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

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Tomasz Rowicki

Faculty of Chemistry, Warsaw University of Technology, ul. Noakowskiego 3, 00-664 Warsaw, Poland
(e-mail: tomek@ch.pw.edu.pl)

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.*

Contents

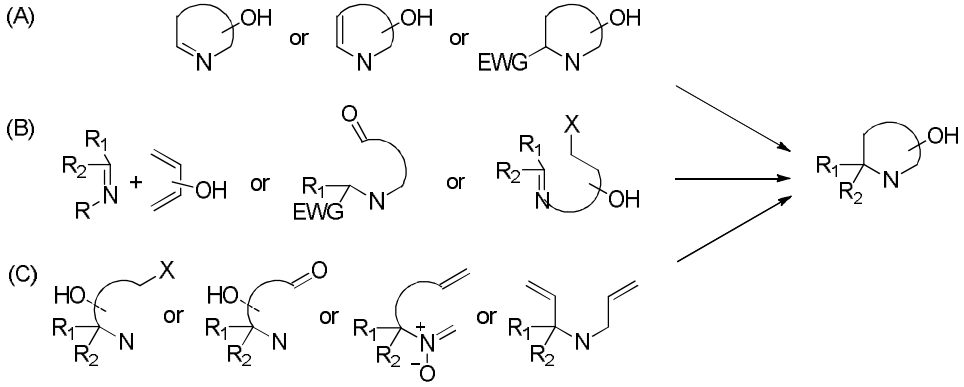
1. Introduction

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.[1] 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 nojirimicine derivatives by Wagner and Vogel.[2]

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.



Scheme 1. Various approaches towards heterocycles with quaternary centre next to nitrogen.

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.

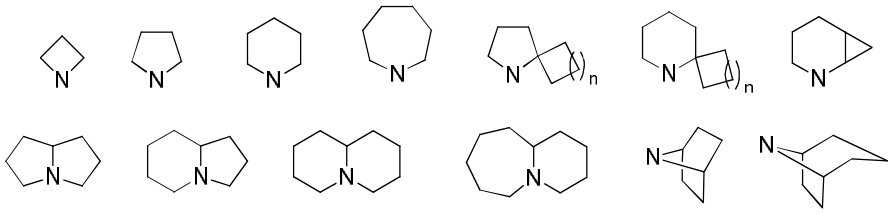
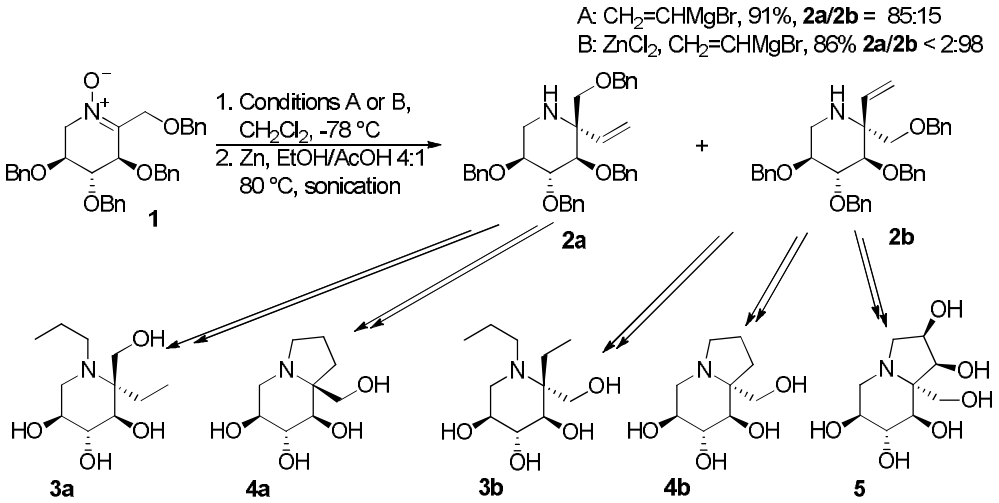


Figure 1. Heterocyclic scaffolds covered within this review.

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).[3] Sterodivergent 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 piperidine or indolizidine based iminosugars **3**, **4** and **5**.

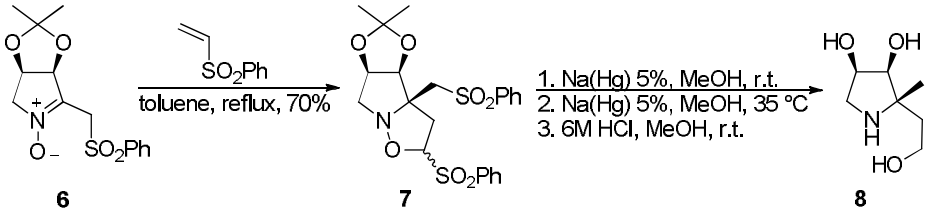


Scheme 2. Synthesis of indolizidine and piperidine iminosugars from L-sorbose-derived cyclic nitrone.

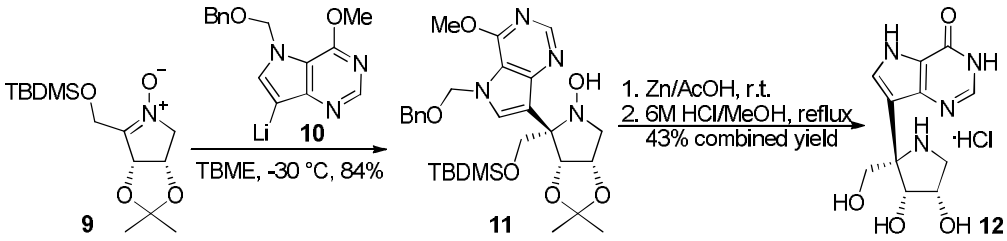
Cycloaddition of phenyl vinyl sulphone to nitrone **6** resulted in the formation of sulphone **7** that was converted into iminosugar **8** with quaternary chiral centre as reported by Díez et. al. (Scheme 3).[4]

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).[5]

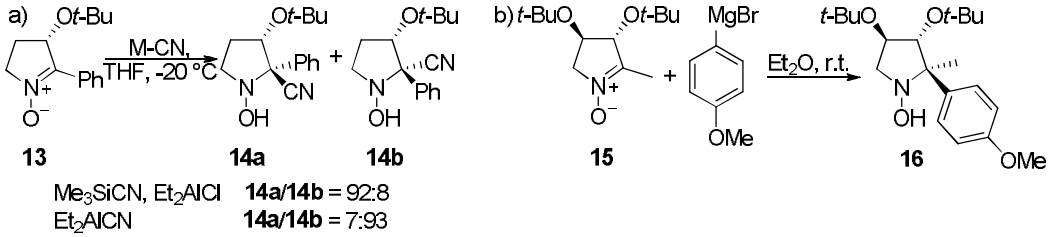


Scheme 3. Synthesis of pyrrolidine **8**.



Scheme 4. Synthesis of aza-*C*-nucleoside **12**.

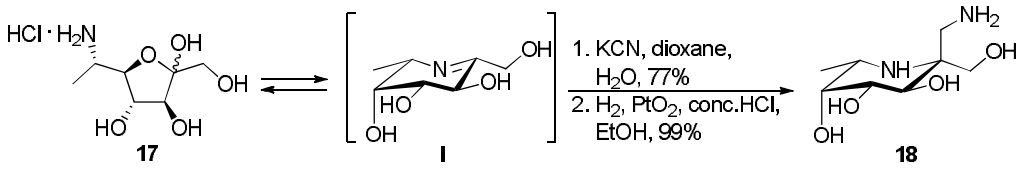
Addition of cyanides to similar nitrone **13** was also studied by Goti and Merino el. al. (Scheme 5a).[6] Variation of the conditions, particularly the cyanide source, allowed to obtain both diestereoisomers **14a** and **14b** with good selectivity. *Tert*-butyl group could be easily deprotected in 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.



Scheme 5. Nucleophilic addition to nitrones **13** and **15**.

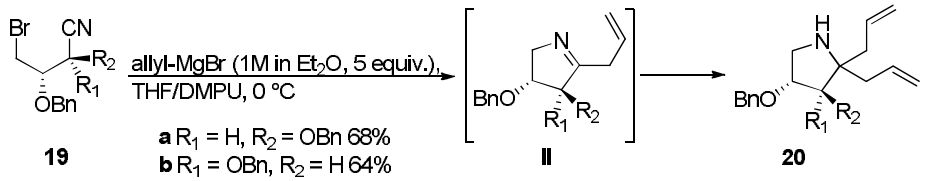
Strecker reaction followed by catalytic reduction was used by Wong et. al. for the synthesis of 2-aminomethyl iminosugar **18** and its derivatization (Scheme 6).[7] Starting 6-aminoheptose hydrochloride **17** was obtained by rabbit muscle aldolase catalysed reaction of dihydroxyacetone phosphate and 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.



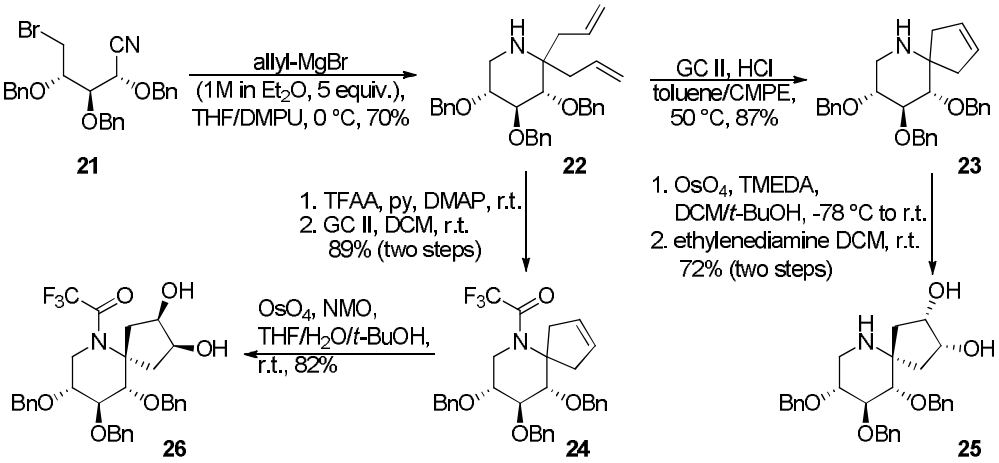
Scheme 6. Synthesis of aminomethyl substituted iminosugar **18**.

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).[8] The formation of quaternary centre was realized by addition of allyl magnesium bromide to intermediate cyclic imine **II**. Synthesis of non-quaternary iminosugar derivarives by reduction of imine **II** was also described.



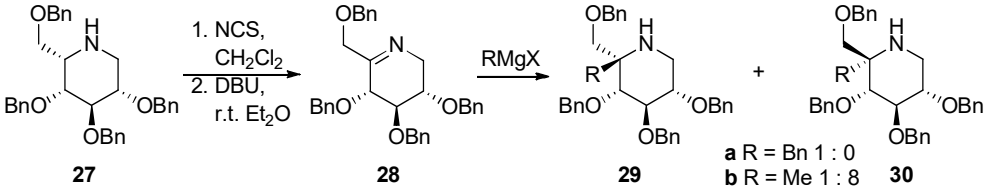
Scheme 7. Reaction of excess of allyl magnesium bromide with 4-bromonitriles **19**.

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).[9]



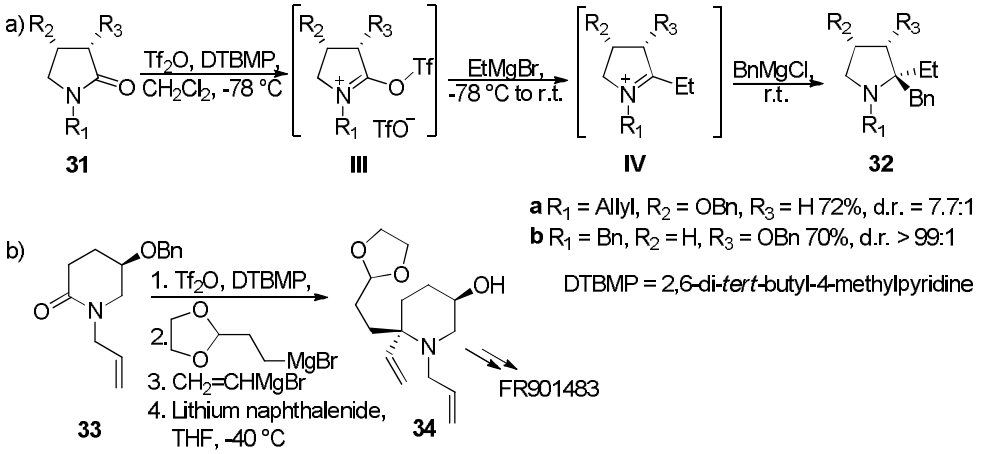
Scheme 8. Synthesis of protected spiro iminosugars **25** and **26**.

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).[10] 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).



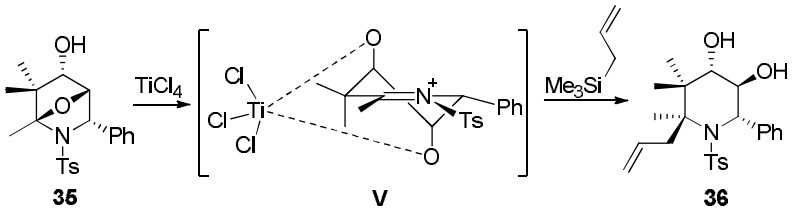
Scheme 9. Addition of Grignard reagents to cyclic imine **28**.

Sequential addition of two organometallic reagents to iminium salts obtained from *N*-substituted lactams after their activation with Tf_2O led to α,α-disubstituted cyclic amines as reported by Huang et. al. (Scheme 10). In case of chiral pyrrolidin-2-ones **31** bearing benzyloxy substituent at 3 or 4 position the products were Bn protected hydroxypyrrolidine derivatives **32** (Scheme 10a).[11] Excellent diastereoselectivity was observed for 3-benzyloxy derivative **32b**. Analogous bis-alkylation of (*R*)-1-allyl-5-(benzyloxy)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).[12]



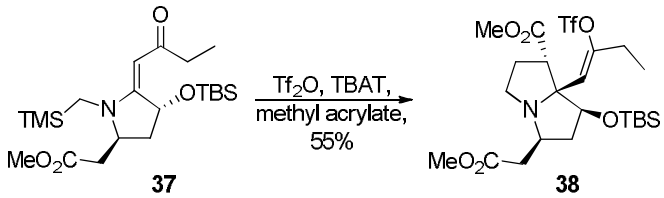
Scheme 10. Bis-alkylation of lactams **31** and **33**.

Highly substituted piperidine-3,4-diol **36** was synthesised by Muthusamy et. al. by $TiCl_4$ 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).[13]



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

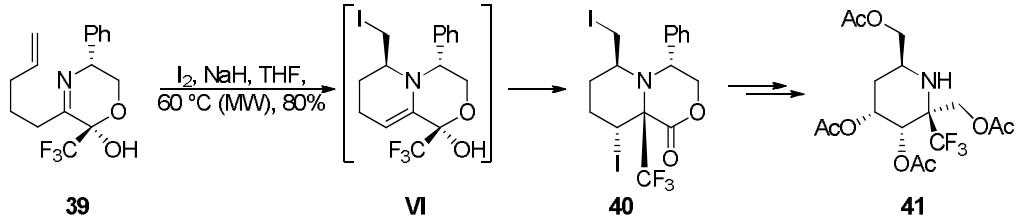
Pyrrolizidine derivative **38** with tert-butyldimethylsilil protected hydroxyl group was synthesised by Gin et. al. via 1,3-dipolar cycloaddition (1,3-DC) of methyl acrylate and azomethine ylide formed from precursor **37** (Scheme 12). Noteworthy, the epimerization of stereogenic centre with *O*-TBS group attached took place during the reaction resulting in predominant stereoisomer **38**.[14]



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

2.2. Addition to enamine-type precursor

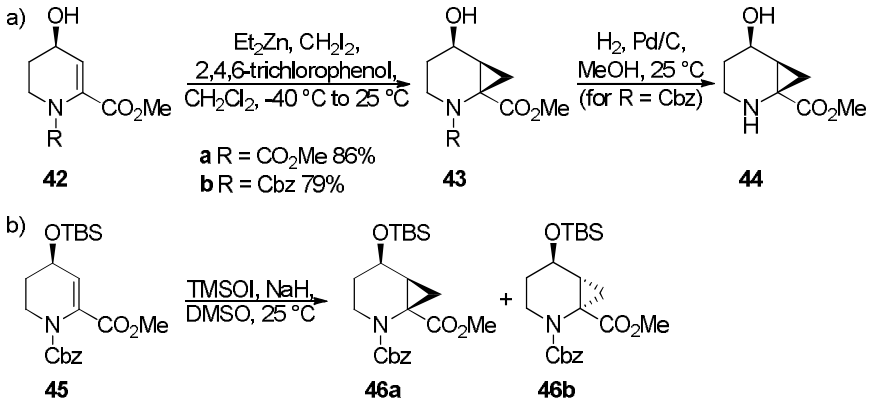
Piperidine-based iminosugar **41** with CF_3 group at α-position was synthesised by Fustero et. al. from imino lactone **39** derived from (*R*)-phenylglycinol (Scheme 13).[15] Key steps were iodocyclization of the starting lactone **39** to enamino lactol **VI** and base mediated rearrangement of the latter affording diiodo intermediate **40**. Further transformations gave final product **41**.



Scheme 13. Synthesis of CF_3 decorated iminosugar **41**.

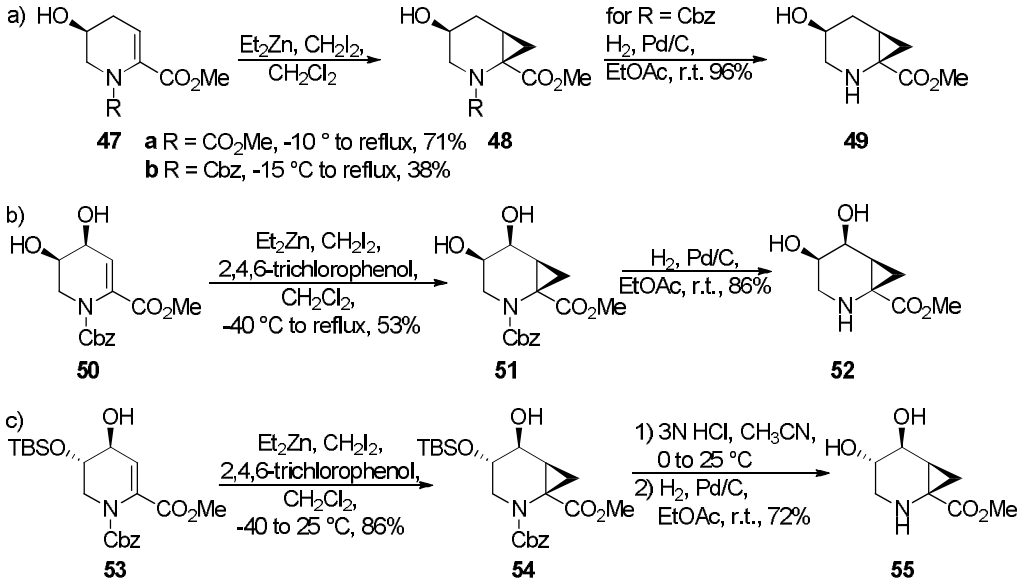
Highly stereoselective cyclopropanation of 4-hydroxypyridine derivatives **42** was studied by Occhiato et. al. and led to 5-hydroxy-2-azabicyclo[4.1.0]heptane-1-carboxylate methyl esters **43**. Catalytic hydrogenation of Cbz protected product **43b** afforded 4-hydroxy-2,3-methanopipecolic acid methyl ester **44** in quantitative yield (Scheme 14a).[16] 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.



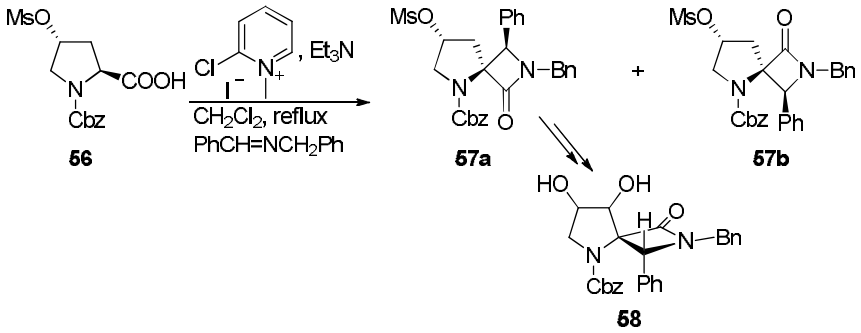
Scheme 14. Synthesis of protected 2,3-methanopipecolic acids esters **44** and **46**.

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



Scheme 15. Synthesis of hydroxylated 2,3-methanopipecolic 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 desctibed by La Rosa et. al. (Scheme 16).[18] 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.[19]

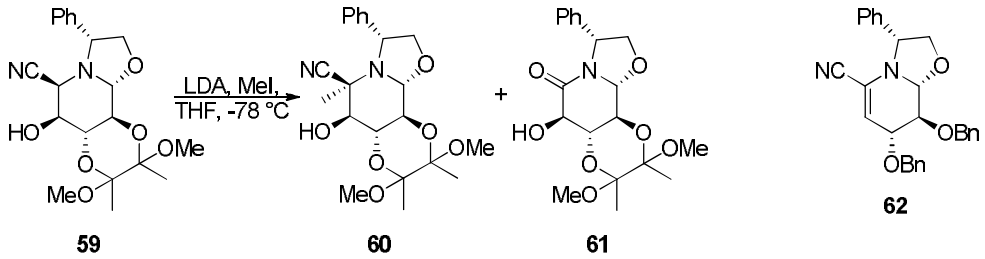


Scheme 16. Synthesis of pyrrolidine-spiro-β-lactam **58**.

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.

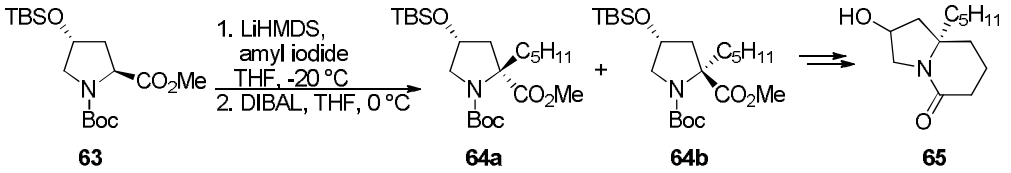
Protected iminosugar nitrile **59** was methylated by Lallemand et. al. to give quaternized product **60** (Scheme 17).[20] The reaction was sensitive for the kind of protective group and also another diastereoisomer of **59** did not give product of substitution but lactame **61** formed instead. In 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.

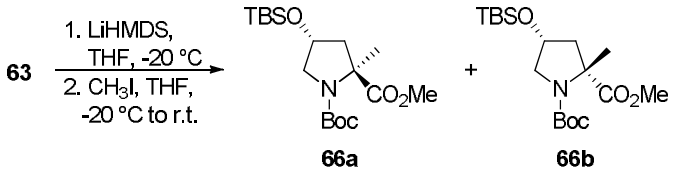
Alkylation and subsequent reduction of fully protected *trans*-4-hydroxyproline **63** leading to respective pyrrolidines **64a** and **64b** was described by Honda and Hisa.[21] Thus, pyrrolidine and indolizidine

derivatives **64** and **65** with quaternary carbon adjacent to nitrogen were obtained during synthesis of (-)-adalinine, a coccinellid alkaloid (Scheme 18).



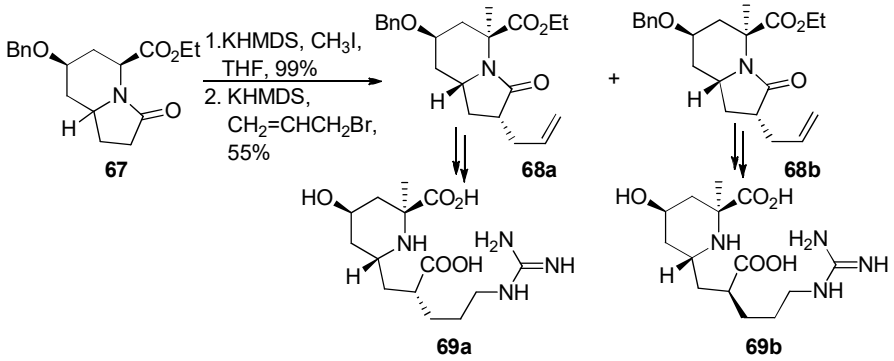
Scheme 18. α-Alkylation of protected *trans*-4-hydroxyproline **63**.

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).[22] The amides were tested as organocatalysts for Michael addition.



Scheme 19. α-Methylation of **63**.

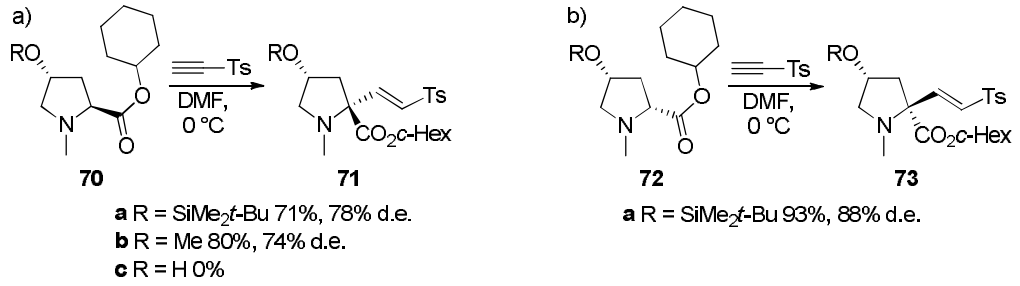
Similar methylation of protected indolizidine **67** to mixture of quaternized products **68** was utilized by Pérard-Viret et. al. for the synthesis of 4-hydroxypipecolic acid derivatives **69** (Scheme 20).[23]



Scheme 20. Synthesis of pipecolic acid esters **69**.

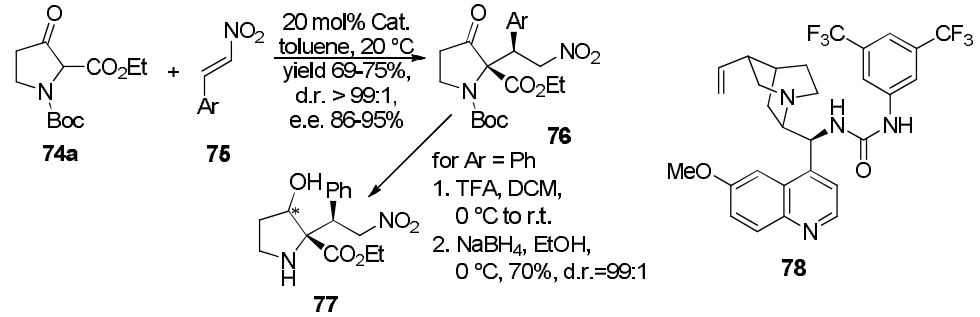
Ethynyl tolyl sulphone reacted with *N,O*-protected 4-hydroxyproline esters **70** and **72** to give respective α-2-tosylvinyl derivatives **71** and **73** as reported by Tayama et. al. (Scheme 21).[24] Both, the yield and d.e. appeared to be higher for *cis*-4-hydroxyproline derivative **73** (Scheme 21b). In contrast to fully

protected substrates *N*-protected ester **70c** with free hydroxyl group gave no product of the tosylvinylation (Scheme 21a).



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 reprted 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 diasteroselectivity. Despite excellent d.r. and very good enantioselectivities only relative configuration of the products were established.



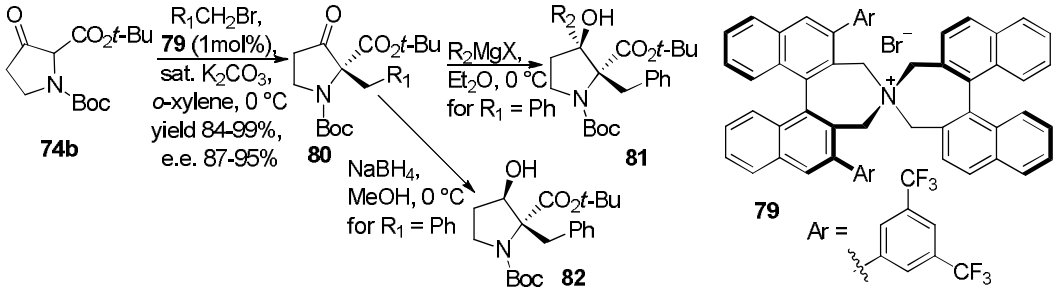
Scheme 22. Synthesis of 3-hydroxyproline derivative **77**.

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.

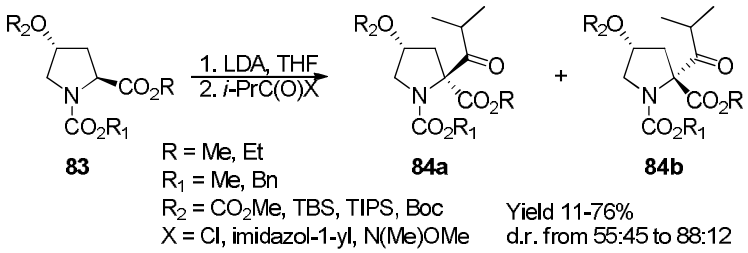
Derivatives of *trans*-4-hydroxyproline **83** were acylated by Hayes et.al. on the approach to formal synthesis of (+)-lactacystin (Scheme 24).[27] Despite the moderate diastereoselectivity of enolate acylation most of the products **84** were obtained as pure diastereomers after chromatography.

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

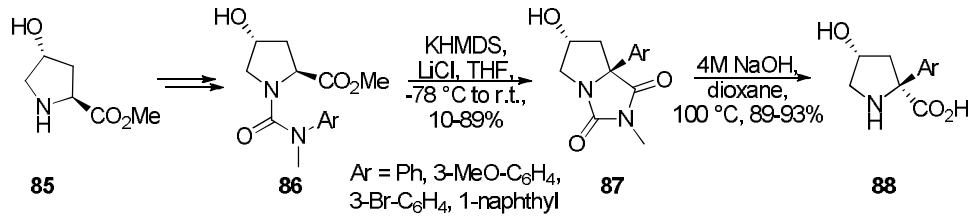
chromatographic separation of intermediate hydantoins **87** and their hydrolysis. Different proline derivatives have been also α-arylated by this methodology and some examples of high d.r. were reported.



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

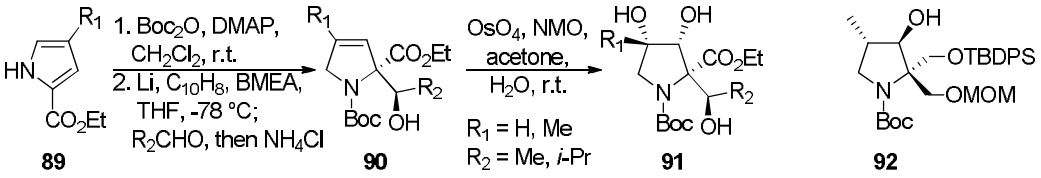


Scheme 24. Acylation of protected *trans*-4-proline derivatives.



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

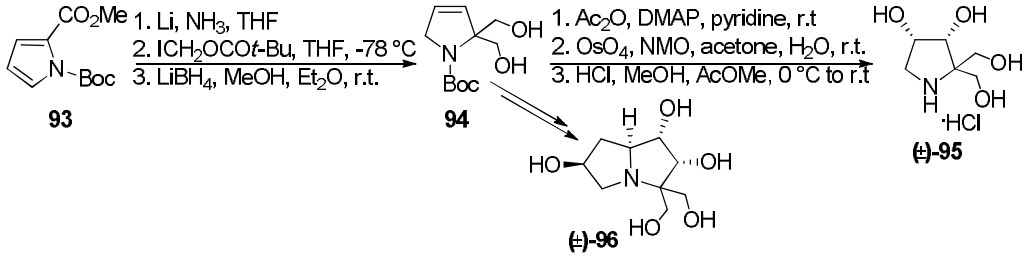
Derivatives of 3,4-dihydroxypyrrolidine **91** were obtained by Donohoe et. al. from respective pyrrole-2-carboxylic esters **89** by reductive aldol reaction of *N*-Boc protected Birch intermediates (not schown) followed by dihydroxylation of double bond in products **90** (Scheme 26).[29]



Scheme 26. Utilization of Birch reduction in formation of quaternary centres.

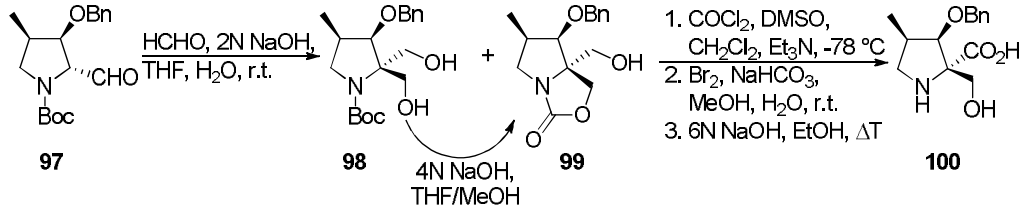
Pyrrolidine **91** was further utilized in the synthesis of KSM-2690 B, a polyene β-lactone possessing antibiotic activity. Similar alkylation of a Birch reduction product also led to the construction of quaternary centre and was utilized by the same group to synthesise chiral pyrrolidine **92**.[30]

Birch reduction of pyrrole-2-carboxylate **93** followed by alkylation with iodomethyl pivalate was utilized by Schieweck and Altenbach for obtaining of *bis*(hydroxymethyl) pyrroline **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. 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 pyrolidine-2-carboxylic acid derivative **100**.[32]

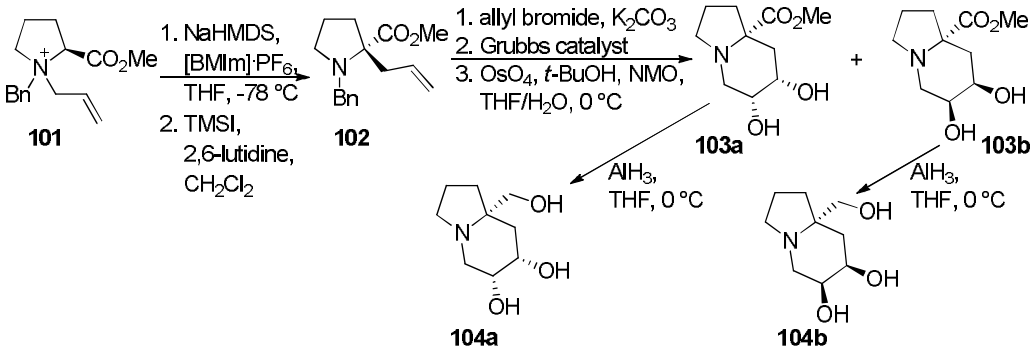


Scheme 28. Utilization of cross-aldol reaction in the formation of quaternary centre.

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

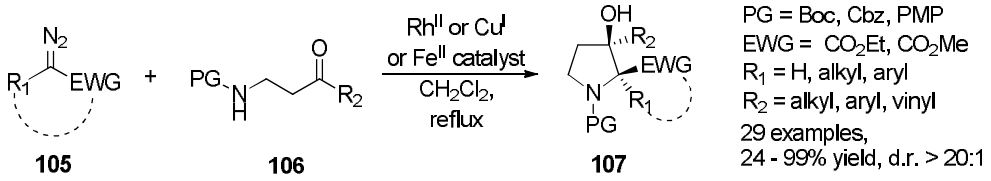
Classification in this category has been made on the basis of the one-step synthesis and does not necessarily means the reaction it simultaneous from the mechanistic point of view. In some cases the formation of quaternary centre may be distinguished from subsequent cyclization although they were not separated during the synthesis.



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

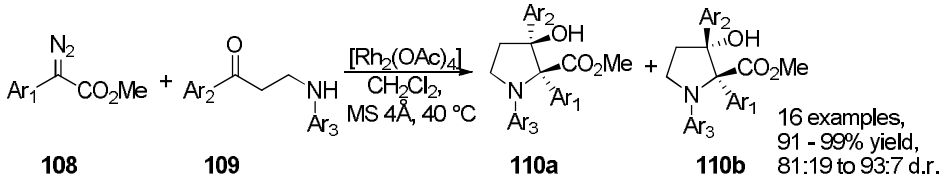
3.1. Intramolecular aldol-type reaction

Substituted 3-hydroxypyrrolidines **107** were synthesised by Moody et. al. through reaction of metallocarbenes with variety of β-aminoketones (Scheme 30).[34] The reaction proceeded in mild conditions with high diastereoselectivity (d.r.> 20:1). Among variation of alkyl and aryl substituents at R_1 and R_2 covering Me, substituted alkyls, Ph, 4-F-C_6H_4, 4-MeO-C_6H_4 and heteroaryls additional two 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.



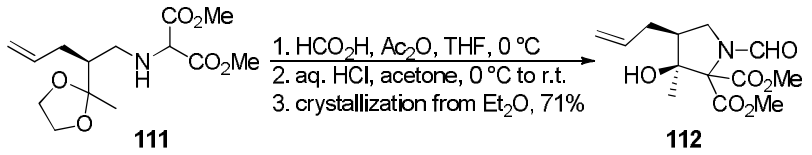
Scheme 30. Synthesis of substituted 3-hydroxypyrrolidines **107**.

Synthesis of similar 3-hydroxypyrrolidines **110** was reported by Hu et. al. via rhodium catalysed reaction.[35] 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 31. Rhodium catalysed synthesis of aryl substituted 3-hydroxypyrrolidines.

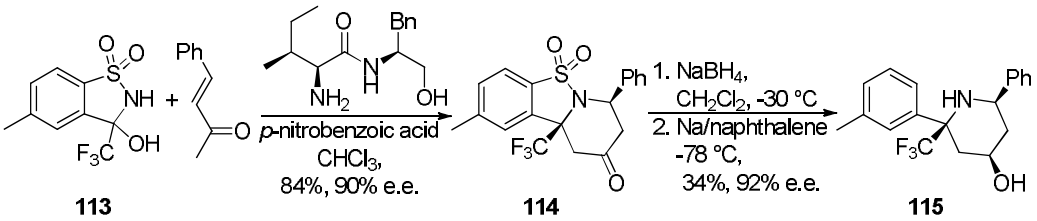
Spontaneous formation of 3-hydroxypyrrolidine **112** from substituted malonate **111** was reported by Fukuyama et. al. on their route to Salinosporamide A (Scheme 32).[36]



Scheme 32. Formation of substituted 3-hydroxypyrrolidine **112**.

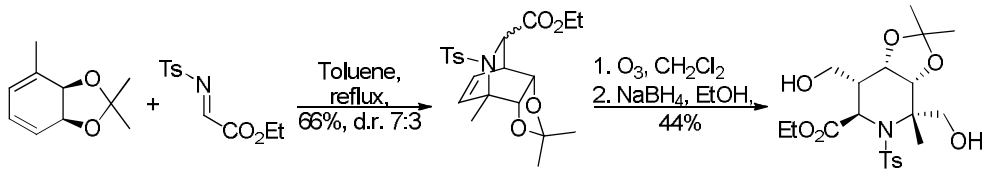
3.2. Cycloaddition

Synthesis of 4-hydroxypiperidine **115** with CF_3 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.

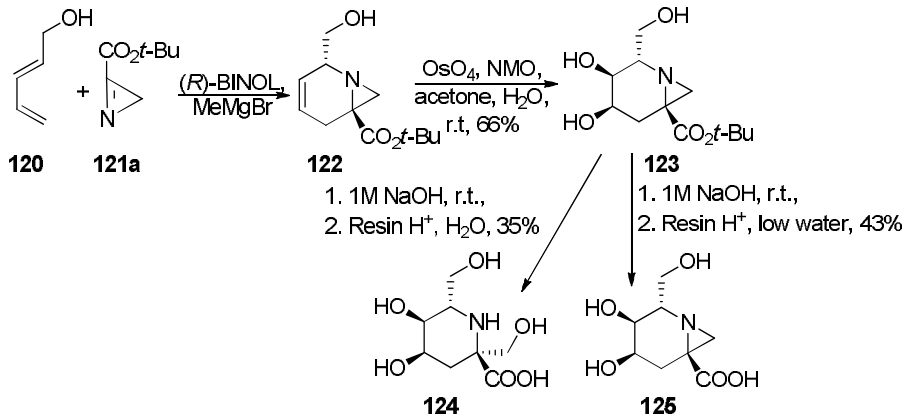
Protected derivative of dihydroxypipecolate ester **119** was synthesised by Carrera et. al. from chiral diene **116** accessed in turn by biotransformation method from toluene (Scheme 34).[38] Formation of quaternary stereogenic centre was achieved by aza-Diels-Alder reaction of the diene with with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



Scheme 34. Synthesis of 3,4-dihydroxypipecolic acid derivative **119**.

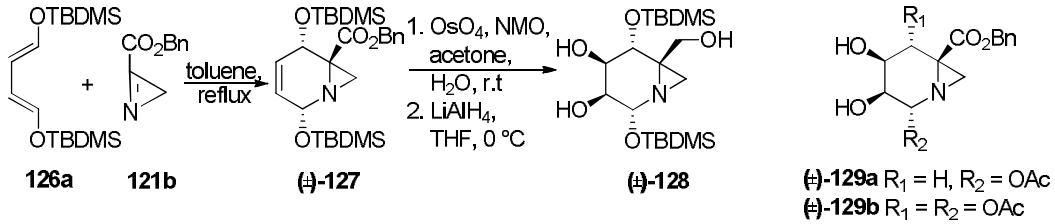
Alves et. al. synthesised another derivatives of pipecolic acid **124** and **125** by enantioselective cycloaddition of (*2E*)-penta-2,4-dien-1-ol **120** and *tert*-butyl *2H*-azirine-3-carboxylate **121a** catalysed by 1,1′-binaphthalene-2,2′-diol (BINOL).[39] Pure enantiomers of cycloadduct **122** 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).



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).[40] 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.



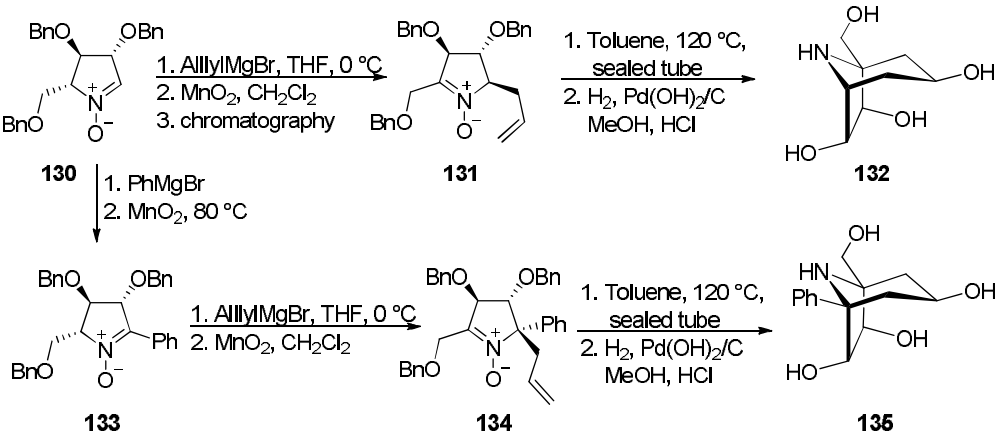
Scheme 36. Utilization of aza-Diels-Alder reaction for the synthesis of iminosugar **128** and esters **129**.

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).[41] 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.

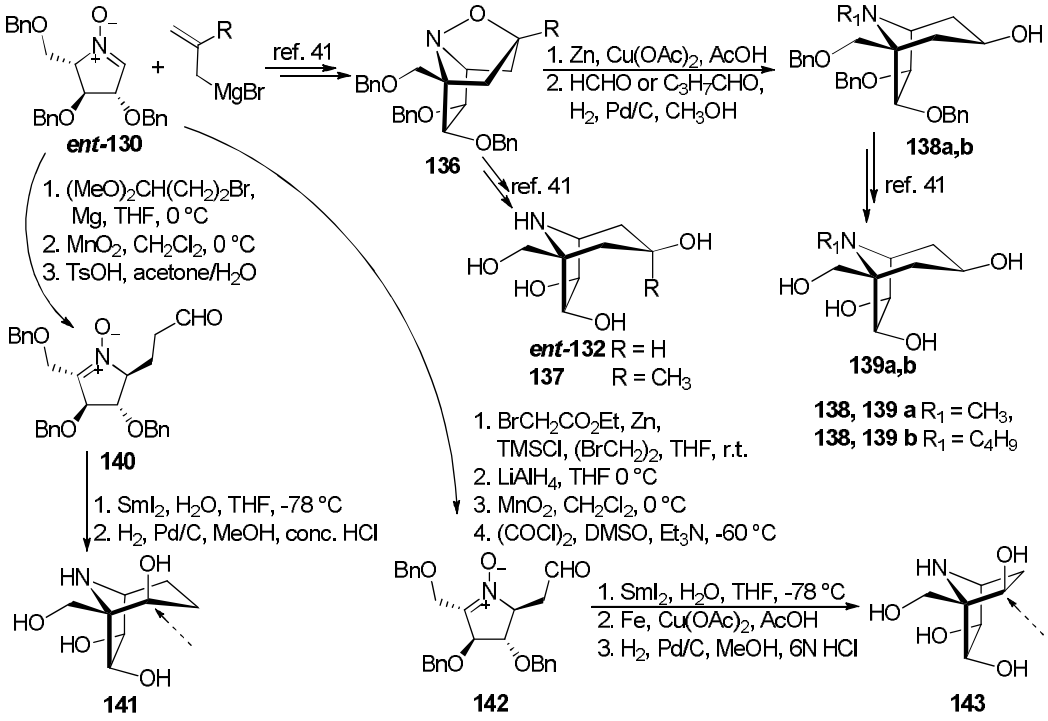
Enantiomeric nortropane iminosugar ***ent*-132** as well as its derivatives **137** and **139** were obtained using the above synthetic approach by Kato, Yu and Hirono et. al. and tested as inhibitors of intestinal α-glucosidases.[42]. Also similar structures **141** and **143** were achieved from respective nitrones **140** and **142** by SmI_2 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).

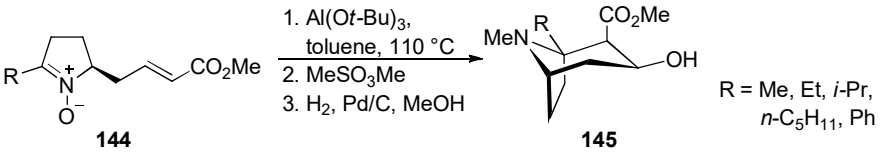
Similar synthetic approach i.e. intramolecular 1,3-DC of 5-allyl cyclic nitrone **144** was used for less hydroxylated cocaine derivative **145** by Davis et. al and Córdova et. al (Scheme 39).[43]



Scheme 37. Synthesis of nortropane iminosugars **132** and **135**.



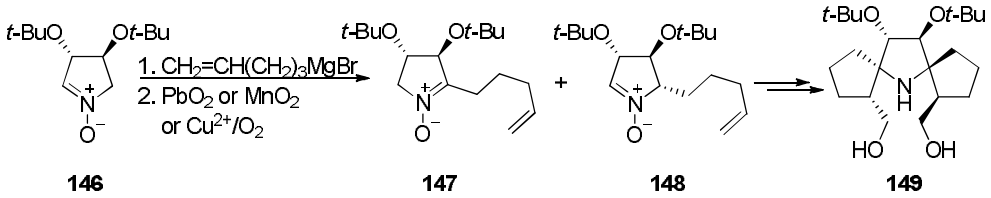
Scheme 38. Synthesis of iminosugars via intramolecular 1,3-DC of sugar-derived cyclic nitrones.



144 **145**

Scheme 39. Synthesis of cocaine derivative **145**.

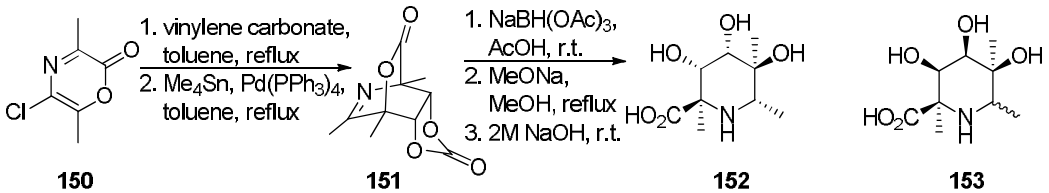
In turn Morozov et. al. applied similar 5-membered cyclic nitrone **146** for the synthesis of spiro pyrrolidine derivative **149** (Scheme 40).[44] It was realized by sequential addition of pent-4-enyl magnesium bromide and oxidation of nitrones **147** and **148**. Final product **149** was obtained from both of them by appropriate altering the reaction sequence.



146 **147** **148** **149**

Scheme 40. Synthesis of dispiropyrrolidine **149**.

Highly substituted racemic pipecolic acid derivatives **152** and **153** were synthesised by Afarinkia et. al. (Scheme 41).[45] 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 pipecolic acid **152**. Also product **153** could be obtained from the second diastereomer of cycloadduct **151**.



150 **151** **152** **153**

Scheme 41. Synthesis of pipecolic acids **152** and **153**.

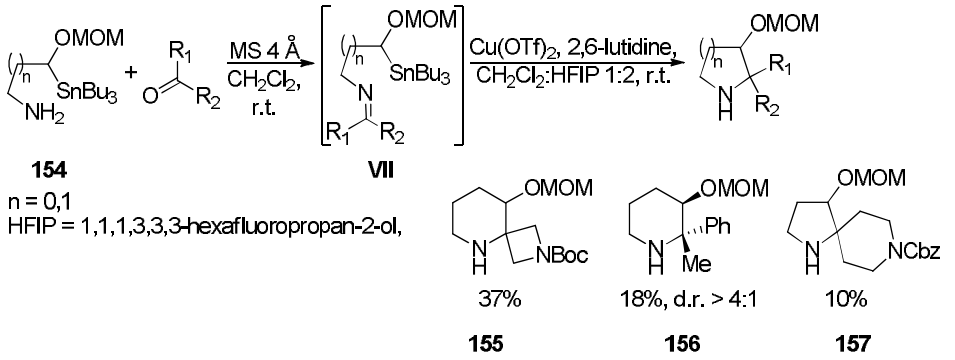
3.3. Intramolecular addition to imine

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).[46] 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 utilised 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

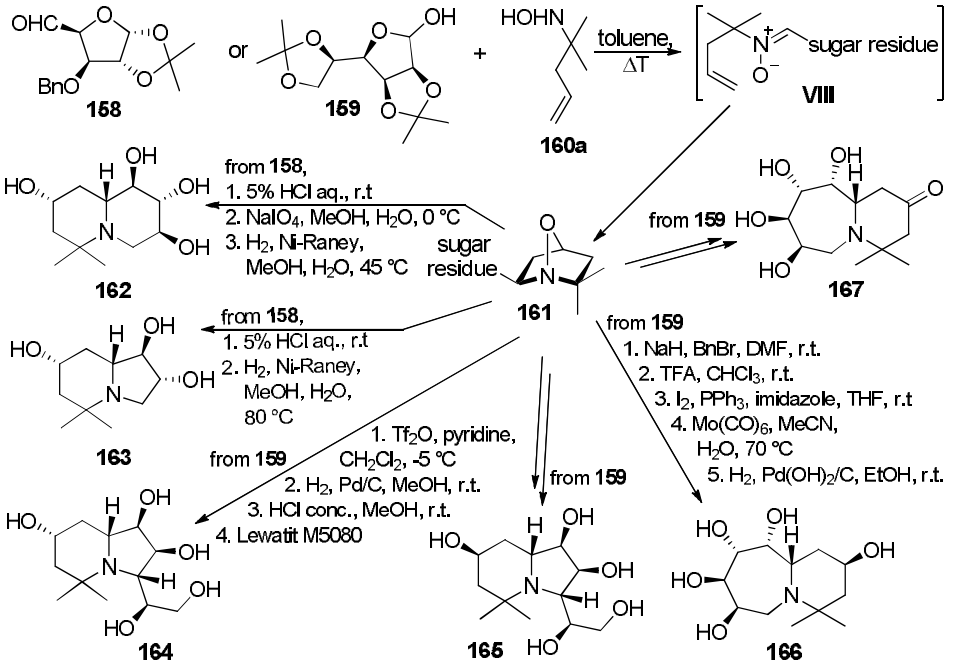
very early stage of the synthesis by rather general methods. The way of the heterocycle formation was consequently more important for the synthetic strategy, although the method of the quaternary centre construction is also outlined.



Scheme 42. Synthesis of MOM protected heterocycles via stannyl reagents.

4.1. Cycloaddition

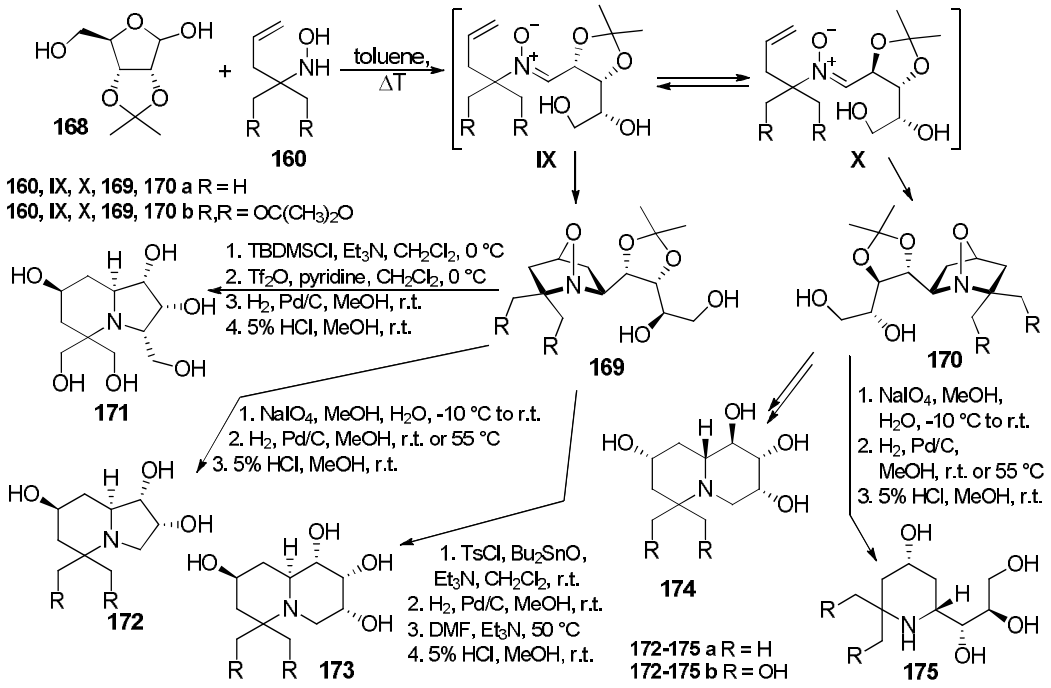
Intramolecular 1,3-DC of N-alkenyl nitrones was utilized for the synthesis of variety of iminosugars reported from our group. The nitrones were obtained either from glucose derived aldehyde **158** or from suitably protected monosugars that can act as aldehydes in the open chain form (Scheme 43).



Scheme 43. Bicyclic iminosugsars 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-D-mannofuranose (**159**) reported by Mironiuk-Puchalska et. al. gave access to bicyclic iminosugars **162**–**167** of expected stereochemistry as depicted on Scheme 43.[47]

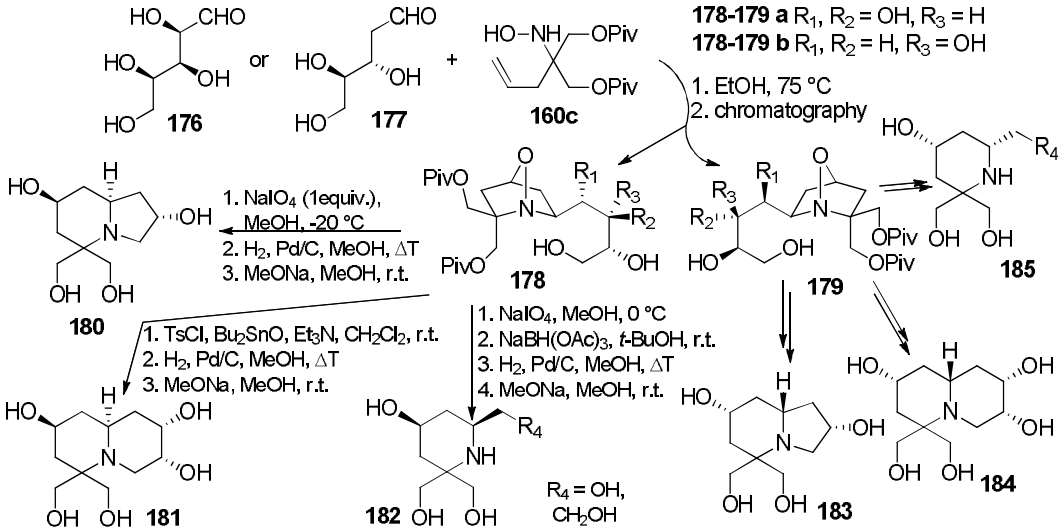
Surprisingly, analogous reaction with protected 2,3-*O*-isopropylidene-D-ribofuranose (**168**) gave the mixture of cycloadducts **169** and **170** differing in configuration of stereocentre of the former atom C2 of sugar (Scheme 44).[48] Since the possibility of sugar epimerization as well as participation of ionic species was excluded experimentally, the mechanism of nitrone α-stereocentre epimerisation via [1,4]-sigmatropic rearrangement was proposed on the basis of DFT calculations.[49] 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**.

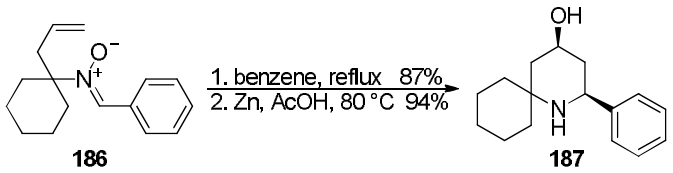
Additionally, we have shown that unprotected monosugars can be utilized in the synthesis of iminosugars through intramolecular cycloaddition of *N*-alkenyl nitrones.[50] Stereoselectivity of 1,3-DC of

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 stereo chemical 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).



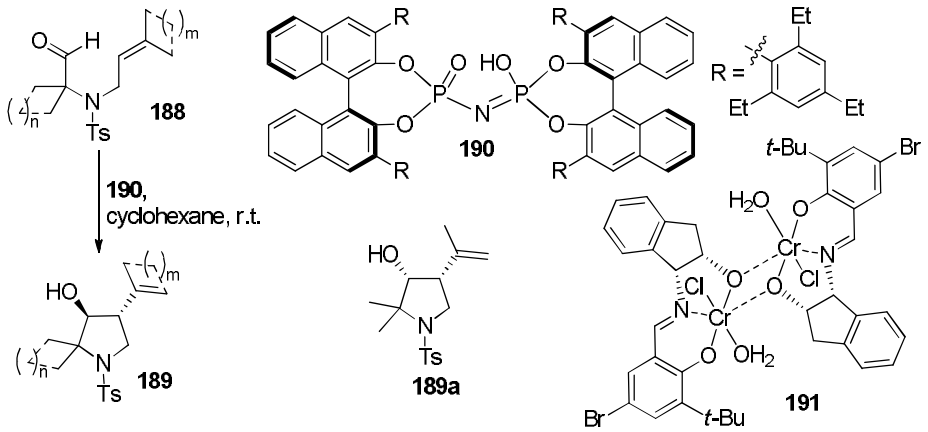
Scheme 45. Utilization of unprotected pentoses in the synthesis of iminosugars.

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).[51]



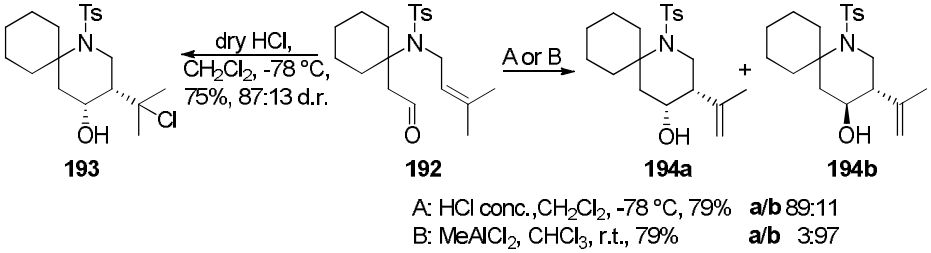
Scheme 46. Synthesis of piperidine **187** via intramolecular 1,3-DC of *N*-alkenyl nitrone.

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).[52] 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.[53]



Scheme 47. Asymmetric carbonyl-ene reaction leading to 3-hydroxypyrrolidine derivatives **189**.

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).[54] Change of the reaction conditions allowed to alternate stereoselectivity between isomers **194a** and **194b**. Palette of piperidines without quaternary carbon was also obtained.



Scheme 48. Spiro-piperidines accessed by carbonyl-ene and Prins reactions.

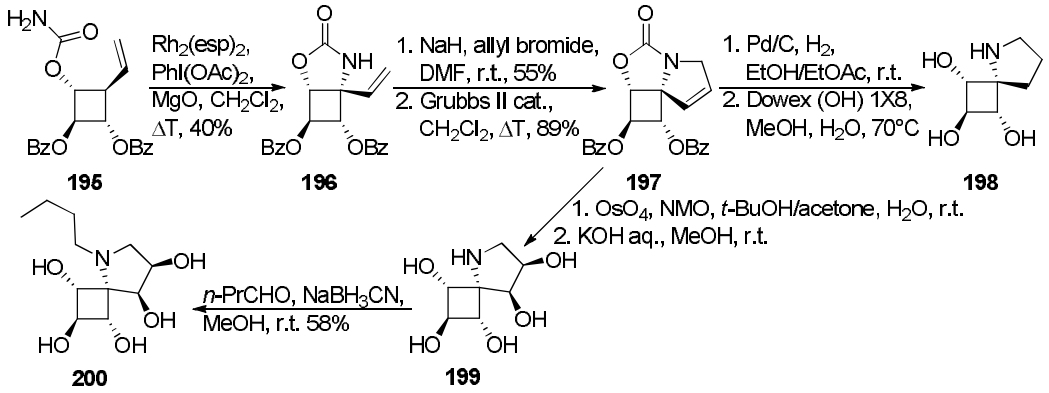
4.2. Metathesis

Interesting spiro-iminosugars of 5-azaspiro[3.4]octane framework were synthesised by Compain et. al. and tested against β-glucocerebrosidase.[55] Formation of quaternary chiral centre was achieved by bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] ($Rh_2(esp)_2$) 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**.

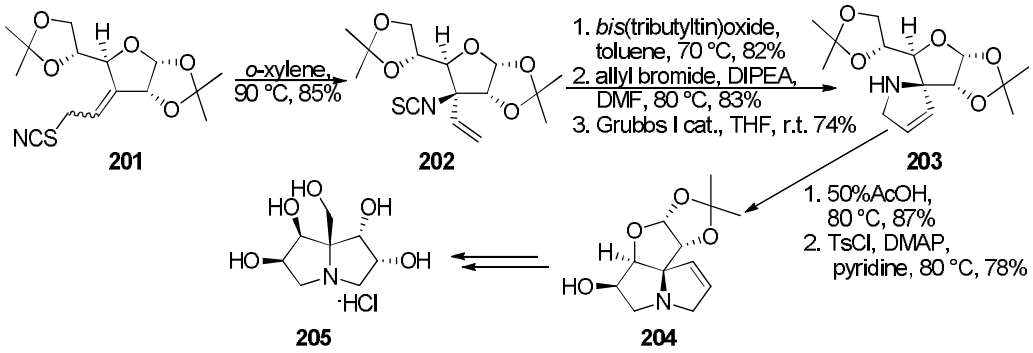
RCM construction of pyrrolidine ring, together with further intramolecular alkylation of nitrogen, was used by Gonda et. al. to synthesise novel pyrrolizidine iminosugar **205** from isothiocyanate **202** bearing quaternary stereogenic centre (Scheme 50).[56a] The latter was previously obtained by [3,3]-sigmatropic rearrangement of sugar derived allylic thiocyanate **201**.[56b]

Epimeric indolizidines **210** were synthesised by Langlois et. al. (Scheme 51).[57] The quaternary chiral centre was formed by stereoselective addition of allyltrimethylsilane to **206**. Hydrolysis and further

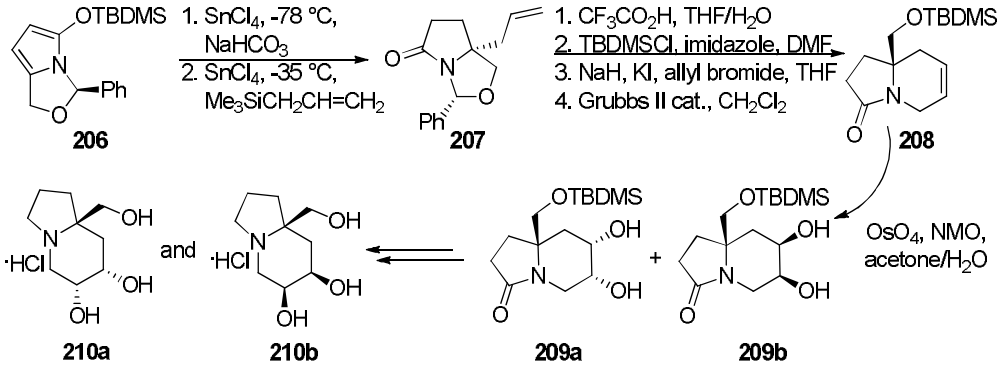
functionalisation of aminal **207** gave chiral product **208**, that was oxidised to the mixture of diastereomeric indolizidinones **209**, that were separated by chromatography. Subsequent steps including reduction and deprotection led to final products **210a** and **210b**.



Scheme 49. Synthesis of 5-azaspiro[3.4]octane based iminosugars.



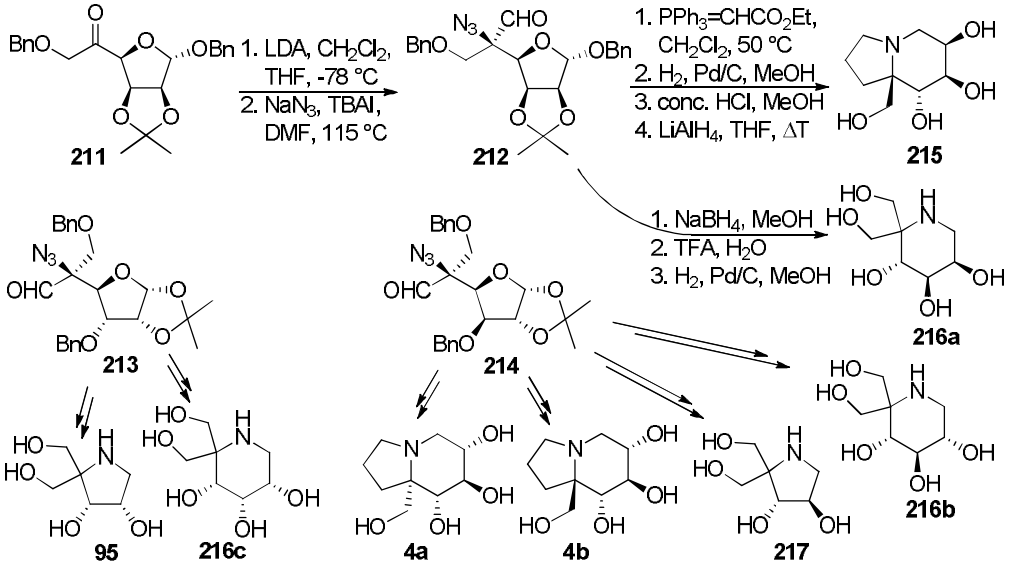
Scheme 50. Synthesis of quaternary pyrrolizidine iminosugar **205**.



Scheme 51. Synthesis of quaternary indolizidines.

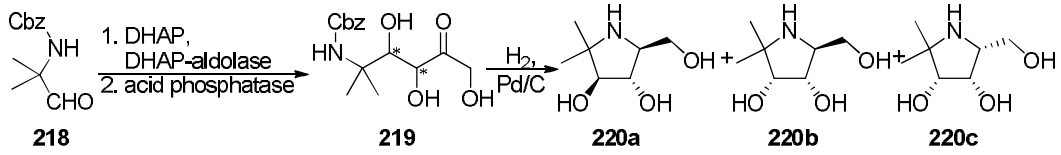
4.3. Reductive aminocyclization

Synthesis of indolizidine, piperidne and pyrrolidine iminosugars bearing hydroxymethyl substituents at quaternary centre was designed by Dhavale et. al. (Scheme 52).[58] Key substrates, azidoaldehydes **212-214** with quaternary stereogenic centre were obtained from carbohydrate-derived ketones such as **211** (for azidoaldehyde **212**) by addition of dichloromethyllithium 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.[3] Synthesis of racemic pyrrolizidine **95** was also reported by Schieweck and Altenbach.[31]



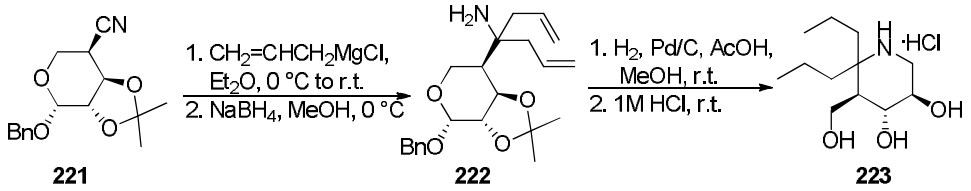
Scheme 52. Synthesis of iminosugars **4**, **95**, **215-217** by reductive aminocyclization.

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).[59] 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.



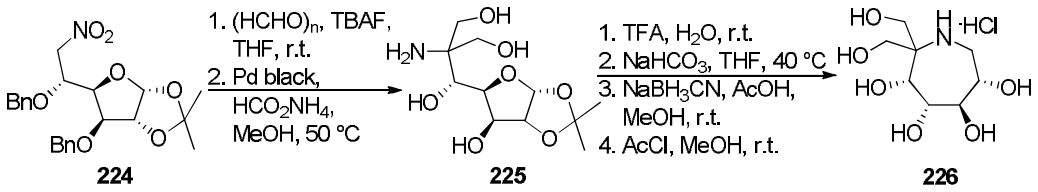
Scheme 53. Reductive aminocyclization of aldol **219**.

Isofagomine derivative **223** was synthesised by Withers et. al. from L-xylose derived nitrile **221** (Scheme 54).[60] Quaternary centre was formed by double addition of Grignard reagent affording amine **222**. Subsequent reductive aminocyclization and deprotection afforded the targeted iminosugar **223**.



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

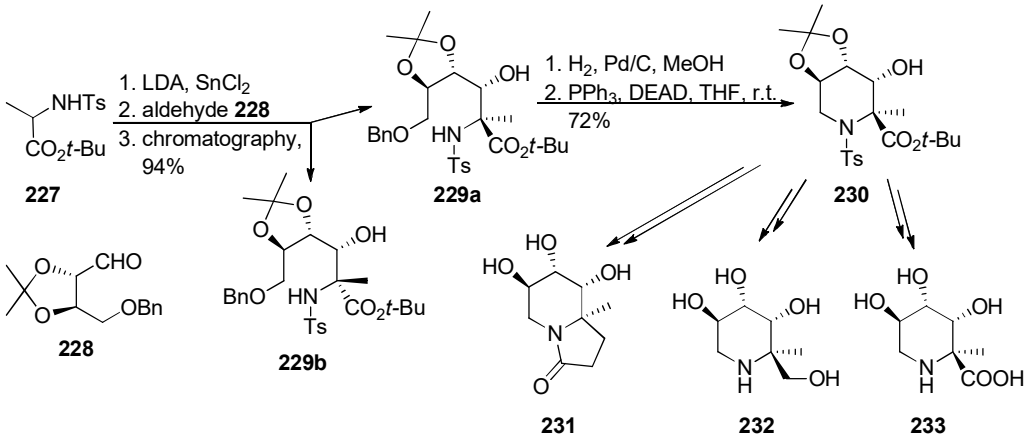
Reductive amination was used by Estévez et. al. to synthesise azepane derived iminosugar **226** (Scheme 55).[61] Amine **225** was obtained by double Henry reaction of sugar nitrocompound **224** followed by catalytic reduction. Deprotection of acetonide in **225** and reductive amination gave product **226**.



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

4.4. Intramolecular alkylation of amines

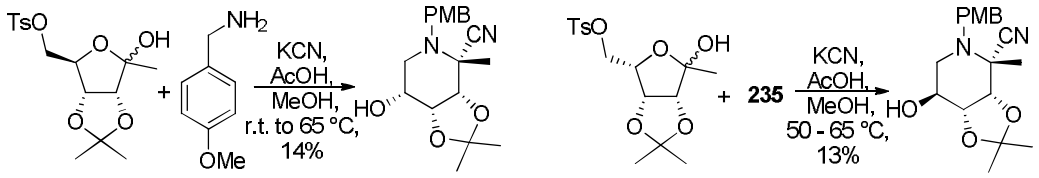
Hydroxylated pipecolic acids and respective hydroxymethyl piperidines as well as related indolizidines were synthesised from *N*-tosyl alanine ester **227** and protected D- or L-treose as reported by Kazmaier et. al. (Scheme 56).[62]



Scheme 56. Utilization of intramolecular Mitsunobu reaction in the synthesis of iminosugars.

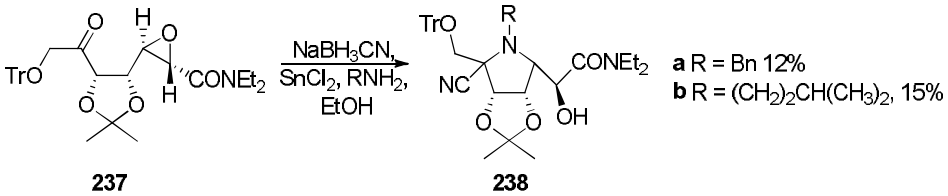
First, aldol reaction of enolate generated form **227** with aldehyde **228** afforded mixture of adducts **229a** and **229b** in 78:22 diastereomeric ratio if excess (2.5 equiv.) of $SnCl_2$ was used. Then, after chomatograpic separation, pure isomers of **229** were submitted for hydrolytic cleavage of benzyl ether followed by Mitsunobu reaction that resulted in formation of protected pipecolic acid as shown for the main isomer **229a**. Further transformations allowed to synthesise indolizidine **231** piperidine **232** and pipecolic 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).[63] 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**.

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).[64]

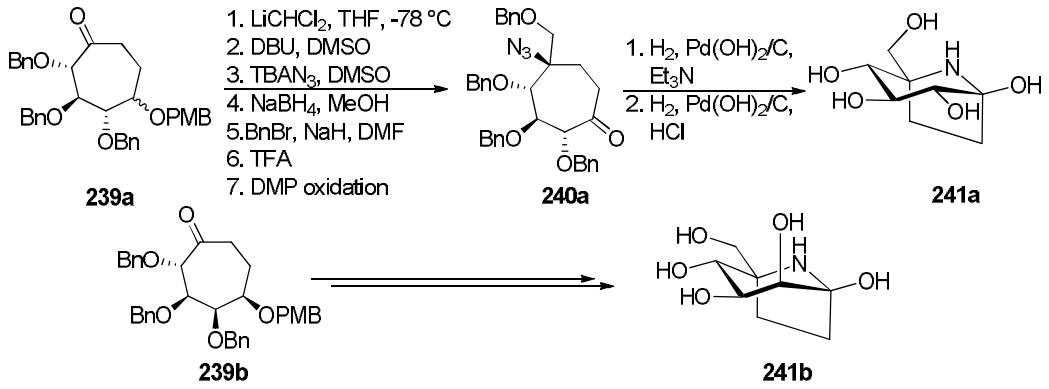


Scheme 58. Formation of nitrile **238** upon reductive amination with $NaBH_3CN$.

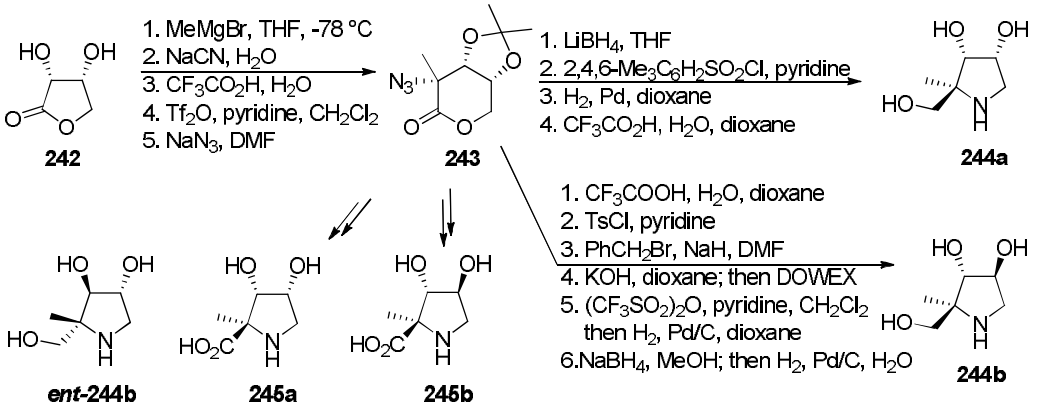
Reduction of azide precursors **240** followed by spontaneous intramolecular formation of stable aminals were utilized by Jensen et. al. to obtain bridged bicyclic imnosugars **241** named nojiristegines as they merge structural motifs of nojirimicin and calystegines (Scheme 59).[65] Formation of quaternary centre was realised by the same method as described by Dhavale et. al. for **212-214**.[58] 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).[66] 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 acetonide 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**.



Scheme 59. Synthesis of nojiristegines **241**.

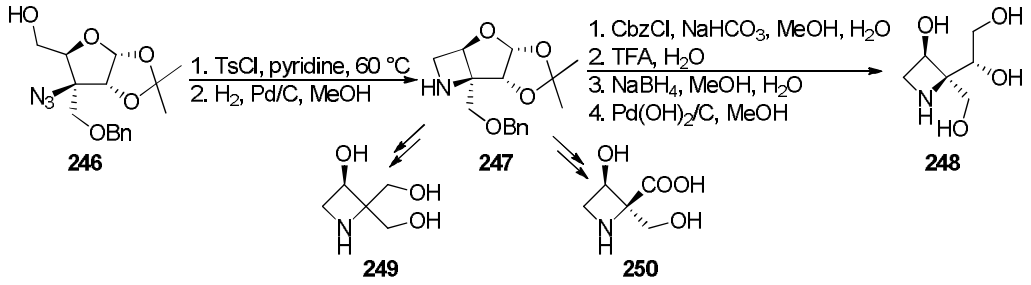


Scheme 60. Synthesis of pyrrolidines **244** and **245**.

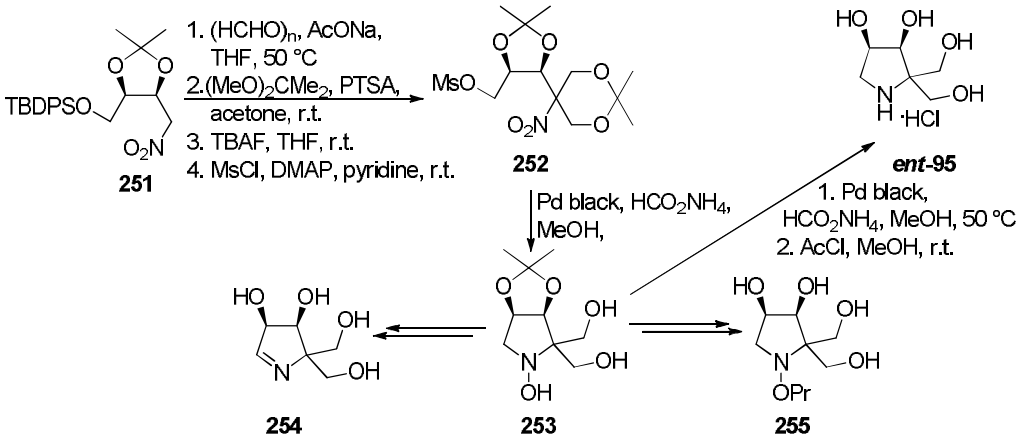
Another sugar azide precursor **246** was utilized by Dhavale et. al. for the synthesis of azetidine iminosugars **248**-**250** (Scheme 61).[67] Tosylation of hydroxyl group followed by the azide reduction gave intermediate **247** with furanose fused azetidine ring as a result of spontaneous cyclization. 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),[68] 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 azetidine iminosugars **248**-**250**.



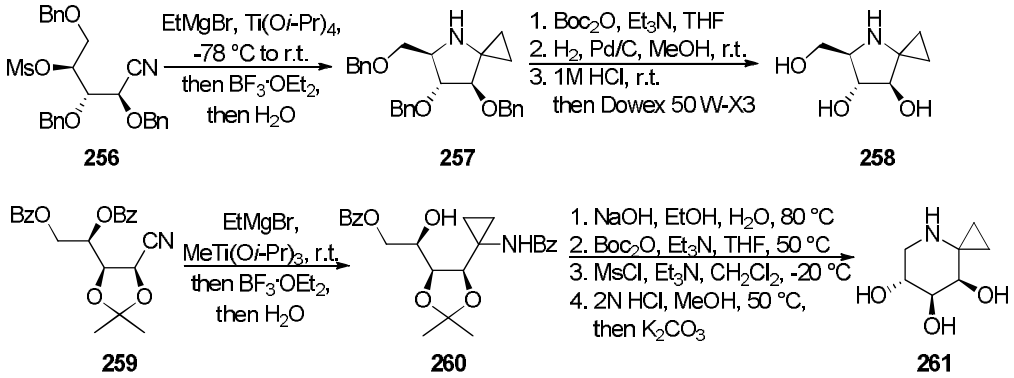
Scheme 62. Synthesis of pyrrolidines *ent*-**95**, **254**, **255**.

Series of spirocyclopropyl pyrrolidines **258** and piperidines **261** were obtained from various aldoses by Behr et. al. (Scheme 63).[69] Key reactions were titanium mediated cyclopropanation of protected nitriles **256** and **259** followed by intramolecular substitution of mesylates 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.

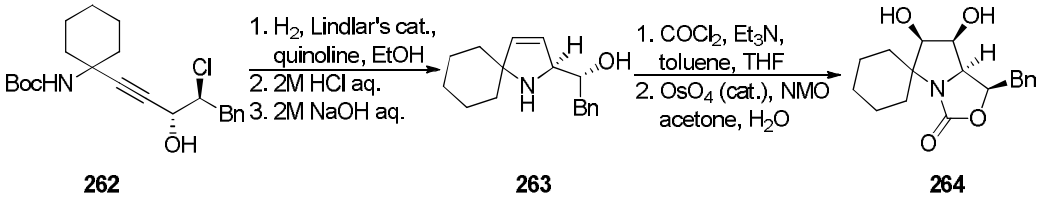
Synthesis of another spiro derivative **264** was reported by Britton et. al. (Scheme 64).[70] Thus, chlorohydrin **262** upon catalytic reduction and alkalization formed dihydropyrrole derivative **263** via presumptive epoxide. Reaction of **263** with phosgene and subsequent dihydroxylation afforded iminosugar product **264**.

Yet another spirocyclopropyl pyrrolidine **268** was obtained by Chen and Pinto using the intramolecular alkylation approach (Scheme 65).[71] Quaternary stereogenic centre was achieved by aldol reaction and subsequent transformation of the aldol **265** to N-Cbz protected amine **266** through Curtius rearrangement.

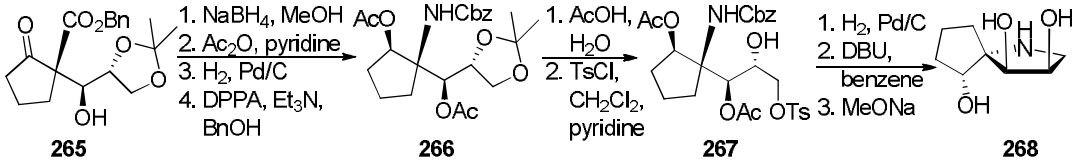
Deprotection of acetonide in compound **266** followed by tosylation led to intermediate **267**, which reductive Cbz cleavage afforded, after complete deprotection, spiro-iminosugar **268**.



Scheme 63. Synthesis of spiro iminosugars **258** and **261**.

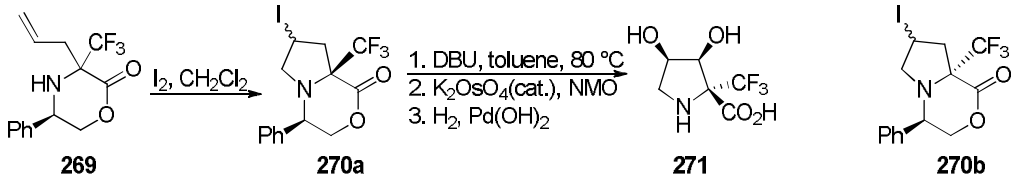


Scheme 64. Synthesis of iminosugar derivative **264**.



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).[72] Enantiomer of the final 2-(trifluoromethyl)proline ***ent*-271** could be obtained from the diastereomeric iodocompound **270b** with opposite configuration of trifluoromethyl group.

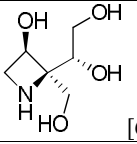
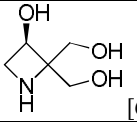
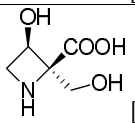
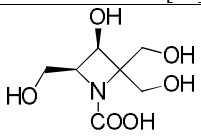
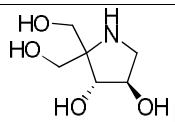
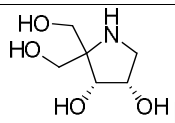
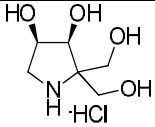
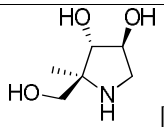


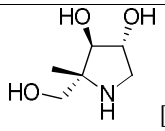
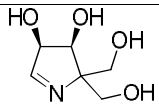
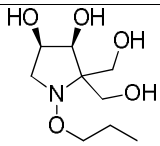
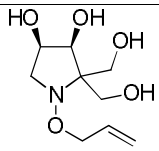
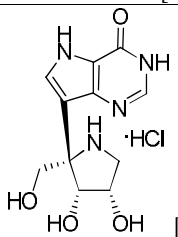
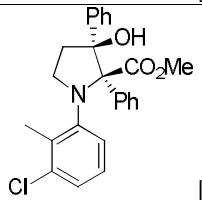
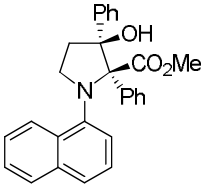
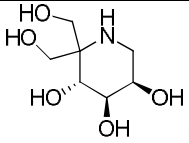
Scheme 66. Synthesis of trifluoromethyl substituted proline **271**.

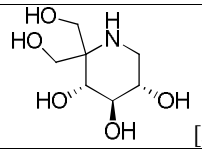
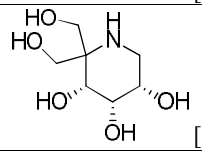
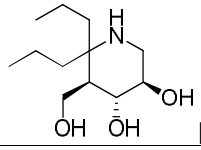
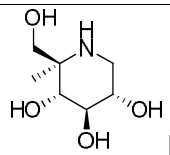
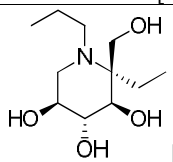
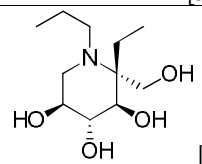
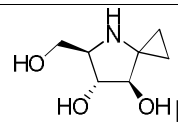
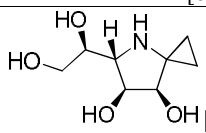
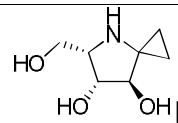
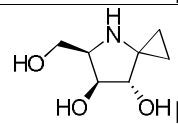
5. Biological activity

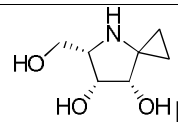
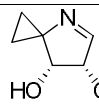
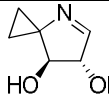
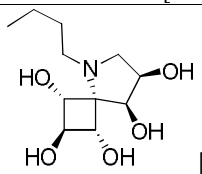
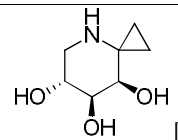
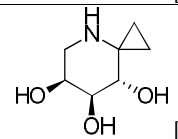
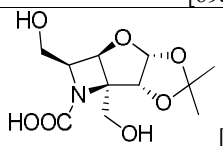
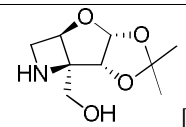
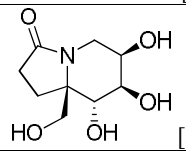
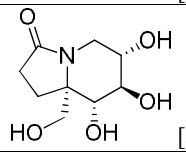
Although in many cases the synthesis of quaternary iminosugars itself was a challenge as with other iminosugars an overriding objective of their obtaining is the search for biologically active compounds. Study of enzyme inhibition is the basic test for assessing the biological activity of iminosugars. 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.

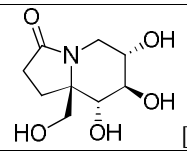
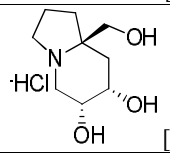
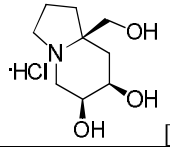
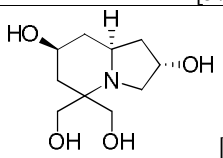
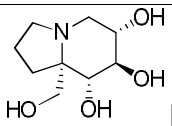
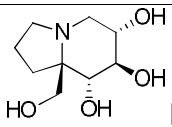
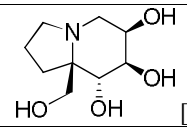
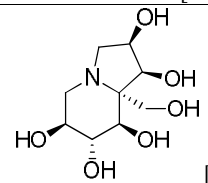
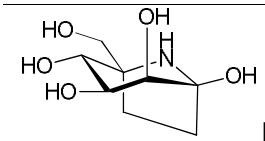
Table 1. Results of enzyme inhibition tests for quaternary iminosugars covered by this review.

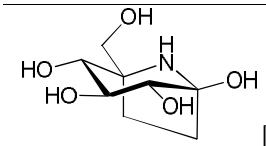
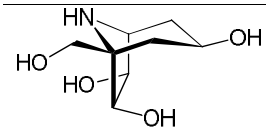
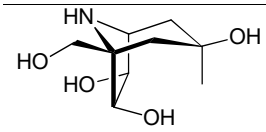
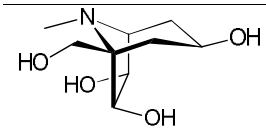
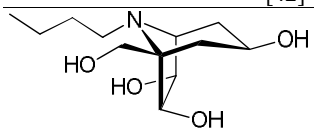
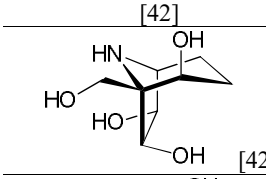
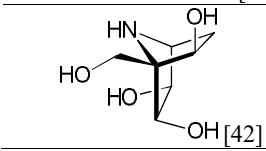
Structure [ref.]	Enzyme inhibition
 [67]	*Aspergillus niger* amyloglucosidase IC_{50} 522μM; K_i 421μM
 [67]	*Aspergillus niger* amyloglucosidase IC_{50} 415μM; K_i 322μM
 [67]	*Aspergillus niger* amyloglucosidase IC_{50} 201μM; K_i 145μM Coffee bean α-galactosidase IC_{50} 103μM; K_i 89μM
 [67]	*Aspergillus niger* amyloglucosidase IC_{50} 1.5μM; K_i 0.8μM
 [58b]	Rice α-glucosidase IC_{50} 0.028μM; K_i 0.083μM Baker's yeast α-glucosidase IC_{50} 128μM; K_i 25μM *Geobacillus sp.* α-galactosidase IC_{50} 14μM; K_i 40μM
 [58b]	Rice α-glucosidase IC_{50} 5μM; K_i 4μM
 [68]	*Bacillus* α-glucosidase 52% inhibition at 0.8mM Coffee bean α-galactosidase 76% inhibition at 0.8mM Bovine liver β-galactosidase 3% inhibition at 0.8mM Bovine kidney α-fucosidase 35% inhibition at 0.8mM Jack bean α-*N*-acetylglucosaminidase 6% inhibition at 0.8mM
 [66a]	Rice α-glucosidase IC_{50} 5.8μM Rat intestinal maltase IC_{50} 2.4μM Rat intestinal isomaltase IC_{50} 5.1μM Rat intestinal sucrase IC_{50} 0.66μM

 [66a]	Rice α-glucosidase IC_{50} 7.1μM Yeast α-glucosidase IC_{50} 1.9μM Rat intestinal maltase IC_{50} 0.74μM Rat intestinal isomaltase IC_{50} 3.4μM Rat intestinal sucrase IC_{50} 0.41μM Rat instestinal trehalase IC_{50} 38μM
 [68]	Baker's yeast α-glucosidase 3% inhibition at 0.8mM *Bacillus* α-glucosidase 21% inhibition at 0.8mM Coffee bean α-galactosidase 10% inhibition at 0.8mM Bovine liver β-galactosidase 80% inhibition at 0.8mM *Penicillium* naringinase 22% inhibition at 0.8mM
 [68]	*Bacillus* α-glucosidase 15% inhibition at 0.8mM Coffee bean α-galactosidase 48% inhibition at 0.8mM Bovine liver β-galactosidase 40% inhibition at 0.8mM *Penicillium* naringinase 7% inhibition at 0.8mM
 [68]	Baker's yeast α-glucosidase 3% inhibition at 0.8mM *Bacillus* α-glucosidase 5% inhibition at 0.8mM Bovine liver β-galactosidase 12% inhibition at 0.8mM Bovine kidney α-*N*-acetylglucosaminidase 5% inhibition at 0.8mM
 [5]	Purine nucleoside phosphorylase IC_{50} 0.1-0.3μM
 [35a]	Protein tyrosine phosphatase 1B IC_{50} 9.03μM
 [35a]	Protein tyrosine phosphatase 1B IC_{50} 5.97μM
 [58b]	Rice α-glucosidase IC_{50} 4μM; K_i 3μM *Geobacillus sp.* α-galactosidase IC_{50} 22μM; K_i 20μM

 [58b]	Rice α-glucosidase IC_{50} 0.032μM; K_i 0.066μM Baker's yeast α-glucosidase IC_{50} 97μM; K_i 20μM *Geobacillus sp.* α-galactosidase IC_{50} 15μM; K_i 13μM
 [58b]	Rice α-glucosidase IC_{50} 0.052μM; K_i 0.083μM Bovine liver β-galactosidase IC_{50} 40μM; K_i 25μM *Geobacillus sp.* α-galactosidase IC_{50} 19μM; K_i 34μM
 [60]	Human glucocerebrosidase K_i 0.6μM
 [10a]	Human α-glucosidase IC_{50} 1μM
 [3]	Baker's yeast α-glucosidase 96% inhibition at 1mM Rice α-glucosidase 95% inhibition at 1mM *Aspergillus orizae* β-galactosidase 6% inhibition at 1mM *Helix pomatia* β-mannosidase 4% inhibition at 1mM
 [3]	Baker's yeast α-glucosidase 95% inhibition at 1mM Rice α-glucosidase IC_{50} 2.3μM Almond β-glucosidase 47% inhibition at 1mM *Aspergillus orizae* β-galactosidase 7% inhibition at 1mM Jack bean α-mannosidase 6% inhibition at 1mM
 [69c]	Bovine kidney α-L-fucosidase 50% inhibition at 1mM Bovine liver β-galactosidase 73% inhibition at 1mM *Aspergillus niger a*mylоglucosidase IC_{50} 100μM *Rhizopus mold a*mylоglucosidase IC_{50} 47μM
 [69c]	Bovine kidney α-L-fucosidase IC_{50} 13μM; K_i 1.6μM Bovine liver β-galactosidase 9% inhibition at 1mM *Aspergillus orizae* β-galactosidase 16% inhibition at 1mM
 [69c]	Bovine kidney α-L-fucosidase 49% inhibition at 1mM Bovine liver β-galactosidase 24% inhibition at 1mM
 [69c]	Bovine kidney α-L-fucosidase 41% inhibition at 1mM Bovine liver β-galactosidase 65% inhibition at 1mM Rice α-glucosidase 11% inhibition at 1mM

 [69c]	Bovine kidney α-L-fucosidase 55% inhibition at 1mM Bovine liver β-galactosidase 49% inhibition at 1mM Rice α-glucosidase 45% inhibition at 1mM Almond β-glucosidase 30% inhibition at 1mM
 [69a]	Bovine kidney α-L-fucosidase 76% inhibition at 1mM *Penicillium decumbens* α-L-rhamnosidase IC_{50} 57μM
 [69a]	Bovine kidney α-L-fucosidase 19% inhibition at 1mM *Penicillium decumbens* α-L-rhamnosidase 72% inhibition at 1mM
 [55a]	β-Glucocerebrosidase IC_{50} >100μM
 [69a]	Bovine kidney α-L-fucosidase IC_{50} 18μM
 [69a]	*Penicillium decumbens* α-L-rhamnosidase 72% inhibition at 1mM
 [67]	*Aspergillus niger* amyloglucosidase IC_{50} 2.8μM; K_i 1.5μM Coffee bean α-galactosidase IC_{50} 45μM; K_i 35μM Rat intestinal β-glucosidase IC_{50} 384μM; K_i 254μM
 [67]	*Aspergillus niger* amyloglucosidase IC_{50} 10.5μM; K_i 5.3μM
 [58a]	Bovine liver β-glucosidase IC_{50} 46μM; K_i 24μM *Aspergillus niger* α-galactosidase IC_{50} 630μM; K_i 68μM Bovine liver β-galactosidase IC_{50} 7.2μM; K_i 3.1μM Jack bean α-mannosidase IC_{50} 1.3μM; K_i 0.9μM
 [58a]	Bovine liver β-glucosidase IC_{50} 22μM; K_i 11μM *Aspergillus niger* α-galactosidase IC_{50} 0.42μM; K_i 0.33μM Bovine liver β-galactosidase IC_{50} 0.8μM; K_i 0.2μM Jack bean α-mannosidase IC_{50} 0.056μM; K_i 0.035μM

 [58a]	Bovine liver β-glucosidase IC_{50} 39μM; K_i 19μM *Aspergillus niger* α-galactosidase IC_{50} 0.130μM; K_i 14μM Bovine liver β-galactosidase IC_{50} 5.6μM; K_i 2.4μM Jack bean α-mannosidase IC_{50} 0.075μM; K_i 0.043μM
 [57]	Baker's yeast α-glucosidase IC_{50} 0.57mM *Escherichia coli* β-galactosidase IC_{50} 0.56mM
 [57]	Baker's yeast α-glucosidase IC_{50} 0.59mM
 [50a]	*Helix pomatia* β-mannosidase 37% inhibition at 1mM
 [3], [58a]	Baker's yeast α-glucosidase 80% inhibition at 1mM [3] Rice α-glucosidase IC_{50} 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 IC_{50} 116μM; K_i 95μM [58a] *Aspergillus niger* α-galactosidase IC_{50} 0.13μM; K_i 0.09μM [58a] Bovine liver β-galactosidase IC_{50} 3.6μM; K_i 1.5μM [58a]
 [3], [58a]	Baker's yeast α-glucosidase 82% inhibition at 1mM [3] Rice α-glucosidase IC_{50} 0.052μM; K_i 0.031μM [3] *Aspergillus niger* α-rhamnosidase 53% inhibition at 1mM [3] Bovine liver β-glucosidase IC_{50} 202μM; K_i 102μM [58a] *Aspergillus niger* α-galactosidase IC_{50} 0.24μM; K_i 0.54μM [58a] Bovine liver β-galactosidase IC_{50} 2.3μM; K_i 1μM [58a]
 [58a]	Bovine liver β-glucosidase IC_{50} 156μM; K_i 86μM *Aspergillus niger* α-galactosidase IC_{50} 0.63μM; K_i 0.44μM Bovine liver β-galactosidase IC_{50} 1.2μM; K_i 0.5μM
 [3]	Baker's yeast α-glucosidase 71% inhibition at 1mM Rice α-glucosidase IC_{50} 1.5μM Almond β-glucosidase 20% inhibition at 1mM *Aspergillus orizae* β-galactosidase 19% inhibition at 1mM Jack beans α-mannosidase 10% inhibition at 1mM *Helix pomatia* β-mannosidase 10% inhibition at 1mM *Aspergillus niger* α-rhamnosidase 90% inhibition at 1mM
 [65]	*Escherichia coli* β-glucuronidase IC_{50} 810μM Porcine kidney α,α-trehalase IC_{50} 420μM

 [65]	Rice α-glucosidase IC_{50} 27μM Rat intestinal maltase IC_{50} 181μM Rat intestinal sucrase IC_{50} 14μM Human lysosome alglucosidase alfa IC_{50} 30μM Human lysosome β-glucocerebrosidase IC_{50} 440μM *Escherichia coli* β-glucuronidase IC_{50} 620μM
 [42]	Rat intestinal maltase IC_{50} 0.15μM Rat intestinal isomaltase IC_{50} 2.8μM Rat intestinal sucrase IC_{50} 0.18μM
 [42]	Rat intestinal maltase IC_{50} 5.1μM Rat intestinal isomaltase IC_{50} 104μM Rat intestinal sucrase IC_{50} 11μM
 [42]	Rat intestinal maltase IC_{50} 33μM Rat intestinal isomaltase IC_{50} 254μM Rat intestinal sucrase IC_{50} 6.6μM
 [42]	Rat intestinal maltase IC_{50} 4.8μM Rat intestinal isomaltase IC_{50} 66μM Rat intestinal sucrase IC_{50} 4.1μM
 [42]	Rat intestinal maltase IC_{50} 1.8μM Rat intestinal isomaltase IC_{50} 4.0μM Rat intestinal sucrase IC_{50} 0.36μM
 [42]	Rat intestinal maltase IC_{50} 66μM Rat intestinal isomaltase IC_{50} 93μM Rat intestinal sucrase IC_{50} 18μM

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

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