IMINOSUGARS AND RELATED HETEROCYCLES  
WITH QUATERNARY CARBON ADJACENT TO NITROGEN:  
SYNTHESIS AND BIOLOGICAL PROPERTIES  

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Abstract. Iminosugars, formerly also called azasugars, are an important class of biologically active compounds and plethora of the structures which have been described in this class. Recently, iminosugars with quaternary carbon atom next to nitrogen have been reported to be potent glycosidase inhibitors. This review aims at covering the synthetic approaches used for this subset of iminosugars as well for similar hydroxylated nitrogen heterocycles e.g. amino acids possessing the above structural motif.  

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1. Introduction  

Synthesis and testing of biological properties of iminosugars attracted considerable attention during recent decades due to their importance as chiral pharmacophores. Introduction on the market of two iminosugar-based drugs against diabetes type 2 (Glyset®) and Gaucher’s disease (Zavesca®) certainly increased interest in the subject. Many synthetic approaches towards naturally occurring iminosugars, or to their synthetic analogues, have been published and the development of general iminosugars chemistry and
representative scope of potential applications can be found in representative literature. Despite this coverage of the discipline, no review on iminosugars bearing quaternary carbon atom has been published to date, although it might be helpful, particularly from the synthetic point of view. It might be a good moment to review the topic as it has been twenty five years since the first synthesis of quaternized nojirimicines by Wagner and Vogel.

Thus, this review fills the gap and summarizes the methods used for the synthesis of iminosugars with quaternary carbon atom adjacent to the nitrogen.

As the construction of quaternary centre alpha to the nitrogen is a primary topic, the literature data was divided on the basis of this feature. There are three synthetic approaches that could be easily distinguished: quaternization of an existing heterocycle (A), construction of quaternary centre simultaneous with formation of the heterocycle (B) and cyclization of compounds already possessing quaternary centre (C) as outlined in Scheme 1. In some cases the quaternary carbon atom was also a stereogenic centre. If so, the formation of the chiral centre in acyclic compounds was also included. Compounds structurally similar to iminosugars e.g. hydroxylated cyclic amino acids may be also synthesised by the methods applied for iminosugars and vice versa. Therefore, some recent examples on the synthesis of proline and pipecolic acid derivatives possessing quaternary centre connected to nitrogen were also included. Nonetheless, the chemistry of cyclic amino acids is obviously too immense to be even slightly discussed in this review, thus besides the examples mentioned no other amino acids derivatives, e.g. pyroglutamates, were covered.

To accurately set the subject of this review, the iminosugars and related heterocycles considered are hydroxylated monocyclic amines pyrrolidines and piperidines or their fused bicyclic derivatives; namely, pyrrolizidines, indolizidines, quinolizidines as well as other structures e.g. fused cyclopropanes (Figure 1). Iminosugars of other structures such as nortropane derivatives and 2-spiro heterocycles were also included. Examples of compounds in which the aforementioned structural motifs are built in more complex polycyclic structures have not been considered as the construction of them becomes in many times a highly individualized task. Additionally, compounds containing aromatic rings fused to the specified structures
were not reviewed. Besides review of synthesis methods of iminosugars and related compounds this article also contains a brief overview of their biological properties.

![Heterocyclic scaffolds covered within this review.](image)

**Figure 1.** Heterocyclic scaffolds covered within this review.

### 2. Construction of quaternary centre at existing heterocycle

#### 2.1. Addition to imine-type precursor

Py et al. completed synthesis of a set of iminosugars through diastereoselective addition of vinylmagnesium bromide to nitrone 1 derived from l-sorbose (Scheme 2). Stereodivergent construction of quaternary chiral centre was achieved by vinylation of the nitrone with CH$_2$=CHMgBr itself, or by performing the reaction in the presence of Lewis acid. Among the acids tested, zinc chloride proved to be the best giving piperidine 2b as a single isomer. Both diastereoisomers 2a and 2b were utilized in the synthesis of respective piperidin or indolizidine based iminosugars 3, 4 and 5.

![Synthesis of indolizidine and piperidine iminosugars from l-sorbose-derived cyclic nitrone.](image)

**Scheme 2.** Synthesis of indolizidine and piperidine iminosugars from l-sorbose-derived cyclic nitrone.

Cycloaddition of phenyl vinyl sulphone to nitrone 6 resulted in the formation of sulphone 7 that was converted into iminosugar 8 with quaternary chiral centre as reported by Díez et al. (Scheme 3). Addition of metalorganic compound to another 5-membered nitrone was used by Kamath et al. for the synthesis of analogue of forodesine HCl, a potent purine nucleoside phosphorylase inhibitor. Thus, the
reaction of nitrone 9 with lithiated 9-deazahypoxantine derivative 10 furnished quaternized pyrrolidine 11 that was subsequently reduced and deprotected to give the final aza-C-nucleoside 12 (Scheme 4). Addition of cyanides to similar nitrone 13 was also studied by Goti and Merino et. al. (Scheme 5a). Variation of the conditions, particularly the cyanide source, allowed to obtain both diastereoisomers 14a and 14b with good selectivity. Tert-butyl group could be easily deprotected in acidic conditions. The authors report also addition of metalorganic compound to nitrone 15 resulting in stereoselective formation of dihydroxypyrrolidine derivative 16 (Scheme 5b), although little information on this reaction is given as nitrone 15 was minor side product in the synthesis of (-)-codonopsinine.

Strecker reaction followed by catalytic reduction was used by Wong et. al. for the synthesis of 2-aminomethyl iminosugar 18 and its derivatization (Scheme 6). Starting 6-aminoheptose hydrochloride 17 was obtained by rabbit muscle aldolase catalysed reaction of dihydroxyacetone phosphate and 3-azido-2-hydroxybutanal followed by the reduction of azide group. Neutralization of 17 set the equilibrium with
prevailing cyclic imine form I that underwent cyanide addition. Further functionalization of primary amine group in 18 was also described.

Malik and Jarosz synthesised two O-benzyl pyrrolidine derivatives 20 via addition of excess of allyl magnesium bromide to sugar-derived 4-bromonitriles 19 (Scheme 7). The formation of quaternary centre was realized by addition of allyl magnesium bromide to intermediate cyclic imine II. Synthesis of non-quaternary iminosugar derivatives by reduction of imine II was also described.

The same strategy was used by Jarosz et. al. to synthesise O-benzyl piperidine derivative 22 from respective 5-bromonitrile 21. The intermediate piperidine iminosugar 22 was first cyclized by RCM to spiro derivatives 23 and 24 that were subsequently transformed into respective O-benzyl protected azaspiro[4.5]decanes 25 and 26 (Scheme 8).
Epimeric O-benzyl protected piperidine iminosugars 29 and 30 could be synthesised by addition of Grignard reagents to imine 28 derived from tetrabenzyl deoxynojirimycin 27 as reported by Davis et. al. (Scheme 9). Addition of methyl magnesium bromide gave mixture of isomers 29b and 30b but application of bulkier nucleophile, benzyl magnesium chloride, resulted in selective formation of iminosugar 29a, although both reaction proceeded in low yield (17% and 19% respectively).

Sequential addition of two organometallic reagents to iminium salts obtained from N-substituted lactams after their activation with Tf2O led to α,α-disubstituted cyclic amines as reported by Huang et. al. (Scheme 10). In case of chiral pyrrolidin-2-ones 31 bearing benzylxy substituent at 3 or 4 position the products were Bn protected hydroxypyrrolidine derivatives 32 (Scheme 10a). Excellent diastereoselectivity was observed for 3-benzylxy pyrrolidine 32b. Analogous bis-alkylation of (R)-1-allyl-5-(benzylxy)piperidin-2-one 33 proceeded with d.r. = 9:1 and after debenzylation afforded 6,6-disubstitutedpiperidin-3-ol 34 that was further employed in the synthesis of immunosuppressant FR901483 (Scheme 10b).

Highly substituted piperidine-3,4-diol 36 was synthesised by Muthusamy et. al. by TiCl4 promoted opening of 7-oxa-2-azabicyclo[2.2.1]heptane ring 35 followed by addition of allyltrimethylsilane to the intermediate N-tosyliminium ion V (Scheme 11).
Pyrrrolizidine derivative 38 with tert-butyldimethylsilyl protected hydroxyl group was synthesised by Gin et. al. via 1,3-dipolar cycloaddition (1,3-DC) of methyl acrylate and azomethine ylide formed from precursor 37 (Scheme 12). Noteworthy, the epimerization of stereogenic centre with O-TBS group attached took place during the reaction resulting in predominant stereoisomer 38.  

**Scheme 11.** Synthesis of piperidine 36.

2.2. Addition to enamine-type precursor

Piperidine-based iminosugar 41 with CF\textsubscript{3} group at \(\alpha\)-position was synthesised by Fustero et. al. from imino lactone 39 derived from (R)-phenylglycinol (Scheme 13). Key steps were iodocyclization of the starting lactone 39 to enamino lactol VI and base mediated rearrangement of the latter affording diido intermediate 40. Further transformations gave final product 41.

**Scheme 12.** OTBS protected pyrrrolizidine 38 synthesis.

**Scheme 13.** Synthesis of CF\textsubscript{3} decorated iminosugar 41.

Highly stereoselective cyclopropanation of 4-hydroxypyridine derivatives 42 was studied by Occhiato et. al. and led to 5-hydroxy-2-azabicyclo[4.1.0]heptane-1-carboxylate methyl esters 43. Catalytic hydrogenation of Cbz protected product 43b afforded 4-hydroxy-2,3-methanopipeolic acid methyl ester 44 in quantitative yield (Scheme 14a). Variation on the substrate and the reaction conditions enabled also to
obtain trans-cyclopropanated compound 46b as major products although the selectivity for trans-stereoisomers was significantly lower and maximal isomer ratio 1:7 for isomers 46a and 46b was achieved (Scheme 14b). The key for inversion of stereoselectivity was change of the reaction conditions since sole introduction of bulky protecting group on hydroxyl did not alternate the stereodirection of the cyclopropanation.

Scheme 14. Synthesis of protected 2,3-methanopipeolic acids esters 44 and 46.

The same cis-cyclopropanation approach also allowed Occhiato et. al. to synthesise similar 2,3-methanopipeolic acids 49, 52 and 55 distinguished in the term of the number or the position of hydroxyl group (Scheme 15).\textsuperscript{17}

Scheme 15. Synthesis of hydroxylated 2,3-methanopipeolic acid esters 49, 52 and 55.
Addition of N-benzylidenebenzylamine to ketene obtained from proline derivative 56 enabled to obtain pyrrolidine-spiro-β-lactams 57 as described by La Rosa et al. (Scheme 16). Among other attempts of synthetic utilization of the spiro-β-lactams isomer 57a has been transformed into diastereoisomeric diol 58 (mixture of isomers, 83:17 d.r.). Synthesis of compounds 57 as well as other spiro-β-lactams of this type was also described by Thiruvazhi et al. 20

![Scheme 16. Synthesis of pyrrolidine-spiro-β-lactam 58.](image)

### 2.3. Alkylation of EWG substituted compounds

Little iminosugar derivatives have been synthesised by this methodology, although is very popular for amino acids functionalization, including amino acids bearing hydroxyl groups. Since quaternization of amino acids is a very broad topic that greatly exceeds the scope of this review, only some recent examples, mostly on 4-hydroxyproline, were cited.

Protected iminosugar nitrile 59 was methylated by Lallemand et al. to give quaternized product 60 (Scheme 17). The reaction was sensitive for the kind of protective group and also another diastereoisomer of 59 did not give product of substitution but lactam 61 formed instead. In other cases e.g. O-benzyl protected substrate elimination product 62 prevailed. Such reactivity is enforced probably by the conformation of whole molecule of type 59 which causes the CN group occupies axial position, thus making it prone for elimination.

![Scheme 17. Attempts on α-methylation of iminosugar nitriles.](image)

Alkylation and subsequent reduction of fully protected trans-4-hydroxyproline 63 leading to respective pyrrolidines 64a and 64b was described by Honda and Hisa. Thus, pyrrolidine and indolizidine
derivatives 64 and 65 with quaternary carbon adjacent to nitrogen were obtained during synthesis of (-)-
adalinine, a coccinellid alkaloid (Scheme 18).

Scheme 18. α-Alkylation of protected trans-4-hydroxyproline 63.

The same substrate 63 was methylated in similar conditions to give the mixture of chromatographically
separable diastereoisomers 66 that were subsequently transformed into N-substituted trans-4-hydroxyproline
amides as described by Kelleher et. al. as well as Manfredi et. al. (Scheme 19). The amides were tested as
organocatalysts for Michael addition.

Scheme 19. α-Methylation of 63.

Similar methylation of protected indolizidine 67 to mixture of quaternized products 68 was utilized by
Pérard-Viret et. al. for the synthesis of 4-hydroxypropeolic acid derivatives 69 (Scheme 20).

Scheme 20. Synthesis of pipelic acid esters 69.

Ethynyl tolyl sulphone reacted with N,O-protected 4-hydroxyproline esters 70 and 72 to give
respective α-2-tosynyl derivatives 71 and 73 as reported by Tayama et. al. (Scheme 21). Both, the yield
and d.e. appeared to be higher for cis-4-hydroxyproline derivative 73 (Scheme 21b). In contrast to fully
protected substrates N-protected ester 70e with free hydroxyl group gave no product of the tosylvinylation (Scheme 21a).

![Diagram 1](image1.png)

Scheme 21. Stereoselective α-2-tosylvinylation of 4-hydroxyproline derivatives.

Organocatalytic Michael addition of 3-oxoproline ester 74a to β-nitrostyrene and its substituted analogues 75 catalysed by quinidine derived urea catalyst 78 or similar organocatalysts gave access to a series of α-substituted 3-oxoproline derivatives 76 as reported by Naicker and Govender et. al. (Scheme 22).25 In an outlined example phenyl derivative was reduced to α-substituted 3-hydroxyproline ethyl ester 77 with excellent diastereoselectivity. Despite excellent d.r. and very good enantioselectivities only relative configuration of the products were established.

![Diagram 2](image2.png)

Scheme 22. Synthesis of 3-hydroxyproline derivative 77.

Similar alkylation of 3-oxoproline ester 74b catalysed by chiral ammonium bromide 79 was reported by Maruoka et. al. (Scheme 23).26 Quaternized product 80a (R = Ph) was reacted with Grignard reagents or reduced to proline derivatives 81 and 82 respectively.

Derivatives of trans-4-hydroxyproline 83 were acylated by Hayes et.al. on the approach to formal synthesis of (+)-lactacystin (Scheme 24).27 Despite the moderate diastereoselectivity of enolate acylation most of the products 84 were obtained as pure diastereomers after chromatography.

Arylation of trans-4-hydroxyproline 85 has been realized by base induced migration of aryl group in derivative N-aryl ureas 86 as reported by Maury and Clayden (Scheme 25).28 Despite moderate stereoselectivity of the migration pure enantiomers of arylated proline 88 were obtained in most cases after
chromatographic separation of intermediate hydantoin 87 and their hydrolysis. Different proline derivatives have been also α-arylated by this methodology and some examples of high d.r. were reported.

![Scheme 23](image)

**Scheme 23.** Synthesis of 3-hydroxyproline derivatives 81 and 82.

**Scheme 24.** Acylation of protected trans-4-proline derivatives.

![Scheme 25](image)

**Scheme 25.** Synthesis of α-arylo-4-hydroxyprolines 88.

Derivatives of 3,4-dihydroxyprorlidine 91 were obtained by Donohoe et al. from respective pyrrole-2-carboxylic esters 89 by reductive aldol reaction of N-Boc protected Birch intermediates (not shown) followed by dihydroxylation of double bond in products 90 (Scheme 26). 29

![Scheme 26](image)

**Scheme 26.** Utilization of Birch reduction in formation of quaternary centres.
Pyrrolidine 91 was further utilized in the synthesis of KSM-2690 B, a polyene β-lactone possessing antibiotic activity. Similar alkylation of a Birch reduction product also led to the construction of quaternary centre and was utilized by the same group to synthesise chiral pyrrolidine 92.30

Birch reduction of pyrrole-2-carboxylate 93 followed by alkylation with iodomethyl pivalate was utilized by Schieweck and Altenbach for obtaining of bis(hydroxymethyl) pyrrolidine 94, that in turn served as a substrate in the synthesis of racemic pyrrolidine and pyrrolizidine iminosugars 95 and 96 respectively (Scheme 27).31

![Scheme 27](image)

**Scheme 27.** Application of Birch reduction for the synthesis of iminosugars 95 and 96.

Mondal and Bera described cross-aldol reaction of formaldehyde with chiral aldehyde 97, that gave bis(hydroxymethyl) pyrrolidine derivative 98 among with predominant oxazolidinone 99 (Scheme 28). Oxidation of hydroxymethyl group of the latter led to pyrrolidine-2-carboxylic acid derivative 100.32

![Scheme 28](image)

**Scheme 28.** Utilization of cross-aldol reaction in the formation of quaternary centre.

Stevens’ rearrangement of proline derived iminium salt 101 was used by Santos et. al. to synthesise quaternary proline ester 102 (Scheme 29). Subsequent non reductive debenzylation followed by allylation, RCM and dihydroxylation led to perhydroindolizine 8a-carboxylates 103, that were reduced to respective indolizidines 104.33

3. **Cyclization with simultaneous formation of quaternary centre**

Classification in this category has been made on the basis of the one-step synthesis and does not necessarily means the reaction is simultaneous from the mechanistic point of view. In some cases the formation of quaternary centre may be distinguished from subsequent cyclization although they were not separated during the synthesis.
relative stereochemistry. Asymmetric synthesis was attempted. Configurations of the stereoisomers depicted on Scheme 30 reflect compounds were tested leading to pyrrolidines affording products in very good yield and diastereomeric ratio (Scheme 31). Derivatives of pyrrolidines were tested leading to pyrrolidines 107 with 2-spiro stereocentre. Also α-substituent in aminoketone 106 was introduced resulting in additional substituent at 4-position of pyrrolidine. Since no asymmetric synthesis was attempted configurations of the stereoisomers depicted on Scheme 30 reflect relative stereochemistry.

3.1. Intramolecular aldol-type reaction

Substituted 3-hydroxypyrrolidines 107 were synthesised by Moody et. al. through reaction of metalloketenes with variety of β-aminoketones (Scheme 30). The reaction proceeded in mild conditions with high diastereoselectivity (d.r. > 20:1). Among variation of alkyl and aryl substituents at R1 and R2 covering Me, substituted alkyls, Ph, 4-F-C₆H₄, 4-MeO-C₆H₄ and heteroaryl intermediate cyclic diazo compounds were tested leading to pyrrolidines 107 with 2-spiro stereocentre. Also α-substituent in aminoketone 106 was introduced resulting in additional substituent at 4-position of pyrrolidine. Since no asymmetric synthesis was attempted configurations of the stereoisomers depicted on Scheme 30 reflect relative stereochemistry.

Synthesis of similar 3-hydroxypyrrolidines 110 was reported by Hu et al. via rhodium catalysed reaction. Palette of aryl substituents either in aminoketones 109 and diazo substrates 108 was studied affording products in very good yield and diastereomeric ratio (Scheme 31). Derivatives of pyrrolidines 110 with additional substituent at 5-position were also obtained by this method.

Scheme 29. Utilization of Stevens rearrangement in the synthesis of iminosugars.

Scheme 30. Synthesis of substituted 3-hydroxypyrrolidines 107.

Scheme 31. Rhodium catalysed synthesis of aryl substituted 3-hydroxypyrrolidines.
Spontaneous formation of 3-hydroxypyrrolidine 112 from substituted malonate 111 was reported by Fukuyama et al. on their route to Salinosporamide A (Scheme 32).36

![Scheme 32. Formation of substituted 3-hydroxypyrrolidine 112.](image)

3.2. Cycloaddition

Synthesis of 4-hydroxypiperidine 115 with CF₃ group attached at quaternary centre was fulfilled by Wang et al. using organocatalytic asymmetric formal aza-Diels-Alder reaction of benzylideneacetone with hemiaminal 113 (Scheme 33).37 Subsequent reduction of carbonyl group in 114 and sultam ring cleavage gave final product 115.

![Scheme 33. Synthesis of 4-hydroxy piperidine 115 with 2-trifluoromethyl group.](image)

Protected derivative of dihydroxypipeolate ester 119 was synthesised by Carrera et al. from chiral diene 116 accessed in turn by biotransformation method from toluene (Scheme 34).38 Formation of quaternary stereogenic centre was achieved byaza-Diels-Alder reaction of the diene with with N-tosyl imine 117. Ozonolysis of cycloadduct 118 followed by reduction of aldehyde groups gave highly substituted piperolic acid ester 119.

![Scheme 34. Synthesis of 3,4-dihydroxypipeolic acid derivative 119.](image)

Alves et al. synthesised another derivatives of piperolic acid 124 and 125 by enantioselective cycloaddition of (2E)-penta-2,4-dien-1-ol 120 and tert-butyl 2H-azirine-3-carboxylate 121a catalysed by 1,1'-binaphthalene-2,2'-dil (BINOL).39 Pure enantiomers of cycloadduct 122 were obtained by altering
chirality of the catalyst. Dihydroxylation of double bond with osmium tetroxide led to compound 123 deprotection of which gave two types of pipecolic acid 124 and 125 with their structures depending on the workup (Scheme 35).

\[ \text{Scheme 35. Pipecolic acids 124 and 125 accessed by aza-Diels-Alder reaction.} \]

Analogous reaction sequence was earlier utilized by Gilchrist et. al. for the synthesis of similar racemic iminosugar 128 and pipecolic acid derivatives 129 (Scheme 36). Thus, aza-Diels-Alder reaction of aziridine 121b and diene 126a gave cycloadduct 127, which subsequent dihydroxylation and reduction led to iminosugar 128. For the synthesis of esters 129 respective dienes and different dihydroxylation conditions were applied.

\[ \text{Scheme 36. Utilization of aza-Diels-Alder reaction for the synthesis of iminosugar 128 and esters 129.} \]

Intramolecular 1,3-DC of sugar-derived cyclic nitrones 131 and 134 obtained from D-arabinose derived nitrone 130 was used by Goti and Merino et. al. for the synthesis of nortropane type iminosugars 132 and 135 (Scheme 37). This reaction, as well as the examples below that also deal with intramolecular 1,3-DC of sugar-derived cyclic nitrones, could be also regarded as quaternization of an existing heterocycle and placed in section 2.1.

Enantiomeric nortropane iminosugar ent-132 as well as its derivatives 137 and 139 were obtained using the above synthetic approach by Kato, Yu and Hirono et. al. and tested as inhibitors of intestinal α-glucosidases. Also similar structures 141 and 143 were achieved from respective nitrones 140 and 142 by Sml2 mediated reductive coupling (Scheme 38). However, the structures of compounds 141 and 143 might be uncertain since drawings in the paper are inconsistent in case of stereocentres pointed by the dashed
arrows (drawings on Scheme 38 reflect the configurations deduced from the names of key intermediates in Experimental Section).

Similar synthetic approach i.e. intramolecular 1,3-DC of 5-allyl cyclic nitrone 144 was used for less hydroxylated cocaine derivative 145 by Davis et. al and Córdova et. al (Scheme 39).  

![Scheme 37. Synthesis of nortropane iminosugars 132 and 135.](image)

![Scheme 38. Synthesis of iminosugars via intramolecular 1,3-DC of sugar-derived cyclic nitrones.](image)
In turn Morozov et al. applied similar 5-membered cyclic nitrones 146 for the synthesis of spiro pyrrolidine derivative 149 (Scheme 40). It was realized by sequential addition of pent-4-enyl magnesium bromide and oxidation of nitrones 147 and 148. Final product 149 was obtained from both of them by appropriate altering the reaction sequence.

Highly substituted racemic piperolic acid derivatives 152 and 153 were synthesized by Afarinkia et al. (Scheme 41). Quaternary centre was formed by aza-Diels-Alder reaction of substituted 1,4-oxazin-2-one 150 with vinylene carbonate. Further transformations of cycloadduct 151 led to polyhydroxy piperolic acid 152. Also product 153 could be obtained from the second diastereomer of cycloadduct 151.

3.3. Intramolecular addition to imine

Luescher and Bode described copper mediated intramolecular cyclization of intermediate imines VII formed from ω-amino stannyl reagents 154 and respective carbonyl compounds (Scheme 42). Although the protocol worked well for aldehydes, the synthesis of pyrrolidine 157 and piperidine derivatives 155 and 156 possessing quaternary centre from ketones gave rather poor yield.

4. Cyclization of precursors already possessing quaternary centre

This was actually the most common strategy utilized for iminosugar synthesis. The method of ring closure is the basis for the classification since quaternary centre was, at least in some cases, introduced at a
very early stage of the synthesis by rather general methods. The way of the heterocycle formation was consequently more important for the synthetic strategy, although the method of the quaternary centre construction is also outlined.

![Scheme 4](image)

**Scheme 4.** Synthesis of MOM protected heterocycles via stannylation reagents.

### 4.1. Cycloaddition

Intramolecular 1,3-DC of N-alkenyl nitrones was utilized for the synthesis of variety of iminosugars reported from our group. The nitrones were obtained either from glucose derived aldehyde 158 or from suitably protected monosugars that can act as aldehydes in the open chain form (Scheme 43).

![Scheme 43](image)

**Scheme 43.** Bicyclic iminosugars accessed by 1,3-DC of N-alkenyl nitrones.
The cycloaddition of nitrones derived from hydroxylamine 160 and protected carbohydrates was highly stereoselective and led to only one stereoisomer of 7-oxa-1-azabicyclo[2.2.1]heptane 161. Thus, syntheses from aldehyde 158 reported by Gębarowski and Sas as well as these from 2,3:5,6-di-O-isopropylidene-β-mannofuranose (159) reported by Mironiuk-Puchalska et al. gave access to bicyclic iminosugars 162–167 of expected stereochemistry as depicted on Scheme 43.  

Surprisingly, analogous reaction with protected 2,3-O-isopropylidene-D-ribofuranose (168) gave the mixture of cycloadducts 169 and 170 differing in configuration of stereocentre of the former atom C2 of sugar (Scheme 44). Since the possibility of sugar epimerization as well as participation of ionic species was excluded experimentally, the mechanism of nitrene α-stereocentre epimerisation via [1,4]-sigmatropic rearrangement was proposed on the basis of DFT calculations. What is worth noting the 1,3-DC of both epimerized and unepimerised nitrones IX and X was still highly stereoselective. Epimerized cycloadducts 170 that are formally derivatives of D-arabinose also served for iminosugar synthesis and, interestingly, significant difference in their reactivity was observed in comparison to the unepimerised D-ribo isomers. Namely, application of conditions used for synthesis of indolizidine 172 from 169 to its stereoisomer 170 did not give respective indolizidine but piperidine 175 formed instead.

Scheme 44. Synthesis of iminosugars from 168 with epimerization of intermediate nitrone IX.

Additionally, we have shown that unprotected monosugars can be utilized in the synthesis of iminosugars through intramolecular cycloaddition of N-alkenyl nitrones. Stereoselectivity of 1,3-DC of
nitrones derived from D-xylose (176) and 2-deoxy-D-ribose (177) was not as high as it was in case of protected derivatives, although cycloadducts 178 and 179 could be separated by chromatography. Beneficially, in case of 176 the stereochemical course of the reaction could be altered by weak Lewis acids such as magnesium bromide. As a result enantiomeric piperidines 182 and 185 as well as diastereomeric indolizidines 180 and 183 and quinolizidines 165 and 168 were synthesised (Scheme 45).

![Scheme 45. Utilization of unprotected pentoses in the synthesis of iminosugars.](image)

Also racemic 4-hydroxypiperidine derivative 187 with 2-spirocyclohexyl substituent was synthesised by this method from nitrone 186 as reported by Chida et al. (Scheme 46).  

![Scheme 46. Synthesis of piperidine 187 via intramolecular 1,3-DC of N-alkenyl nitrene.](image)

Enantioselective carbonyl-ene reaction catalysed by chiral Bronsted acid 190 was applied by List et al. to synthesise a series of 3-hydroxypyrrolidines 189 and some other five membered rings (Scheme 47). Derivatives of 2,2-dimethyl pyrrolidine (n=0) with propen-2-yl (m=0) or cyclic alkenyl substituents (m=3-4) at 4 position were obtained with high yield as well as enantio and diastereoselectivity. Also 2-spiro-pyrrolidines of various ring size (n=1-3, m=0) were obtained. In all cases trans-trans-diastereoselectivity was observed what made the process complementary to the example of cis-diastereoselectivity reported previously by Jacobsen et al. with catalyst 191 that allowed to synthesise 2,2-dimethyl pyrrolidine derivative 189a as pure enantiomer (d.r.>30:1, e.e.=95%) in high yield.  

![Scheme 47. Enantioselective carbonyl-ene reaction catalysed by chiral Bronsted acid.](image)
Spiro-piperidines 193 and 194 were synthesised from aldehyde 192 by Prins and carbonyl-ene reaction respectively as reported by Snaith et. al. (Scheme 48). Change of the reaction conditions allowed to alternate stereoselectivity between isomers 194a and 194b. Palette of piperidines without quaternary carbon was also obtained.

4.2. Metathesis

Interesting spiro-iminosugars of 5-azaspiro[3.4]octane framework were synthesised by Compain et. al. and tested against β-glucocerebrosidase. Formation of quaternary chiral centre was achieved by bis[rhodium(α,α,α'-tetramethyl-1,3-benzenedipropionic acid)](Rh(esp)) catalysed C(sp^3)-H amination of highly substituted cyclobutane 195 (obtainable from vitamin C) while alkylation of 196 and Grubbs II catalysed RCM served for pyrrolidine ring closure leading to 197 (Scheme 49). Subsequent dihydroxylation, deprotection and reductive alkylation, in case of 200, led to the targeted compounds 198-200.

RCM construction of pyrrolidine ring, together with further intramolecular alkylation of nitrogen, was used by Gonda et. al. to synthesise novel pyrrolizidine iminosugar 205 from isothiocyanate 202 bearing quaternary stereogenic centre (Scheme 50). The latter was previously obtained by [3,3]-sigmatropic rearrangement of sugar derived allylic thiocyanate 201.

Epimeric indolizidines 210 were synthesised by Langlois et. al. (Scheme 51). The quaternary chiral centre was formed by stereoselective addition of allyltrimethylsilane to 206. Hydrolysis and further
functionalisation of aminal 207 gave chiral product 208, that was oxidised to the mixture of diastereomeric indolizidinones 209, that were separated by chromatography. Subsequent steps including reduction and deprotection led to final products 210a and 210b.


Scheme 50. Synthesis of quaternary pyrroliizidine iminosugar 205.

Scheme 51. Synthesis of quaternary indolizidines.
4.3. Reductive aminocyclization

Synthesis of indolizidine, piperidine and pyrrolidine iminosugars bearing hydroxymethyl substituents at quaternary centre was designed by Dhaevel et. al. (Scheme 52). Key substrates, azidoaldehydes 212-214 with quaternary stereogenic centre were obtained from carbohydrate-derived ketones such as 211 (for azidoaldehyde 212) by addition of dichloromethylithium followed by addition of sodium azide. Heterocyclic rings were in all cases constructed by reductive amination of suitably prepared carbonyl precursors as shown for the synthesis of indolizidine 215 and piperidine 216a from 212. Isomeric iminosugars 4, 95, 216-217 were obtained from azidoaldehydes 213 and 214 in similar manner. Indolizidines 4 were independently obtained by Py et. al. from piperidines 2 by allylation, RCM and deprotection of hydroxyl groups. Synthesis of racemic pyrrolizidine 95 was also reported by Schieweck and Altenbach.

Reductive amination was employed for the synthesis of 3,4-dihydroxy pyrrolidine derivatives 220 from respective polyhydroxyl γ-aminoketones 219 as reported by Clapés et. al (Scheme 53). Starting chiral γ-aminoketones 219 were obtained from aldol reaction of dihydroxyacetone phosphate (DHAP) with N-Cbz-amino aldehyde 218 catalysed by DHAP-dependent aldolases i.e. l-rhamnulose-1-phosphate aldolase (RhuA) or l-fuculose-1-phosphate aldolase(FucA). Product ratio was dependent on type of aldolase used.

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Scheme 52. Synthesis of iminosugars 4, 95, 215-217 by reductive aminocyclization.

Scheme 53. Reductive aminocyclization of aldol 219.
Isofagomine derivative 223 was synthesised by Withers et al. from 1-xylose derived nitrile 221 (Scheme 54). Quaternary centre was formed by double addition of Grignard reagent affording amine 222. Subsequent reductive aminocyclization and deprotection afforded the targeted iminosugar 223.

Reductive amination was used by Estévez et al. to synthesise azepane derived iminosugar 226 (Scheme 55). Amine 225 was obtained by double Henry reaction of sugar nitrocompound 224 followed by catalytic reduction. Deprotection of acetonide in 225 and reductive amination gave product 226.

4.4. Intramolecular alkylation of amines

Hydroxylated picolic acids and respective hydroxymethyl piperidines as well as related indolizidines were synthesised from N-tosyl alanine ester 227 and protected D- or L-treose as reported by Kazmaier et al. (Scheme 56).

**Scheme 54.** Synthesis of isofagomine derivative 223.

**Scheme 55.** Synthesis of azepane iminosugar 226.

**Scheme 56.** Utilization of intramolecular Mitsunobu reaction in the synthesis of iminosugars.
First, aldol reaction of enolate generated form 227 with aldehyde 228 afforded mixture of adducts 229a and 229b in 78:22 diastereomeric ratio if excess (2.5 equiv.) of SnCl₂ was used. Then, after chromatographic separation, pure isomers of 229 were submitted for hydrolytic cleavage of benzyl ether followed by Mitsunobu reaction that resulted in formation of protected picolic acid as shown for the main isomer 229a. Further transformations allowed to synthesise indolizidine 231 piperidine 232 and piperolic acid 233. Enantiomers of the compounds shown at Scheme 56 were obtained while starting from L-treose.

Tandem Strecker reaction and iminocyclization of Ts activated ketoses 234 was used by Ayers and Fleet for the synthesis of piperidine α-iminonitriles 236 (Scheme 57). However, since the one-pot procedure was used it was not determined whether the addition of cyanide precede or follow cyclization, so this item might as well be placed in paragraph 2.1. Nonetheless, the synthesis from ketoses that lead to products 236 with quaternary carbon proceeded with rather low yield, contrary to similar process from aldoses which was much more effective.

![Scheme 57. Synthesis of piperidine nitriles 236.](image)

Formation of similar pyrrolidine α-iminonitrile as minor side products was also observed by Pino-González and Assiego during reductive amination with sodium cyanoborohydride (Scheme 58).

![Scheme 58. Formation of nitrile 238 upon reductive amination with NaBH₄CN.](image)

Reduction of azide precursors 240 followed by spontaneous intramolecular formation of stable aminals were utilized by Jensen et. al to obtain bridged bicyclic iminosugars 241 named nojirimicin and calystegines (Scheme 59). Formation of quaternary centre was realised by the same method as described by Dhavale et. al. for 212-214. Starting cycloheptanones 239a and 239b were obtained from glucose and mannose respectively.

Pyrrolidine iminosugars were obtained from azides by spontaneous intramolecular alkylation of an amine formed by reduction of azide group as reported by Fleet et. al. (Scheme 60). The key synthetic intermediate, azide 243 was synthesised from sugar lactone 242 in five steps. Reduction of lactone, selective activation of hydroxyl group as sulfonic ester and azide reduction followed by spontaneous cyclization and,
at least acetone hydrolysis gave pyrrolidine 244a. Epimeric pyrrolidine 244b was also obtained as depicted on Scheme 60. Respective proline derivatives 245 were synthesised by similar methods as well as pyrrolidine ent-244b obtained from enantiomeric lactone ent-242.

Another sugar azide precursor 246 was utilized by Dhavale et al. for the synthesis of azetidine iminosugars 248-250 (Scheme 61). Tosylation of hydroxyl group followed by the azide reduction gave intermediate 247 with furanose fused azetidine ring as a result of spontaneous cyclization. Further transformations of the intermediate 247 led to final iminosugars 248-250.

Intramolecular substitution of terminal mesylate by hydroxylamine group formed in situ by reduction of nitro group in compound 252 was applied by Estévez et al. for synthesis of bis(hydroxymethyl) pyrrolidine iminosugar ent-95 (Scheme 62), which is enantiomer of compound 95 obtained later by Dhavale et al. Quaternary centre in 252 was formed by double Henry reaction of nitro compound 251 with formaldehyde. Intermediate hydroxylamine 253 served also for the synthesis of other related compounds 254
and 255. However, harsher reduction conditions of nitromesylate 252 i.e. elevated temperature and prolonged time led directly to pyrrolidine ent-95.

![Scheme 61. Synthesis of azetidinone iminosugars 248-250.](image)

Series of spirocyclopropyl pyrrolidines 258 and piperidines 261 were obtained from various aldoses by Behr et. al. (Scheme 63). 259 Key reactions were titanium mediated cyclopropanation of protected nitriles 256 and 259 followed by intramolecular substitution of mesyates with free or N-Boc protected aminosugars. Nitriles similar to 256 and 259 but of different configurations of stereocenters were also synthesised from various sugars and used for the synthesis of iminosugars of type 258 and 261 but of different stereochemistry.

Synthesis of another spiro derivative 264 was reported by Britton et. al. (Scheme 64). 270 Thus, chlorohydrin 262 upon catalytic reduction and alkalization formed dihydropyrrole derivative 263 via presumptive epoxide. Reaction of 263 with phosgene and subsequent dihydroxylation afforded iminosugar product 264.

Yet another spirocyclopropyl pyrrolidine 268 was obtained by Chen and Pinto using the intramolecular alkylation approach (Scheme 65). 271 Quaternary stereogenic centre was achieved by aldol reaction and subsequent transformation of the aldol 265 to N-Cbz protected amine 266 through Curtius rearrangement.
Deprotection of acetonide in compound 266 followed by tosylation led to intermediate 267, which reductive Cbz cleavage afforded, after complete deprotection, spiro-iminosugar 268.

Scheme 63. Synthesis of spiro iminosugars 258 and 261.

Scheme 64. Synthesis of iminosugar derivative 264.

Scheme 65. Synthesis of spiro iminosugars 268.

Synthesis of 2-(trifluoromethyl)proline derivative 271 was accomplished by Brigaud et. al. through iodocyclization of allyl morpholinone 269 to iodocompound 270a and its further transformation (Scheme 66). Enantiomer of the final 2-(trifluoromethyl)proline ent-271 could be obtained from the diastereomeric iodocompound 270b with opposite configuration of trifluoromethyl group.

Scheme 66. Synthesis of trifluoromethyl substituted proline 271.
5. Biological activity

Although in many cases the synthesis of quaternary iminosugars itself was a challenge as with other iminosugars an overriding objective of their obtaining is the search for biologically active compounds. Study of enzyme inhibition is the basic test for assessing the biological activity of iminosugars. Only these data are available for quaternary iminosugars, as it is a subclass at relatively early stage of development. Even in this case, a list of all tested compounds exceeds the volume of this review, thus only compounds marked as active in the original papers were included in the table.

Table 1. Results of enzyme inhibition tests for quaternary iminosugars covered by this review.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Enzyme inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td>Aspergillus niger amylglucosidase IC₅₀ 522μM; Kᵢ 421μM</td>
</tr>
<tr>
<td><img src="image2" alt="Structure 2" /></td>
<td>Aspergillus niger amylglucosidase IC₅₀ 415μM; Kᵢ 322μM</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>Aspergillus niger amylglucosidase IC₅₀ 201μM; Kᵢ 145μM</td>
</tr>
<tr>
<td><img src="image4" alt="Structure 4" /></td>
<td>Aspergillus niger amylglucosidase IC₅₀ 1.5μM; Kᵢ 0.8μM</td>
</tr>
<tr>
<td><img src="image5" alt="Structure 5" /></td>
<td>Rice α-glucosidase IC₅₀ 0.028μM; Kᵢ 0.083μM</td>
</tr>
<tr>
<td><img src="image6" alt="Structure 6" /></td>
<td>Rice α-glucosidase IC₅₀ 5μM; Kᵢ 4μM</td>
</tr>
<tr>
<td><img src="image7" alt="Structure 7" /></td>
<td>Bacillus α-glucosidase 52% inhibition at 0.8mM</td>
</tr>
<tr>
<td><img src="image8" alt="Structure 8" /></td>
<td>Rice α-glucosidase IC₅₀ 5.8μM</td>
</tr>
<tr>
<td><img src="image9" alt="Structure 9" /></td>
<td>Rat intestinal maltase IC₅₀ 2.4μM</td>
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<td><img src="image10" alt="Structure 10" /></td>
<td>Rat intestinal isomaltase IC₅₀ 5.1μM</td>
</tr>
<tr>
<td><img src="image11" alt="Structure 11" /></td>
<td>Rat intestinal sucrase IC₅₀ 0.66μM</td>
</tr>
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<td>Enzyme Type</td>
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</tr>
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<td>-----------------------------</td>
<td>-----------------------</td>
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<td>Yeast α-glucosidase</td>
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<td>3% inhibition at 0.8 mM</td>
</tr>
<tr>
<td><em>Bacillus</em> α-glucosidase</td>
<td>21% inhibition at 0.8 mM</td>
</tr>
<tr>
<td>Coffee bean α-galactosidase</td>
<td>10% inhibition at 0.8 mM</td>
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<tr>
<td>Bovine liver β-galactosidase</td>
<td>80% inhibition at 0.8 mM</td>
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<tr>
<td>Geobacillus sp. α-galactosidase</td>
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<tr>
<td>Purine nucleoside phosphorylase</td>
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</tr>
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<td>IC&lt;sub&gt;50&lt;/sub&gt; 9.03 μM</td>
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<tr>
<td>Human α-glucosidase</td>
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<td>Helix pomatia β-mannosidase</td>
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<tr>
<td>Jack bean α-mannosidase</td>
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<td>Jack bean α-mannosidase</td>
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<td>Rice α-glucosidase</td>
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[69c]
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<td><img src="image2" alt="Chemical Structure" /></td>
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<td>Rice α-glucosidase 45% inhibition at 1mM</td>
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<td>Almond β-glucosidase 30% inhibition at 1mM</td>
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<td><img src="image5" alt="Chemical Structure" /></td>
<td>Bovine kidney α-L-fucosidase 76% inhibition at 1mM</td>
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<td>Bovine kidney α-L-fucosidase 19% inhibition at 1mM</td>
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<td><img src="image8" alt="Chemical Structure" /></td>
<td><em>Penicillium decumbens</em> α-L-rhamnosidase 72% inhibition at 1mM</td>
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<td>β-Glucocerebrosidase IC₅₀ &gt;100μM</td>
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<td><em>Penicillium decumbens</em> α-L-rhamnosidase 72% inhibition at 1mM</td>
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<td>Coffee bean α-galactosidase IC₅₀ 45μM; Kᵢ 35μM</td>
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<td><img src="image14" alt="Chemical Structure" /></td>
<td>Rat intestinal β-glucosidase IC₅₀ 384μM; Kᵢ 254μM</td>
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<td><img src="image19" alt="Chemical Structure" /></td>
<td>Jack bean α-mannosidase IC₅₀ 1.3μM; Kᵢ 0.9μM</td>
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<td>Bovine liver β-glucosidase IC₅₀ 22μM; Kᵢ 11μM</td>
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<td><img src="image22" alt="Chemical Structure" /></td>
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<tr>
<td><img src="image23" alt="Chemical Structure" /></td>
<td>Jack bean α-mannosidase IC₅₀ 0.056μM; Kᵢ 0.035μM</td>
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</table>
Bovine liver β-glucosidase IC₅₀ 39μM; Kᵢ 19μM

Aspergillus niger α-galactosidase IC₅₀ 0.130μM; Kᵢ 14μM

Bovine liver β-galactosidase IC₅₀ 5.6μM; Kᵢ 2.4μM

Jack bean α-mannosidase IC₅₀ 0.075μM; Kᵢ 0.043μM

Aspergillus niger α-galactosidase IC₅₀ 0.130μM; Kᵢ 0.09μM

Bovine liver β-galactosidase IC₅₀ 5.6μM; Kᵢ 2.4μM

Jack bean α-mannosidase 37% inhibition at 1mM

Baker’s yeast α-glucosidase IC₅₀ 0.57mM

Baker’s yeast α-glucosidase IC₅₀ 0.59mM

Helix pomatia β-mannosidase 37% inhibition at 1mM

Baker’s yeast α-glucosidase 82% inhibition at 1mM [3]

Rice α-glucosidase IC₅₀ 2.2μM [3]

Almond β-glucosidase 89% inhibition at 1mM [3]

Aspergillus orizae β-galactosidase 10% inhibition at 1mM [3]

Aspergillus niger α-rhamnosidase 53% inhibition at 1mM [3]

Bovine liver β-glucosidase IC₅₀ 116μM; Kᵢ 95μM [58a]

Aspergillus niger α-galactosidase IC₅₀ 0.13μM; Kᵢ 0.09μM [58a]

Bovine liver β-galactosidase IC₅₀ 1.2μM; Kᵢ 0.5μM [58a]

Aspergillus orizae β-galactosidase 19% inhibition at 1mM [3]

Helix pomatia β-mannosidase 10% inhibition at 1mM

Baker’s yeast α-glucosidase 71% inhibition at 1mM

Rice α-glucosidase IC₅₀ 0.052μM; Kᵢ 0.031μM [3]

Aspergillus orizae α-rhamnosidase 53% inhibition at 1mM [3]

Bovine liver β-glucosidase IC₅₀ 202μM; Kᵢ 102μM [58a]

Aspergillus niger α-galactosidase IC₅₀ 0.24μM; Kᵢ 0.54μM [58a]

Bovine liver β-galactosidase IC₅₀ 3.6μM; Kᵢ 1.5μM [58a]

Aspergillus niger α-rhamnosidase 90% inhibition at 1mM

Baker’s yeast α-glucosidase 67% inhibition at 1mM

Rice α-glucosidase IC₅₀ 1.5μM

Almond β-glucosidase 20% inhibition at 1mM

Aspergillus orizae β-galactosidase 19% inhibition at 1mM [3]

Jack beans α-mannosidase 10% inhibition at 1mM

Helix pomatia β-mannosidase 10% inhibition at 1mM

Aspergillus niger α-rhamnosidase 90% inhibition at 1mM

Escherichia coli β-glucuronidase IC₅₀ 810μM

Porcine kidney α,α-trehalase IC₅₀ 420μM

[3]

[50a]

[58a]
6. Conclusions

Among the published methods majority of syntheses of iminosugars with quaternary carbon atom next to nitrogen rely on cyclization of compounds already possessing quaternary centre via intramolecular alkylation of amine, reductive aminocyclization or intramolecular cycloaddition. Also quaternization of cyclic precursors particularly by addition of nucleophiles to cyclic imines or cyclic nitrones was frequently used. As chemistry of the latter has been intensively studied during recent years it might be attractive approach. Thus, despite relatively small number of papers on iminosugars quaternary carbon atom next to nitrogen (if compared to whole iminosugars) various synthetic approaches towards the subclass have been developed. This indicates the group ready to launch for more intensive studies that seem very likely in the context of some highly active inhibitors that were identified among the class during recent years. Nowadays
the challenges lie rather in precise identification of structural elements responsible for biological activity than synthetic limitations.

Acknowledgment
Funding from Warsaw University of Technology, Faculty of Chemistry is gratefully acknowledged.

References