Spiro Iminosugars: Structural Diversity and Synthetic Strategies

Damien Hazelard, Raphael Hensienne, Jean-Bernard Behr, Philippe Compain

Spiro Iminosugars: Structural Diversity and Synthetic Strategies

Damien Hazelard[a], Raphaël Hensienne[a], Jean-Bernard Behr[b], and Philippe Compain[a]

a) Laboratoire d'Innovation Moléculaire et Applications
Univ. de Strasbourg | Univ. de Haute-Alsace | CNRS | LIMA (UMR 7042)
Equipe de Synthèse Organique et Molécules Bioactives (SYBIO), ECPM
25 Rue Becquerel, 67000 Strasbourg, France
b) Institut de Chimie Moléculaire de Reims
Univ. Reims Champagne Ardenne | CNRS (UMR 7312)
Méthodologie en Synthèse Organique (MSO)
Moulin de la Housse, 51687 Reims Cedex 2, France.

e-mails: philippe.compain@unistra.fr; *jb.behr@univ-reims.fr*

Abstract From their discovery in the late 1960's, iminosugars have undergone an expansion from an area of science limited to a few researchers to a field that now attracts the interest of members of the whole synthetic organic chemistry community. Indeed, many tasks concern structural modifications of standard iminosugars in order to improve their biological and pharmacological properties. In this way, the introduction of an adjoining *spiro* cycle afforded unprecedented polyhydroxyazaspiranes, the structures and syntheses of which are presented in this chapter. Special attention is paid to the key steps involved in the generation of the pivotal quaternary spiro-atom.

Keywords iminosugars, spiro compounds, conformational constraint, glycochemistry, glycosidase inhibitors, glycomimetics

Contents

1 Introduction

Azaspirocycles represent structural motifs found in a diversity of natural products and biologically active compounds including alkaloids, such as the neurotoxin histrionicotoxins, or spirocyclic nucleosides related to hydantocidin [1]. The list includes also stemonamine [1e], nankakurine A [1f], halichlorine and cephalotaxine [1]. Inspired by Nature, chemists have recently designed original glycomimetics based on spiranic frameworks. In view of the biological importance of carbohydrate mimics with nitrogen atom replacing the ring oxygen, increasing efforts are directed toward the synthesis of "spiro iminosugars". Historically known as potent glycosidase inhibitors, iminosugars have been shown to inhibit an ever-growing number of therapeutically relevant carbohydrate-processing enzymes such as glycogen phosphorylases, and most recently also, enzymes that act on non-sugar-substrates [2-8]. Since the discovery of their potential as anti-diabetic agents in the 70's, the interest of chemists and clinical researchers for iminosugars has been steadily strengthened by important breakthroughs. The list includes the development of the pharmacological chaperone concept that culminated in 2016 with the approval of Galafold™ as the first oral drug for the treatment of Fabry disease [9] or the discovery of large multivalent effects in glycosidase inhibition in the late 2000's [10-12] (Fig. 1). In this review, a spiro iminosugar is defined as a glycomimetic based on a polyhydroxylated spiroazacycle. Such structures combine the advantages of classical iminosugars and of spirocycles. The ability of endocyclic amines to become protonated at physiological pH may induce effective biological activity by mimicking the structure of the enzymatic oxocarbenium ion-like transition state and/or by promoting strong electrostatic interactions with carboxylate residues in the enzyme active site [2,13]. The introduction of a spiranic center is expected to provide conformational rigidity and give access to a diversity of conformations other than the traditional chair or boat of six-membered rings. The original distributions of hydroxyl groups thus obtained are thought to be of likely significance for receptor recognition purposes. Constraining a given structure in orientations that fit the enzymatic active site or binding pocket of the biological target is a strategy widely used in drug discovery [14,15]. Within the context of glycomimetic-based inhibitors/ligands, holding hydroxyl groups in precisely defined arrangements may be a promising tool to gain specificity for a particular protein. In addition, this approach allows the exploration of unfrequented regions of chemical and intellectual property spaces. In contrast to fused bicyclic

iminosugars based on pyrrolizidine or indolizidine skeletons such as castanospermine, swainsonine or australine (Fig. 1) [16], the field of spiro iminosugars has emerged only recently. Although the first description of polyhydroxylated spiroazacycles dates back to almost 50 years [17], increased scientific interest for such structures has emerged only in the early 2000's. This may be explained in part by the synthetic difficulties associated with spiranic structures including the stereocontrolled formation of the stereogenic quaternary spirocyclic center and the functionalization of the newly formed ring system [18].

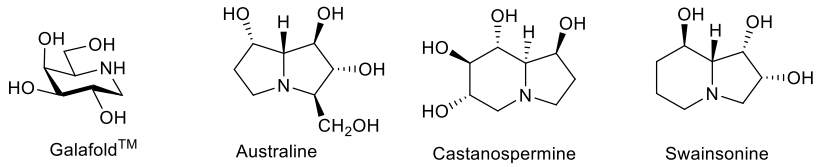


Figure 1 Some representative mono- and bicyclic iminosugars

The purpose of this review is to give an overview of the synthetic strategies designed to address the multiple challenges posed by such structures. Our intent is to focus on the key steps leading to the formation of spiro iminosugars. The review will be organized in three sections: cyclitol-based azaspiranes, glycoside-based azaspiranes and iminosugars spiro-linked with carba-, oxa-, or azacycles (Fig. 2).

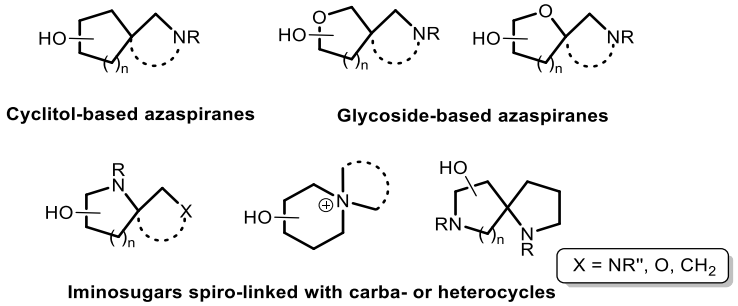
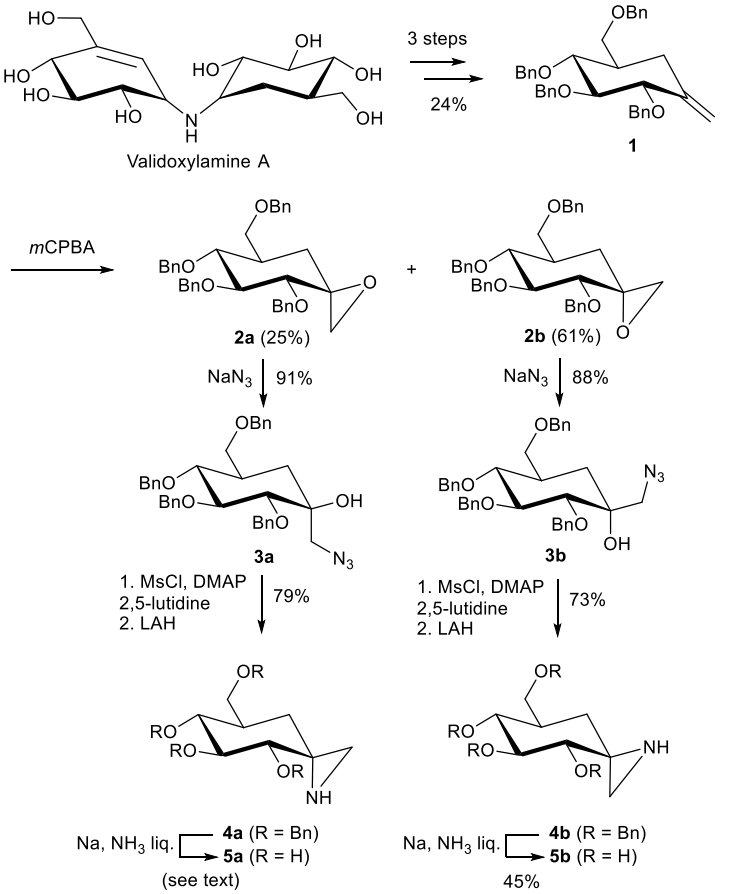


Figure 2 Spiro iminosugar structures

We hope that this review will stimulate further research in the area by providing a description of the different types of spiro iminosugars that have been reported so far. Data on their biological activity will be also given whenever such data are available.

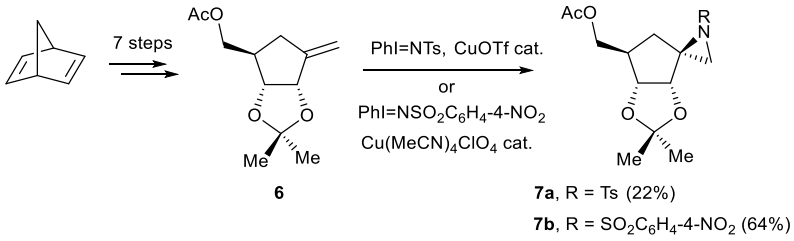
2 Cyclitol-based Azaspiranes

A limited number of polyhydroxylated spiroazacycles in which the hydroxyl groups are positioned on a cycloalkane ring has been described in the literature so far. In 2003, Vasella *et al.* reported the synthesis of spiroaziridines **5** (Scheme 1) [19]. These compounds were designed as mechanistic probes to study the impact of the position of the basic nitrogen atom on the inhibition profile towards a panel of glycosidases. The key alkene intermediate **1** was prepared in three steps from validoxylamine A (Scheme 1). The targeted aziridines were synthesized *via* the corresponding epoxides **2** obtained as a mixture of diastereomers after treatment of **1** with *m*CPBA (86% yield, d. r. 2.4:1 in favor of **2b**). Attempts to convert exocyclic alkene **1** into the corresponding *N*-tosyl aziridine using chloramine T and phenyl(trimethyl)ammonium tribromide led to poor yields. After separation by HPLC, epoxides **2a** and **2b** were treated with NaN_3. The resulting ring-opening products **3** were converted to the corresponding azido methanesulfonate intermediates which were transformed into aziridines **4** by treatment with $LiAlH_4$ in THF. Debenzylation of the spiroaziridines under Birch conditions provided the expected deprotected aziridines **5**. Spiroaziridine **5a** was found to be particularly unstable and was obtained with a small amount of an unidentified by-product after purification by Sephadex chromatography. Evaluation of azaspiranes **5** towards a panel of three glycosidases indicated that **5b** was a weak irreversible inhibitor of the β-glucosidase from *Caldocellum saccharolyticum* and a weak reversible inhibitor of the β-glucosidase from yeast. No inhibition was observed for β-glucosidase from sweet almonds. Spiroaziridine **5a** was a poor inhibitor of the three enzymes.



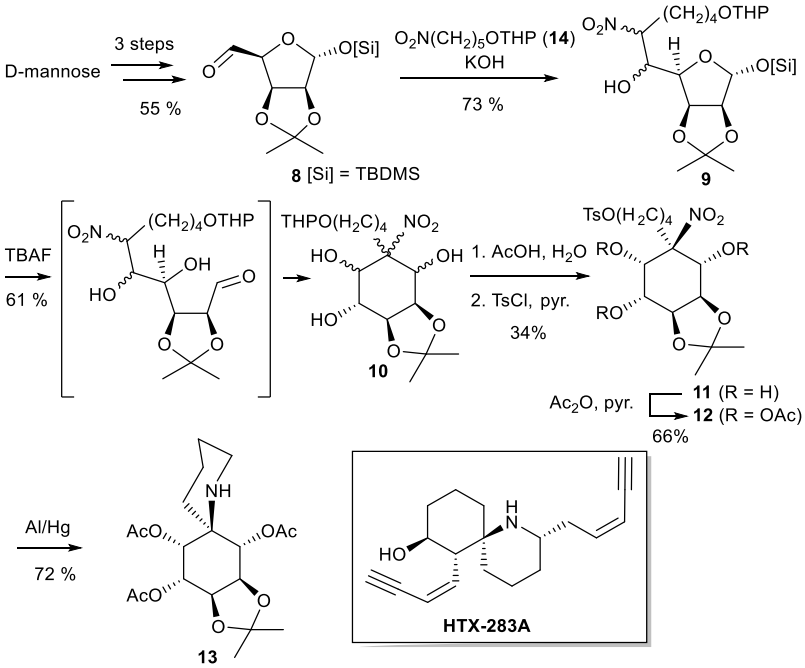
Scheme 1 Synthesis of spiroaziridines **5**

Phosphoribosyl transferase is an attractive target for anti-protozoal chemotherapy. Within the context of the synthesis of carbocyclic phosphoribosyl transferase transition state analogues, Borhani and co-workers reported the synthesis of protected spiroaziridines **7** based on a 5-membered carbasugar [20]. Interestingly, direct copper-catalyzed aziridination of exocylic alkene **6** using PhI=NTs provided aziridine **7a** as a single diastereomer, albeit in low yields (Scheme 2). The structure of **7a** was unequivocally confirmed by X-ray analysis of the corresponding ring-opening product obtained after treatment with Li_2NiBr_4. The yield of the aziridination reaction could be significantly improved using [(4-nitrobenzenesulfonyl)-imino]-phenyliodinane and $Cu(MeCN)_4ClO_4$ as the catalyst.



Scheme 2 Synthesis of spiroaziridines **7** *via* copper-catalyzed aziridination

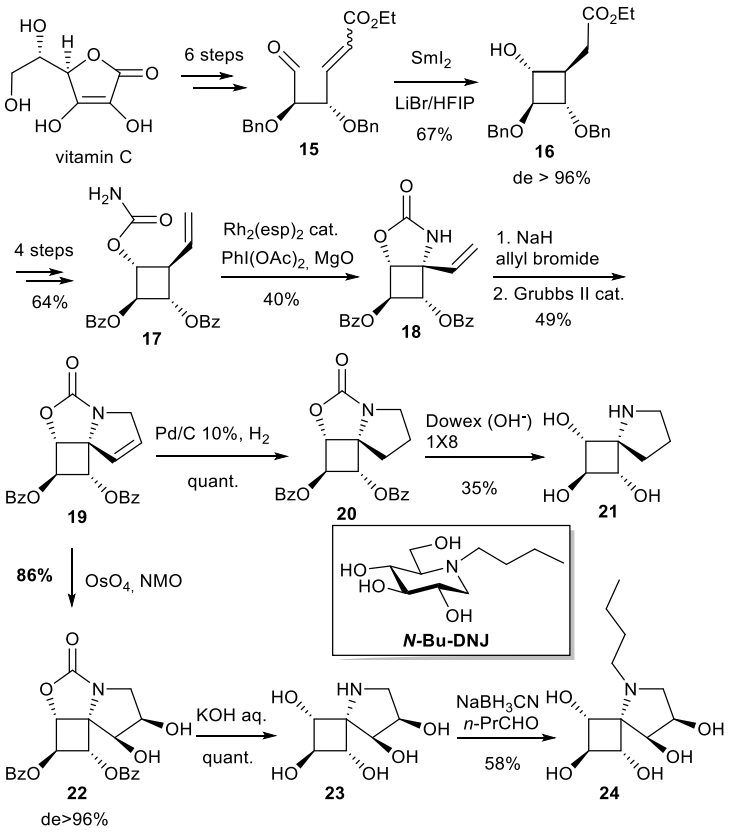
In 1987, the group of Harrisson reported a model study toward the total synthesis of enantiomerically pure (-)-histrionicotoxins (HTX) from D-mannose (Scheme 3) [21]. Their strategy was to take advantage of the chirality of carbohydrates to access enantiopure natural products and related compounds. The 1-azaspiro[5.5]undecane ring system was synthesized by way of successive inter- and intra-molecular Henry reaction. KOH-catalyzed addition of protected 5-nitro-pentan-1-ol **14** onto aldehyde **8** obtained in three steps from D-mannose afforded nitro alcohols **9** as a complex mixture of diastereomers. Treatment of the 1-*O*-silyl protected furanose **9** with TBAF liberated the anomeric aldehyde group giving rise to an intramolecular Henry reaction. This process afforded the formation of the key quaternary C-N bond of the 1-azaspiro[5.5]undecane skeleton. The nitrocyclitols **10** were however obtained as a mixture of diastereomers (61% yield). It is noteworthy that, quite remarkably, the related 2-step sequence afforded only a single diastereomer in 70% yield when nitroethane is used instead of **14**. As a prelude to the formation of the piperidine ring by way of intramolecular S_N2, the tetrahydropyranyl group was deprotected and the corresponding alcohol was tosylated to afford **11**. At this stage, after purification on silica gel, the synthesis was performed on the major diastereomer. Acetylation of diastereomerically pure triol **11** with acetic anhydride in the presence of pyridine provided the nitro derivative **12** which was reduced with aluminum amalgam. Spontaneous ring-closing then afforded the expected polyoxygenated azaspirane **13** in 72% yield.



Scheme 3 Synthesis of polyoxygenated 1-azaspiro[5.5]undecane **13** by way of inter and intramolecular Henry reactions.

Other examples of spiro iminosugars with a nitrogen atom directly connected to the quaternary spiro carbon atom were recently described by the group of Compain [22,23]. The key step of the synthesis was the stereocontrolled formation of the pivotal C–N bond *via* nitrene insertion into a C-H bond at the spiro carbon atom (Scheme 4). This process which is catalyzed by rhodium(II) complexes occurs with retention of configuration. However, applying such a reaction to polyoxygenated substrates represents a challenge in terms of regioselectivity since insertion is known to be favoured in α-ethereal C–H bonds. The first part of the synthesis is the preparation of the functionalized square carbasugar **16** [24,25]. This key intermediate was obtained in 67% yield by way of SmI_2-mediated intramolecular coupling reaction of γ,δ-unsaturated aldehyde **15** prepared in 6 steps from vitamin C [24]. To achieve a complete regiocontrol in the pivotal C-H amination step, a strategy using a combination of activating and electron-withdrawing groups has to be followed. The mere introduction of a vinylic group was indeed not sufficient to reach high regioselectivity at the spiro carbon atom; electron-withdrawing protecting groups were also required to reduce the electron density at the undesired C–H insertion site in α-position to the carbamate group. After various attempts, the best C-H amination substrate was found to be carbamate **17** obtained in 4 steps from the cyclization product **16**. After having generated the pivotal C–N bond of the final targets with retention of configuration

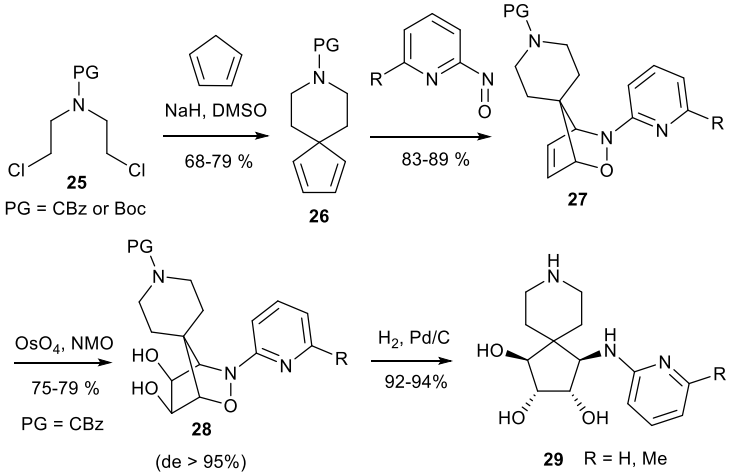
and high regiocontrol, the final key step of the synthesis entailed the formation of the azacycle by ring-closing metathesis. Despite the additional ring strain generated by the 5-membered ring closure, the expected tricyclic spirocycle derivative **19** was obtained in high yield using 5 mol% of Grubbs II catalyst. Unprecedented constrained iminosugars **21** and **23-24** were then obtained in 2 or 3 steps from the common intermediate **19** thus generated (Scheme 4). Preliminary biological evaluations were performed and led to the identification of a new class of correctors of defective F508del-CFTR gating involved in cystic fibrosis (CFTR : Cystic Fibrosis Transmembrane conductance Regulator). The best corrector of the spiranic series, iminosugar **24**, displayed a F508del-CFTR activity rescue not significantly different from the *N*-Bu DNJ-induced one [23]. *N*-Bu DNJ - also named miglustat - is a clinical candidate for the treatment of cystic fibrosis.



Scheme 4 Synthesis of 4-membered cyclitol-based spiro iminosugars

Cyclitol-based iminosugars where the nitrogen is not directly connected to the quaternary spirocarbon have been described by the group of Miller [26]. The spirocyclic skeleton was efficiently constructed *via* the dialkylation of

cyclopentadiene with *N*-protected bis-2-chloroethylamines **25** (Scheme 5). The spiranic dienes **26** were then engaged in a series of iminonitroso Diels-Alder reactions to yield the corresponding cycloadducts **27** in good yields. In addition to the stereocontrolled formation of two carbon-heteroatom bonds, one advantage of this cycloaddition process is that the resulting endocyclic alkenes are converted into the corresponding diols **28** with high diastereoselectivity under Upjohn reaction conditions (OsO_4, *N*-methyl morpholine-*N*-oxide, NMO). The one-step cleavage of the N-O bond and deprotection of the Cbz group provided the 4-amino-8-azaspiro[4.5]decanols **29** in high yields (racemic form).



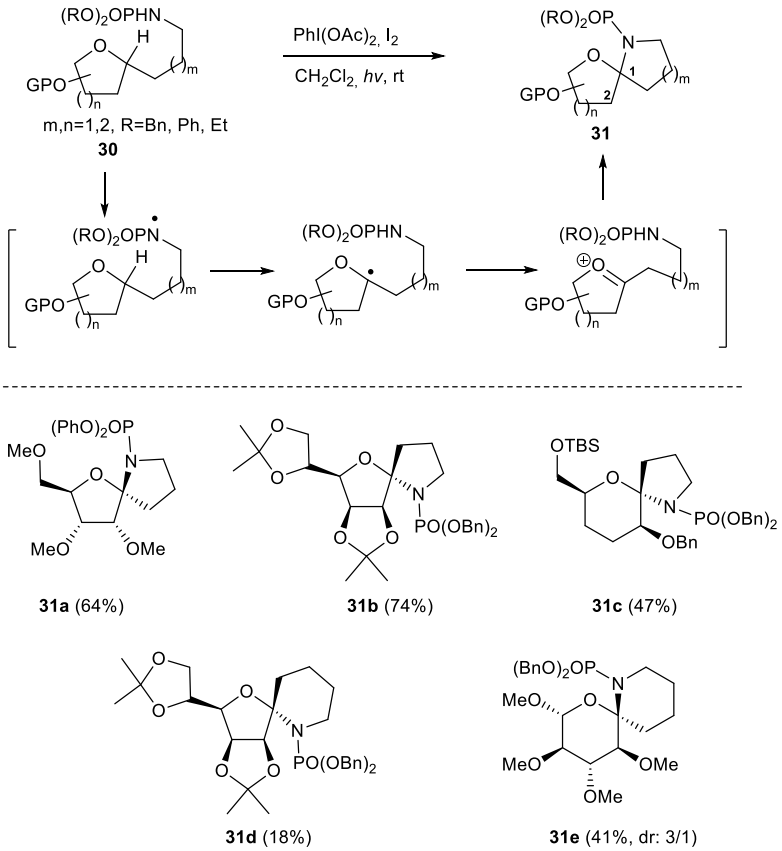
Scheme 5 Synthesis of 4-amino-8-azaspiro[4.5]decanols **29**

3 Carbohydrate-based Azaspiranes

It is not surprising that several synthetic carbohydrate-based spiroazacycles have been described in the literature. The preparation of such compounds takes indeed advantage of the use of carbohydrates as starting materials. Biologically relevant carbohydrate-based azaspiranes are also found in Nature as shown by the herbicide hydantocidin, a nucleoside having a unique structure with a spiro-annelated hydantoin and ribose [27].

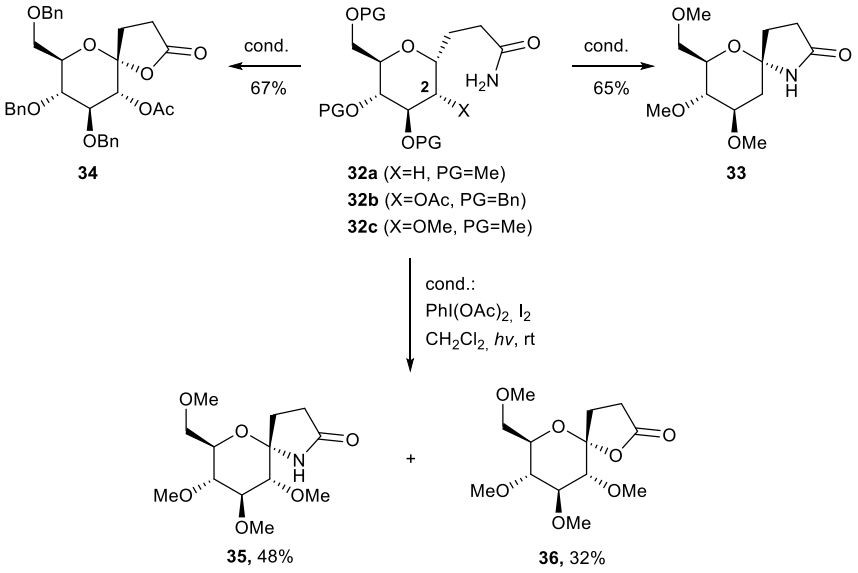
3.1 Systems with a nitrogen atom at α-position to the spirocyclic center

Suarez and co-workers reported the regio- and stereoselective formation of oxa-1-azaspirocycles by way of intramolecular hydrogen atom transfer (HAT) (Scheme 6) [28,29]. This strategy is based on the formation of an electrophilic *N*-radical followed by subsequent abstraction of a hydrogen atom at the *pseudo* anomeric position. The nucleophilic *C*-radical thus formed is oxidized to an oxonium ion which reacts with the amine group [30]. The authors synthesized several carbohydrate substrates **30** with different ring sizes and protecting groups. Irradiation of compounds **30** in the presence of molecular iodine and $PhI(OAc)_2$ afforded spiroaminals **31** [28,29,1a]. Better yields were obtained for the formation of five membered in comparison to six membered rings. This difference of reactivity could be explained by a more favourable 1,5 HAT through a six membered transition state. Furthermore, the methodology described was compatible with the most common protecting groups in carbohydrate chemistry. However, the introduction of an electron withdrawing protecting group (acetate) at C-2 inhibits the radical abstraction at C-1 and the substrate was recovered unchanged.



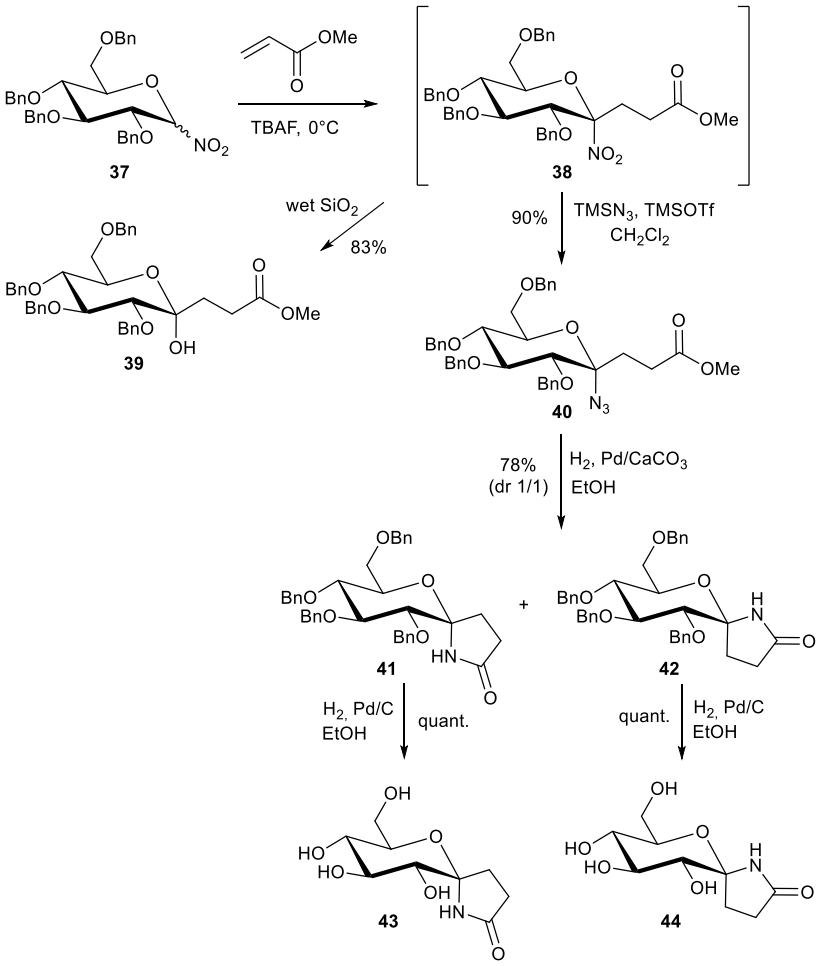
Scheme 6 Synthesis of 1-azaspirocycles **31** by intramolecular hydrogen atom transfer

The same group has applied the HAT strategy to the synthesis of spirolactams involving amidyl radicals [31] (Scheme 7). It is noteworthy that depending on the substitution at C-2, spirolactones or spirolactams are obtained. Indeed, 2-deoxysugar **32a** afforded lactam **33**, whereas 2-acetyl-D-glucose **32b** gave spirolactone **34** in good yield. This difference of reactivity is explained by the authors on the basis of the hard and soft acids and bases (HSAB) principle. In the case of **32b**, the oxocarbenium ion intermediate is a harder electrophile than **32a** due to the presence of the electron-withdrawing group at C-2. As the oxygen atom of the amide is considered to be a harder nucleophile than the nitrogen atom, it attacks the hard electrophilic oxocarbenium ion. In the case of **32c**, substituted at C-2 with an electron-donating group, a mixture of spirolactam **35** and spirolactone **36** was obtained. The highly stereoselective formation of the products with axial C-O (N) bonds is explained by a better stability of the bicyclic products **33**-**36** due to the anomeric effect.



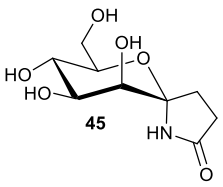
Scheme 7 Synthesis of carbohydrate-based spirolactams or spirolactones by intramolecular hydrogen abstraction

Spirolactams have also been obtained from nitrosugars by way of Michael addition (Scheme 8) [32]. For example, reaction of nitrosugar **37** [33] with methyl acrylate in the presence of TBAF gave unstable adduct **38** which after column chromatography produced **39** in good yield [32,34]. On the other hand, azidation of the crude Michael adducts **38** with $TMSN_3$ in the presence of TMSOTf afforded 1-azido sugar **40** in 90% yield as a single diastereomer. This methodology has also been applied to other electrophiles such as acrylonitrile or ethyl propiolate and in other sugar series (D-manno). Amides **41** and **42** were then obtained after reduction of 1-azido sugar **40** and subsequent cyclization. Ring-opening of the transient glucosylamine intermediate formed during the process followed by ring-closing of the corresponding open imine led to the formation of a mixture of epimeric spirolactams **41** and **42** [32]. Deprotection of the benzyloxy groups afforded the final products **43** and **44** in 70% yields from nitrosugar **37**. Related spiro-carbamate and spiro-sulfamate glycosides were obtained by means of intramolecular rhodium-catalyzed amination of pseudo anomeric C-H bond in 2-deoxy *C*-glycosides [35].

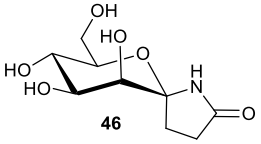


Scheme 8 Synthesis of carbohydrate-based spirolactams **43** and **44** from nitrosugar **37**

Spiroaminals **45** and **46** were obtained following a similar strategy [32]. The inhibitory activities of compounds **43**-**46** were evaluated on several commercially available glycosidases (Fig. 3). These compounds showed no inhibition against yeast α-glucosidase and Jack beans α-mannosidase [32]. Among the spirolactams tested, compound **43** with a glucose core gave the most interesting result as a highly selective inhibitor of bovine β-galactosidase.



45

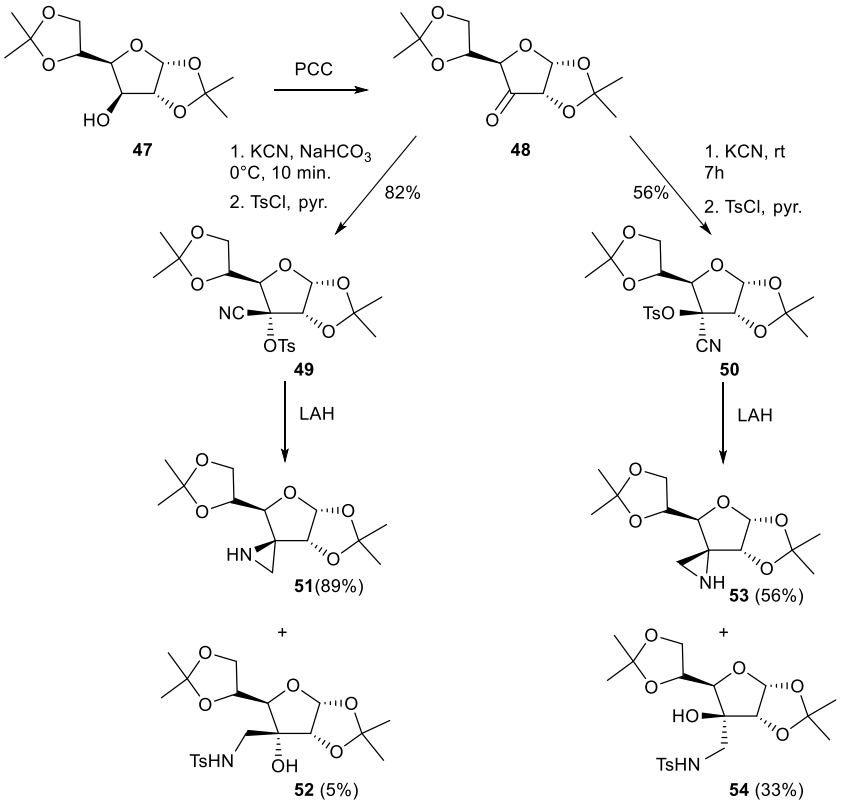


46

Enzyme	IC_{50} (μM)			
	43	**44**	**45**	**46**
α-glucosidase (yeast)	NI	NI	NI	NI
β-glucosidase (almonds)	NI	200	NI	NI
α-galactosidase (coffee beans)	NI	77	NI	NI
β-galactosidase (bovine)	207	160	NI	400
α-mannosidase (Jack beans)	NI	NI	NI	NI

Figure 3 Inhibition profile of spirolactams **43**-**46**

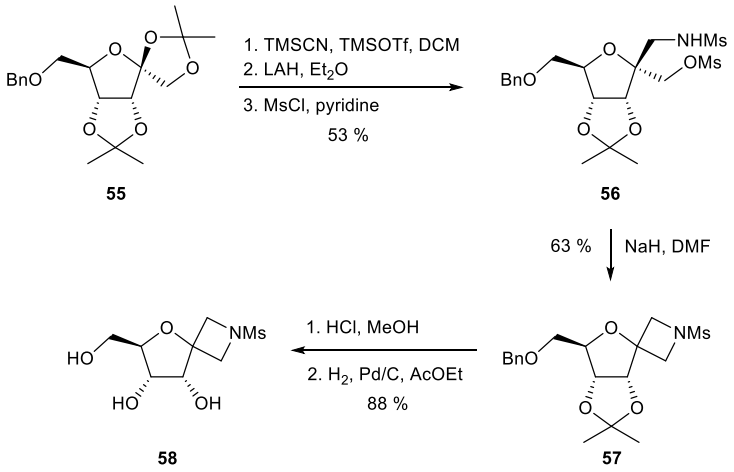
Several authors prepared original spiroaziridines as valuable intermediates for the synthesis of carbohydrate derivatives of interest [17, 36-38]. In the course of their study on carbohydrate-based spiro 1,3-oxazolidinine-2-thiones, Tatibouët *et al.* reported the synthesis of spiroaziridines **51** and **53** (Scheme 9) [37]. The strategy was based on the stereoselective formation of cyanohydrin derivatives **49** and **50**. The stereochemistry of the new stereogenic center could be controlled under kinetic or thermodynamic conditions from ketone **48**, obtained after oxidation of alcohol **47** [37-39]. Reduction of nitriles **49** and **50** afforded, after spontaneous intramolecular cyclization, aziridines **51** and **53**, respectively. However, amino alcohols **52** and **54** resulting from competing tosyl migration were also obtained in yields up to 33%.



Scheme 9 Synthesis of spiroaziridines **51** and **53**

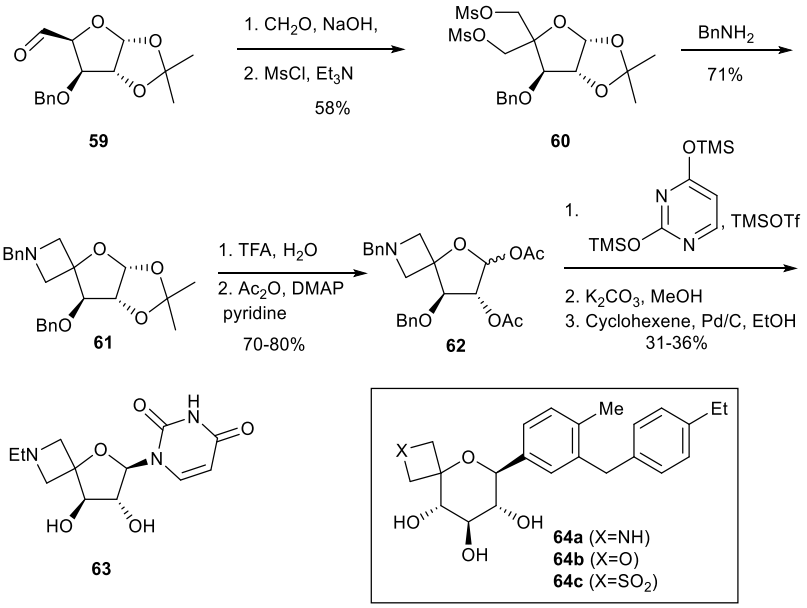
3.2 Systems with a nitrogen atom at β-position to the spirocyclic center

Several authors have reported the formation of carbohydrates spiro-linked with an azetidine [40-43]. The first examples were described by the groups of Fuentes and Mandal in 2006 [40, 41a]. Fuentes and co-workers reported the formation of sulfoazetidine spiro-*C*-glycosides from ketose acetals [40]. For example, treatment of spiroacetal **55** obtained in 4 steps from D-fructose [44] with trimethylsilyl cyanide followed by reduction of the nitrile and dimesylation of the corresponding amino alcohol intermediate afforded compound **56** in 53% yield (3 steps) [40,45]. Base-mediated cyclization of **56** and deprotection of the resulting azetidine gave spiro iminosugar **58** in good yield (Scheme 10).



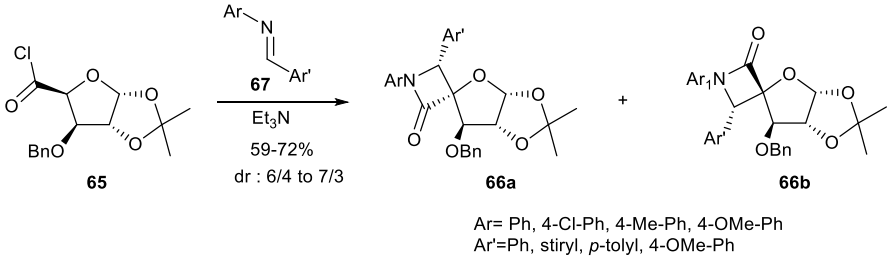
Scheme 10 Synthesis of spiroazetidine **58**

During their studies on the synthesis of spironucleosides [41], Mandal and co-workers reported the formation of nitrogen-containing spirosugars **61-63** through an aldol/Cannizzaro sequence (Scheme 11). Compound **59**, easily obtained from **47**, was treated by formaldehyde and sodium hydroxide to afford the corresponding diol which was then subjected to mesylation reaction with MsCl and Et_3N [41a]. The resulting dimesylate **60** was reacted with benzylamine providing spiroazetidine **61**. After cleavage of the acetonide group and acetylation, a nucleobase could be introduced by treatment of compound **62** with 2,4-bis-(trimethylsilyloxy)pyrimidine. Deacetylation and debenzylation steps furnished spironucleoside **63**. Interestingly, during the debenzylation step using transfer hydrogenolysis with cyclohexene, introduction of an ethyl group on the amine was observed. The authors explained the formation of *N*-alkyl derivative **63** by the Pd-catalysed oxidation of ethanol to acetaldehyde. Free amine may then condense with acetaldehyde to form an iminium which could be reduced *in situ* [41b]. Spirocyclic *C*-glycosides **64** have been obtained by a related synthetic strategy using an aldol/Cannizzaro sequence (Scheme 11) [42]. These compounds have been evaluated as SGLT2 (Sodium Glucose Transporter of type 2) inhibitors. SGLT2 inhibitors are expected to display interesting therapeutic applications, in particular as anti-diabetic agents [42]. Evaluation of compounds **64** indicated that **64b** and **64c** were potent and selective SGLT2 inhibitors. Azaspironucleoside **64a** with IC_{50} values in the micromolar range was found to be up to 1500-fold less potent as SGLT2 inhibitors than **64b** and **64c**.



Scheme 11 Synthesis of spironucleosides **63** and **64** *via* Cannizzaro and cyclisation reactions

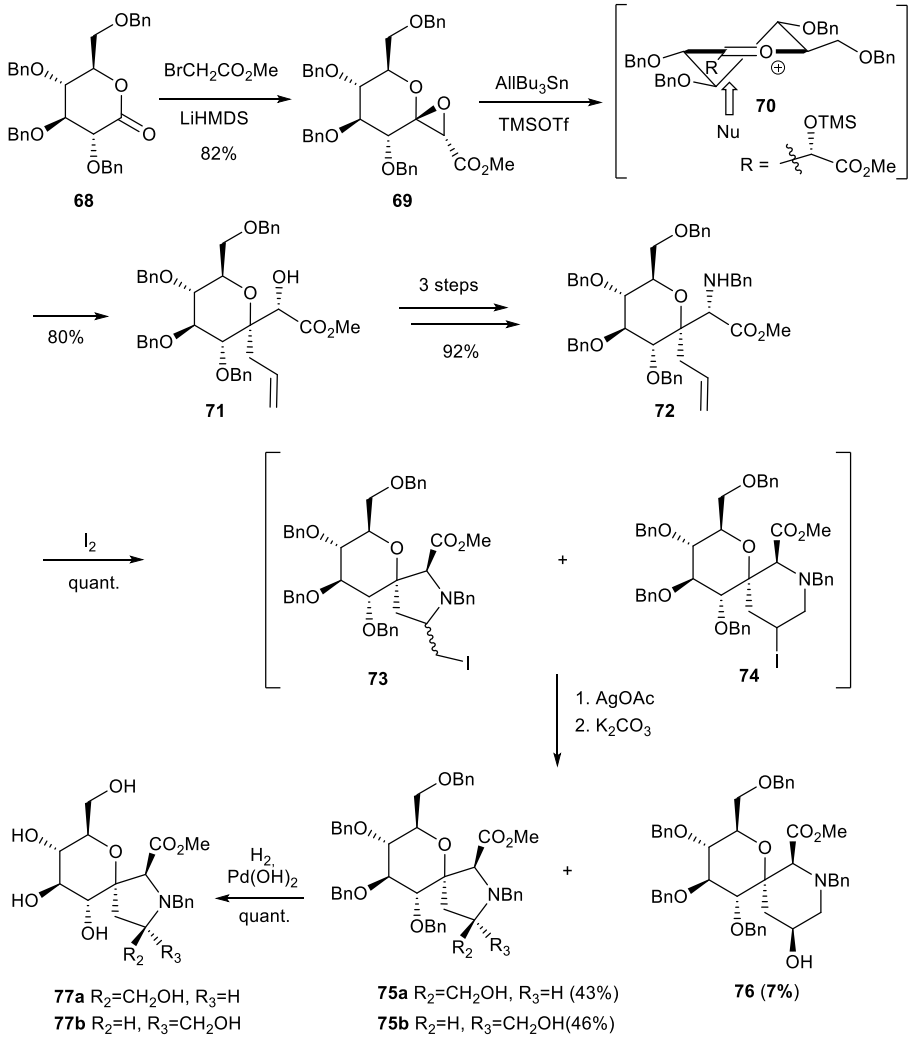
Related carbohydrates spiro-linked with an azetidine may be also obtained by means of Staudinger cycloaddition (Scheme 12) [43]. Acid chloride **65** was prepared from D-glucose in five steps and was used as a ketene precursor which can react with imines **67** to provide lactams **66a** and **66b** (d. r. 6/4 to 7/3 in favour of **66a**). The [2+2] cycloaddition reaction proceeded with a good level of stereoselectivity; only two d diastereomers were obtained among the four theoretically possible. The stereoselectivity observed could be rationalized by the torquoelectronic model.



Scheme 12 Synthesis of lactams **66** *via* Staudinger cycloaddition

Zhang and Schweizer reported the synthesis of carbohydrate-based azaspiranes with a piperidine or pyrrolidine moiety from 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**68**) [46]. The first key step of the synthesis involved the highly diastereoselective TMSOTf-mediated *C*-glycosylation of the exocyclic glucose-

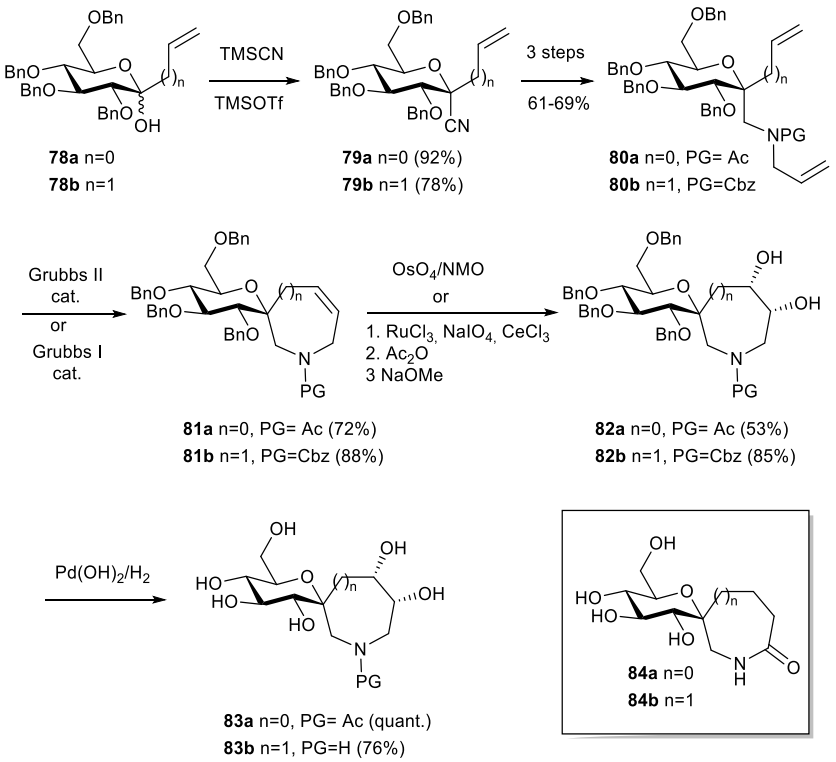
based epoxyde **69** with allyltributylstannane (Scheme 13). The α-selectivity observed may be rationalized by preferential nucleophilic attack along axial trajectory on the most favoured half-chair of the glycosyl cation intermediate **70** in which all the substituents are *pseudo*-equatorial. The resulting *C*-ketoside **71** was obtained in 80% yield. Conversion to the corresponding α-amino ester **72** was performed by way of reductive amination. The iodocylisation reaction in the presence of molecular iodine turned out to be not completely regioselective; iodocompounds **73** and **74** were obtained in quantitative yield as an inseparable mixture of spirocyclic products of various ring sizes. Attack of the amino group at the most substituted site of the cyclic iodonium intermediate was found to be favoured and occurred without stereocontrol. Treatment of **73** and **74** with silver acetate followed by saponification of the resulting acetates afforded alcohols **75-76** that could be separated by flash chromatography. Their structures and stereochemistry were established in part by NMR analysis and NOE experiments. *Pseudo* iminosugars **77** were finally obtained after deprotection of spirocyclic pyrrolidines **75** in the presence of Pearlman's catalyst. The authors reported also the synthesis of analogues of **77** in which the primary alcohol of the D-glucose moiety has been replaced by an amine [46b].



Scheme 13 Synthesis of spiroiminosugars *via* iodocyclisation

Ring-closing metathesis (RCM) is one of the most powerful methods to access amine-containing heterocycles in particular for the formation of medium or large rings [47]. The group of Vankar has used this methodology for the formation of oxa-aza spiro sugars containing a piperidine or azepane ring (Scheme 14) [48]. Intermediates **78** were prepared from gluconolactone **68** by addition of vinyl- or allylmagnesium bromide. *C*-glycosylation using trimethylsilyl cyanide in the presence of TMSOTf afforded nitriles **79** in good yields and high diastereoselectivity. Key RCM precursors **80** were then synthesized following a 3-step sequence: reduction of nitrile group, protection of the resulting amine and *N*-allylation. Ring

closing metathesis of dienes **80** gave the corresponding azacycles **81** in good yields. It is noteworthy that compound **81a** was not formed in the presence of Grubbs I catalyst. Substantial substrate reactivity differences were also observed for the dihydroxylation step. Whereas treatment of **81b** with osmium tetroxyde in the presence of *N*-methyl morpholine-*N*-oxide (NMO) provided diol **82b** in good yield and as a single diastereomer, no conversion was observed when the same conditions were applied to piperidine **81a**. To overcome this lack of reactivity, bis-hydroxylation was performed with $RuCl_3$ in the presence of $NaIO_4$ and $CeCl_3$ to give the expected diol which was directly acetylated, and then deprotected to afford **82a** in 53% yield for the three steps. Spiro iminosugars **83** were obtained after debenzylation. A related synthetic strategy was used for the formation of lactams **84**. Evaluation of spiro compounds **83**-**84** as inhibitors of a panel of five glycosidases indicated that **83** were weak but selective inhibitors of Jack beans α-mannosidase. Furthermore lactams **84** showed no inhibition or inhibition in the mM range.



Scheme 14 Synthesis of spiroiminosugars *via* ring-closing metathesis

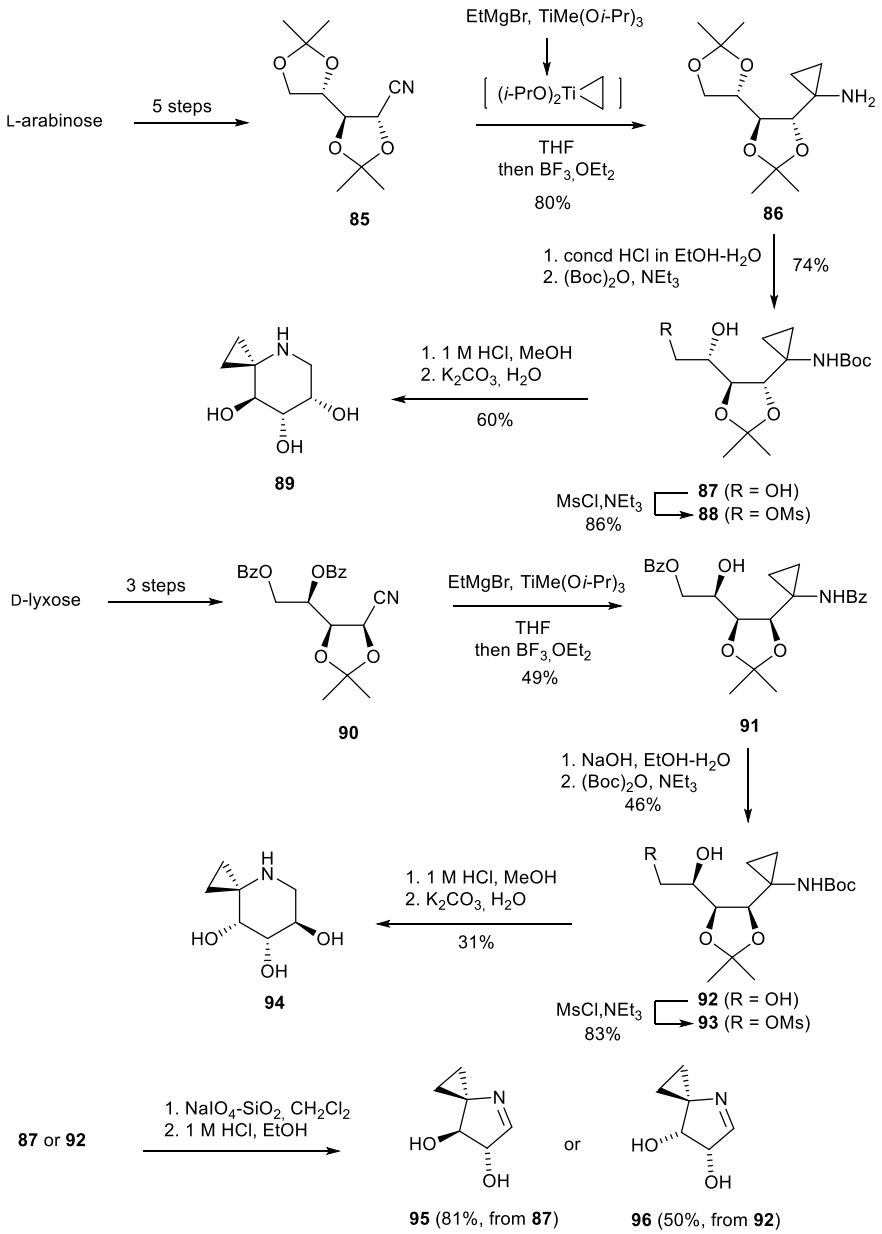
4 Iminosugars Spiro-linked with Carba, Oxa and Azacyles

In addition to the structures presented before, in which an aza-cycle is attached to a polyhydroxylated scaffold, spiro compounds featuring a nitrogen-containing heterocyclic polyol have also attracted great attention. Aside from compounds **24** (Scheme 4) and **83** (Scheme 14) encompassing multiple OH on both the N and X (X=C,O) cycles, a number of additional spiro-iminoalditols have been built in an attempt to affect the peculiar biological properties of their monocyclic templates. Simple aminocyclitols are usually tailored to adapt the catalytic site of a given glycoenzyme, mimicking the corresponding glycoside to be processed [2]. Spiro-linked iminoalditols might be structurally related to fused bicyclic iminosugars (Fig. 1) however, the peculiar orthogonal orientation of the extra spiro-cycle offers scope for unprecedented interactions in the active site. Furthermore, synthetic issues to access the two kinds of adjoined cycles are rather distinct. Contrarily to their fused analogues [47a, 49], the construction of spirocyclic iminoalditols has been scarcely reviewed [50]. Main strategies are described below.

4.1 Iminosugar-carbacycle spiro systems

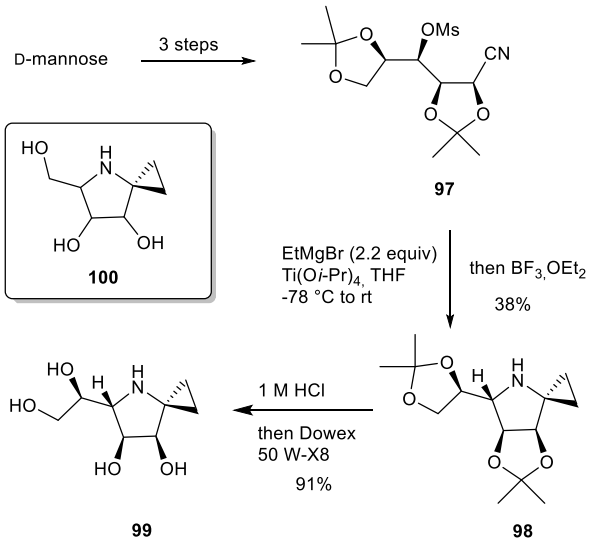
L-Fucose and L-rhamnose are 6-deoxyhexoses commonly found in complex carbohydrates from all organisms, the trimming of which is performed by fucosidases and rhamnosidases. Simple iminosugars featuring both the methyl substituent and the adequate hydroxyl distribution are generally potent inhibitors of these enzymes. Analogues with a spiro carbacycle in place of the C-5 methyl group have been designed in order to evaluate the tolerance of the corresponding binding pocket to steric strain and to improve either potency or hydrophobicity. To access spirocyclopropyl iminosugars in L-fuco or L-rhamno series, the group of Behr applied a Kulinkovich-Szymoniak-Bertus cyclopropanation of designed glyconitriles. This reaction of very wide application [51] is based on the generation of a titanacyclopropane intermediate, a bis-anionic reactive species able to add twice to the –CN electrophilic partner to afford a spirocyclopropyl primary amine (Scheme 15). Hence, D-lyxose or L-arabinose derived nitriles **85** or **90**, gave linear cyclopropylamines **86** (80%) and **91** (49%), the latter being formed after in situ Bz transfer [52,53]. A game of protection/deprotection combined with activation of the primary hydroxyl to induce intramolecular nucleophilic displacement furnished the expected spirocyclopropyl piperidines **89** and **94**, analogues of L-rhamnose and L-fucose, respectively. Unsaturated pyrroline **95** was obtained from intermediate **87** after oxidative cleavage of the free vicinal diol and isopropylidene deprotection. The same synthetic sequence was applied for the preparation of **96**, the C-3 epimer of **95**, from **92**. Spirocyclopropyl-iminosugars showed some activi-

ty against fucosidase and rhamnosidase, best results being obtained with **94** (K_i=18 μM against α-fucosidase from bovine kidney).



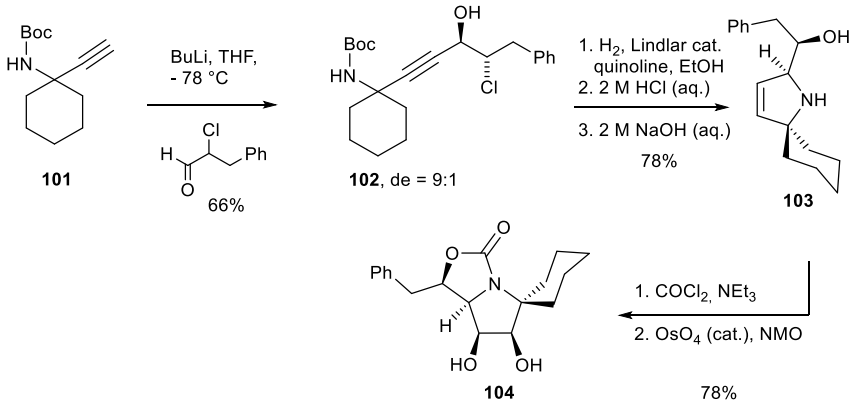
Scheme 15 Synthesis of spiroiminosugars from glyconitriles

To access spirocyclopropyl pyrrolidines, the same group adapted their strategy to 4-methanesulfonyl-glyconontriles such as **97** (Scheme 16), the cyclopropanation of which was accompanied by concomitant cyclization [54,55]. By this very straightforward method spirocyclopropyliminocyclitol **99** was obtained in only five steps starting from D-mannose. Further stereoisomeric pyrrolidines of general structure **100** were prepared following the same strategy through variation of the starting sugar. Among these, only **99** showed inhibition potency in the micromolar range (K_i=1.6 μM against α-fucosidase from bovine kidney). In general, biological assays with such compounds suggest that the replacement of a methyl substituent by a spirocyclopropyl group reduces the inhibitory potency towards the corresponding enzymes.



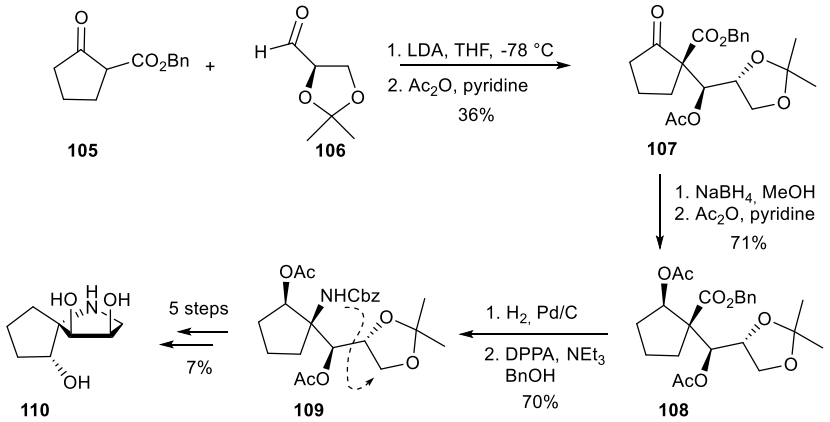
Scheme 16 Synthesis of spiroiminosugar **99**

A spirocyclohexyl analogue of **99** was synthesized more recently in the racemic series from a hydroxyalkyldihydropyrrole precursor [56]. Elaboration of these latter substances involved the coupling of propargylamines with α-chloroaldehydes, followed by alkyne reduction and one-pot epoxide formation/ring-opening sequence (Scheme 17). Thus, the alkynyl chlorohydrin **102** was prepared first following addition of Boc-protected propargylamine **101** to 2-chlorocinnamaldehyde. Then, Lindlar reduction followed by acidic treatment of the crude product afforded the expected dihydropyrrole **103** in good overall yield (78%) after neutralization. It was then converted into spirocyclohexyl-iminosugar **104** *via* reaction with phosgene and subsequent dihydroxylation. The relative stereochemistry of final compound **104** was assessed by 1D NOESY spectra.



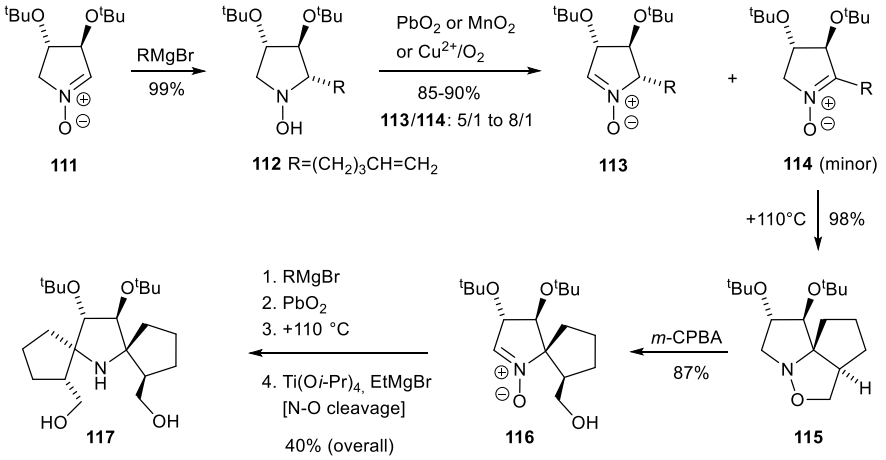
Scheme 17 Synthesis of spirocyclohexyliminosugar **104** *via* dihydropyrrole intermediate

In such aza-spiroheterocycles, partial hydroxylation of the hydrocarbon portion could afford new binding contributions to improve inhibition potencies against a given enzyme. Therefore, Pinto and Chen prepared swainsonine analogue **110** (Scheme 18), which was expected to interact strongly with the hydrophobic pocket of Tyr727, Phe206 and Trp415 in Drosophila Golgi α-mannosidase II [57]. The key quaternary center was formed stereoselectively by aldol condensation of ketone **105** with (*R*)-isopropylidene glyceraldehyde **106** and subsequent acylation. From the four possible stereoisomers (ratio 30:6:5:1), the desired compound **107** was isolated by silica gel chromatography and reduced/acylated to obtain **108**. A Curtius rearrangement allowed the introduction of the amine-derived functional group at this stage, affording carbamate **109**. Additional standard procedures comprising ring closure by intramolecular nucleophilic displacement delivered target compound **110**. Unfortunately, it did not show effective inhibition of human maltase glucoamylase or Golgi mannosidase II.



Scheme 18 Synthesis of swainsonine analogue **110** *via* Curtius rearrangement

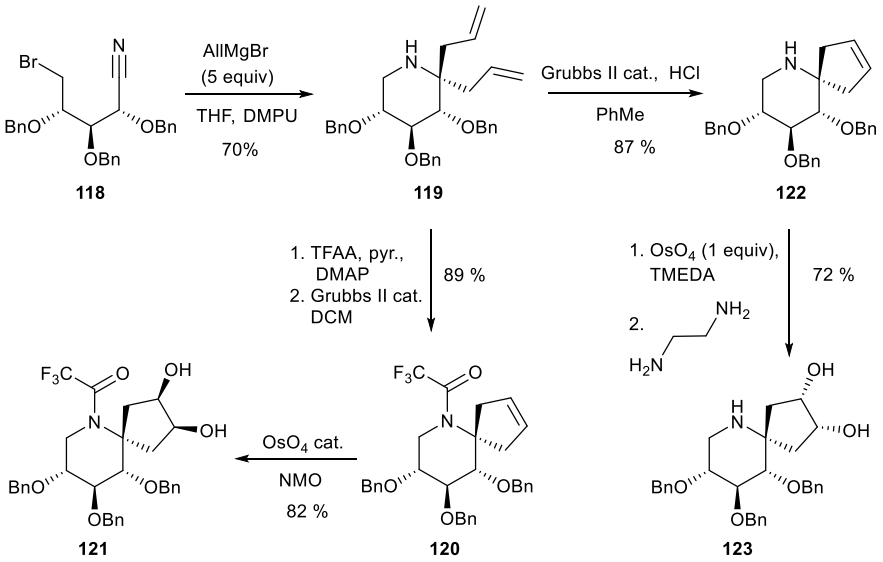
An analogue of **110**, the bis-spiranic C_2-symmetric pyrrolidine **117**, was successfully synthesized by Morozov *et al. via* iterative nitrone chemistry [58]. As depicted in Scheme 19, quaternization of the two α-carbon atoms resulted from successive completely regio- and stereoselective organometallic addition and intramolecular cycloaddition reactions on nitrones **111** and **116**. Transient oxidation of hydroxylamine **112** proved however moderately regioselective, affording the two isomeric nitrone intermediates **113** and **114**. Following the iterative synthetic strategy, *tert*-butoxy protected dispiro-pyrrolidine **117** was eventually obtained in reasonable overall yield.



Scheme 19 Synthesis of bis-spiranic pyrrolidine **117** *via* iterative nitrone chemistry

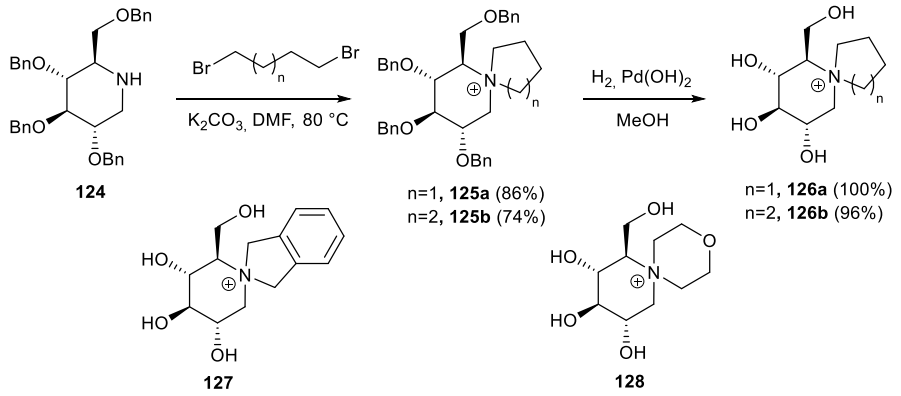
Jarosz and co-workers prepared a series of highly hydroxylated spiro-iminosugars, *i. e.* azaspiro[4.5]decanes **121** and **123**, using a double addition of allyl Grignard to polyhydroxylated ω-bromonitrile **118** (Scheme 20) [59]. While monoallylated product was isolated in good yields when 1.3 equivalents of allylMgBr were used, the reaction with 5 equivalents of this same reagent afforded the bis-allylated piperidine **119** in 70% yield. The presence of DMPU or HMPA clearly favoured the addition of a second allyl nucleophile to the putative imine intermediate [60]. Protection of the free NH proved somewhat tricky due to the presence of bulky substituents in the proximity of the nitrogen atom. However **119** was efficiently protected as a trifluoroacetate, which was subsequently subjected to RCM (Grubbs-II catalyst) to afford azaspiro[4.5]decene **120**. Upcoming osmylation of **120** with osmium tetroxide and *N*-methyl morpholine-*N*-oxide (NMO) was completely stereoselective and the configuration of the formed diol **121** was firmly assigned by X-ray analysis of a hexaacetate derivative. RCM was also applied to amine **119** by using transient *in situ* protection with a Brønsted acid. Interestingly, osmylation occurred from the opposite face with spirodecene **122** than it did in the case of

olefin **120**, the free amine certainly acting as a directing group in such transformations.



Scheme 20 Synthesis of azaspiro[4.5]decanes **121** and **123** *via* RCM

Finally, spirocycles were also installed at the nitrogen atom of iminosugars to generate a permanent positive charge (as a quaternary ammonium salt) in order to favour ionic interactions at the catalytic site of glycosidases [61]. To this end, a double nucleophilic substitution reaction on tetrabenzylated DNJ **124** with either 1,4-dibromobutane or 1,5-dibromopentane followed by hydrogenolysis afforded *N*-spirofused iminosugars **126a,b** (Scheme 21). An analogous strategy gave 1-deoxynojirimycin derivatives **127** and **128** with isoindoline and morpholino extra rings, respectively. The glycosidase inhibition activities of the bromide salts of **126-128** were evaluated at 500 μM concentration on various commercially available glycosidases from different natural origins (α-mannosidase from Jack bean, α-glucosidase from *S. cerevisiae*, amyloglucosidase from *A. niger*). Best results were obtained with **126b** for which 30% residual activity was observed towards amyloglucosidase. Ammonium salts are also frequently used as antibacterial agents, disrupting cell membranes through ionic interactions. Therefore, along with their antiglycosidase potential, antibacterial effect of *N*-spirofused iminosugars was evaluated on the Gram positive *S. aureus* and the Gram negative *E. coli*. However, no activity against the two selected microorganisms could be detected up to 5 μM.



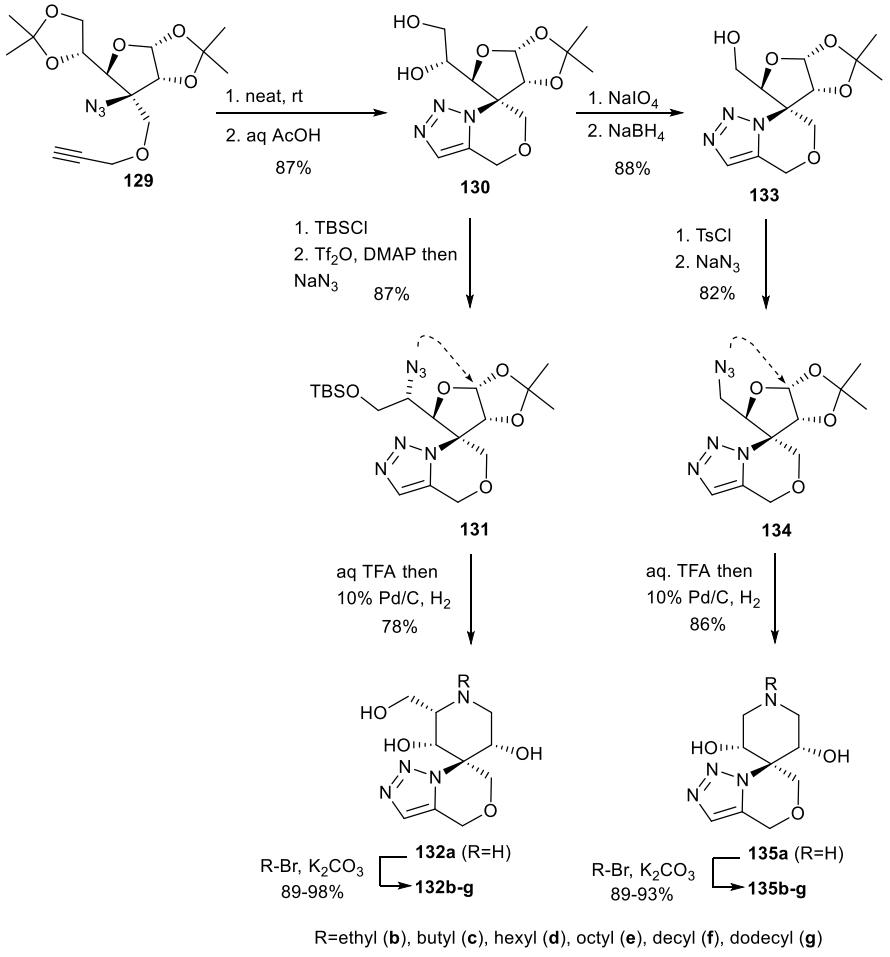
Scheme 21 Synthesis of *N*-spirofused derivatives of DNJ

Compound **128** prepared by the same method differs from its congeners by the presence of an oxygen atom in the additional spirocycle. Other examples of such iminosugars with an adjoining oxa-cycle are given in the next section below.

4.2 Iminosugar-oxacycle spiro systems

In medicinal chemistry, hybrid drugs in which two pharmacophores are present in one molecule have attracted a great deal of interest. The resulting molecule might show dual therapeutic mechanism with possible synergism in bio-activity. In this direction, some iminosugars tethered with additional pharmacophores have been prepared to improve or localize the delivery of an anticancer-active iminosugar [62]. Dhavale and co-workers designed a series of azepines and piperidines spiro-linked with morpholine-fused 1,2,3-triazole, which combine the glycosidase inhibitory potency of the iminosugar platform with the antifungal potential of the 1,2,3-triazole pharmacophore [63]. Quaternization of the C-3 carbon of D-glucose affords unstable 1,2;5,6-di-*O*-isopropylidene-3-*O*-propargyl-3-azido-D-glucofuranose **129**, prone to intramolecular azide-alkyne cycloaddition (AAC) at ambient temperature [64]. The triazole **130** thus obtained is a pivotal intermediate in the synthesis of the targeted compounds (Scheme 22). Access to the morpholino-piperidines required the installation of an azido function at C-5 of the D-gluco moiety yielding **131**, or **134** when azidation was coupled with periodate degradation. Amination of the anomeric carbon under reductive conditions afforded the expected spirofused piperidines **132a** and **135a**, which were *N*-alkylated further to generate the library of compounds **132b-g** and **135b-g**. Their glycosidase inhibitory and antifungal activities were evaluated. Compounds **132a** (IC_{50} = 0.075 μM) and **135a** (IC_{50} = 0.036 μM) showed potent α-glucosidase (rice) activity when

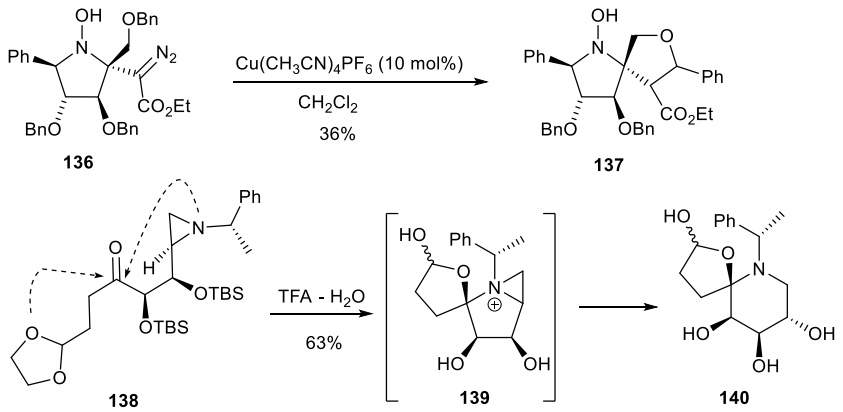
compared to the standard miglitol (IC_{50} = 0.100 µM) and proved highly active against *Candida albicans* yeast cells with minimum inhibition concentration (MIC) = 0.85 µM and MIC = 0.025 µM, respectively.



Scheme 22 Synthesis of morpholino-piperidines *via* intramolecular AAC

Alternatively, other spiroiminosugar-oxacycle molecules were obtained, rather as reaction intermediates. Thus, during their study on metal-catalyzed reactions of α-diazo-ß-hydroxyamino esters such as **136**, Py and co-workers observed the unexpected formation of the spirotetrahydrofuran **137** in 36% yield in the presence of a copper catalyst (Scheme 23) [65]. The compound arose from C–H insertion of the transient carbenoid into a benzylic C–H bond of the nearby OBn substituent.

Regioselective ring-opening of functionalized aziridines has been exploited by Eum *et al.* for the synthesis of pyrrolizidines and indolizidines [66]. During the synthesis of a non-natural analogue of castanospermine, the spiro-hemiaminal intermediate **140** could be isolated and characterized (Scheme 23). The treatment of aziridine **138** in strongly acidic media afforded aziridinium **139** through intramolecular hemiaminal/hemiacetal formation. A subsequent nucleophilic opening reaction with water from the less hindered *si*-face at the more substituted carbon gave spiro-piperidine **140** which was further transformed into the targeted indolizidine.

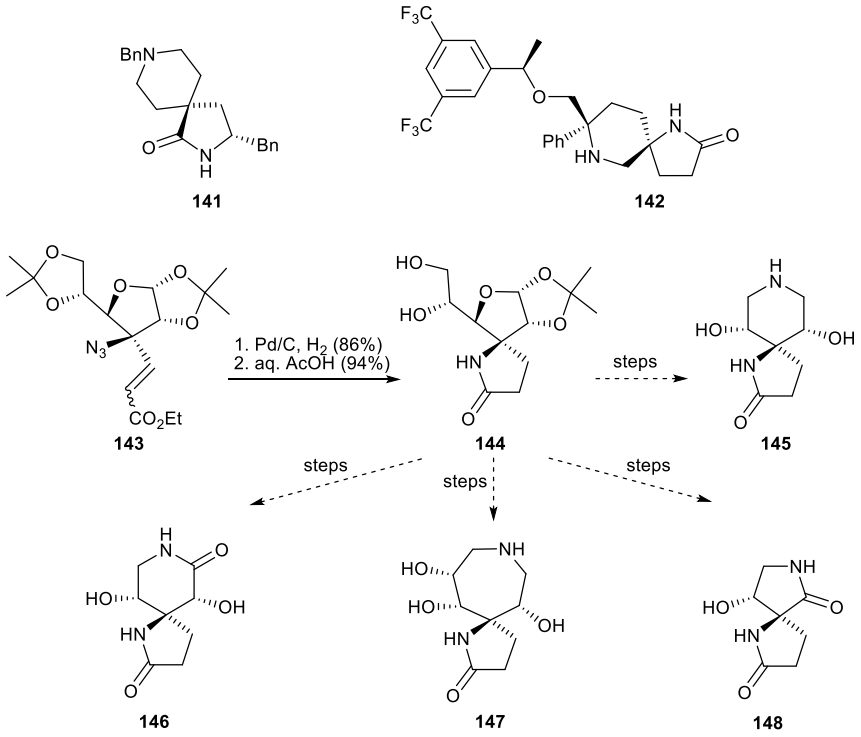


Scheme 23 Synthesis of spiroiminosugar-oxacycles **137** and **140**

4.3 Iminosugar-azacycle spiro systems

The synthesis of a new class of diazaspiro-iminosugars has been reported by Dhavale and co-workers, the structures of which comprise a nitrogen atom in both rings [67]. Diazaspiro skeleton is an important structural motif in biologically active molecules as exemplified by spirocyclic pyrrolidone **141**, a HIV-1 protease inhibitor [68], or the NK1 receptor antagonist **142** [69]. Glucose-derived azido compound **143** with a geminal α,ß-unsaturated ester was used as building block to access the expected spirolactams **145-148** (Scheme 24). Intramolecular lactamization occurred spontaneously after azide reduction, to furnish the spiro-γ-lactam **144** after selective 5,6-O-acetonide hydrolysis. This key intermediate was then converted into the targeted iminosugars following strategies analogue to those described in Scheme 22. Spiro-*bis*lactams **146** and **148** were obtained by additional Schmidt-Boyer-Aube rearrangement that took place between azide and carbonyl functions in an intramolecular fashion. Glycosidase inhibitory activity of diazaspiro-iminosugars **145-148** was studied against α-mannosidase (Jack bean), α-

galactosidase (green coffee bean) and α-glucosidase (yeast). Strong inhibition of the galactosidase occurred with **147** (IC_{50} = 0.029 μM), whereas **148** was a potent inhibitor of Jack bean α-mannosidase (IC_{50} = 0.080 μM).



Scheme 24 Synthesis of diazaspiroiminosugars **145-148**

5 Conclusion and Outlook

Nitrogen-containing analogues of carbohydrates are not only important in medicinal chemistry as therapeutic agents and as biological tools to study carbohydrate-processing enzymes, but they represent also fascinating chemical targets for synthetic organic chemists. A number of novel methodologies have found application in the synthesis of unprecedented iminosugar-like structures. As a consequence, a growing number of non-natural amino-polyols have emerged in the literature, presenting a wide spectrum of chemical profiling. Among them, spiro-iminosugars have the unusual particularity to merge sub-structures by means of a quaternary apical carbon in almost perpendicular planes. The design and synthesis of aza spirocycles has been largely guided by this distinctive structural feature enabling

conformational diversity and unprecedented interactions with biological receptors. As exemplified in this chapter, the main issue to be addressed during the synthesis of spiro-iminosugars is the installation of the pivotal quaternary spiro-atom. It might rarely originate from the starting material but it is mostly elaborated throughout the synthesis prior to or concomitantly with cyclization. On a biological point of view, in some cases the extra ring hinders recognition for a given target due to deleterious steric interactions. But, encouragingly, some aza spirocycles showed more potent or at least distinct biological activities than their non-spirocyclic homologues. This feature should stimulate research and innovation for the development of further structures of this kind to complement the repertoire of iminosugar analogues.

References

[1] (a) Sinibaldi ME, Canet, I (2008) Eur. J. Org. Chem. 4391-4399; (b) Dake, G (2006) Tetrahedron 62:3467-3492; (c) Galliford CV, Scheidt, KA (2007) Angew. Chem. Int. Ed. 46:8748-8758; (d) Singh, GS, Desta, ZY (2012) Chem. Rev. 112:6104-6155; (e) Fujita S, Nishikawa K, Iwata T, Tomiyama T, Ikenaga H, Mastumoto K, Shindo M (2018) Chem. Eur. J. 24:1539-11543; (f) Altman RA, Nilsson BL, Overman LE, Read de Alaniz J, Rohde JM, Taupin V (2010) J. Org. Chem. 75:7519-7534; (g) Burkhard JA, Wagner B, Fischer H, Schuler F, Müller K, Carreira EM, (2010) Angew. Chem., Int. Ed. 49:3524-3527

[2] Compain P, Martin OR (2007) Iminosugars from synthesis to therapeutic applications. Wiley, Weinheim

[3] Winchester BG (2009) Tetrahedron: Asymm. 20:645-651

[4] Nash RJ, Kato A, Yu CY, Fleet GWJ (2011) Future Med. Chem. 3:1513-1521

[5] Horne G., Wilson FX (2011) Prog. Med. Chem., 50:135-176

[6] Orsato A, Barbagallo E, Costa, B, Olivieri S, De Gioia L, Nicotra F, La Ferla B (2011) Eur. J. Org. Chem. 5012-5019

[7] Decroocq C, Stauffert F, Pamlard O, Oulaïdi F, Gallienne E, Martin OR, Guillou C, Compain P (2015) Bioorg. Med. Chem. Lett. 25:830-833

[8] Santos C, Stauffert F, Ballereau S, Dehoux C, Rodriguez F, Bodlenner A, Compain P, Génisson Y (2017) Bioorg. Med. Chem. 25:1984-1989

[9] Markham A, (2016) Drugs 11:1147-1152

[10] Compain P, Decroocq C, Iehl J, Holler M, Hazelard D, Mena Barragán T, Ortiz Mellet C, Nierengarten JF (2010) Angew. Chem., Int. Ed. 49:5753-5756

[11] Compain P, Bodlenner A (2014) ChemBioChem 15:1239-1251

[12] Gouin S (2014) Chem. Eur. J. 20:11616-11628

[13] (a) Lillelund VH, Jensen HH, Liang X, Bols M (2002) Chem. Rev. 102:515-553; (b) Gloster TM, Davies, GJ (2010) Org. Biomol. Chem. 8:305-320

[14] Zheng Y, Tice CM, Singh SB (2014) Bioorg. Med. Chem. Lett. 24:3673-3682

[15] For a review on conformationally restricted glycoside derivatives see: Maaliki C, Gauthier C, Massinon O, Sagar R, Vincent SP, Blériot Y (2014) in Carbohydrate Chemistry, ed. Pilar Rauter A, Lindhorst T, Queneau Y, Royal Society of Chemistry, Cambridge, 2014, Ch. 20, pp. 418-444

[16] Lahiri R, Ansari AA, Vankar YD (2013) Chem. Soc. Rev. 42:5102-5118

[17] Yanagisawa H, Kinoshita M, Umezawa S (1971) Bull. Chem. Soc. Jap. 44:3399-3405
[18] (a) Rios R (2012) Chem. Soc. Rev. 41:1060-1074 ; Ding A, Meazza M, Guo H, Yang JW, Rios R (2018) Chem. Soc. Rev. 47:5946-5996.
[19] Kapferer P, Birault V, Poisson JF, Vasella A. (2003) Helv. Chim. Acta 86:2210-2227.
[20] Ahmadian M, Khare NK, Riordan JM, Klon AE, Borhani DW (2001) Tetrahedron 57:9899-9909
[21] Brewster K, Harrison JM, Inch TD, Williams NJ (1987) J. Chem. Soc. Perkin Trans. 1 21-26
[22] Nocquet PA, Hensienne R, Wencel-Delord J, Wimmer E, Hazelard D, Compain P (2015) Org. Biomol. Chem. 13:9176-9180
[23] Nocquet PA, Hensienne R, Wencel-Delord J, Laigre, E, Sidelarbi K, Becq F, Norez C, Hazelard D, Compain P (2016) Org. Biomol. Chem. 14:2780-2796
[24] Nocquet PA, Hazelard D, Gruntz G, Compain P (2013) J. Org. Chem. 78:6751-6757
[25] For a review on square sugars see: Hazelard D, Compain P (2017) Org. Biomol. Chem. 15:3806-3827
[26] Lin W, Gupta A, Kim KH, Mendel D, Miller MJ (2009) Org. Lett. 11:449-452
[27] (a) Haruyama H, Takayama T, Kinoshita T, Kondo M, Nakajima M, Haneishi T (1991) J. Chem. Soc. Perkin Trans. 1 1637-1640; (b) Nakajima M, Itoi K, Takamatsu Y, Kinoshita T, Okazaki T, Kawakubo K, Shindo M, Honma T, Tohjigamori M, Haneishi T (1991) J. Antibiot. 44:293–300; (c) Soengas RG, da Silva G, Estévez JC (2017) Molecules 22:2028
[28] Freire R, Martín A, Pérez-Martín I, Suárez E (2002) Tetrahedron Lett. 43:5113-5116
[29] Martín A, Pérez-Martín I, Suárez E (2009) Tetrahedron 65:6147-6155
[30] Fransisco, CG, Herrera AJ, Martín A, Pérez-Martín I, Suárez E (2007) Tetrahedron Lett. 48:6384-6388
[31] Martín A, Pérez-Martín I, Suárez E (2015) Org. Lett. 7:2027-2030
[32] Pal APJ, Vankar YD (2010) Tetrahedron Lett. 51:2519-2524
[33] Aebisher B, Vasella A (1983) Helv. Chem. Acta 66:789-794
[34] For a review on carbanionic reactivity of the anomeric center in carbohydrates, see: Somsák L (2001) Chem. Rev. 101:81-135
[35] Toumieux S, Compain P, Martin OR (2005) Tetrahedron Lett. 46:4731-4735
[36] Alves RJ, Castillon S, Dessinges A, Herczegh P, Lopez JC, Lukacs G, Olesker A, Thang TT (1988) J. Org. Chem. 53:4616-4618
[37] Tardy S, Vicente JL, Tatibouët A, Dujardin G, Rollin P (2008) Synthesis 3108-3120.
[38] (a) Bourgeois JM (1976) Helv. Chem. Acta 59:2114-2124; (b) Bourgeois JM (1974) Helv. Chem. Acta 57:2553-2557
[39] Bourgeois JM (1975) Helv. Chem. Acta 58:363-372
[40] Sayago FJ, Pradera MÁ, Gasch C, Fuentes J (2006) Tetrahedron 62:915-921
[41] (a) Roy A, Achari B, Mandal SB (2006) Tetrahedron Lett. 47:3875-3879; (b) Maity JK, Ghosh R, Drew MGB, Achari B, Mandal SB (2008) J. Org. Chem. 73:4305-4308
[42] Mascitti V, Robinson RP, Préville C, Thuma, BA, Carr CL, Resse MR, Maguire RJ, Leininger MT, Lowe A, Steppan CM (2010) Tetrahedron Lett. 51:1880-1883
[43] Chincholkbar PM, Puranik VG, Deshmukh ARAS (2007) Tetrahedron 63:9179-9187
[44] Mio S, Kumagawa Y, Sugai S (1991) Tetrahedron 47:2133-2144
[45] Sano H, Mio S, Kitagawa J, Sugai S (1994) Tetrahedron: Asymm. 5:2233-2240
[46] (a) Zhang K, Schweizer F (2005) Synlett 3111-3115; (b) Zhang K, Schweizer F (2009) Carbohydr. Res. 344:576-585
[47] For selected reviews see: (a) Hazelard D, Compain P (2017) Top. Heterocycl. Chem. 47:111-154; (b) Compain P (2007) Adv. Synth. Catal. 349:1829-1846; (c) Felpin FX, Lebreton J (2003) Eur. J. Org. Chem. 3693-371; (d) Dragutan I, Dragutan V, Mitan C,

Vosloo HCM, Delaude L, Demonceau A (2011) Belstein J. Org. Chem. 699-716; (e) Deiters A, Martin SF (2004) Chem. Rev. 104:2199-2238
[48] Pal APJ, Gupta P, Reddy YS, Vankar YD (2010) Eur. J. Org. Chem. 6957-6966
[49] (a) Robertson J, Stevens K (2017) Nat. Prod. Rep. 34:62–89; (b) Davies SG, Fletcher AM, Roberts PM, Thomson JE (2017) Synlett 2697–2706; (c) Pansare SV, Thorat RG (2013) Targets Heterocycl. Syst. 17:57–86; (d) Kim IS, Jung YH (2011) Heterocycles 83:2489-2507
[50] Rowicki T (2016) Targets Heterocycl. Syst. 20:409–447
[51] (a) Forcher G, Clousier N, Beauseigneur A, Setzer P, Boeda F, Pearson-Long MSM, Karoyan P, Szymoniak J, Bertus P (2015) Synthesis 992-1006 ; (b) Szalata C, Szymoniak J, Fabis F, Butt-Gueule S, Rault S, Bertus P, Gerard S, Sapi J (2013) ChemMedChem 8:70-73; (c) Wolan A, Six Y (2010) Tetrahedron 66:15–61; (d) Bertus P, Szymoniak J, Jeanneau E, Docsa T, Gergely P, Praly JP, Vidal S (2008) Bioorg. Med. Chem. Lett. 18:4774-4778; (e) Bertus P, Szymoniak J (2007) Synlett 1346–1356
[52] Pearson MSM, Plantier-Royon R, Szymoniak J, Bertus P, Behr JB (2007) Synthesis 3589-3594
[53] Pearson MSM, Floquet N, Bello C, Vogel P, Plantier-Royon R, Szymoniak J, Bertus P, Behr JB (2009) Bioorg. Med. Chem. 17:8020-8026
[54] Laroche C, Plantier-Royon R, Szymoniak J, Bertus P, Behr JB (2006) Synlett 223-226
[55] Laroche C, Behr JB, Szymoniak J, Bertus P, Schütz C, Vogel P, Plantier-Royon R (2006) Bioorg. Med. Chem. 14:4047-4054
[56] Dhand V, Draper JA, Moore J, Britton R (2013) Org. Lett. 15:1914-1917
[57] Chen W, Pinto B M (2007) Carbohydr. Res. 342:2163-2172
[58] Morozov DA, Kirilyuk IA, Komarov DA, Goti A, Bagryanskaya IY, Kuratieva NV, Grigor'ev IA (2012) J. Org. Chem. 77:10688-10698
[59] Malik M, Witkowski G, Ceborska M, Jarosz S (2013) Org. Lett. 15:6214-6217
[60] Behr JB, Kalla A, Harakat D, Plantier-Royon R (2008) J. Org. Chem. 73:3612-3615
[61] D'Orazio G, Martorana AM, Filippi G, Polissi A, De Gioia L, La Ferla B (2016) ChemistrySelect 1:2444-2447
[62] (a) Hottin A, Scandolera A, Duca L, Wright DW, Davies GJ, Behr JB (2016) Bioorg. Med. Chem. Lett. 26:1546-1549; (b) Hottin A, Wright DW, Dubar F, Steenackers A, Delannoy P, Biot C, Davies GJ, Behr JB (2013) Chem. Eur. J. 19:9526-9533; (c) Hottin A, Dubar F, Steenackers A, Delannoy P, Biot C, Behr JB (2012) Org. Biomol. Chem. 10:5592-5597; (d) Garcia-Moreno MI, Diaz-Perez P, Ortiz Mellet, C, Garcia Fernandez JM (2002) Chem. Commun. 848-849; (e) Zhou Y, Zhao Y, Boyle KMO, Murphy PV (2008) Bioorg. Med. Chem. 18:954-958
[63] Chavan SR, Gavale KS, Khan A, Joshi R, Kumbhar N, Chakravarty D, Dhavale DD (2017) ACS Omega 2:7203-7218
[64] Chavan SR, Gavale KS, Kamble KM, Pingale SS, Dhavale DD (2017) Tetrahedron 73:365-372
[65] Kui EL, Kanazawa A, Philouze C, Poisson JF, Py S (2017) Eur. J. Org. Chem. 363-372
[66] Eum H, Choi J, Cho CG, Ha HJ (2015) Asian J. Org. Chem. 4:1399-1409
[67] Parihar VS, Pawar NJ, Ghosh S, Chopade B, Kumbhar N, Dhavale DD (2015) RSC Adv. 5:52907-52915
[68] Kazmierski WM, Furfine E, Spaltenstein A, Wright LL (2002) Bioorg. Med. Chem. Lett. 12:3431-3433
[69] Duffy RA, Morgan C, Naylor R, Higgins GA, Varty GB, Lachowicz JE, Parker EM (2012) Pharmacol. Biochem. Behav. 102:95-100