Conformationally constrained fused bicyclic iminosugars: synthetic challenges and opportunities

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Abstract

This review presents an overview of the synthetic approaches developed towards the preparation of fused bicyclic iminosugars containing a three or four-membered ring, as well as their biological activity whenever such data are available. Challenges associated with the incorporation of a small ring in chiral polyhydroxylated molecules are also highlighted.

Keywords: Constrained iminosugars, fused azetidines, aziridines, cyclopropanes, glycosidase inhibitors
1. Introduction

Many hundreds of iminosugars have been studied since the discovery half a century ago of nojirimycin (1), the first example of a naturally occurring glycomimetic in which the ring oxygen is replaced by a nitrogen atom (Figure 1).\(^1,2\) In the early days of the field, research was conducted to identify new antibiotics from natural sources.\(^3,4\) At the time, it would have been hard to predict the scope of iminosugars in glycobiology and drug discoveries. The interest of chemists and biologists for this exciting class of glycomimetics has steadily increased over the years in parallel with increasing numbers of biological targets “hit” by iminosugars, including enzymes binding non-sugar substrates. First recognized as glycosidase inhibitors in the 1970’s,\(^1\) the scope of their biological interest has been further extended to other important classes of carbohydrate-processing enzymes such as glycosyltransferases\(^5,6\) and glycogen phosphorylases.\(^2,7\) Recently, iminosugars have also demonstrated their interest as inhibitors of metalloproteinases,\(^8\) protein kinases\(^9\) and cholinesterases,\(^10\) but also as ligands of the ceramide transfer protein (CERT).\(^11,12\) As a consequence, iminosugars have been lead compounds for the development of clinical candidates towards a wide range of diseases including diabetes, cancers, rare genetic diseases and viral infections.\(^2,13\) Three iminosugar drugs, all based on a piperidine skeleton, have successfully completed clinical trials to date. After the commercialization of Glyset\textsuperscript{TM} (2, against type II diabetes) in 1996, two other iminosugars, Zavesca\textsuperscript{TM} (3) and Galafold\textsuperscript{TM} (4) have been licensed recently as the first oral drugs for the treatment of two lysosomal storage disorders, Gaucher disease and Fabry disease, respectively.

![Figure 1. Some representative mono- and bicyclic iminosugars.](image)

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However, the ability of iminosugars to strike a wide range of biological targets may be also seen as a threat for the development of drug candidates as illustrated by the pyrrolizidine-containing swainsonine (5). Despite its powerful effect on Golgi α-mannosidase II, this naturally-occurring bicyclic iminosugar failed as an anticancer agent in human clinical trials because of unacceptable toxicity.\textsuperscript{14} Castanospermine (6), a famous indolizidine-containing iminosugar, and its prodrug Celgosivir\textsuperscript{TM} (7), have raised many hopes due to their promising antiviral activities.\textsuperscript{15} However, Celgosivir\textsuperscript{TM} has yet to make its way to the clinic, with only few reported trials in humans (with modest success).\textsuperscript{16} A number of strategies have been deployed to increase iminosugar selectivity and modulate efficacy, the most recent one being the use of multivalent design.\textsuperscript{17-19}

Another approach to improve receptor specificity is the incorporation of conformational constraints into analogues of biologically active iminosugars. Conformationally constrained compounds with lesser degree of freedom may bind more efficiently to the receptor of the specific biological target.\textsuperscript{20,21} In addition to lowering the entropic barrier to complex formation, iminosugars are forced to adopt unusual conformations; the original distributions of hydroxyl groups thus obtained may be highly relevant for receptor recognition purposes. Inspired by two emblematic leads of Nature, swainsonine and castanospermine, chemists have designed fused bicyclic systems incorporating small rings.\textsuperscript{22,23} These compounds may indeed be seen as analogues of naturally-occurring pyrrolizidine- and indolizidine-based iminosugars. For some systems, especially the ones incorporating a 3-membered ring, the objective is more to obtain relevant analogues of monocyclic iminosugars such as 1-deoxynojirimycin derivatives by rigidifying their structure. Analogues of the bicyclic natural product cyclophellitol (8) that contain an aziridine in place of the epoxide have been also designed (Figure 2). These pseudo iminosugars have been used as selective activity-based glycosidase probes.

![3-Membered ring-containing systems](image1)

![4-Membered ring-containing systems](image2)

**Figure 2.** Unusual fused bicyclic iminosugar structures incorporating a small ring. Structure of the natural product cyclophellitol.

Incorporating a small ring in polyhydroxylated azacycles with a high density of asymmetric centers raises many synthetic challenges. The purpose of this review is to present an overview of the innovative approaches that have been developed towards the synthesis of fused bicyclic iminosugars containing a 3- or 4-membered ring. The review will be organized in two main sections, according to the size of the fused small ring (Figure 2). Coverage includes essentially the total syntheses of conformationally constrained iminoalditols designed for biological purposes, but also examples of structures obtained as intermediates or transient species in the synthesis of other classes of compounds. Relevant biological activity will be also highlighted whenever such data are available.
2. Three-membered Ring-containing Iminosugars

2.1 Aziridine-based bicyclic iminosugars

Aziridine-based bicyclic iminosugars have been designed as potential glycosidase inactivators. Indeed, aziridine may react with carboxylate residues involved in most mechanisms of enzyme-assisted glycoside hydrolysis. In this context, Ganem et al. reported the first synthesis of iminosugars incorporating an aziridine ring (Scheme 1). Compound 9 was converted to intermediate 10 via conversion of the primary alcohol to a leaving group and deprotection/protection steps. Deprotonation of the endocyclic amine followed by cyclisation afforded after deprotection desired aziridine 11 in moderate yield. Compound 11, which may be seen as a constrained analog of Galafold\textsuperscript{TM} (4) has been evaluated to a panel of four glycosidases (green coffee bean α-galactosidase, yeast α-glucosidase, Jack bean α-mannosidase and bovine β-galactosidase). Iminosugar 11 is a selective irreversible inhibitor of α-galactosidase from green coffee beans. Following the same sequence, the enantiomer of compound 11 has been obtained and evaluated as inhibitor of α-L-fucosidase.

![Scheme 1. Synthesis of aziridinyl iminosugar 11.](image)

Using the same strategy, several aziridine-based bicyclic iminosugars have been synthesized. Martín et al. reported the synthesis of iminosugar-derived aziridine 17 (Scheme 2). The required precursor 15 was obtained in five steps from glucolactone 12. Addition of (methoxymethoxy)methylithium followed by reduction and oxidation of the resulting diol provided diketone 14. Double reductive amination which generated two stereocenters (C1 and C5) in a highly stereocontrolled manner provided 15 as a single diastereomer after deprotection of the MOM group. Selective tosylation of the primary alcohol function led to 16 which was converted to aziridine 17 after basic treatment and deprotection of benzyl groups. It is noteworthy that the harsh conditions of the debenzylation step (Ca, NH\textsubscript{3}) did not affect the aziridine group although product 17 and similar compounds are prone to be quite unstable.
Scheme 2. Preparation of aziridinyl iminosugar 17.

The same group have reported the synthesis of two analogues of 17, the fused iminosugars 24 and 25 (Scheme 3). \(^{28-30}\) Intermediates 21 were obtained by the same sequence involving Wittig and two consecutive Mitsunobu reactions. Compound 21a was converted into the iodo-ammonium salt 22 then into aziridine 24 after basic treatment. \(^{28}\) On the other hand, removal of the phthalimido group in 21b and cyclisation promoted by NIS led to the iodo derivative 23 with good diastereoselectivity in favor of the \(\alpha\)-diastereoisomer. \(^{29,30}\) While cyclisation of compound 23 to the corresponding aziridine in the presence of DBU was successful, all attempts to deprotect the benzyl groups led to degradation or to cleavage of the aziridine ring. To circumvent this problem, the deprotection step using trimethylsilyl iodide was performed before cyclisation. Evaluation of bicyclic iminosugar 25 on a panel of commercially available glycosidases indicated that this compound displayed slightly better inhibitory activity than fagomine, the parent monocyclic iminosugar. Furthermore, no evidence for irreversible inhibition was observed with aziridine 25. \(^{29,30}\)

Scheme 3. Synthesis of aziridinyl iminosugars 24 and 25.
Py et al. reported recently an original strategy for the synthesis of aziridinyl iminosugars (Scheme 4). The strategy is based on cycloaddition of cyclic nitrones with alkynes followed by highly diastereoselective Baldwin rearrangement. Treatment of several nitrones with various alkynes afforded isoxazolines which were converted to acylaziridines by heating. Some representative examples are shown in Scheme 4. The scope of the synthetic approach described is relatively broad. However, disubstituted ketonitrones and failed to react with phenylacetylene. Furthermore, Baldwin rearrangement of compound which is obtained in good yield from the corresponding nitrone led to a complex mixture of products.

Scheme 4. Synthesis of acylaziridines via Baldwin rearrangement.

Aziridines were converted into deprotected bicyclic iminosugars after treatment with NaBH₄ and Birch reduction (Scheme 5). Compounds were obtained in good yields after a 2-step sequence while Birch reduction was unsuccessful with aziridine. Birch conditions were not applied to aziridines as these compounds are prone to ring-opening upon treatment with single-electron reducing agents.
Scheme 5. Synthesis of bicyclic iminosugars 30 from 28.

Aziridinyl iminosugars were also obtained from decomposition of corresponding dihydrotriazoles (Scheme 6).\textsuperscript{36,37} For example, Vasella et al. reported the synthesis of compound 32 by intramolecular cycloaddition of azido-alkene 31.\textsuperscript{36,38} Several conditions were tested for the transformation of 32 to aziridine 33: photolysis, thermolysis or acid treatment.\textsuperscript{36} The best results were obtained by the reaction of 32 with acetic acid. Using a similar approach, Murphy et al. synthesized aziridinyl iminosugar 36 as an advanced intermediate in the synthesis of deoxynojirimycin derivatives.\textsuperscript{37} Compound 36 was isolated in moderate yield due to its instability and its formation was supported only by mass spectrometry.

Scheme 6. Synthesis of aziridinyl iminosugars 33 and 36 via azide-alkene cycloaddition.

Aza-Diels-Alder reactions using azirines constitute an efficient strategy to rapidly generate 1-azabicyclo[4.1.0]heptene skeletons with an endocyclic double bond used as a masked diol and up to three asymmetric centers. In 2002, the group of Gilchrist reported the rapid \textit{de novo} synthesis of protected iminosugar 42 by Diels-Alder reaction using azirine 39 as the dienophile partner (Scheme 7).\textsuperscript{39} Reaction of 39, generated from 2-azidoacrylate ester 38, with diene 40 afforded bicyclic iminosugars 41 as a racemic mixture.
Dihydroxylation under classical osmylation conditions led to the corresponding diol in 93% yield. Finally, the ester group was reduced with LAH to give disilylated aziridine-based bicyclic iminosugar 42.\(^{39}\)

Scheme 7. Synthesis of iminosugar 42 via Diels-Alder cycloaddition.

It is noteworthy that under the same conditions, no dihydroxylation reaction was observed when the TBDMS protecting groups are replaced by acetate functions.\(^{39}\)

In 2014, the synthesis of an aziridinyl iminosugar by way of enantioselective Diels-Alder cycloaddition was reported (Scheme 8).\(^{40}\) Diene 43 and dienophile 44 were treated with (R)-BINOL in the presence of MeMgBr and Me\(_2\)Zn to generate a bimetallic complex of zinc and magnesium tethered to the enantiopure diol ligand. In these conditions, desired aziridine 45a was obtained as a single enantiomer as confirmed by \(^1\)H NMR analysis of the (S)-camphanoate derivative of 45a. In this process, minor product 45b, which was formed by aziridine ring-opening due to water content in the reaction solvent, was also isolated. Diol 45b was converted quantitatively to compound 45a by simple basic treatment using N-methylmorpholine. The rather unexpected formation of aziridine 45a was explained by a hydrogen bond leading to the formation of a pseudo six-membered ring (45b'). In this rigidified system, the hydroxymethylene group is more prone to nucleophilic attack (Scheme 8).\(^{40}\) Dihydroxylation of 45a followed by hydrolysis of the ester group provided the pipecolic acid derivative 47.
2.2 Cyclopropane-based bicyclic systems
The only methodology reported to date for the formation of cyclopropane-based bicyclic iminosugars is the cyclopropanation of the appropriate alkene derivatives.\textsuperscript{41-43} Using this methodology, fused iminosugar 51 was prepared in three steps from imino glucal 49 which was synthesized by treatment of 48 with oxalyl chloride (Scheme 9).\textsuperscript{41} Cyclopropanation of 49 using diethylzinc and diiodomethane led to compound 50 in 64% yield after deprotection of the Fmoc group. The cyclopropanation step was highly diastereoselective as only one stereoisomer was formed. To explain this stereoselectivity, the authors suggest that glucal 49 adopts a half chair conformation. Then the carbenoid would react in \textit{anti} to the OBn group at C3.\textsuperscript{41} For the final synthetic steps, hydrogenation conditions must be finely tuned in order to obtain the desired products. Debenzylation using palladium on carbon in the presence of HCl afforded the desired iminosugar 51. Interestingly, the cyclopropane was cleaved without concomitant debenzylation when hydrogenation was performed with palladium hydroxide in the absence of HCl. Under these conditions, piperidine 52 was isolated in 79% yield. Hydrogenolysis of the benzyl groups in acidic conditions afforded compound 53. Iminosugars 51 and 53 were found to display weak inhibitory activity against mannosidase from Jack bean with inhibition values in the mM range.\textsuperscript{41}
Scheme 9. Synthesis of original iminosugars by way of cyclopropanation of enamine 49.

In 2014, Ochiato et al. reported the synthesis of several cyclopropane-based pipecolic acid analogues. In their strategy, the key step was performed using a zinc carbenoid cyclopropanating reagent. The synthesis began with the conversion of compound 54 into enamine 55 in 2 steps via the formation of the corresponding enol phosphate and its carbonylation. Removal of the acetal group was then performed under acidic conditions to afford intermediate 56 in 60% yield. Simmons-Smith cyclopropanation in the presence of diethylzinc, diiodomethane and 2,4,6-trichlorophenol yielded cyclopropane 57 as a single stereoisomer. The stereoselectivity could be explained by the presence of an allylic alcohol in 56 which directs the attack of the carbenoid on the same face. The final deprotection step gave piperidine 58 in good yield (Scheme 10).

Scheme 10. Synthesis of pipecolic acid derivative 58.

Recently, the synthesis of fused iminosugars based on a 2-azabicyclo[4.1.0]heptane skeleton using a sulfur ylid cyclopropanation as the key step has been reported in the literature. Treatment of enaminone 59 with (2-ethoxy-2oxoethyl)dimethylsulfonium and DBU under microwave heating afforded, after reduction, the
racemic cyclopropane 60 in high diastereoselectivity (Scheme 11). Dehydration of compound 60 by Grieco elimination furnished alkene 61 in 83% yield. Non-stereoselective dihydroxylation of compound 61 gave diols 62. Finally, esters 62a and 62b were reduced to afford triols 63a and 63b.

Scheme 11. Synthesis of cyclopropane-based bicyclic iminosugars via a sulfur ylid cyclopropanation.

2.3 Aziridine-based bicyclic cyclitols
Cyclophellitol-aziridine (66) is an analogue of the natural product cyclophellitol (8). These two compounds are irreversible, mechanism-based retaining glucosidase inhibitors. Several syntheses of cyclophellitol-aziridine and its derivatives have been described in the literature. The first synthesis of cyclophellitol-aziridine (66) was reported by the group of Tatsuta in the early 1990s (Scheme 12). This compound was obtained from 1,6-epi-cyclophellitol (64) in four steps. Perbenzylation of tetraol 64 followed by ring-opening of the epoxide by NaN₃ provided a mixture of regioisomers 65. A Staudinger type reaction was then performed by treatment of the mixture of 65a and 65b with PPh₃ to afford the corresponding perbenzylated cyclophellitol-aziridine in 60% yield. Deprotection using Birch conditions yielded the desired compound 66. In the same manner, 1,6-epi-cyclophellitol-aziridine (67) was obtained from cyclophellitol (8). The authors reported also the synthesis of derivatives 68 and 69 from 66 by a two-steps sequence involving alkylation or acylation reactions. Evaluation of aziridines 66-69 indicated that these compounds were inhibitors of β-glucosidase from almond with the exception of 69b. Furthermore, cyclophellitol-aziridine (66) is a stronger inhibitor (IC₅₀ = 0.22 μg/mL) than its epimer 67 (IC₅₀ = 32 μg/mL) and cyclophellitol (8) (IC₅₀ = 0.8 μg/mL).
Scheme 12. Synthesis of cyclophellitol-aziridine 66 and derivatives 67-69 by Tatsuta et al.

The group of Overkleeft was also interested in the synthesis of cyclophellitol-aziridine (66) as well as analogs\textsuperscript{44} for their potential biological interest as glycosidase inhibitors or as selective activity-based glycosidase probes.\textsuperscript{48-53} The synthesis of compound 66 by Overkleeft et al. started from aldehyde 70 which was treated with ethyl 4-bromocrotonate in an indium-mediated reaction to afford diene 71 in good yield and excellent diastereoselectivity (scheme 13).\textsuperscript{54} Diene 71 was converted to cyclohexene 72 by ring closing metathesis and reduction of the ester group. Introduction of a trichloroacetimidate function followed by iodo cyclization led to iodide 73 with total stereocontrol. Compound 73 was then converted to the target cyclophellitol-aziridine (66) by acidic hydrolysis of the trichloroacetimidate group followed by base-induced intramolecular S\textsubscript{N}2 reaction and removal of the benzyl groups. Birch conditions were used for the deprotection step since palladium-catalyzed hydrogenolysis conditions led to partial reduction of the aziridine while Lewis-acid-mediated debenzylolation proved unsuccessful. Bicyclic aziridine 76, the pseudo D-galacto analog of 66, was obtained following a similar sequence from the same intermediate 70.\textsuperscript{55} For this synthesis, the two asymmetric centers corresponding to C4 and C5 in the parent pyranose were created by aldolization of 70 with the Evans oxazolidinone 74 affording compound 75 in 80\% yield (Scheme 13). Overkleeft et al. reported also the preparation of 77 from the enantiomer of 70.\textsuperscript{56}
Scheme 13. Synthesis of cyclophellitol-aziridine (66) and analogs 76-77.

Other examples of cyclophellitol-aziridine derivatives possessing interesting biological activities have been described by Overkleeft and other groups (Figure 3). Compounds 78-80 were obtained in two steps from 66 and evaluated on the following three retaining glucosidases: GBA, GBA2 and GBA3. All the evaluated compounds 78-80 were good inhibitors of the three enzymes, in particular N-alkyl derivative 78 which is a nanomolar inhibitor of GBA (IC₅₀ = 17 nM) and GBA2 (IC₅₀ = 3 nM). Compounds 81 and 82 were obtained from the appropriate epoxide following a similar sequence to the one described by Tatsuta et al. (see Scheme 12) involving ring-opening of the epoxide by NaN₃ and PPh₃-mediated cyclisation to form the aziridine ring. Alternatively, aziridines 82 could also been prepared from tetrabenzylinositol. The N-alkylaziridines 82b-82d were evaluated as inhibitors of human β-glucocerebrosidase (GBA1), the enzyme involved in Gaucher disease. The results indicated that the Kᵢ values were inversely correlated with the length of the alkyl chain. N-octyl conduritol aziridine 82d, a specific covalent inactivator of GBA1 (Kᵢ = 4.8 nM), was indeed found to be 500-fold more potent than 82b, its N-butyl analog.
Figure 3. Examples of bioactive cyclophellitol-aziridine derivatives.

In 2015, Llebaria et al. reported the synthesis of D-galacto configured N-aminoaziridines as analogs of compound 76 (Scheme 13). Aziridination of compound 83, obtained from diene 75 with quinazolinone 84 in the presence of phenyl iododiacetate afforded the key intermediate 85 as a single diastereoisomer (Scheme 14). First attempts to remove the protecting groups under Birch conditions were unsuccessful. An alternative way was to perform the hydrazinolysis of N-aminoaziridine 85 first and then to deprotect the benzyl groups. This two-step sequence enabled the formation of the desired compound 87 in good yields. N-Iminoaziridine 88 was then obtained quantitatively by treatment of 87 with acetone. A diversity of cyclophellitol-aziridine analogues could be easily obtained by reaction of N-aminoaziridines such as 86 with a variety of carbonyl compounds. N-aminoaziridines 87 and 88 are potent irreversible inhibitors of Aspergillus oryzae and Escherichia coli β-galactosidases.

Scheme 14. Synthesis of N-aminoaziridines 87 and 88.
The synthesis and biological evaluation of aminocyclopentitols have also been reported.\textsuperscript{65-67} The groups of Burger and Ganem independently described the racemic synthesis of polyhydroxylated aziridinyl cyclopentanes 93 and 94 using the photolysis of $N$-alkylpyridinium intermediates as the key step (Scheme 15).\textsuperscript{65,66} Under these conditions, several bridged aziridines 92 were obtained in moderate to excellent yields. Compound 92 is presumably formed via the isomerization of pyridinium salt 89 to azoniabenzvalene 90. Due to high steric strain, 90 opens to give the allylic cation 91 which is subsequently trapped by solvent addition on its less hindered face.\textsuperscript{65,68} Aminocyclopentitols 93 and 94 were prepared by dihydroxylation of alkene 92. Evaluation of aminocyclopentitols 93b and 94b indicated that 94b is a specific, reversible competitive inhibitor of Jack bean $\alpha$-mannosidase ($K_i = 8.0 \mu$M).\textsuperscript{66}

Scheme 15. Synthesis of aminocyclopentitols via photolysis of $N$-alkylpyridiniums.

Bols \textit{et al.} reported the synthesis of aziridine-based bicyclic cyclitols 98 and 100 using a 1,3 dipolar cycloaddition as the key step (Scheme 16).\textsuperscript{67} Precursor 96, obtained in four steps from methyl-D-glucopyranoside 95, was treated with $N$-benzylhydroxylamine affording 1,2 oxazine 97. Reduction of the N-O bond was carried out by hydrogenolysis using Ni Raney and the corresponding aziridine was isolated in 48% yield. Deprotection of the benzoate and benzyl groups gave the target compound 98. Compounds 98 and its stereoisomer 100 obtained in a similar sequence from methyl D-mannoside 99 were found to be poor inhibitors or not inhibitors of $\alpha$-glucosidase (yeast), $\beta$-glucosidase (almonds) and $\alpha$-fucosidase (bovine kidney).\textsuperscript{67}
Scheme 16. Synthesis of bicyclic aziridines 98 and 100.

Aziridine-based cyclitols were also used as intermediates in the synthesis of natural products. During their studies on the synthesis of (+)-lycoricidine, Yadav et al. reported the formation of aziridine 103 via two synthetic strategies (Scheme 17). In the first approach, aziridination of cyclohexene 101, obtained in eight steps from D-mannose, yielded N-tosylaziridine 102 as a single stereoisomer. Removal of the tosyl group was performed by treatment of 102 with sodium naphthalenide. In the second approach, 101 was converted to 103 in five steps. Reaction of 101 with NBS afforded a mixture of bromohydrins, which under basic conditions, provided epoxide 104. Regioselective epoxide ring-opening with NaN₃, followed by mesylation gave compound 106. Desired aziridine-cyclohexitol 103 was then obtained by treatment with triphenylphosphine and diisopropylethylamine in a Staudinger-type reaction.

Scheme 17. Synthesis of aziridine 103 by aziridination of alkene 101 or via ring-opening of epoxide 104.
During their studies on the synthesis of several *Amaryllidaceae* alkaloids, Hudlicky et al. reported the formation of aziridines 111-113 as advanced synthetic intermediates (Scheme 18).\(^{70,71}\) The synthesis began with the chemoenzymatic dihydroxylation of bromobenzene (107) with recombinant *E. coli* JM109(pDTG601) to provide diol 108 as a single enantiomer.\(^{72,73}\) Protection of the diol moiety as an acetonide followed by regioselective aziridination furnished compound 109.\(^{74,75}\) Dehalogenation of vinylbromide 109 with tributyltin hydride afforded allyl aziridine 110 in 76% yield.\(^{70,71}\) Epoxidation of cyclohexene 110 yielded a mixture of epoxides 111 and 112,\(^{70,71}\) whereas dihydroxylation furnished diol 113 as a single diastereoisomer.\(^{71}\) Ring-opening of epoxide 111 by the alane derived from alkyne 114 provided compound 115 after protection of the resulting alcohol.\(^{70}\)

![Scheme 18. Synthesis of aziridines 111-113 via chemoenzymatic dihydroxylation of bromobenzene.](image)

In 2014, Yan’s group reported a new method for olefin aziridination using *N*-aminophtalimide 116 as the amine precursor and sodium 2-iodoxybenzoate 118 as the oxidant.\(^{76}\) Sodium 2-iodoxybenzoate was formed *in situ* by reaction of IBX with sodium carbonate. The methodology was applied on several acyclic and cyclic alkenes including polyoxygenated cyclohexene 117. Under these conditions aziridine 119, a potential intermediate in the synthesis of *Amaryllidaceae* alkaloids, was obtained in 70% yield in high diastereoselectivity (Scheme 19).\(^{76}\)
Scheme 19. Sodium-iodoxybenzoate mediated aziridination of polyoxygenated cyclohexene 117.

3. Four-membered Ring-containing Iminosugars

3.1 Bicyclic systems with nitrogen at the ring junction

In most four-membered ring-containing fused bicyclic iminosugars described to date, nitrogen atom is part of the ring junction – with their second ring size ranging from five- to seven-membered. The first occurrence of naturally-occurring pyrrolizidine/indolizidine iminosugar analogues was published in 1993 by Alcaide et al. In the course of their work on mono- and bicyclic β-lactams, they developed an efficient synthesis of carbapenam derivatives 122 and 123 (Scheme 20).77 Iminoketones 120, readily prepared from corresponding oxoalkanals and methyl glycinate, were engaged in a Staudinger cycloaddition with in situ generated benzyloxyketene, affording β-lactams 121. It is noteworthy that, at this stage, only cis diastereoisomers were formed. The appropriately functionalized cis-β-lactams 121 were then submitted to an intramolecular aldol-type condensation in order to reach the targeted bicyclic skeleton. Only the cis diastereoisomers 122 were obtained under kinetic control, while thermodynamic conditions led exclusively to the trans diastereoisomers 123. Based on mechanistic experiments, the authors proposed that the trans configuration was reached through the epimerization of 121 via an equilibrium with bicyclic compound 122 rather than a straightforward epimerization of 122 itself.

Scheme 20. Synthesis of carbapenam derivatives 122 and 123.
More recent syntheses of iminosugars based on 1-azabicyclo[3.2.0]heptane skeleton all feature a cycloaddition involving sugar derived nitrones.\textsuperscript{78-82} The Kinugasa reaction is of particular interest in this regard. This reaction involves a cycloaddition between a nitron and a copper acetylide followed by a rearrangement giving corresponding β-lactams.\textsuperscript{79} The use of cyclic nitrones allows the direct formation of bicyclic iminosugars with a β-lactam scaffold (Scheme 21). Khangarot and Kaliappan used this reaction on various pairs of sugar-derived nitrones and alkynes, producing a library of sugar-conjugated polyhydroxylated bicyclic β-lactams.\textsuperscript{78} For example, treatment of the cyclic nitrone \textsuperscript{124} with alkyne \textsuperscript{125} in the presence of copper iodide afforded the β-lactam \textsuperscript{126} in good yield and high diastereoselectivity (Scheme 21).\textsuperscript{78} This strategy has also been applied by Chmielewski \textit{et al.} for the synthesis of a library of carbapenam derivatives.\textsuperscript{80-82} A case worth highlighting is the double addition of nitrone \textsuperscript{128} to diyne \textsuperscript{127}, affording the bis-adduct \textsuperscript{129} (Scheme 21).\textsuperscript{82}

\begin{center}
\textbf{Scheme 21.} Synthesis of polyhydroxylated bicyclic β-lactams \textit{via} the Kinugasa reaction.
\end{center}

Cycloaddition partners other than alkynes can be used. Since no spontaneous rearrangement then occurs, more steps are required in order to reach the desired 1-azabicyclo[3.2.0]heptane skeleton. Nitrones \textsuperscript{132}, derived from 2-deoxy-D-ribose, and α,β-unsaturated lactones \textsuperscript{130-131} or ethyl crotonate were thus employed by Chmielewski \textit{et al.} in a sequence in which the 1,3-dipolar cycloaddition is followed by \textit{N}-\textit{O} bond cleavage. Subsequent β-lactam ring formation was effected \textit{via} intramolecular \textit{N}-acylation (Schemes 22-23).\textsuperscript{83,84} When applied to six-membered lactones \textsuperscript{130} and \textsuperscript{131}, this strategy led to carbapenem analogues \textsuperscript{137} and \textsuperscript{138} with high stereoselectivity (Scheme 22).\textsuperscript{83} Cycloaddition reaction between \textsuperscript{132a} and \textsuperscript{130} or \textsuperscript{131} afforded cycloadducts \textsuperscript{133} and \textsuperscript{134}, respectively, in high yields. Cleavage of the N-O bond was performed by reduction with zinc. Saponification of the lactone followed by protection step yielded compounds \textsuperscript{135} and \textsuperscript{136}. These products were treated by 2-chloro-1-methylpyridinium iodide (Mukayama’s salt) to afford \textsuperscript{137} or \textsuperscript{138} after deprotection/protection steps in high overall yields from \textsuperscript{133} and \textsuperscript{134} (Scheme 22).\textsuperscript{83} When the same sequence was applied to γ-lactones, epimerization as well as side-reactions were observed and the corresponding fused iminosugars were obtained in low yields.\textsuperscript{83}
Scheme 22. Synthesis of carbapenems analogues 137-138 from α,β-unsaturated lactones 130-131.

Chmielewski et al applied the same strategy starting from ethyl crotonate for the synthesis of compounds 141 which are intermediates in the synthesis of the antibiotic Thienamycin (Scheme 23).\textsuperscript{84}

Scheme 23. Synthesis of carbapenam derivatives 141 from ethyl crotonate.
Reissig et al. reported the synthesis of azabicyclotetrol 147 from L-erythrose-derived nitrone 142. The key step was the addition of lithiated 2-(trimethylsilyl)-ethoxyallene on nitrone 142 affording compound 143 which cyclized spontaneously in the presence of drying reagent MgSO₄ to form bicyclic 1,2-oxazine 144 in 72% yield (Scheme 24). The introduction of a hydroxyl group at C-5 of the oxazine was performed by hydroboration and subsequent oxidation affording after mesylation compound 145 as a single diastereoisomer. Cleavage of the N-O bond and protection of the primary alcohol gave mesylate 146. The four-membered ring closure was performed by basic treatment yielding, after deprotection step, azabicyclotetrol 147 bearing the characteristic hydroxymethyl group that is present in most hexopyranosides. Inhibitory properties of compound 147 were assessed on eleven commercially available glycosidases, without any significant activity being observed.

Scheme 24. Synthesis of azabicyclotetrol 147.

Many examples of four-membered ring-containing synthetic fused bicyclic iminosugars feature a conidine skeleton (Schemes 25-29). Dhavale et al. reported recently the synthesis of trihydroxylated conidine alkaloids 151 (Scheme 25). The sugar-bearing β-amino acid 149 was obtained in two steps through a moderately stereoselective Michael addition from the glucose-derived product 148. The azetidine ring was then formed by way of an efficient lactamization-reduction sequence. Finally, acetal hydrolysis followed by benzyl group cleavage under hydrogenolysis conditions induced piperidine ring closure via reductive amination, leading to azabicyclopriol 151. Regardless of the ring junction stereochemistry, conidine derivatives 151 were found to be weak inhibitors of the four tested glycosidases. The group of Tiwari also described the synthesis of compound 151b following a similar sequence, except for the azetidine ring formation which was generated via Mitsunobu reaction after hydride reduction of ester 152 to alcohol 153 (Scheme 25).
Scheme 25. Synthesis of trihydroxylated conidine alkaloids 151 via a lactamization-reduction sequence or a Mitsunobu reaction.

Fleet et al. synthesized trihydroxyconidine derivatives 158 and 160\textsuperscript{89} from D-altrose, obtained through enzymatic isomerization of D-fructose.\textsuperscript{89,90} D-altrose was converted into mono-acetonide 154 which was transformed to the 3,5-di-O-triflate 155 (Scheme 26).\textsuperscript{89} Condensation of benzylamine to this intermediate afforded the tricyclic azetidine 156. The modest yield observed for this reaction may be due to TBDS-induced steric crowding in the transition state. Removal of acetal and silyl groups followed by a Wittig reaction led to monocyclic α,β-unsaturated ester 157. Subsequent transfer hydrogenation allowed both the desired lactamization reaction and a competing lactonization, explaining the low isolated yield obtained for compound 158. Attempts to prevent the aforementioned side reaction by protecting alcohols of 157 as TBDS-ethers did not improve the cyclization process and bicyclic lactam 159 was obtained in 23% yield from 157. Finally, lactam reduction followed by acidic treatment delivered trihydroxyconidine 160. Evaluation of the biological activity of conidine derivatives 158 and 160 on a panel of glycosidases resulted in weak inhibition of β-galactosidase (for both compounds) and α-mannosidase (for 160 only).\textsuperscript{89} The same group also synthesized tetrahydroxyconidine 161, starting from L-arabinose and applying a similar synthetic sequence (Scheme 26).\textsuperscript{91,92} Out of eighteen glycosidases, only rat intestinal lactase (IC\textsubscript{50} = 418 µM) and Rhizopus sp. amyloglucosidase (IC\textsubscript{50} = 532 µM) were weakly inhibited by compound 161.\textsuperscript{92}
Scheme 26. Synthesis of tri- and tetra-hydroxyconidine derivatives 158, 160 and 161.

Beyond a lactamization reaction or classical $S_N 2$ process, the conidine skeleton may be also generated through photocatalytic cyclization. In the course of their work on glycosidase inhibitors, Pal and Dumbre thereby published the synthesis of trihydroxyconidine 167 (Scheme 27). Aldehyde 162 and amine 163 (prepared from L-(+)-tartaric acid and 3-aminopropanol, respectively) were coupled in 71% yield via reductive amination. The free alcohol was then mesylated, allowing in situ azetidine ring closure. Piperidine formation was accomplished in 35% yield by way of highly stereoselective photo-induced 6-exo-dig radical cyclisation of compound 165. Finally, azabicycle 166 was converted in four steps into the hydrochloride (167) of trihydroxyconidine. The hydrochloride was found to be a weak inhibitor of *Aspergillus oryzae* β-galactosidase ($K_i = 114 \, \mu M$) as well as a moderate inhibitor of almond β-glucosidase ($K_i = 7.6 \, \mu M$). The group of Pandey described a synthesis of β-lactam-iminosugar hybrid 171 and its enantiomer using a similar strategy (Scheme 27). Compound 164 was converted in one step into 1,3-oxazine 168. The piperidine ring was then formed in 60% yield by means of photo-induced 6-exo-dig radical cyclisation, affording the oxa-azabicycle 169 which was in turn converted in nine steps into the β-amino acid 170. Finally, deprotection of the amine followed by lactamization reaction provided deprotected bicyclic β-lactam 171 after debenzylation in 50% overall yield (three steps from 170). The biological activity of this compound and its enantiomer was evaluated on α- and β-galactosidases, α- and β-glucosidases and α- and β-mannosidases. Bicyclic iminosugar 171 showed weak to moderate inhibitory properties against α- and β-galactosidases whereas no inhibition was observed for the corresponding enantiomer.
Scheme 27. Photochemical synthesis of trihydroxyconidine derivatives 167 and 171.

Following their work on carbapenems (Scheme 20), Alcaide et al. extended the scope of their efforts to the synthesis of carbacephem derivatives such as 175 (Scheme 28). The cis-β-lactam 172, prepared via enantioselective Staudinger cycloaddition, was engaged in a deacetalization-silylation-oxidation sequence which afforded aldehyde 174. In order to avoid loss of material during purification process, crude 174 was directly treated with BF$_3$·Et$_2$O, leading to the formation of cycloadduct 175 through ene cyclization (36% yield from 173). The authors proposed a six-membered, cyclic chair-like transition-state model to explain the stereochemical outcome of this reaction. The use of a more resistant silyl ether protecting group (TBS instead of TMS) considerably improved the cyclization yield by preventing desilylation to occur, however this was shown to reduce the diastereoselectivity of the reaction as illustrated with the conversion of 176 to 177 and 178.
Scheme 28. Synthesis of carbacepham derivatives via ene cyclization.

The group of Grande also synthesized carbacepham derivatives from stereoselective Staudinger cycloaddition products (Scheme 29). The cis-2-azetidinone 179 and its diastereoisomer were readily prepared by reaction of methoxyacetyl chloride with a D-glucosamine-derived imine. Compound 179 was submitted to diithioacetal deprotection conditions to afford the corresponding aldehyde which was directly engaged in a Wittig reaction. Using this sequence, acrylate ester 180 was obtained in high yields. Regioselective epoxidation of the more electron-rich alkene provided compound 181 with low diastereoselectivity. Efficient ozonolysis of the remaining double bond yielded epoxyaldehyde 182 in quantitative yield. Treatment by in situ generated TiCp₂Cl induced homolytic cleavage of the epoxide, triggering a radical cyclization that ultimately delivered the carbacepham derivative 183 in moderate yield (pathway a, Scheme 29). Same reaction was performed on the more sterically hindered epoxyester 181 and expected bicyclic compound 184 was obtained in 52% yield. This cyclization was found to compete with β-elimination of the titanium-coordinated oxygen (pathway b, Scheme 29), hence the reversion to diene 180. It is noteworthy that, in the case of the C5,C6 diastereoisomer of 181, no cyclization product was observed and only the diene 180 was isolated.
Scheme 29. Synthesis of carbacephem derivatives 183 and 184 via radical cyclization.

Madsen et al. reported a unique example of a bicyclic iminosugar featuring an azepane ring, as a byproduct *en route* to the synthesis of castanospermine 6 (Figure 1). Conversion of methyl α-D-glucopyranoside 95 to the corresponding 6-iodopyranoside followed by perbenzylation and zinc-mediated fragmentation efficiently provided enal 185 (Scheme 30). In order to avoid epimerization upon standing, the crude 185 was directly submitted to reductive amination, leading to homoallylamine 186 in 89% yield. After treatment with trifluoroacetic anhydride, the resulting diene 187 was engaged in a ring-closing metathesis reaction which required extensive optimization to favor the desired product 189 over byproducts such as 190 or the homodimer of 187. The use of Grubbs catalyst 188 and its dropwise addition over 20 h allowed the formation of the nine-membered N-heterocycle 189 in 78% yield along with 7% of its eight-membered counterpart 190. Subsequent epoxidation by the *in situ* generated dioxirane of 1,1,1-trifluoroacetone followed by base-mediated N-deprotection/transannular cyclization delivered both tribenzylated castanospermine 191 and the bicyclic azepane derivative 192 in 44% and 15% yield, respectively. This constitutes an interesting example of a skeleton-diversity-oriented reaction.
Scheme 30. Divergent synthesis of bicyclic iminosugars 191 and 192.

3.2 Bicyclic systems with nitrogen not at the ring junction

There are few examples of fused bicyclic iminosugars for which the nitrogen atom is not part of the ring junction. Recently, the group of Compain reported the synthesis of such compounds, based on a 6-aza-bicyclo[3.2.0]heptane skeleton (Schemes 31-32). When treated with TMSOTf and Et$_3$N, β-lactam diester 193, readily prepared from L-glutamic acid, underwent a cationic Dieckmann-type cyclisation leading, after desilylation, to the desired bicyclic intermediate 194 in 81% yield on a gram-scale. In order to reach analogues bearing three hydroxyl groups on the cyclopentane ring, ketone 194 was converted to enone 195 in 70% yield via IBX-mediated desaturation. Unreactive towards both dihydroxylation and epoxidation, this key intermediate 195 underwent efficient chemo- and diastereoselective Luche’s reduction into allylic alcohol 196 with good diastereoselectivity (5/1 dr). The major diastereoisomer 196 was in turn converted in two steps to the advanced intermediate 197, which proved to be a suitable substrate for further functionalization. Diastereoselective dihydroxylation of 197 under Upjohn’s conditions indeed led to 198 as the sole diastereoisomer, in 80% yield. Sequential benzylation, reduction and debenzylation afforded in good overall yield bicyclic amino-tetrol 199 (racemic) which may be seen as an analog of Galafold. N-butyl derivative 200 was then obtained through reductive amination (Scheme 31).
Scheme 31. Synthesis of constrained bicyclic iminosugars via cationic Dieckmann-type cyclisation.

The same authors reported the synthesis of diastereoisomers of 199 and 200 via the m-CPBA oxidation of alkene 197 which provided epoxide 201 as a single diastereoisomer in 88% yield (Scheme 32). After benzylation of the hydroxymethyl group, epoxide-ring opening could be efficiently achieved, with complete regioselectivity, using catalytic sulfuric acid in acetic acid. Applying the same end game sequence used for the preparation of compounds 199-200 yielded 1-deoxygulonojirimycin bicyclic analogue 203 as well as its N-butyl derivative 204 (racemic form). Unfortunately, none of the four amino-tetrols 199, 200, 203 and 204 were potent inhibitors of any glycosidase among the test panel (Saccharomyces cerevisiae α-glucosidase, almond β-glucosidase, green coffee beans α-galactosidase, E. coli β-galactosidase and Jack bean α-mannosidase).

In the course of their work towards the 6-azabicyclo[3.2.1]octane ring system, Grainger et al. synthesized the bicyclic β-lactam diols 210 and 211 as well as triol 212 (Scheme 33). Starting from compound 205, carbamoyl diethyldithiocarbamate 206 was readily prepared in two steps. The bicyclic skeleton was then formed in 84% yield by way of photo-induced 4-exo-trig radical cyclisation, with the dithiocarbamate moiety being transferred to the less hindered face of the resulting β-lactam 207 – obtained as the sole isolated product. Regioselectivity of the following dithiocarbamate elimination was found to be dependent on the methodology used: α,β-unsaturated β-lactam 208 was thus formed almost quantitatively through base mediation, whereas thermal reaction led to its β,γ-unsaturated counterpart 209 in 80% yield. Dihydroxylation of lactam 208 afforded syn-diol 210 in good yield. In the other hand, β-lactam 211 was obtained following a two-step sequence; the trans relationship was achieved through epoxidation of lactam 208 followed by regioselective opening. Three hydroxyl groups could be introduced elegantly into β,γ-unsaturated β-lactam 209. Regioselective base-mediated ring-opening of the epoxide generated from 209 afforded an allylic alcohol intermediate which was subjected to dihydroxylation reaction after protection as a benzoate ester to give β-lactam 212 in good overall yield (56% from 209).
3.3 Bicyclic systems having an additional ring heteroatom

Few examples of constrained bicyclic iminosugars containing an additional endocyclic heteroatom have been described. β,δ-Dilactam 217 was obtained as an intermediate in the synthesis of carbacephem precursors developed by the group of Saito (Scheme 34).\(^\text{104}\) Starting from enantiopure aldehyde 213, the β-lactam ring...
was formed by way of Staudinger cycloaddition using in situ generated azidoketene, leading to the cis-β-lactam 214 as a single diastereoisomer. After protecting group manipulation, the one-pot debenzylation / azido reduction and Boc-protection of the resulting amine efficiently afforded 215. TEMPO-like oxidation of the free primary alcohol using 216 triggered the formation of a hemiaminal intermediate which was further oxidized to a δ-lactam, thus providing bicyclic dilactam 217 in 87% yield.

Rai et al. reported an original synthesis of fused iminosugar β-lactams 219 by way of iodine/ionic liquid-catalyzed [1C+2C+1N] three-components one-pot coupling (Scheme 35). Unprotected carbohydrates, 2-phenyl-2-oxazolan-5-one 218, and aromatic amines were used as one carbon, two carbons and nitrogen sources, respectively. In this process, imidazolium hydroxide-mediated deprotonation of 218 is expected to trigger a Mannich-type reaction affording adducts 221. The β-lactam ring is then formed upon activation of the carbonyl moiety by iodine, leading to 219 through intermediate 222. This methodology was applied to D-glucose and D-xylose in the presence of aniline derivatives. All resulting fused iminosugar β-lactams 219 were obtained in good yields and with a high cis diastereoselectivity.

While working on the synthesis of polyhydroxylated azetidines, the group of Dhavale obtained unprecedented furan-based bicyclic iminosugars 231 and 232 (Scheme 36). D-Glucose derivative 223 was engaged in a Corey-Link and Jocic-Reeve-type protocol, affording 225 through azidation of an in situ generated chlorooxirane intermediate. Compound 225 was then converted in three steps to the key intermediate 226. Oxidative cleavage of the free diol followed by reduction and activation of the resulting primary alcohol led to tosylate 227. Subsequent reduction of the azide to amine function triggered the azetidine ring closure, providing fused sugar azetidine 228 in 79% yield. Compound 226 could also undergo selective benzylation of its primary alcohol. In this case, straightforward activation of the remaining free hydroxyl group followed by azide to amine reduction did not allow the formation of the expected bicyclic product. Instead, the azido group had to be reduced first and the resulting amine protected as a carbamate before performing an alcohol mesylation in order to reach the actual cyclisation precursor 229. Fused sugar azetidine 230 was obtained in

Scheme 34. Synthesis of the bicyclic β,δ-dilactam 217.
95% yield by treatment of mesylate 229 with potassium carbonate. Interestingly, hydrogenolysis of 230 led to the corresponding \( N \)-COOH derivative 231. The key role of the 5-CH$_2$OBn moiety in 228 in the outcome of this final deprotection step is illustrated by the synthesis of free bicyclic azetidine 232 obtained after full cleavage of both benzyl and carbamate protecting groups. Fused furanose azetidines 231 and 232 were found to be moderate inhibitors of \textit{Aspergillus niger} amyloglucosidase. Diol 231 is also a moderate inhibitor of coffee bean \( \alpha \)-galactosidase as well as a weak inhibitor of rat intestinal \( \beta \)-glucosidase.$^{106}$

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\text{Scheme 35. Synthesis of fused iminosugar } \beta \text{-lactams 219 via iodine/ionic liquid-catalyzed [1C+2C+1N] three-components one-pot coupling.}
\]
4. Conclusions

The design and synthesis of unprecedented constrained bicyclic iminosugars reaches far beyond an academic exercise. As analogues of biologically relevant naturally-occurring alkaloids, the interest of such structures is manifold. First the challenge raised by these unusual chiral polyfunctionalized structures bearing a four- or three-membered ring is a source of progress in organic synthesis and serves as a testing ground for well-established synthetic methodologies. Conformational constraints associated with original distributions of hydroxyl groups present in these glycomimetics offer the possibility to explore the glycochemical space and to access mechanistic probes or more specific pharmacological leads. Most examples presented in this review have been published after 2000 and almost 50% after 2010. Despite these reported achievements, there remains much to be done. Only few biological assays reported to date have been performed on therapeutically relevant carbohydrate-processing enzymes and the real clinical potential of constrained
bicyclic iminosugars is still to be explored. The field is thus wide open for exciting discoveries and organic chemistry has an important role in designing and synthesizing promising molecules.

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