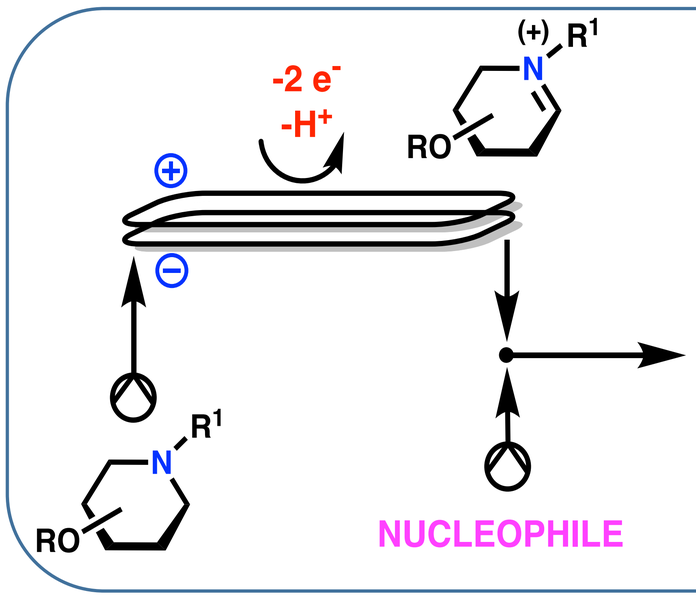
IMINO-DISACCHARIDE

X = O, S, N, carbon chain



IMINOSUGAR CLUSTER

Since the syntheses of imino-disaccharides and iminosugar clusters are usually quite long and not very efficient, we propose the *electrochemical C-H activation* of very stable 1-deoxy-iminosugar (e.g. 1-deoxy-Nojirimycin) *bearing no leaving groups* at the (pseudo)anomeric position (high atom economy), to afford an iminium intermediate to which is *then added* the suitable nucleophile (e.g. a sugar alcohol or a polyol scaffold) to give new *O*-, *S*-, *N*- or *C*-linked *imino-disaccharides* and *iminosugar-clusters*. The above-mentioned electrochemical activation approach has been recently exploited by Chiba and co-workers for the functionalization of proline derivatives as well for the synthesis of azanucleosides from protected prolinols (i.e. *pyrrolidine* derivatives). However, the application to iminopyranoses (i.e. *piperidine* derivatives) has never been explored. The electrochemical experiments will be carried out in the ElectraSyn (IKA) flow cell apparatus already available in our laboratory.
Although the electrochemical synthesis allows reactions difficult or even impossible to achieve by conventional methods, this *technology remains underutilized*.

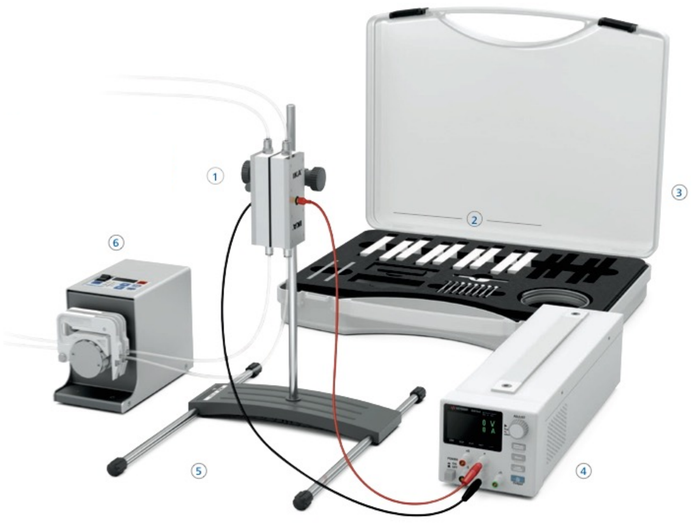


NUCLEOPHILE

IMINO-DISACCHARIDES

or

IMINOSUGAR CLUSTERS



ElectraSyn flow cell (IKA)

Further reading: our reviews and articles related to the topic

Organic & Biomolecular Chemistry (2021)


Organic & Biomolecular Chemistry

Volume 19, Number 25, 7 July 2021, Pages 5429–5662

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Mycobacterium tuberculosis cell wall polysaccharides

GLYCOSYLTRANSFERASES

SUGAR (substrate)

INHIBITORS (enzyme inhibitors)

The sick child
E. Munch, 1896

ISSN 1477-0520

ROYAL SOCIETY OF CHEMISTRY

REVIEW ARTICLE
Irene Conforti and Alberto Marra
Iminosugars as glycosyltransferase inhibitors


Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

REVIEW

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Iminosugars as glycosyltransferase inhibitors†

Irene Conforti and Alberto Marra*

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1. Introduction

Iminosugars,[1] sometimes called azasugars,[2] are naturally occurring monocyclic and bicyclic compounds closely related to carbohydrates since they feature a basic nitrogen instead of the endocyclic oxygen atom (Fig. 1). It is worth noting that most iminosugars are 1-deoxy (e.g. 1,4-dideoxy-1,4-imino-*arabinitol* (DAB) and 1-deoxynojirimycin (DNJ)) or *C*-glycosides (e.g. 2*R*,5*R*-dihydroxymethyl-3*R*,4*R*-dihydroxy-pyrrolidine (DMDP)) derivatives and therefore their chemical and enzymatic stability largely exceeds that of the natural carbohydrates, molecules existing mainly as hemiacetals (aldoses) and hemiketals (ketoses) or acetals and ketals (*O*-glycosides). These products are known to be strong inhibitors of the glycoside hydrolases (glycosidases), the enzymes that catalyse the cleavage of glycosidic bonds in oligosaccharides and glycoconjugates. However, they are also good inhibitors of the glycosyltransferases (GTs), the enzymes that catalyse the formation of the glycosidic bond starting from a sugar donor bearing a leaving group at the anomeric position.

Since the isolation[3a,b] of the isofagomine (Fig. 1) from *Streptomyces ravuconensmorgens* and *S. lavendulae* in 1967 and nojirimycin[3c] (Fig. 1) from white mulberry root barks in 1976, hundreds of unnatural iminosugars

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† Electronic supplementary information (ESI) available: Fig. S1–S11. See DOI: 10.1039/d1ob00384h

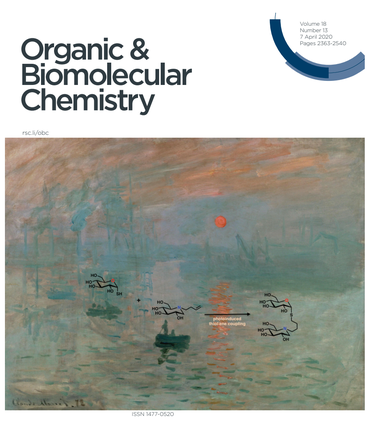

Irene Conforti

Irene Conforti graduated in Pharmaceutical Sciences from the University of Rome "La Sapienza" (Italy) spending eight months at the Laboratory of Pharmaceutical Chemistry of the King's College London (UK) to prepare her degree thesis. After a six-month period at the University of Copenhagen (Denmark) as Research Assistant, she earned a Marie Skłodowska-Curie ITN PhD fellowship at the University of Montpellier under the supervision of Prof. A. Marra. Her research topic is focused on the iminosugar-based inhibitors of NAMPT glycosyltransferase.


Alberto Marra

Alberto Marra graduated in Pharmaceutical Sciences from the University of Pisa (Italy) and obtained his PhD degree from the University of Paris VI (France) under the supervision of Prof. P. Sinaÿ. After a post-doctoral fellowship at the University of Zurich (Switzerland) with Prof. A. Vasella, he joined the group of Prof. A. Dondoni at the University of Ferrara (Italy). In 1998 he became Professor in Organic Chemistry and in 2012 he moved to the University of Montpellier (France) where he was appointed as full Professor. Recent work is dealing with the metal-free synthesis of multivalent sugars and iminosugars.

Organic & Biomolecular Chemistry (2020)


Organic & Biomolecular Chemistry

Volume 18, Number 13, 7 April 2020, Pages 2363–2540

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The Mulberry Tree (V. van Gogh, 1889)

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ROYAL SOCIETY OF CHEMISTRY

PERSPECTIVE
Alberto Marra et al.
Synthesis and biological properties of multivalent iminosugars

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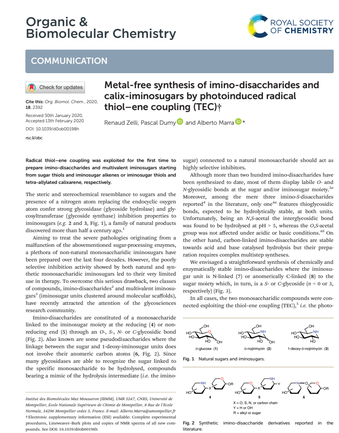
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ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

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Metal-free synthesis of imino-disaccharides and calix-iminosugars by photoinduced radical thiol–ene coupling (TEC)†

Renaud Zelli, Pascal Dumy and Alberto Marra*

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DOI: 10.1039/d0ob00198h
rsc.li/obc

Radical thiol–ene coupling was exploited for the first time to prepare imino-disaccharides and multivalent iminosugars starting from sugar thiols and iminosugar alkenes or iminosugar thiols and tetra-allylated calixarene, respectively.

The steric and stereochemical resemblance to sugars and the presence of a nitrogen atom replacing the endocyclic oxygen atom confer strong glycosidase (glycoside hydrolase) and glycosyltransferase (glycoside synthase) inhibition properties to iminosugars (*e.g.* 2 and 3, Fig. 1), a family of natural products discovered more than half a century ago.[1]

Aiming to treat the severe pathologies originating from a malfunction of the above-mentioned sugar-processing enzymes, a plethora of non-natural monosaccharidic iminosugars have been prepared over the last four decades. However, the poorly selective inhibition activity showed by both natural and synthetic monosaccharidic iminosugars led to their very limited use in therapy. To overcome this serious drawback, two classes of compounds, imino-disaccharides[2] and multivalent iminosugars[3] (iminosugar units clustered around molecular scaffolds), have recently attracted the attention of the glycosciences research community.

Imino-disaccharides are constituted of a monosaccharide linked to the iminosugar moiety at the reducing (**1**) or non-reducing end (**5**) through an *O*-, *S*-, *N*- or *C*-glycosidic bond (Fig. 2). Also known are some pseudodisaccharides where the linkage between the sugar and 1-deoxy-iminosugar units does not involve their anomeric carbon atoms (**6**, Fig. 2). Since many glycosidases are able to recognize the sugar linked to the specific monosaccharide to be hydrolysed, compounds bearing a mimic of the hydrolysis intermediate (*i.e.* the iminosugar) connected to a natural monosaccharide should act as highly selective inhibitors.

Although more than two hundred imino-disaccharides have been synthesised to date, most of them display labile *O*- and *N*-glycosidic bonds at the sugar and/or iminosugar moiety.[2a] Moreover, among the mere three imino-*S*-disaccharides reported[4] in the literature, only one[4a] features thioglycosidic bonds, expected to be hydrolytically stable, at both units. Unfortunately, being an *N*,*S*-acetal the iminothioglycoside bond was found to be hydrolysed at pH > 5, whereas the *O*,*S*-acetal group was not affected under acidic or basic conditions.[4b] On the other hand, carbon-linked imino-disaccharides are stable towards acid and base catalysed hydrolysis but their preparation requires complex multistep synthèses.

We envisaged a straightforward synthesis of chemically and enzymatically stable imino-disaccharides where the iminosugar unit is *N*-linked (**7**) or anomerically *C*-linked (**8** to **10**) to the sugar moiety which, in turn, is a *S*- or *C*-glycoside (*n* = 0 or 1, respectively) (Fig. 3).

In all cases, the two monosaccharidic compounds were connected exploiting the thiol–ene coupling (TEC),[5] *i.e.* the photo-


(+)-gabosine (**7**) | 1-nojirimycin (**2**) | 1-deoxy-D-nojirimycin (**3**)

Fig. 1 Natural sugars and iminosugars.


X = O, S, N, or carbon chain
R = alkyl
R = alkyl or sugar

Fig. 2 Synthetic imino-disaccharides derivatives reported in the literature.

RSC Specialist Periodical Reports - Carbohydrate Chemistry (2018)

Specialist Periodical Reports

Carbohydrate Chemistry

Chemical and Biological Approaches

Volume 43

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ROYAL SOCIETY OF CHEMISTRY

Synthesis and biological properties of imino-disaccharides and -oligosaccharides

Alberto Marra*[a] and Renaud Zelli[b]

DOI: 10.1039/9781788010641-00001

Since 1985, various *O*-, *S*-, *N*- and *C*-linked imino-disaccharides and imino-oligosaccharides have been designed as potent and more selective glycosidase inhibitors.

1 Introduction

Iminosugars,[1] in the past erroneously called azasugars,[2] are polyhydroxylated monocyclic (pyrrolidine, piperidine, azepane) and bicyclic (pyrrolizidine, indolizidine, nortropane) nitrogenated compounds that can be considered carbohydrate analogues bearing a basic nitrogen instead of the endocyclic oxygen atom (Fig. 1). These naturally occurring products are strong inhibitors of both glycosidases, the enzymes that catalyse the cleavage of glycosidic bonds in oligosaccharides and glycoconjugates, and glycosyltransferases, the enzymes that catalyse the formation of the glycosidic bond starting from an activated sugar donor. Besides the sterical and stereochemical resemblance to sugars, their inhibition activity arises from the protonated endocyclic nitrogen, at physiological pH, which leads to strong electrostatic interactions with the carboxylate ion located in the active site of the enzyme.

In order to find new treatments for the severe pathologies originated by a malfunction of the above sugar processing enzymes, many synthetic monosaccharidic iminosugar have been prepared over the last four decades.[3] However, in spite of designed and synthesized imino-disaccharidic derivatives such as the iminosugar clusters and the imino-disaccharides and -oligosaccharides. While the former class of compound has been extensively reviewed,[4] only two review articles and a book's chapter have been dedicated to the latter family of iminosugars, two dealing[5] exclusively with the carbon-linked disaccharides (*imino-C*-disaccharides, see section 5), the other focused[6] mainly on the synthesis and biological properties of the imino-*O*-disaccharides (see section 2). The interest in the di- and oligosaccharidic iminosugar, *i.e.* carbohydrates constituted of an iminosugar moiety linked to one or more sugar units, resides in their expected stronger and more selective glycosidases inhibition. Indeed, these enzymes are not totally selective for the monosaccharides (*e.g.* α-glucose, α-mannose, *etc.*) and the anomeric linkage (α or β) to be cleaved, and thus also the iminosugar-based inhibitors are poorly

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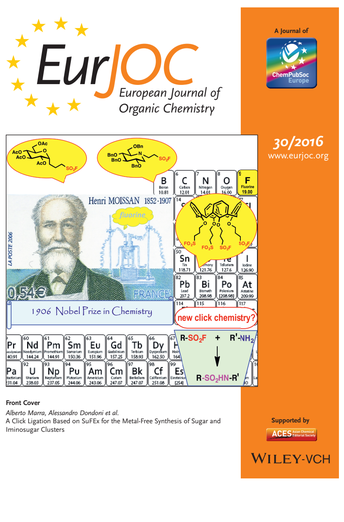
European Journal of Organic Chemistry (2016)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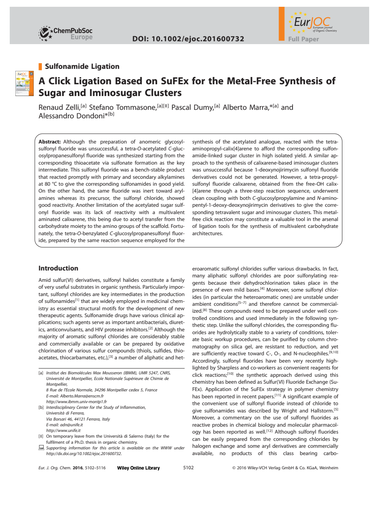
Alberto Marra, Alessandro Dondoni et al.
A Click Ligation Based on SuFEx for the Metal-Free Synthesis of Sugar and Iminosugar Clusters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DOI: 10.1002/ejoc.201600732

EurJOC Full Paper

Sulfonamide Ligation

A Click Ligation Based on SuFEx for the Metal-Free Synthesis of Sugar and Iminosugar Clusters

Renaud Zelli,[a,b] Stefano Tommasone,[a][‡] Pascal Dumy,[a] Alberto Marra,*[a] and Alessandro Dondoni*[a,b]

Abstract: Although the preparation of anomeric glycosyl-*sulfonyl* fluoride was unsuccessful, a tetra-*O*-acetylated *C*-glucosylpropane*sulfonyl* fluoride was synthesized starting from the corresponding thioacetate via sulfonate formation as the key intermediate. This sulfonyl fluoride was a bench-stable product that reacted promptly with primary and secondary alkylamines at 80 °C to give the corresponding sulfonamides in good yield. On the other hand, the same fluoride was inert toward aryl-amines whereas its precursor, the sulfonyl chloride, showed good reactivity. Another limitation of the acetylated sugar sulfonyl fluoride was its lack of reactivity with a multivalent aminated calixarene, this being due to acetyl transfer from the carbohydrate moiety to the amino groups of the sulfinil. Fortunately, the tetra-*O*-benzylated *C*-glucosylpropanesulfonyl fluoride, prepared by the same reaction sequence employed for the synthesis of the acetylated analogue, reacted with the tetra-aminopropyl-calix[4]arene to afford the corresponding sulfonamide-linked sugar cluster in high isolated yield. A similar approach to the synthesis of calixarene-based iminosugar clusters was unsuccessful because 1-deoxynojirimycin sulfonyl fluoride derivatives could not be generated. However, a tetra-propyl-*sulfonyl* fluoride calixarene, obtained from the free-OH calix-[4]arene through a three-step reaction sequence, underwent clean coupling with both *C*-glucosylpropylamine and 4-amino-pentyl-1-deoxy-deoxynojirimycin derivatives to give the corresponding tetravalent sugar and iminosugar clusters. This metal-free click reaction may constitute a valuable tool in the arsenal of ligation tools for the synthesis of multivalent carbohydrate architectures.

Introduction

Amid sulfur(VI) derivatives, sulfonyl halides constitute a family of very useful substrates in organic synthesis. Particularly important, sulfonyl chlorides are key intermediates in the production of sulfonamides[1] that are widely employed in medicinal chemistry as essential structural motifs for the development of new therapeutic agents. Sulfonamide drugs have various clinical applications; such agents serve as important antibacterials, diuretics, anticonvulsants, and HIV protease inhibitors.[2] Although the majority of aromatic sulfonyl chlorides are considerably stable and commercially available or can be prepared by oxidative chlorination of various sulfur compounds (thiols, sulfides, thioacetates, thiocarbamates, etc.),[3] a number of aliphatic and heteroaromatic sulfonyl chlorides suffer various drawbacks. In fact, many aliphatic sulfonyl chlorides are poor sulforylating reagents because their dehydrochlorination takes place in the presence of even mild bases.[4a] Moreover, some sulfonyl chlorides (in particular the heteroaromatic ones) are unstable under ambient conditions[4b–d] and therefore cannot be commercialized.[4e] Those compounds need to be prepared under well controlled conditions and used immediately in the following synthetic step. Unlike the sulfonyl chlorides, the corresponding fluorides are hydrolytically stable to a variety of conditions, tolerate basic workup procedures, can be purified by column chromatography on silica gel, are resistant to reduction, and yet are sufficiently reactive toward C-, O-, and N-nucleophiles.[4c,5] Accordingly, sulfonyl fluorides have been very recently highlighted by Sharpless and co-workers as convenient reagents for click reactions;[6a] the synthetic approach derived using this chemistry has been defined as SuFEx(VI) Fluoride Exchange (Sulfur(VI) Fluoride Exchange). The SuFEx strategy in polymer chemistry has been reported in recent papers.[6b,c] A significant example of the convenient use of sulfonyl fluoride instead of chloride to give sulfonamides was described by Wright and Hallstrom.[6d] Moreover, a commentary on the use of sulfonyl fluorides as reactive probes in chemical biology and molecular pharmacology has been reported as well.[6e] Although sulfonyl fluorides can be easily prepared from the corresponding chlorides by halogen exchange and some aryl derivatives are commercially available, no products of this class bearing carbo-

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The Mulberry Tree (V. van Gogh, 1889)

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Synthesis and biological properties of multivalent iminosugars

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Synthesis and biological properties of multivalent iminosugars

Renaud Zelli, Jean-François Longevial, Pascal Dumy and Alberto Marra*

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www.rsc.org/njc

Glycosidases are extremely widespread enzymes responsible for the cleavage of glycosidic bonds in glycoconjugates found in living organisms. Although it was well-known that the naturally occurring iminosugars are powerful glycosidase inhibitors, the development of inhibitors based on iminosugar clusters was not explored for a long period of time. However, over the past few years, several studies demonstrated that multivalent iminosugars can strongly inhibit the above-mentioned enzymes. In this review, we will focus on the different strategies developed to synthesize these multivalent architectures, from the total synthesis of divalent iminosugars to the preparation of complex systems bearing twenty-five iminosugar units. The enzyme inhibitory properties of the various multivalent iminosugars prepared to date will also be compared in order to infer the valence and the three-dimensional arrangement required for the most efficient inhibition activity.

1. Introduction

The isolation of nojirimycin from *Streptomyces ravuconensmorgens* and *S. lavendulae* in the sixties,[1] followed by the isolation of 1-deoxynojirimycin (DNJ) from white mulberry root barks a decade later,[2] paved the way to intense research in the field of iminosugar chemistry and biology (Fig. 1).[3] The interest in these carbohydrate analogues bearing a nitrogen instead of an oxygen atom came from their ability to strongly inhibit glycoside hydrolases (glycosidases), the ubiquitary enzymes that catalyse the cleavage[4] of glycosidic bonds in oligosaccharides and glycoconjugates involved in essential biological processes. Nowadays, two monovalent *N*-alkylated iminosugars are on the drug market, *N*-hydroxyethyl-deoxynojirimycin (Miglitol), to treat type 2 diabetes, and *N*-butyl-deoxynojirimycin (Miglustat), to treat lysosomal storage disorders (Fig. 1).

It is worth noting that the synthesis as well as the pharmacological evaluation of multivalent iminosugars has been neglected for decades since the discovery, half a century ago, of nojirimycin. This behavior is in sharp contrast with the extensive studies devoted to the multivalency approach in the carbohydrate–lectin

Renaud Zelli

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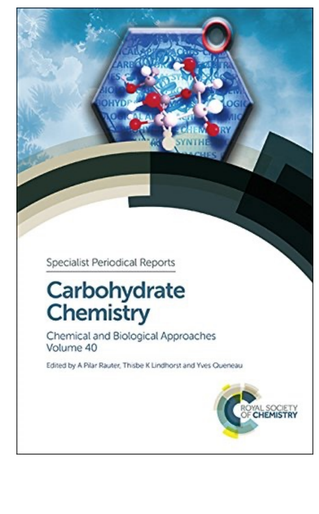
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Electrochemical glycosylation

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During the last three decades, electrochemical glycosylation performed by anodic oxidation of *O*-, *S*-, *Se*- and *Te*-glycosides or by cathodic reduction of glycosyl halides has allowed the synthesis of a large number of complex *O*-, *N*-, and *C*-glycosyl derivatives.

1 Introduction

Glycosciences have recently experienced a steady increase in interest in the fields at the chemistry/biology interface, particularly in the understanding, at molecular level, of the role exerted by glycoproteins and glycolipids in physiological or pathological events that occur in living organisms.[1] To this aim, meaningful quantities of pure oligosaccharides and glycoconjugates are required. Since these compounds are difficult to access from natural sources, many efficient glycosylation methodologies have been developed during the last years.[2] However, among the numerous methods investigated by a large number of researchers all over the world, only a limited number of them are dealt with the electrochemical glycosylation. We will describe hereafter the progress in this area made by several research groups during the last three decades.

2 Electrooxidative glycosylation

The electrochemical glycosylations, like every electrolysis, take places in electrochemical reactors, commonly called cells, that contain the reactants, the polar (*e.g.* CH_3CN, MeOH) or apolar (*e.g.* THF, CH_2Cl_2) solvents, the electrolytes, *i.e.* the salts that release the ions required to make the solution conductive, and the two electrodes. The latter are usually made of platinum, stainless steel or carbon, though, in some cases, a metal (Zn, Pb) that is consumed during the reaction is used for their fabrication (sacrificial electrodes). Also the reactors are available in two different layouts since both divided and undivided cells can be used for the electrochemical transformations. In a typical undivided cell the electrodes, connected to a potentiostat, are immersed in the solution of electroactive species, electrolyte, and solvent that is stirred in a vial, a flask or other kind of glassware. In the undivided cell, reduction and oxidation occur in the same compartment, therefore the substrate and the product are exposed to all species present in the medium. On the contrary, in a divided cell (very often a reactor having a H-shape), the anodic and the cathodic

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