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Conformationally constrained fused bicyclic iminosugars: synthetic challenges and opportunities

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Dedicated to Prof. Stephen Hanessian in recognition of his incomparable achievements in the field of organic chemistry on the occasion of his 84th anniversary

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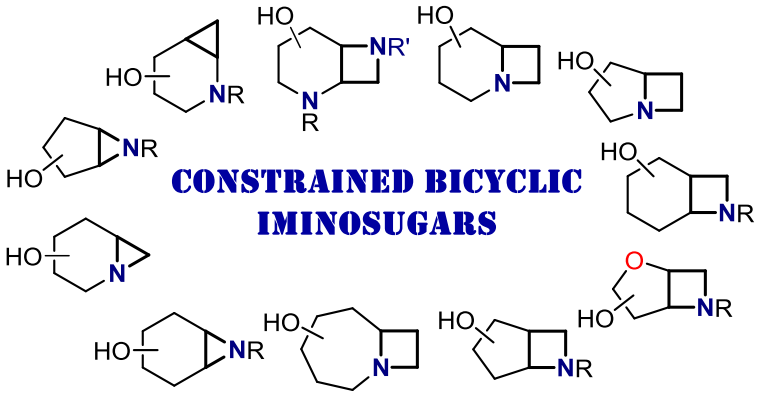
Abstract

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



Keywords: Constrained iminosugars, fused azetidines, aziridines, cyclopropanes, glycosidase inhibitors

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1. Introduction

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

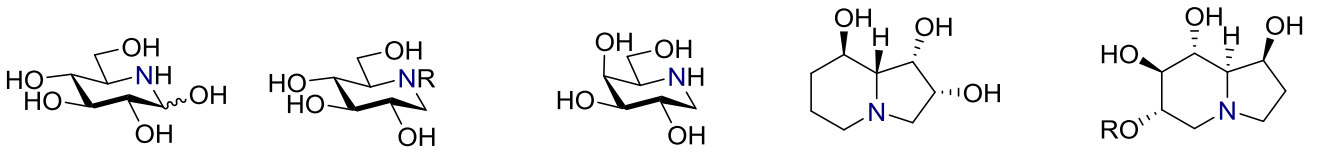

Figure 1. Some representative mono- and bicyclic iminosugars.

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However, the ability of iminosugars to strike a wide range of biological targets may be also seen as a threat for the development of drug candidates as illustrated by the pyrrolizidine-containing swainsonine (**5**). Despite its powerful effect on Golgi α-mannosidase II, this naturally-occurring bicyclic iminosugar failed as an anticancer agent in human clinical trials because of unacceptable toxicity.[14] Castanospermine (**6**), a famous indolizidine-containing iminosugar, and its prodrug Celgosivir™ (**7**), have raised many hopes due to their promising antiviral activities.[15] However, Celgosivir™ has yet to make its way to the clinic, with only few reported trials in humans (with modest success).[16] A number of strategies have been deployed to increase iminosugar selectivity and modulate efficacy, the most recent one being the use of multivalent design.[17-19] Another approach to improve receptor specificity is the incorporation of conformational constraints into analogues of biologically active iminosugars. Conformationally constrained compounds with lesser degree of freedom may bind more efficiently to the receptor of the specific biological target.[20,21] In addition to lowering the entropic barrier to complex formation, iminosugars are forced to adopt unusual conformations; the original distributions of hydroxyl groups thus obtained may be highly relevant for receptor recognition purposes. Inspired by two emblematic leads of Nature, swainsonine and castanospermine, chemists have designed fused bicyclic systems incorporating small rings.[22,23] These compounds may indeed be seen as analogues of naturally-occurring pyrrolizidine- and indolizidine-based iminosugars. For some systems, especially the ones incorporating a 3-membered ring, the objective is more to obtain relevant analogues of monocyclic iminosugars such as 1-deoxynojirimycin derivatives by rigidifying their structure. Analogues of the bicyclic natural product cyclophellitol (**8**) that contain an aziridine in place of the epoxide have been also designed (Figure 2). These pseudo iminosugars have been used as selective activity-based glycosidase probes.

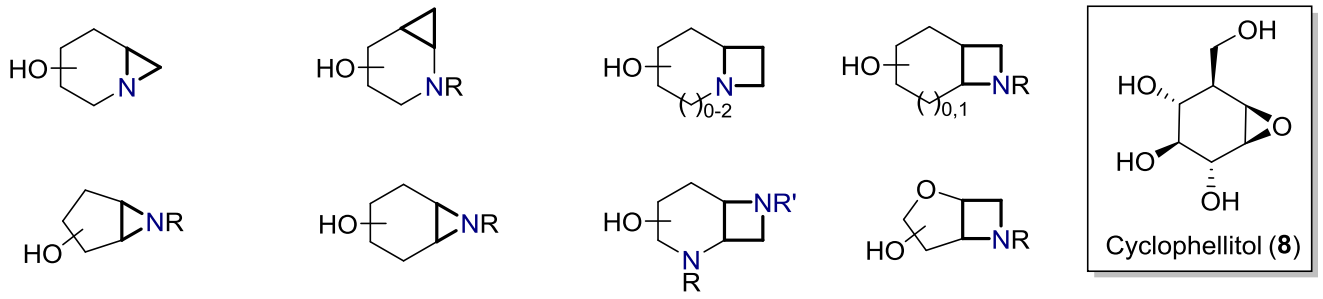

Figure 2. Unusual fused bicyclic iminosugar structures incorporating a small ring. Structure of the natural product cyclophellitol.

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

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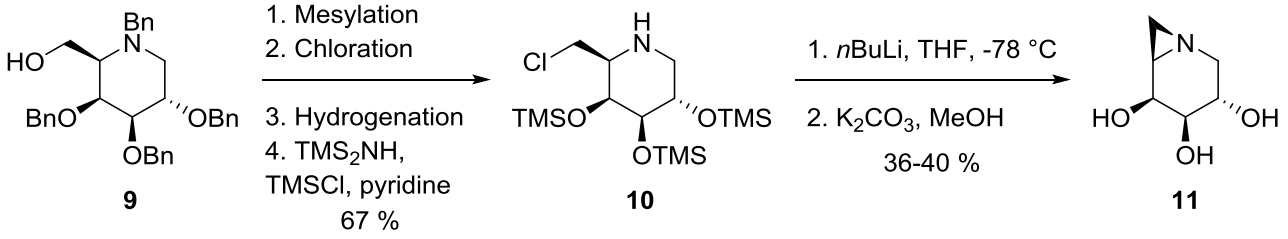
2. Three-membered Ring-containing Iminosugars

2.1 Aziridine-based bicyclic iminosugars

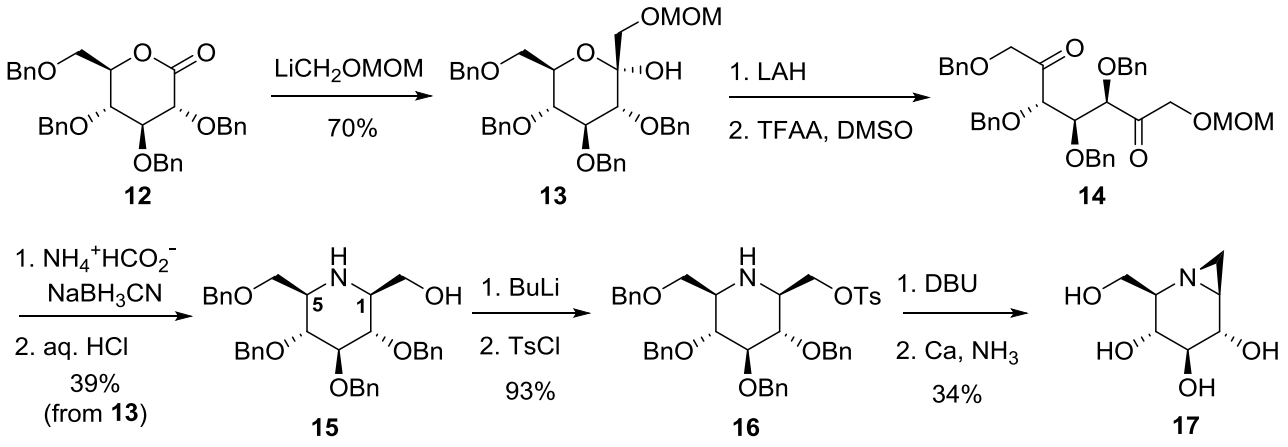
Aziridine-based bicyclic iminosugars have been designed as potential glycosidase inactivators.[24-30] Indeed, aziridine may react with carboxylate residues involved in most mechanisms of enzyme-assisted glycoside hydrolysis.[24,25,31] In this context, Ganem *et al.* reported the first synthesis of iminosugars incorporating an aziridine ring (Scheme 1).[25] Compound **9**[32] was converted to intermediate **10** *via* conversion of the primary alcohol to a leaving group and deprotection/protection steps. Deprotonation of the endocyclic amine followed by cyclisation afforded after deprotection desired aziridine **11** in moderate yield. Compound **11**, which may be seen as a constrained analog of Galafold™ (**4**) has been evaluated to a panel of four glycosidases (green coffee bean α-galactosidase, yeast α-glucosidase, Jack bean α-mannosidase and bovine β-galactosidase). Iminosugar **11** is a selective irreversible inhibitor of α-galactosidase from green coffee beans.[25] Following the same sequence, the enantiomer of compound **11** has been obtained and evaluated as inhibitor of α-L-fucosidase.[26]



9 **10** **11**

Scheme 1. Synthesis of aziridinyl iminosugar **11.**

Using the same strategy, several aziridine-based bicyclic iminosugars have been synthesized.[27-30,33] Martin *et al*. reported the synthesis of iminosugar-derived aziridine **17** (Scheme 2).[27] The required precursor **15** was obtained in five steps from glucolactone **12**. Addition of (methoxymethoxy)methylithium followed by reduction and oxidation of the resulting diol provided diketone **14**. Double reductive amination which generated two stereocenters (C1 and C5) in a highly stereocontrolled manner provided **15** as a single diastereomer after deprotection of the MOM group. Selective tosylation of the primary alcohol function led to **16** which was converted to aziridine **17** after basic treatment and deprotection of benzyl groups. It is noteworthy that the harsh conditions of the debenzylation step (Ca, NH_3) did not affect the aziridine group although product **17** and similar compounds are prone to be quite unstable.[26,27]



12 **13** **14** **15** **16** **17**

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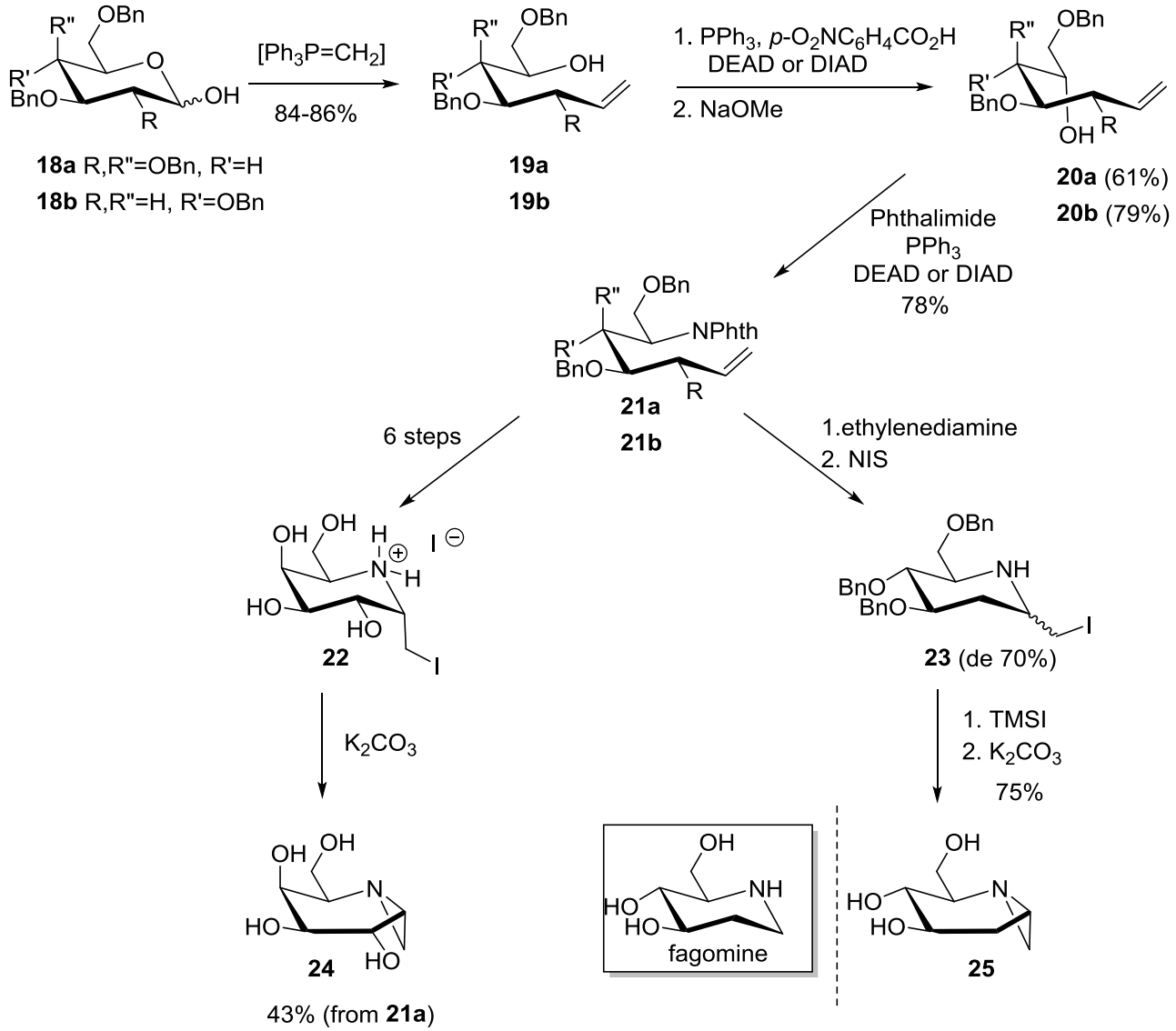
Scheme 2. Preparation of aziridinyl iminosugar **17.**

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



Scheme 3. Synthesis of aziridinyl iminosugars **24** and **25.**

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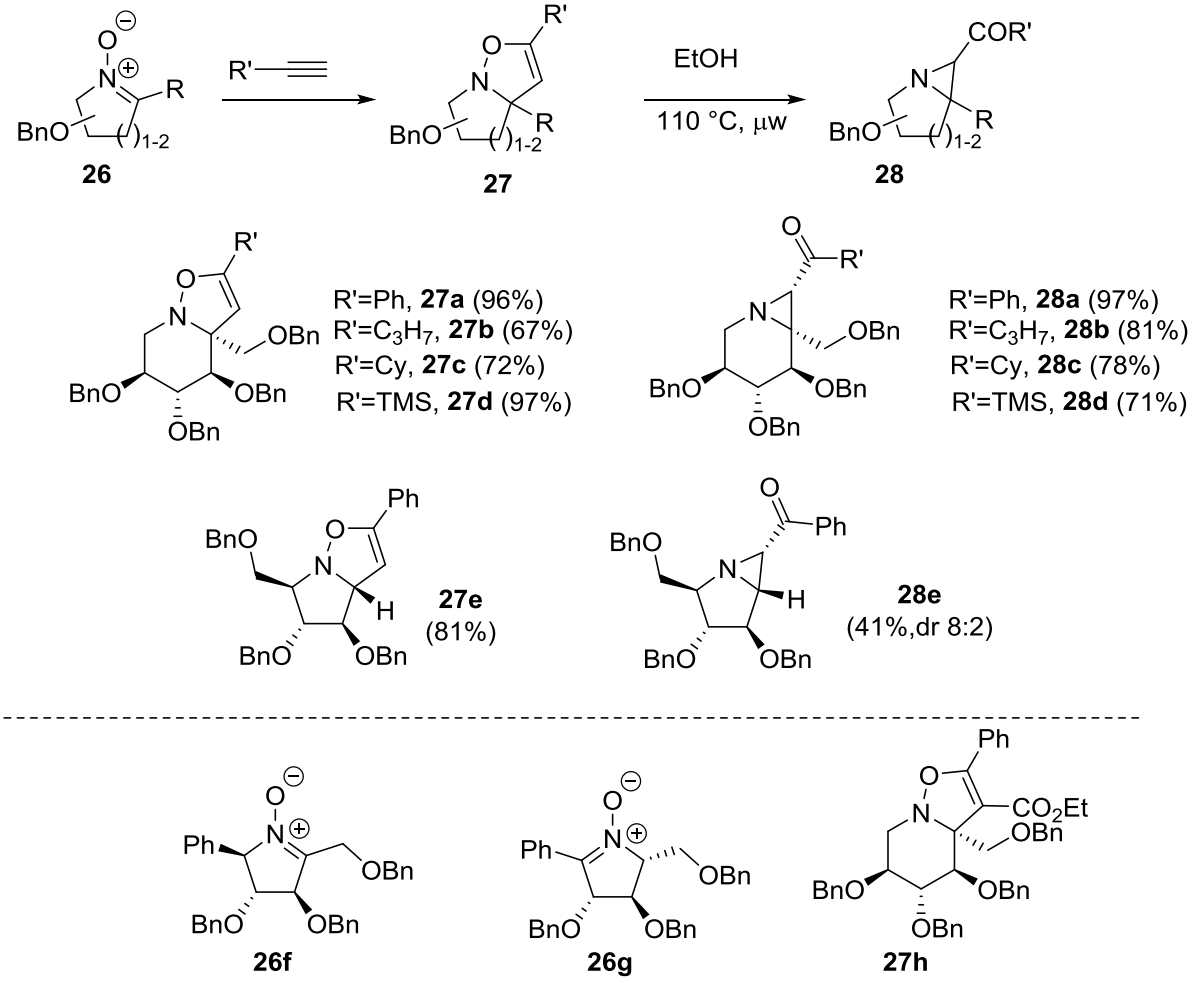
Py *et al.* reported recently an original strategy for the synthesis of aziridinyl iminosugars (Scheme 4).[34] The strategy is based on cycloaddition of cyclic nitrones with alkynes followed by highly diastereoselective Baldwin rearrangement.[35] Treatment of several nitrones **26** with various alkynes afforded isoxazolines **27** which were converted to acylaziridines **28** by heating.[34] Some representative examples are shown in Scheme 4. The scope of the synthetic approach described is relatively broad. However, disubstituted ketonitrones **26f** and **26g** failed to react with phenylacetylene. Furthermore, Baldwin rearrangement of compound **27h** which is obtained in good yield from the corresponding nitrone led to a complex mixture of products.



Scheme 4. Synthesis of acylaziridines **28** *via* Baldwin rearrangement.

Aziridines **28a-c** were converted into deprotected bicyclic iminosugars **30a-c** after treatment with $NaBH_4$ and Birch reduction (Scheme 5).[34] Compounds **30b-c** were obtained in good yields after a 2-step sequence while Birch reduction was unsuccessful with aziridine **29a**. Birch conditions were not applied to aziridines **28** as these compounds are prone to ring-opening upon treatment with single-electron reducing agents.[34]

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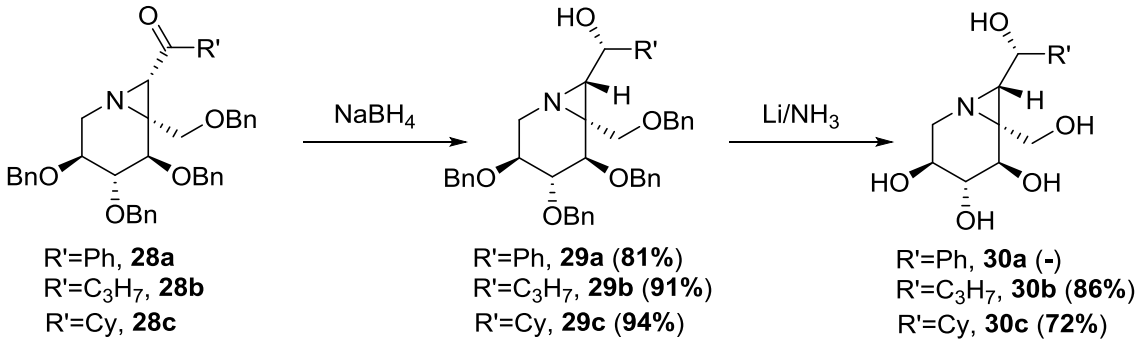
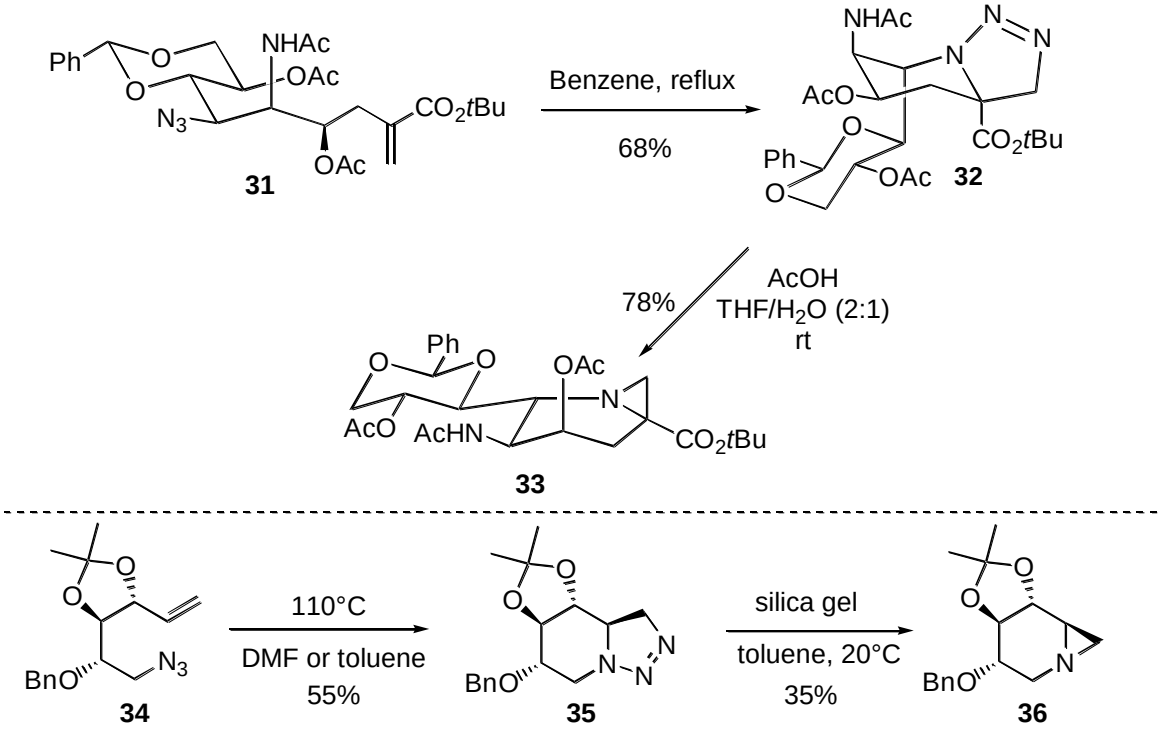


Scheme 5. Synthesis of bicyclic iminosugars **30** from **28**.

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



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

Aza-Diels-Alder reactions using azirines constitute an efficient strategy to rapidly generate 1-azabicyclo[4.1.0] heptene skeletons with an endocyclic double bond used as a masked diol and up to three asymmetric centers. In 2002, the group of Gilchrist reported the rapid *de novo* synthesis of protected iminosugar **42** by Diels-Alder reaction using azirine **39** as the dienophile partner (Scheme 7).[39] Reaction of **39**, generated from 2-azidoacrylate ester **38**, with diene **40** afforded bicyclic iminosugars **41** as a racemic mixture.

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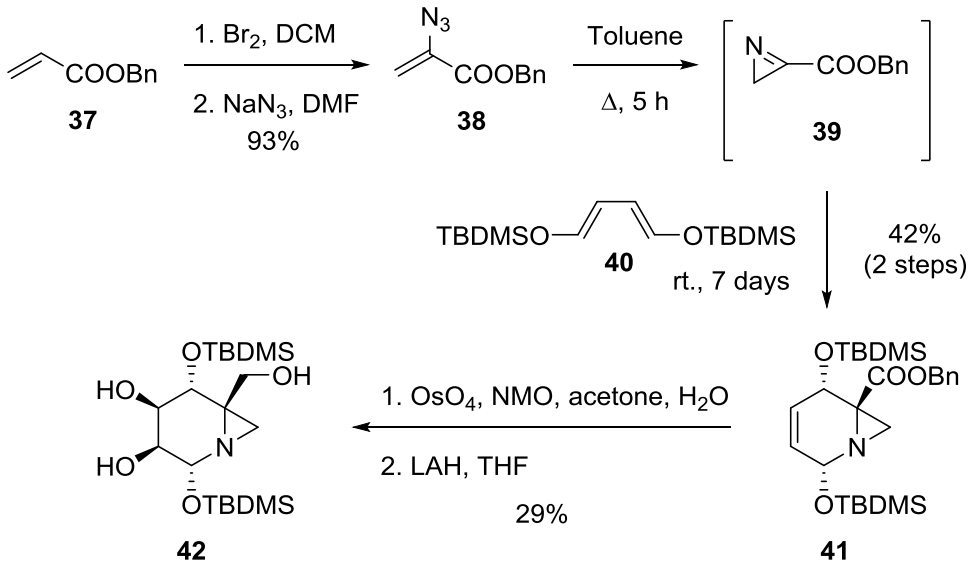
Dihydroxylation under classical osmylation conditions led to the corresponding diol in 93% yield. Finally, the ester group was reduced with LAH to give disilylated aziridine-based bicyclic iminosugar **42**.[39]



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

It is noteworthy that under the same conditions, no dihydroxylation reaction was observed when the TBDMS protecting groups are replaced by acetate functions.[39]

In 2014, the synthesis of an aziridinyl iminosugar by way of enantioselective Diels-Alder cycloaddition was reported (Scheme 8).[40] Diene **43** and dienophile **44** were treated with (*R)*-BINOL in the presence of MeMgBr and Me_2Zn to generate a bimetallic complex of zinc and magnesium tethered to the enantiopure diol ligand. In these conditions, desired aziridine **45a** was obtained as a single enantiomer as confirmed by ^{1}H NMR analysis of the (*S*)-camphanoate derivative of **45a**. In this process, minor product **45b**, which was formed by aziridine ring-opening due to water content in the reaction solvent, was also isolated. Diol **45b** was converted quantitatively to compound **45a** by simple basic treatment using *N*-methylmorpholine. The rather unexpected formation of aziridine **45a** was explained by a hydrogen bond leading to the formation of a *pseudo* six-membered ring (**45b'**). In this rigidified system, the hydroxymethylene group is more prone to nucleophilic attack (Scheme 8).[40] Dihydroxylation of **45a** followed by hydrolysis of the ester group provided the pipecolic acid derivative **47**.

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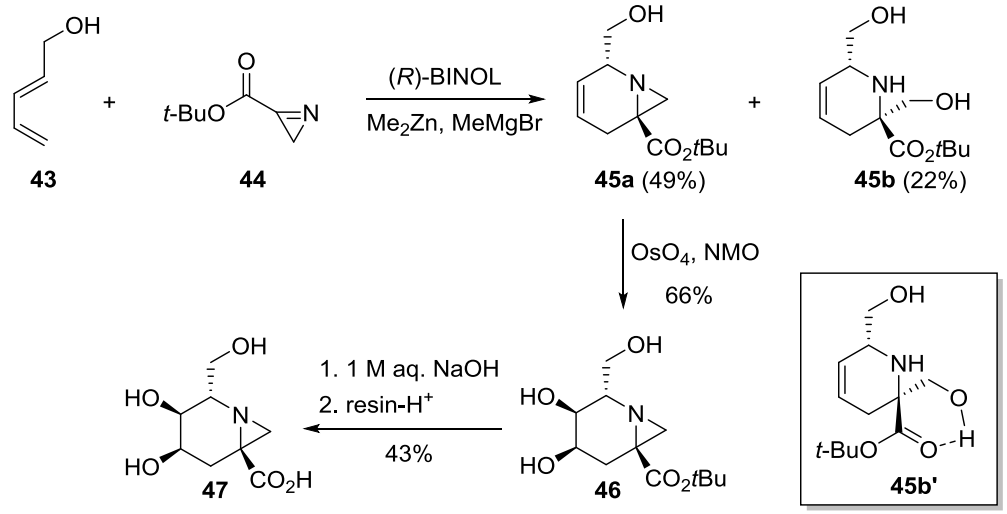

Scheme 8. Synthesis of iminosugar **47** *via* enantioselective Diels-Alder cycloaddition.

2.2 Cyclopropane-based bicyclic systems

The only methodology reported to date for the formation of cyclopropane-based bicyclic iminosugars is the cyclopropanation of the appropriate alkene derivatives.[41-43] Using this methodology, fused iminosugar **51** was prepared in three steps from imino glucal **49** which was synthesized by treatment of **48** with oxalyl chloride (Scheme 9).[41] Cyclopropanation of **49** using diethylzinc and diiodomethane led to compound **50** in 64% yield after deprotection of the Fmoc group. The cyclopropanation step was highly diastereoselective as only one stereoisomer was formed. To explain this stereoselectivity, the authors suggest that glucal **49** adopts a half chair conformation. Then the carbenoid would react in *anti* to the OBn group at C3.[41] For the final synthetic steps, hydrogenation conditions must be finely tuned in order to obtain the desired products. Debenzylation using palladium on carbon in the presence of HCl afforded the desired iminosugar **51**. Interestingly, the cyclopropane was cleaved without concomitant debenzylation when hydrogenation was performed with palladium hydroxide in the absence of HCl. Under these conditions, piperidine **52** was isolated in 79% yield. Hydrogenolysis of the benzyl groups in acidic conditions afforded compound **53**. Iminosugars **51** and **53** were found to display weak inhibitory activity against mannosidase from Jack bean with inhibition values in the mM range.[41]

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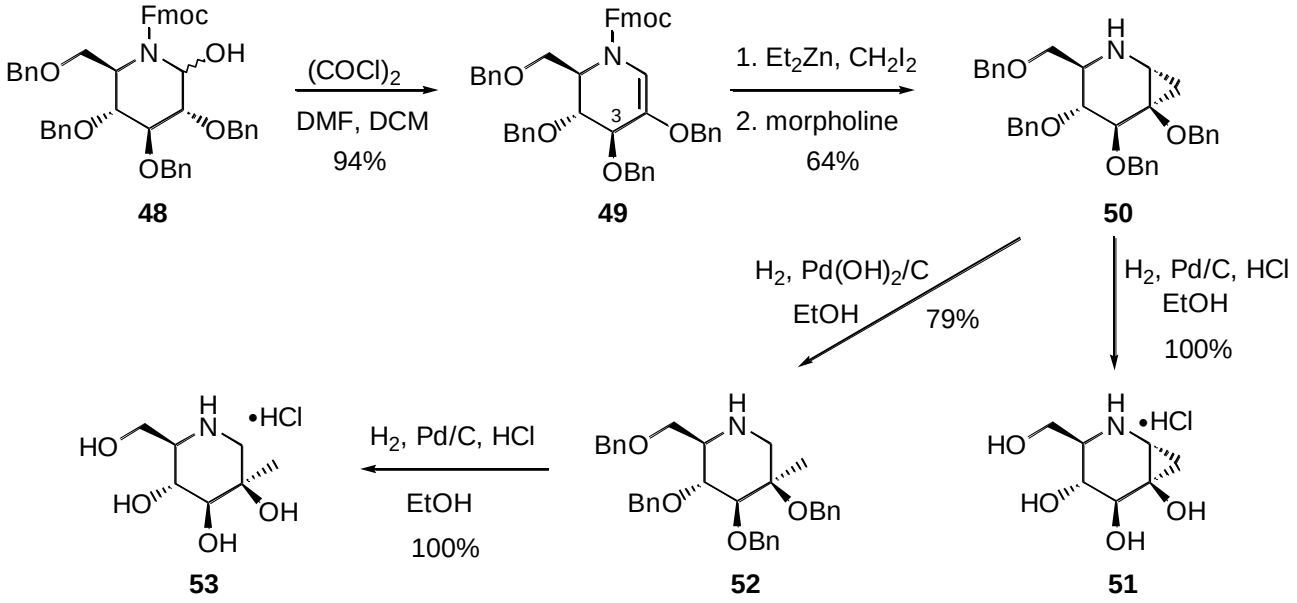
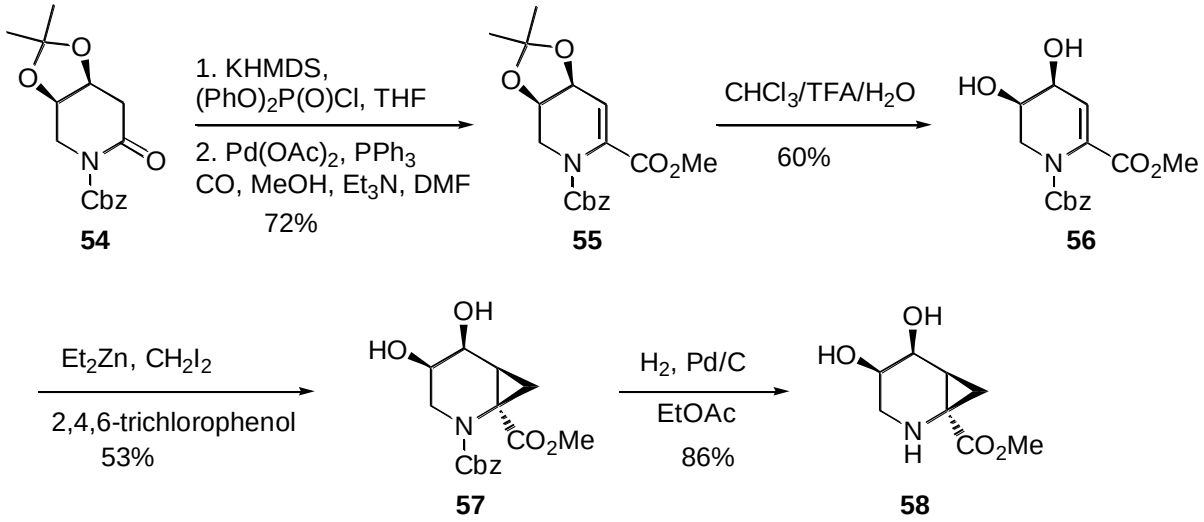


Scheme 9. Synthesis of original iminosugars by way of cyclopropanation of enamine **49.**

In 2014, Ochiato *et al.* reported the synthesis of several cyclopropane-based pipecolic acid analogues.[42] In their strategy, the key step was performed using a zinc carbenoid cyclopropanating reagent. The synthesis began with the conversion of compound **54** into enamine **55** in 2 steps *via* the formation of the corresponding enol phosphate and its carbonylation. Removal of the acetal group was then performed under acidic conditions to afford intermediate **56** in 60% yield. Simmons-Smith cyclopropanation in the presence of diethylzinc, diiodomethane and 2,4,6-trichlorophenol yielded cyclopropane **57** as a single stereoisomer. The stereoselectivity could be explained by the presence of an allylic alcohol in **56** which directs the attack of the carbenoid on the same face. The final deprotection step gave piperidine **58** in good yield (Scheme 10).



Scheme 10. Synthesis of pipecolic acid derivative **58.**

Recently, the synthesis of fused iminosugars based on a 2-azabicyclo[4.1.0]heptane skeleton using a sulfur ylid cyclopropanation as the key step has been reported in the literature.[43] Treatment of enaminone **59** with (2-ethoxy-2oxoethyl)dimethylsulfonium and DBU under microwave heating afforded, after reduction, the

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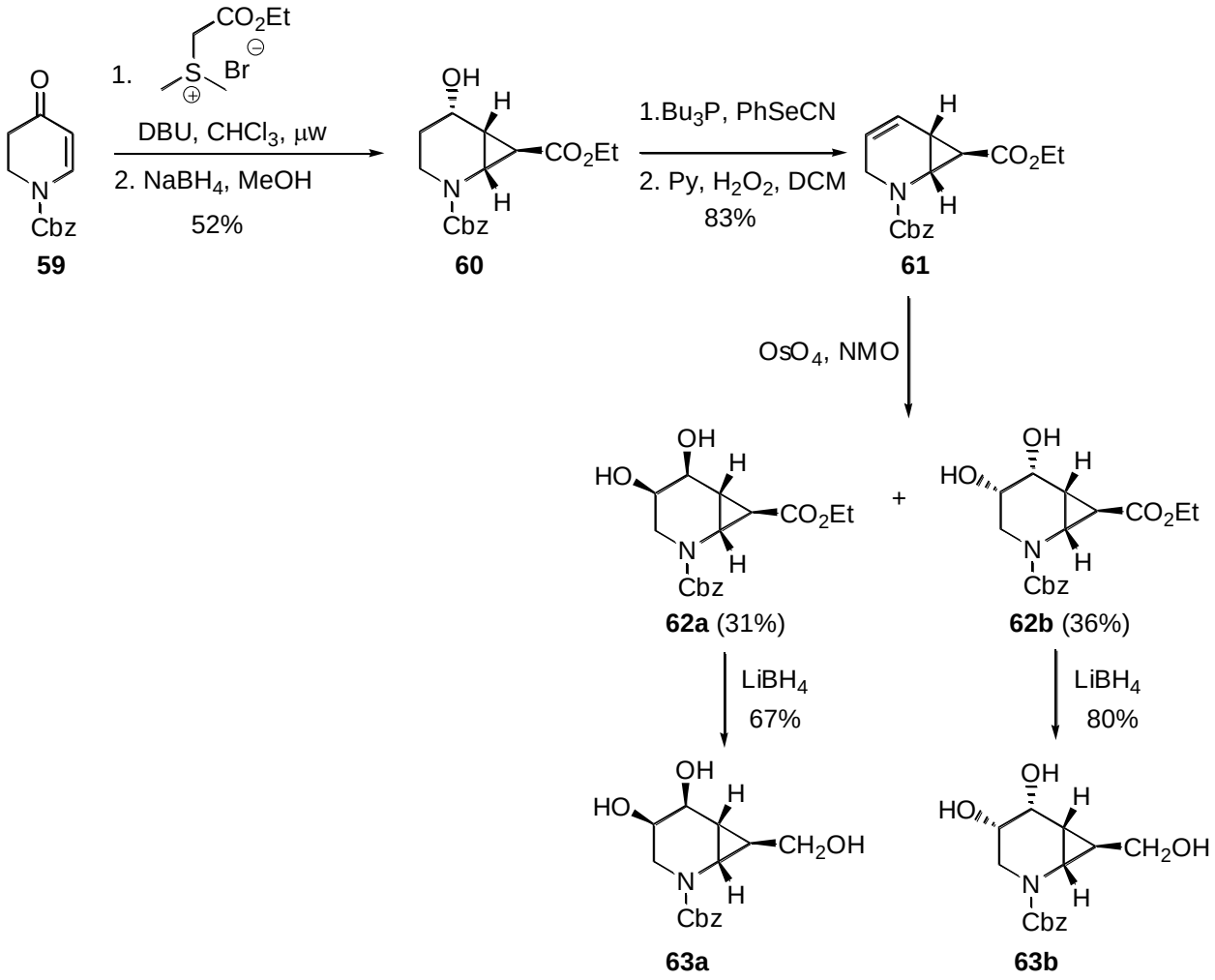
racemic cyclopropane **60** in high diastereoselectivity (Scheme 11). Dehydration of compound **60** by Grieco elimination furnished alkene **61** in 83% yield. Non-stereoselective dihydroxylation of compound **61** gave diols **62**. Finally, esters **62a** and **62b** were reduced to afford triols **63a** and **63b**.



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

2.3 Aziridine-based bicyclic cyclitols

Cyclophellitol-aziridine (**66**) is an analogue of the natural product cyclophellitol (**8**). These two compounds are irreversible, mechanism-based retaining glucosidase inhibitors. Several syntheses of cyclophellitol-aziridine and its derivatives have been described in the literature.[44] The first synthesis of cyclophellitol-aziridine (**66**) was reported by the group of Tatsuta in the early 1990s (Scheme 12).[45,46] This compound was obtained from 1,6-*epi*-cyclophellitol (**64**)[47] in four steps. Perbenzylation of tetraol **64** followed by ring-opening of the epoxide by NaN_3 provided a mixture of regioisomers **65**.[45] A Staudinger type reaction was then performed by treatment of the mixture of **65a** and **65b** with PPh_3 to afford the corresponding perbenzylated cyclophellitol-aziridine in 60% yield. Deprotection using Birch conditions yielded the desired compound **66**. In the same manner, 1,6-*epi*-cyclophellitol-aziridine (**67**) was obtained from cyclophellitol (**8**).[46] The authors reported also the synthesis of derivatives **68** and **69** from **66** by a two-steps sequence involving alkylation or acylation reactions.[46] Evaluation of aziridines **66-69** indicated that these compounds were inhibitors of β-glucosidase from almond with the exception of **69b**.[45,46] Furthermore, cyclophellitol-aziridine (**66**) is a stronger inhibitor (IC_{50} = 0.22 μg/mL) than its epimer **67** (IC_{50} = 32 μg/mL) and cyclophellitol (**8**) (IC_{50} = 0.8 μg/mL).[45,46]

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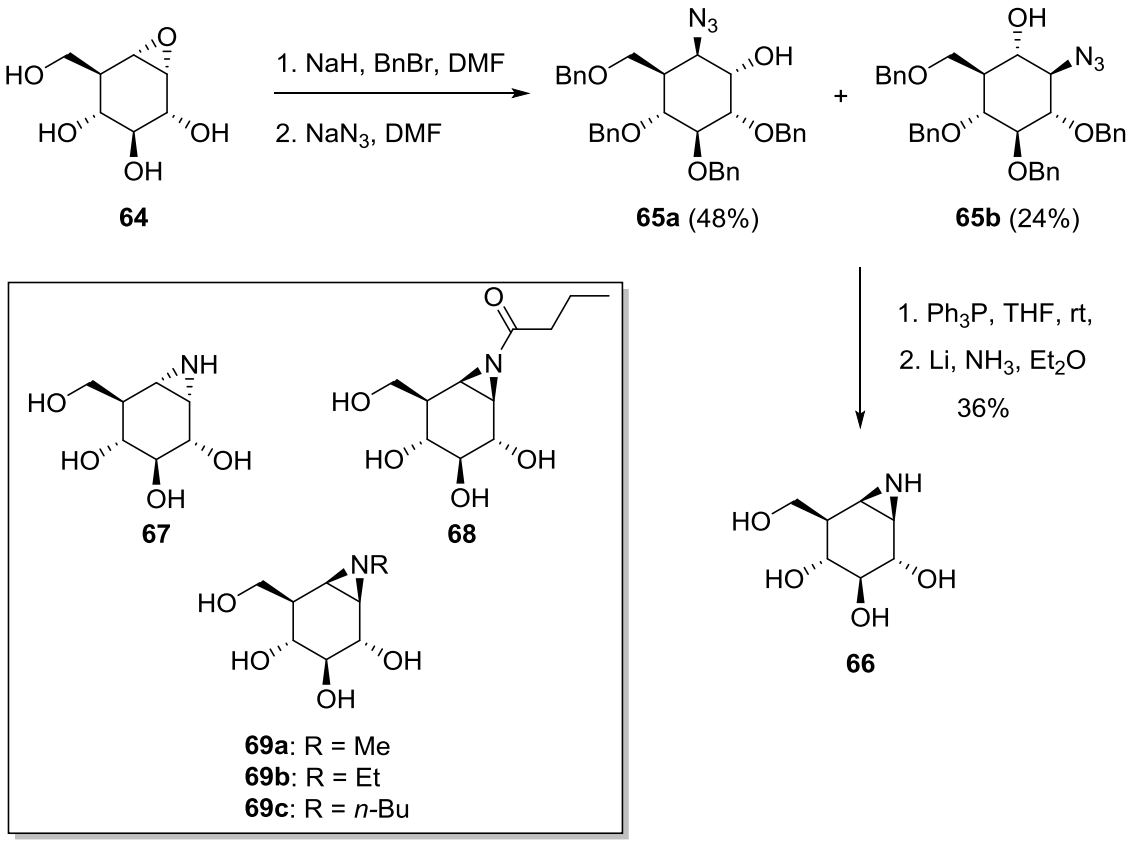

Scheme 12. Synthesis of cyclophellitol-aziridine **66** and derivatives **67-69** by Tatsuta *et al.*

The group of Overkleeft was also interested in the synthesis of cyclophellitol-aziridine (**66**) as well as analogs[44] for their potential biological interest as glycosidase inhibitors or as selective activity-based glycosidase probes.[48-53] The synthesis of compound **66** by Overkleeft *et al.* started from aldehyde **70** which was treated with ethyl 4-bromocrotonate in an indium-mediated reaction to afford diene **71** in good yield and excellent diastereoselectivity (scheme 13).[54] Diene **71** was converted to cyclohexene **72** by ring closing metathesis and reduction of the ester group. Introduction of a trichloroacetimidate function followed by iodocyclization led to iodide **73** with total stereocontrol. Compound **73** was then converted to the target cyclophellitol-aziridine (**66**) by acidic hydrolysis of the trichloroacetimidate group followed by base-induced intramolecular S_N2 reaction and removal of the benzyl groups. Birch conditions were used for the deprotection step since palladium-catalyzed hydrogenolysis conditions led to partial reduction of the aziridine while Lewis-acid-mediated debenzylation proved unsuccessful. Bicyclic aziridine **76**, the *pseudo* D-*galacto* analog of **66**, was obtained following a similar sequence from the same intermediate **70**.[55] For this synthesis, the two asymmetric centers corresponding to C4 and C5 in the parent pyranose were created by aldolization of **70** with the Evans oxazolidinone **74** affording compound **75** in 80% yield (Scheme 13). Overkleeft *et al.* reported also the preparation of **77** from the enantiomer of **70**.[56]

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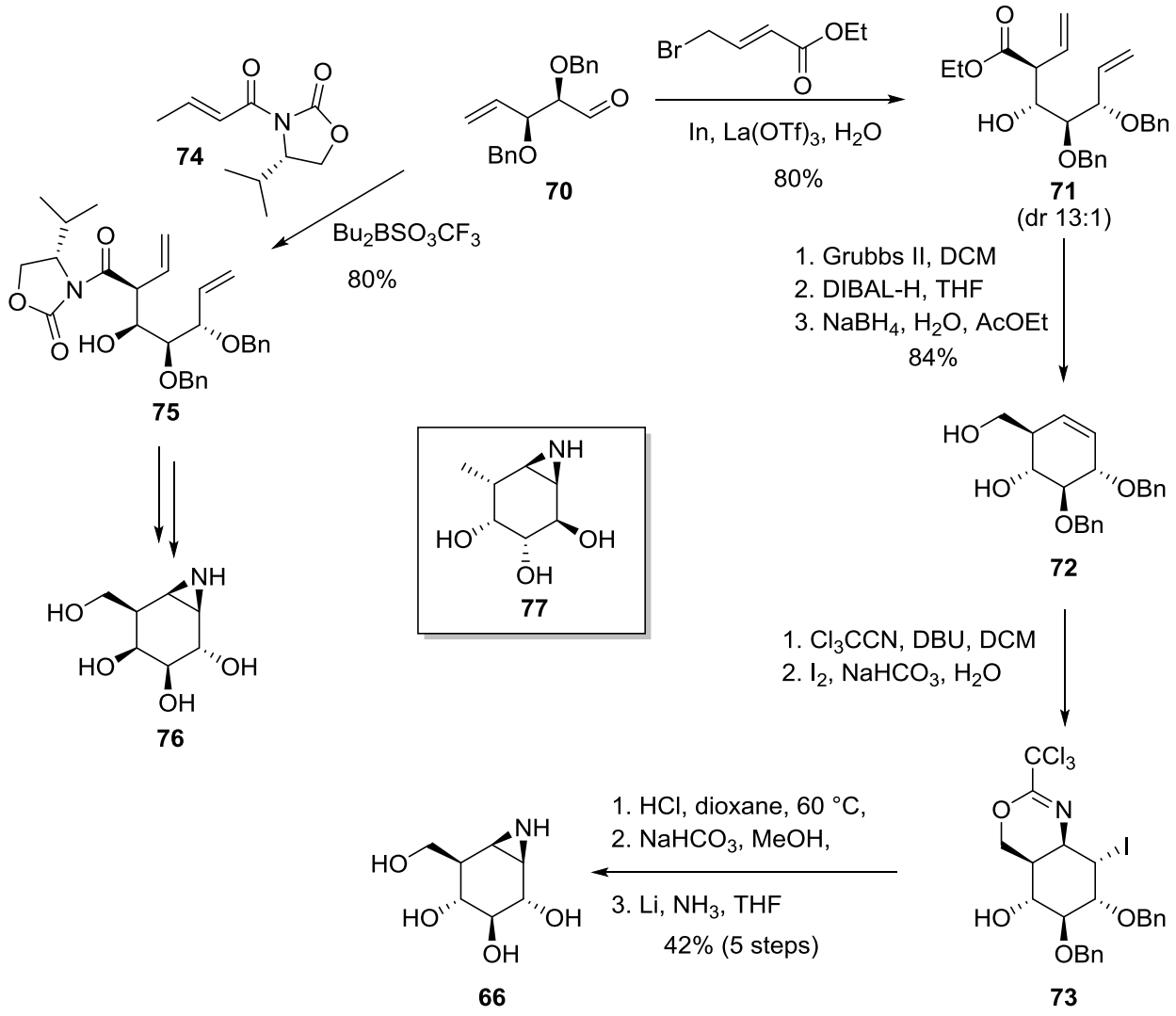

Scheme 13. Synthesis of cyclophellitol-aziridine (**66**) and analogs **76-77.**

Other examples of cyclophellitol-aziridine derivatives possessing interesting biological activities have been described by Overkleeft and other groups (Figure 3). Compounds **78-80** were obtained in two steps from **66** and evaluated on the following three retaining glucosidases: GBA, GBA2 and GBA3.[57] All the evaluated compounds **78-80** were good inhibitors of the three enzymes, in particular *N*-alkyl derivative **78** which is a nanomolar inhibitor of GBA (IC_{50} = 17 nM) and GBA2 (IC_{50} = 3 nM). Compounds **81** and **82** were obtained from the appropriate epoxide following a similar sequence to the one described by Tatsuta *et al.* (see Scheme 12) involving ring-opening of the epoxide by NaN_3 and PPh_3-mediated cyclisation to form the aziridine ring.[58,59] Alternatively, aziridines **82** could also been prepared from tetrabenzylinositol.[60,61] The *N*-alkylaziridines **82b-82d** were evaluated as inhibitors of human β-glucocerebrosidase (GBA1), the enzyme involved in Gaucher disease.[60] The results indicated that the K_i values were inversely correlated with the length of the alkyl chain. *N*-octyl conduritol aziridine **82d,** a specific covalent inactivator of GBA1 (K_i = 4.8 nM), was indeed found to be 500-fold more potent than **82b**, its *N*-butyl analog.[60]

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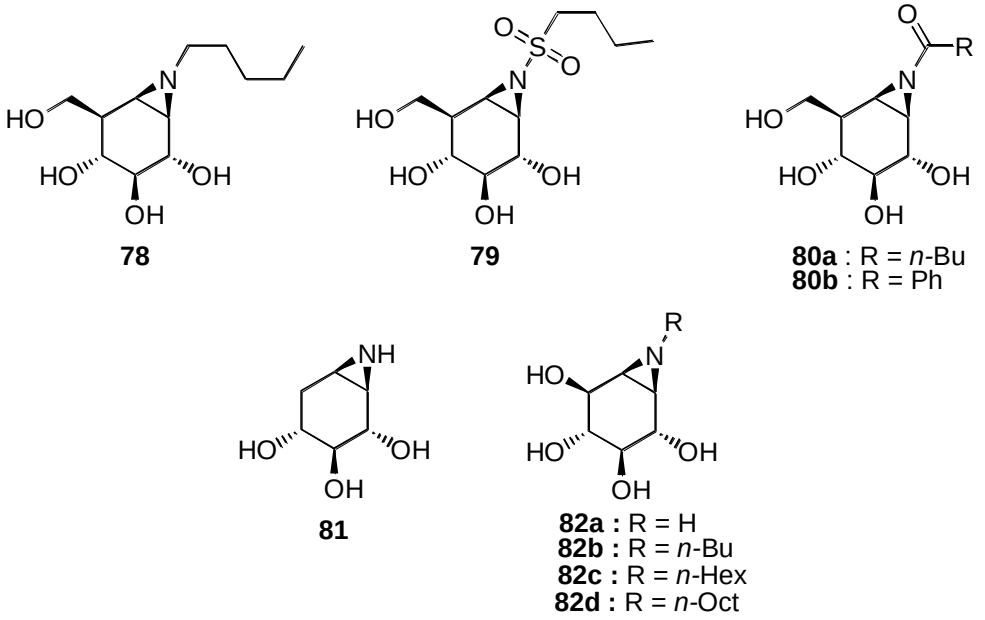
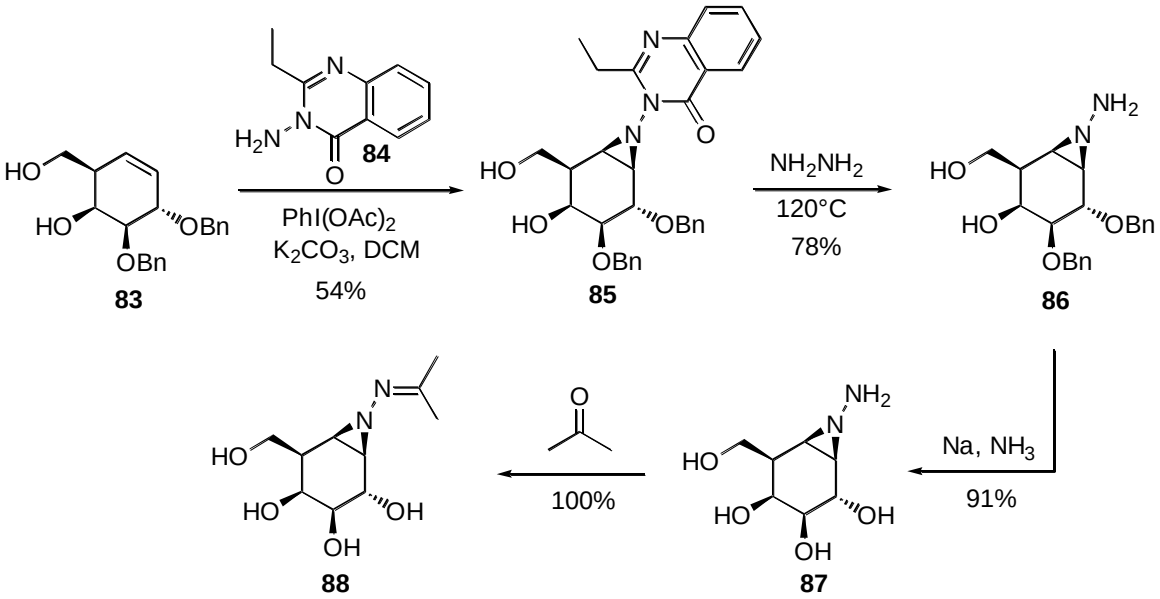


Figure 3. Examples of bioactive cyclophellitol-aziridine derivatives.

In 2015, Llebaria *et al.* reported the synthesis of D-*galacto* configured *N*-aminoaziridines as analogs of compound **76** (Scheme 13).[62] Aziridination of compound **83**,[62,63] obtained from diene **75**,[55,64] with quinazolinone **84** in the presence of phenyl iododiacetate afforded the key intermediate **85** as a single diastereoisomer (Scheme 14).[62] First attempts to remove the protecting groups under Birch conditions were unsuccessful. An alternative way was to perform the hydrazinolysis of *N*-aminoaziridine **85** first and then to deprotect the benzyl groups. This two-step sequence enabled the formation of the desired compound **87** in good yields. *N*-Iminoaziridine **88** was then obtained quantitatively by treatment of **87** with acetone. A diversity of cyclophellitol-aziridine analogues could be easily obtained by reaction of *N*-aminoaziridines such as **86** with a variety of carbonyl compounds. *N*-aminoaziridines **87** and **88** are potent irreversible inhibitors of *Aspergillus oryzae* and *Escherichia coli* β-galactosidases.[62]



Scheme 14. Synthesis of *N*-aminoaziridines **87** and **88.**

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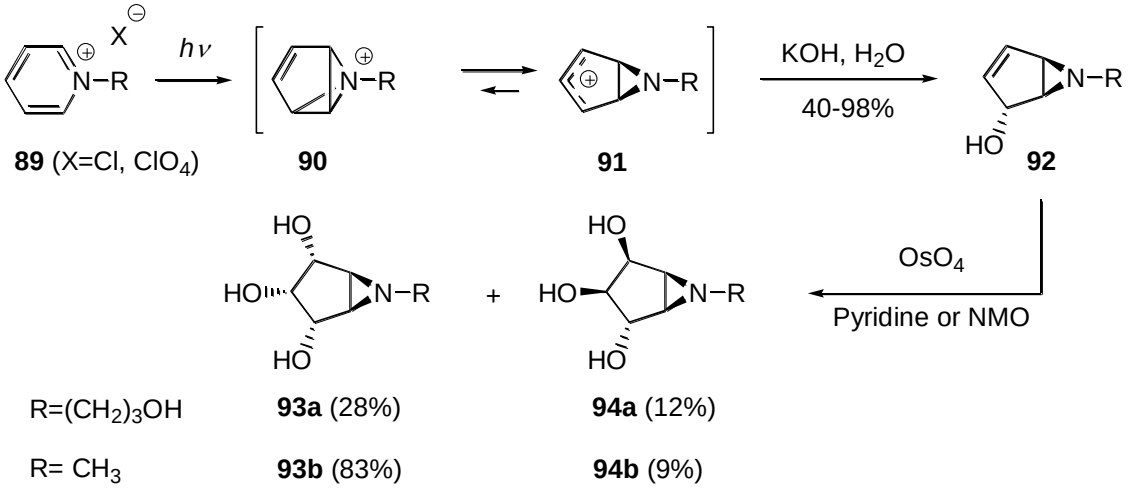
The synthesis and biological evaluation of aminocyclopentitols have also been reported.[65-67] The groups of Burger and Ganem independently described the racemic synthesis of polyhydroxylated aziridinyl cyclopentanes **93** and **94** using the photolysis of *N*-alkylpyridinium intermediates as the key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



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

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

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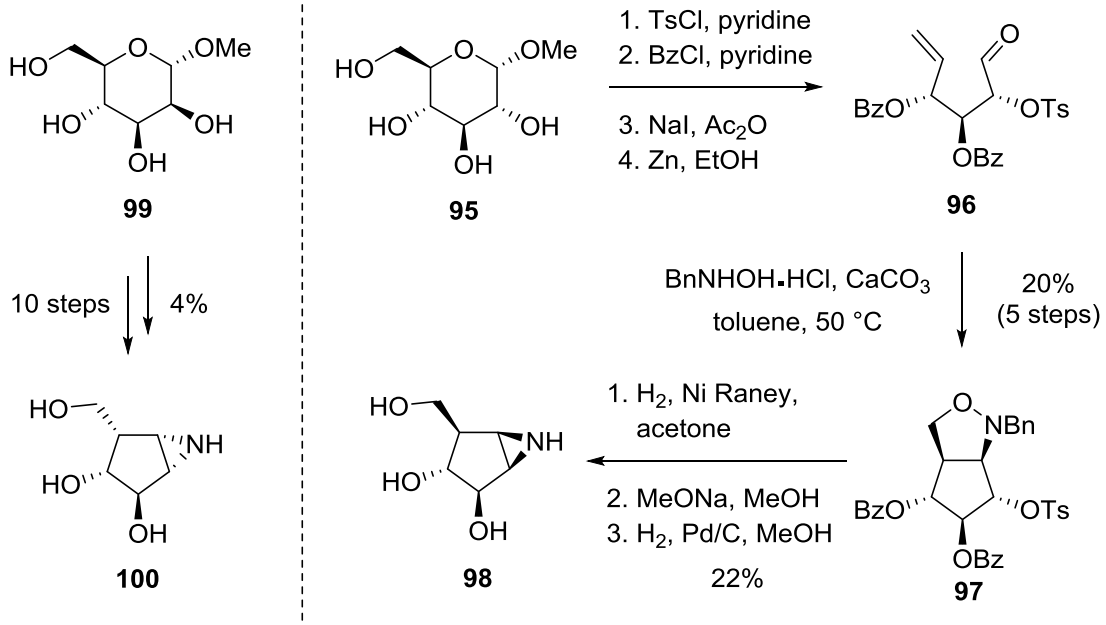
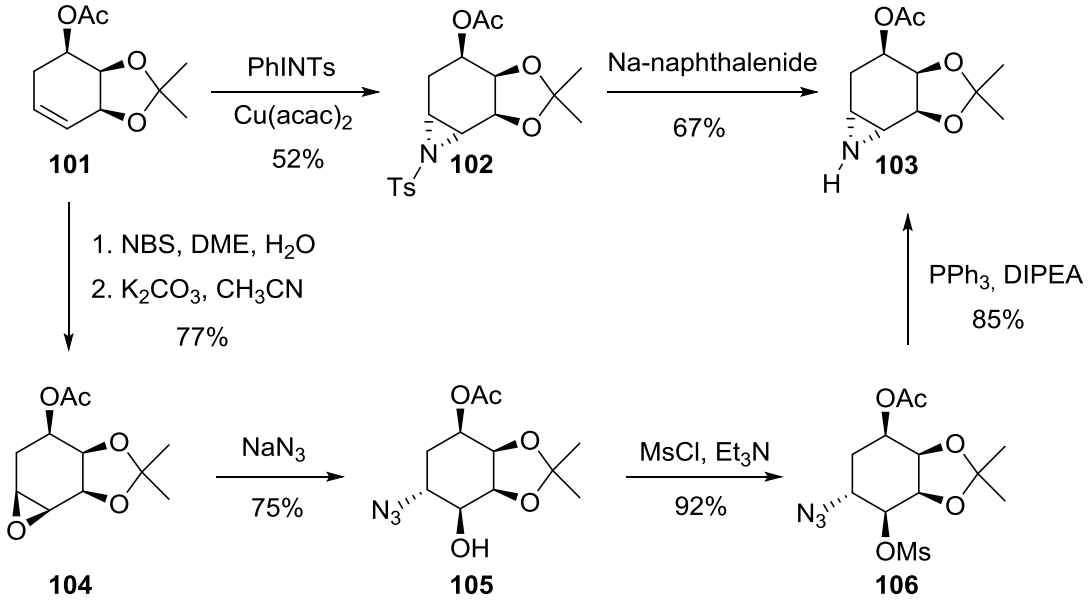


Scheme 16. Synthesis of bicyclic aziridines **98** and **100.**

Aziridine-based cyclitols were also used as intermediates in the synthesis of natural products. During their studies on the synthesis of (+)-lycoricidine, Yadav *et al.* reported the formation of aziridine **103** *via* two synthetic strategies (Scheme 17).[69] In the first approach, aziridination of cyclohexene **101**, obtained in eight steps from D-mannose, yielded *N*-tosylaziridine **102** as a single stereoisomer. Removal of the tosyl group was performed by treatment of **102** with sodium naphthalenide. In the second approach, **101** was converted to **103** in five steps. Reaction of **101** with NBS afforded a mixture of bromohydrins, which under basic conditions, provided epoxide **104**. Regioselective epoxide ring-opening with NaN_3, followed by mesylation gave compound **106**. Desired aziridine-cyclohexitol **103** was then obtained by treatment with triphenylphosphine and diisopropylethylamine in a Staudinger-type reaction.



Scheme 17. Synthesis of aziridine **103** by aziridination of alkene **101** or *via* ring-opening of epoxide **104.**

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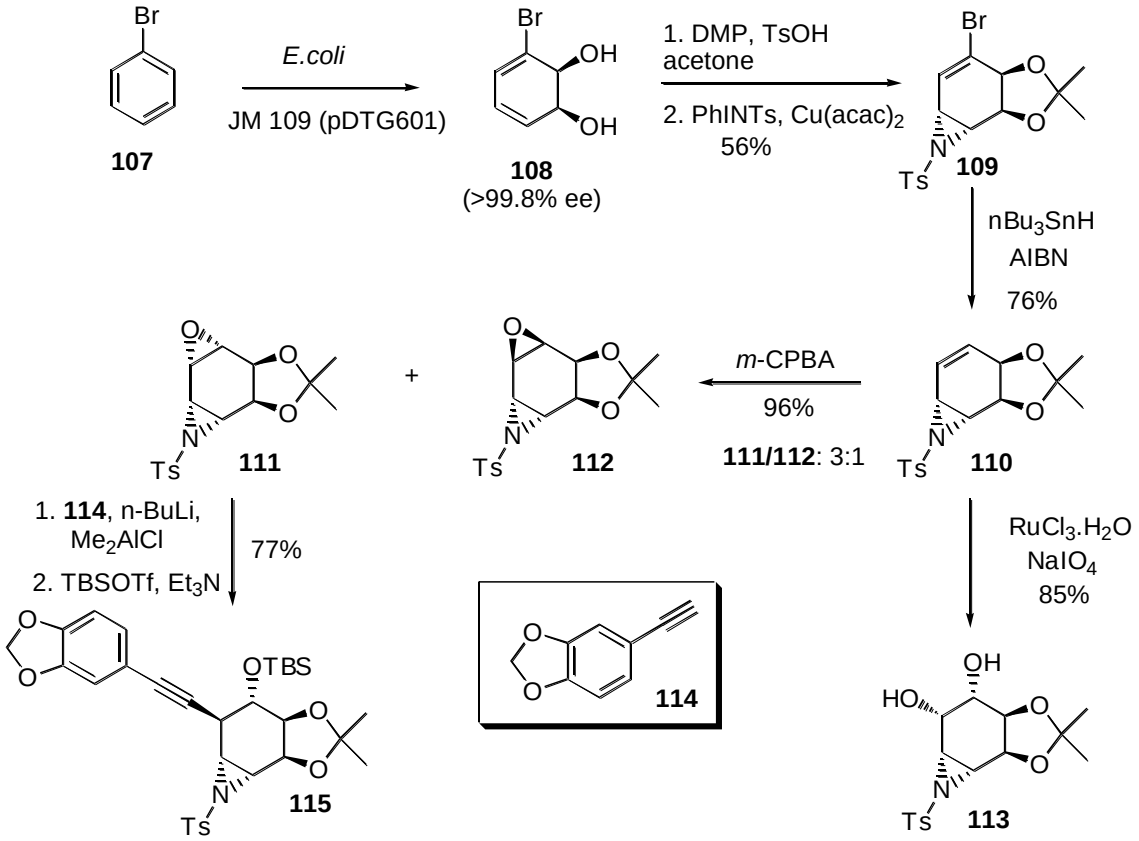
During their studies on the synthesis of several *Amaryllidaceae* alkaloids, Hudlicky *et al.* reported the formation of aziridines **111-113** as advanced synthetic intermediates (Scheme 18).[70,71] The synthesis began with the chemoenzymatic dihydroxylation of bromobenzene (**107**) with recombinant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



Scheme 18. Synthesis of aziridines **111-113** *via* chemoenzymatic dihydroxylation of bromobenzene.

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

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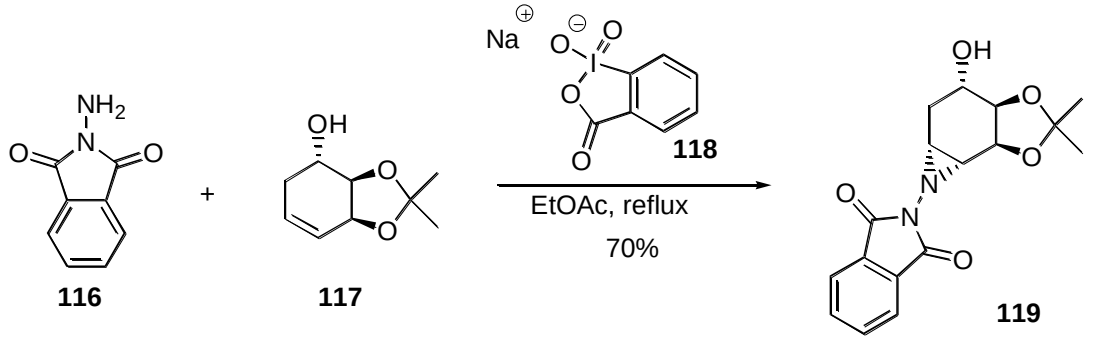
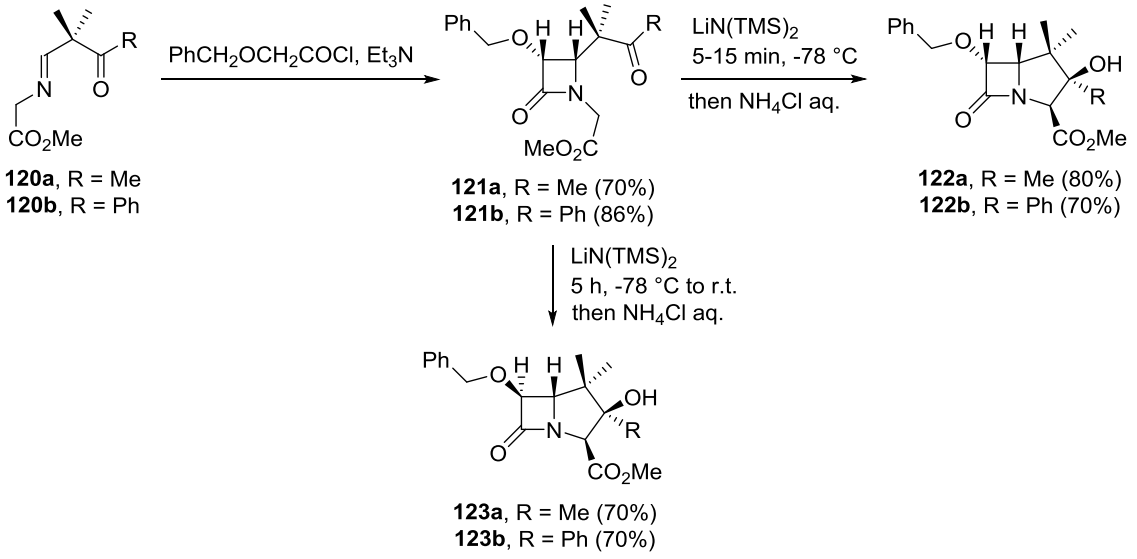


Scheme 19. Sodium-iodoxybenzoate mediated aziridination of polyoxygenated cyclohexene **117.**

3. Four-membered Ring-containing Iminosugars

3.1 Bicyclic systems with nitrogen at the ring junction

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



Scheme 20. Synthesis of carbapenam derivatives **122** and **123.**

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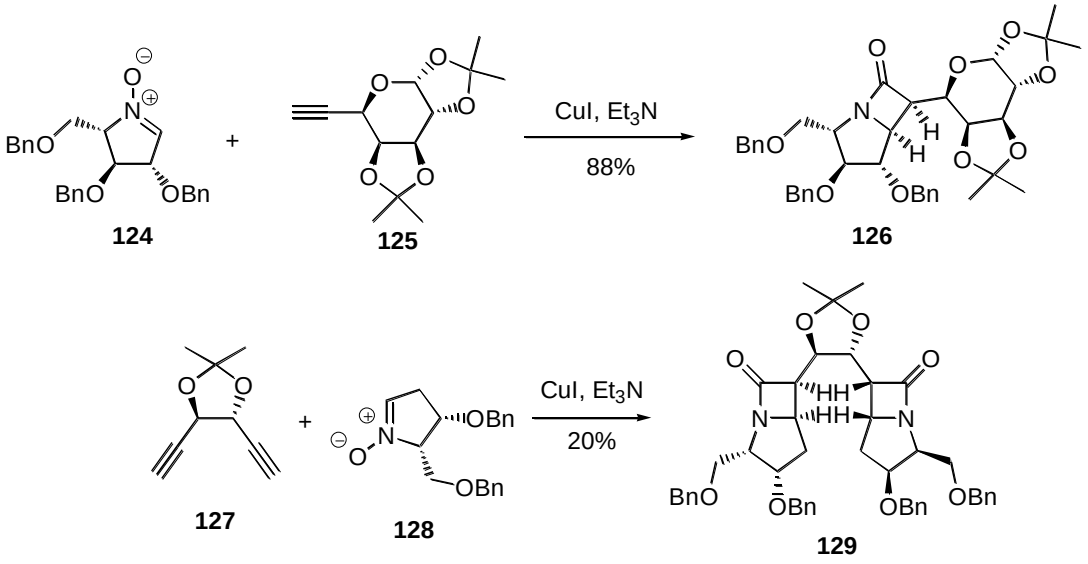
More recent syntheses of iminosugars based on 1-azabicyclo[3.2.0]heptane skeleton all feature a cycloaddition involving sugar derived nitrones.[78-82] The Kinugasa reaction is of particular interest in this regard. This reaction involves a cycloaddition between a nitrone and a copper acetylide followed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



Scheme 21. Synthesis of polyhydroxylated bicyclic β-lactams *via* the Kinugasa reaction.

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

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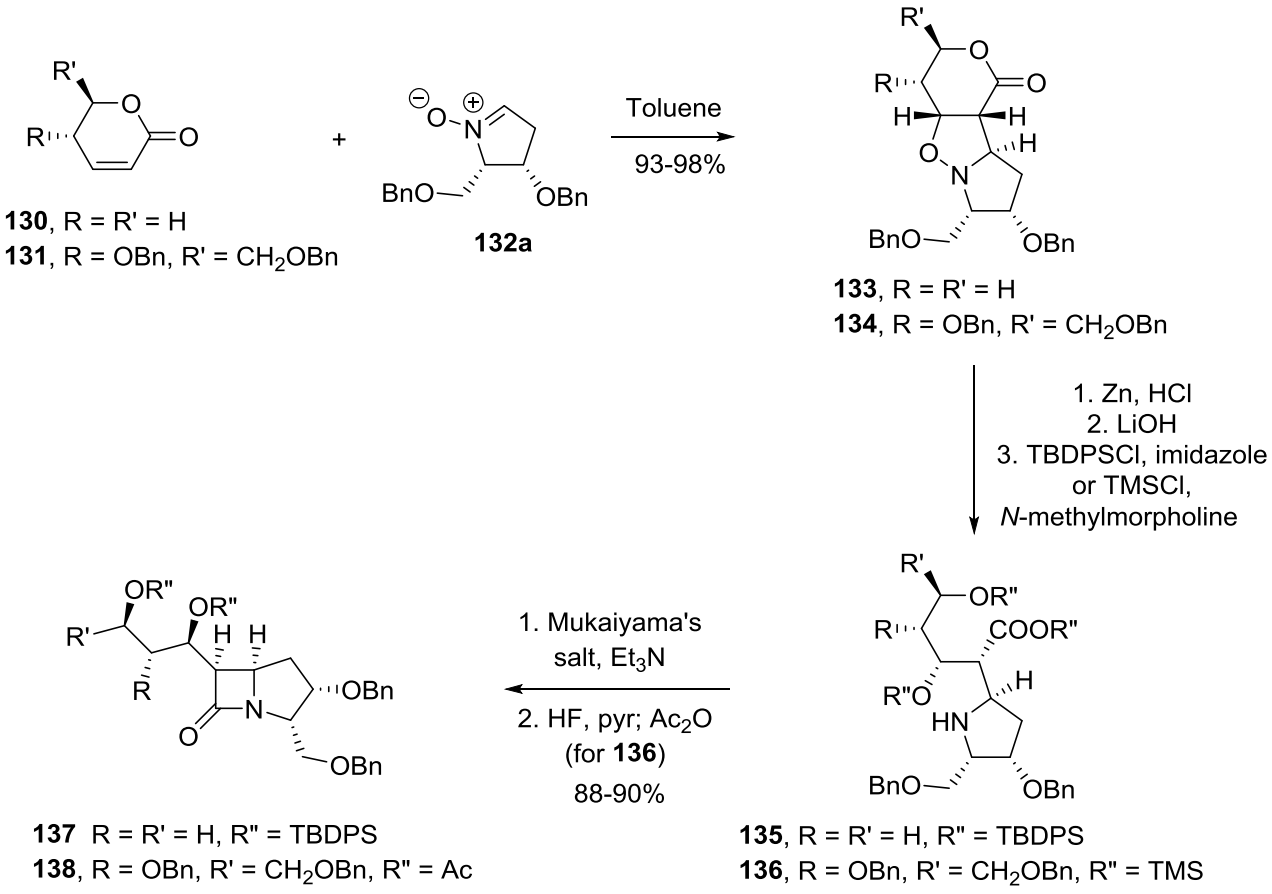


130, R = R' = H
131, R = OBn, R' = CH_2OBn

132a

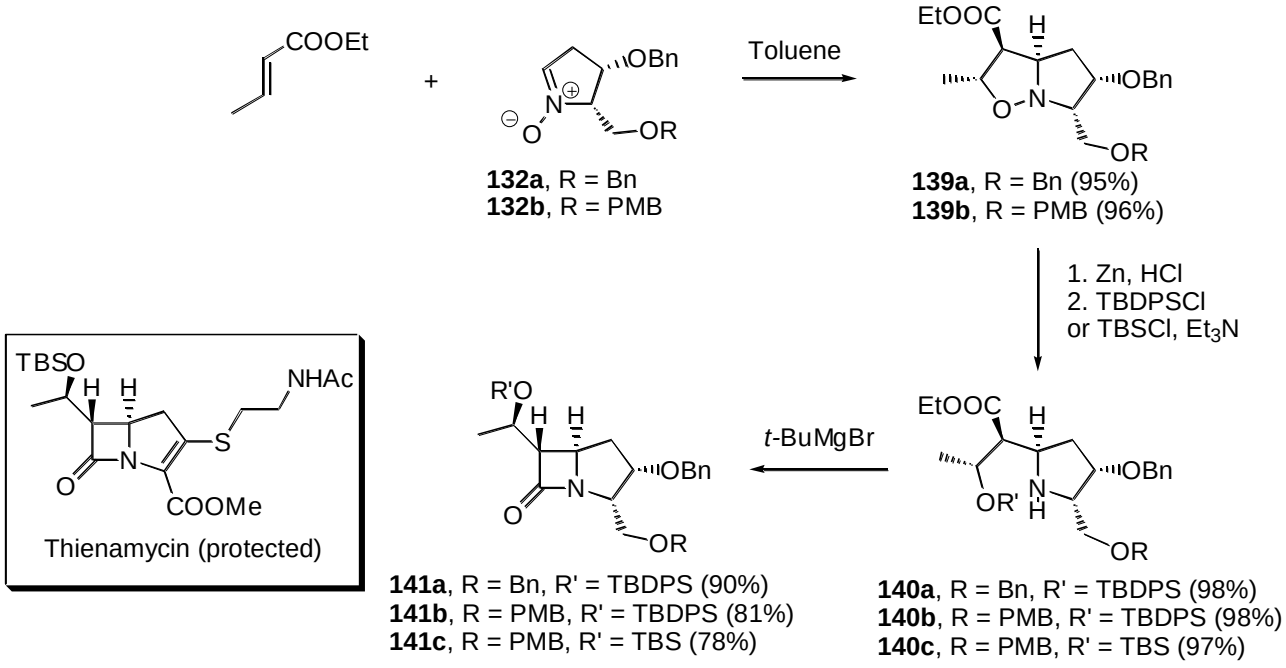
133, R = R' = H
134, R = OBn, R' = CH_2OBn

137 R = R' = H, R" = TBDPS
138, R = OBn, R' = CH_2OBn, R" = Ac

135, R = R' = H, R" = TBDPS
136, R = OBn, R' = CH_2OBn, R" = TMS

Scheme 22. Synthesis of carbapenems analogues **137-138** from α,β-unsaturated lactones **130-131.**

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



132a, R = Bn
132b, R = PMB

139a, R = Bn (95%)
139b, R = PMB (96%)

141a, R = Bn, R' = TBDPS (90%)
141b, R = PMB, R' = TBDPS (81%)
141c, R = PMB, R' = TBS (78%)

140a, R = Bn, R' = TBDPS (98%)
140b, R = PMB, R' = TBDPS (98%)
140c, R = PMB, R' = TBS (97%)

Scheme 23. Synthesis of carbapenam derivatives **141** from ethyl crotonate.

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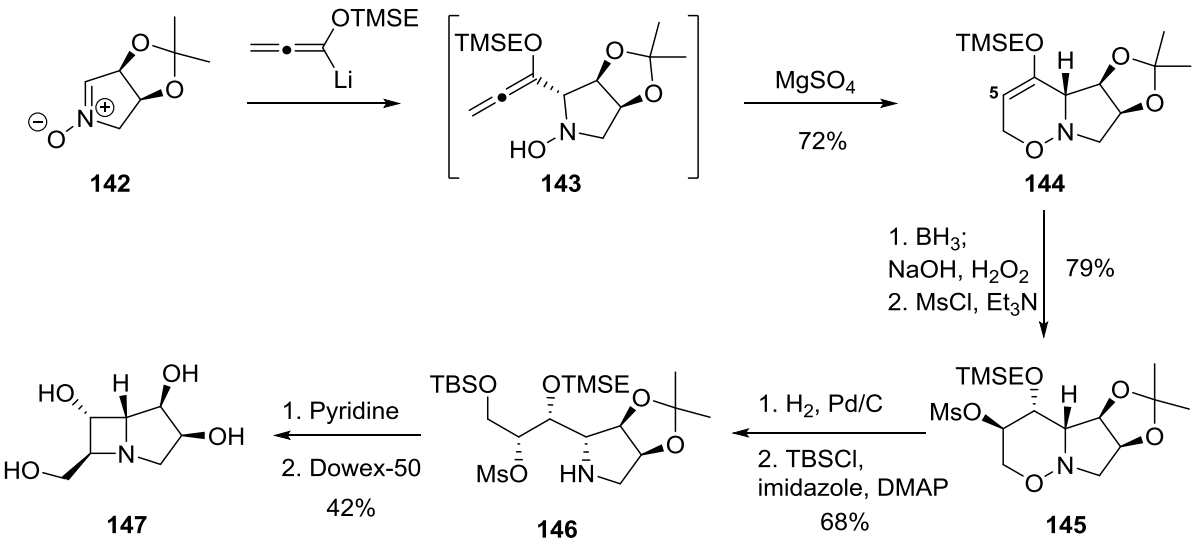
Reissig *et al.* reported the synthesis of azabicyclotetrol **147** from L-erythrose-derived nitrone **142**. The key step was the addition of lithiated 2-(trimethylsilyl)-ethoxyallene on nitrone **142** affording compound **143** which cyclized spontaneously in the presence of drying reagent $MgSO_4$ to form bicyclic 1,2-oxazine **144** in 72% yield (Scheme 24).[85] The introduction of a hydroxyl group at C-5 of the oxazine was performed by hydroboration and subsequent oxidation affording after mesylation compound **145** as a single diastereoisomer. Cleavage of the N-O bond and protection of the primary alcohol gave mesylate **146**. The four-membered ring closure was performed by basic treatment yielding, after deprotection step, azabicyclotetrol **147** bearing the characteristic hydroxymethyl group that is present in most hexopyranosides. Inhibitory properties of compound **147** were assessed on eleven commercially available glycosidases, without any significant activity being observed.[85]



142 **143** **144** **145** **146** **147**

Scheme 24. Synthesis of azabicyclotetrol **147.**

Many examples of four-membered ring-containing synthetic fused bicyclic iminosugars feature a conidine skeleton (Schemes 25-29). Dhavale *et al.* reported recently the synthesis of trihydroxylated conidine alkaloids **151** (Scheme 25).[86] The sugar-bearing β-amino acid **149** was obtained in two steps through a moderately stereoselective Michael addition from the glucose-derived product **148**.[87] The azetidine ring was then formed by way of an efficient lactamization-reduction sequence. Finally, acetal hydrolysis followed by benzyl group cleavage under hydrogenolysis conditions induced piperidine ring closure *via* reductive amination, leading to azabicyclotriols **151**. Regardless of the ring junction stereochemistry, conidine derivatives **151** were found to be weak inhibitors of the four tested glycosidases.[86] The group of Tiwari also described the synthesis of compound **151b** following a similar sequence, except for the azetidine ring formation which was generated *via* Mitsunobu reaction after hydride reduction of ester **152** to alcohol **153** (Scheme 25).[88]

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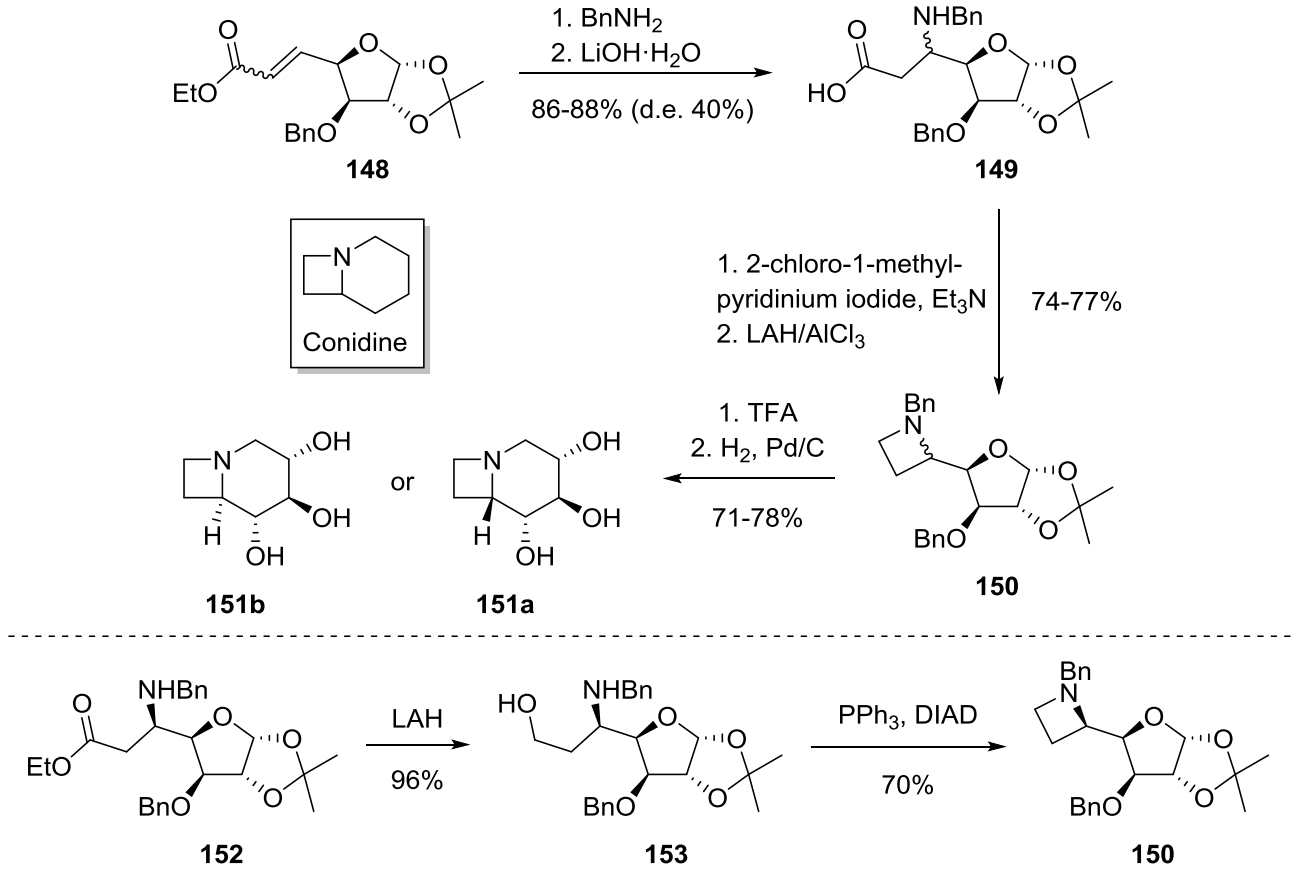

Scheme 25. Synthesis of trihydroxylated conidine alkaloids **151** *via* a lactamization-reduction sequence or a Mitsunobu reaction.

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

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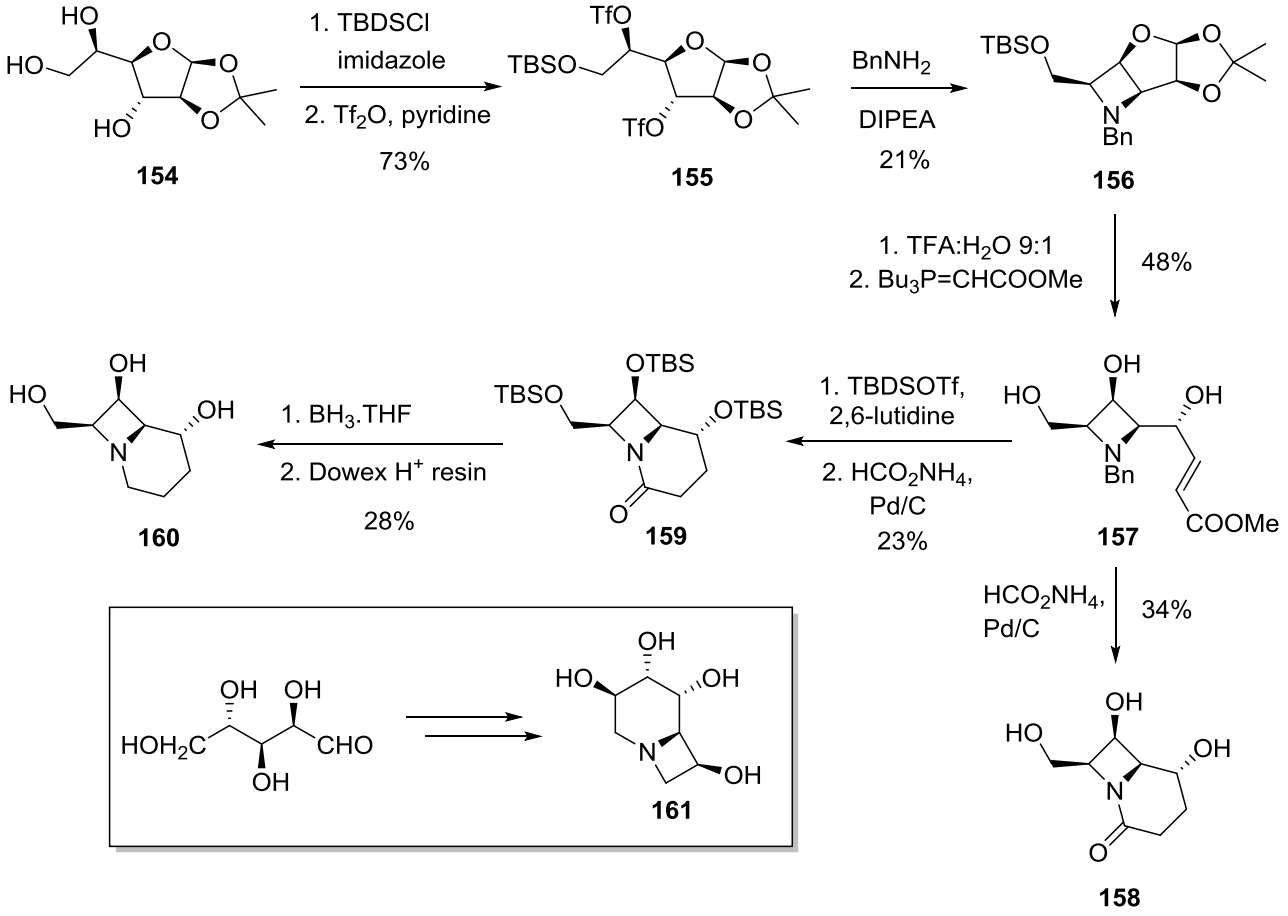

Scheme 26. Synthesis of tri- and tetra-hydroxyconidine derivatives **158**, **160** and **161.**

Beyond a lactamization reaction or classical S_N2 process, the conidine skeleton may be also generated through photocatalytic cyclization. In the course of their work on glycosidase inhibitors, Pal and Dumbre thereby published the synthesis of trihydroxyconidine **167** (Scheme 27).[93,94] Aldehyde **162** and amine **163** (prepared from L-(+)-tartaric acid and 3-aminopropanol, respectively) were coupled in 71% yield *via* reductive amination.[93] The free alcohol was then mesylated, allowing *in situ* azetidine ring closure. Piperidine formation was accomplished in 35% yield by way of highly stereoselective photo-induced 6-*exo*-*dig* radical cyclisation of compound **165**.[94] Finally, azabicycle **166** was converted in four steps into the hydrochloride (**167**) of trihydroxyconidine . The hydrochloride was found to be a weak inhibitor of *Aspergillus oryzae* β-galactosidase (K_i = 114 μM) as well as a moderate inhibitor of almond β-glucosidase (K_i = 7.6 μM).[94] The group of Pandey described a synthesis of β-lactam-iminosugar hybrid **171** and its enantiomer using a similar strategy (Scheme 27).[95] Compound **164** was converted in one step into 1,3-oxazine **168**. The piperidine ring was then formed in 60% yield by means of photo-induced 6-*exo*-*dig* radical cyclisation, affording the oxa-azabicycle **169** which was in turn converted in nine steps into the β-amino acid **170**. Finally, deprotection of the amine followed by lactamization reaction provided deprotected bicyclic β-lactam **171** after debenzylation in 50% overall yield (three steps from **170**). The biological activity of this compound and its enantiomer was evaluated on α- and β-galactosidases, α- and β-glucosidases and α- and β-mannosidases. Bicyclic iminosugar **171** showed weak to moderate inhibitory properties against α- and β-galactosidases whereas no inhibition was observed for the corresponding enantiomer.[95]

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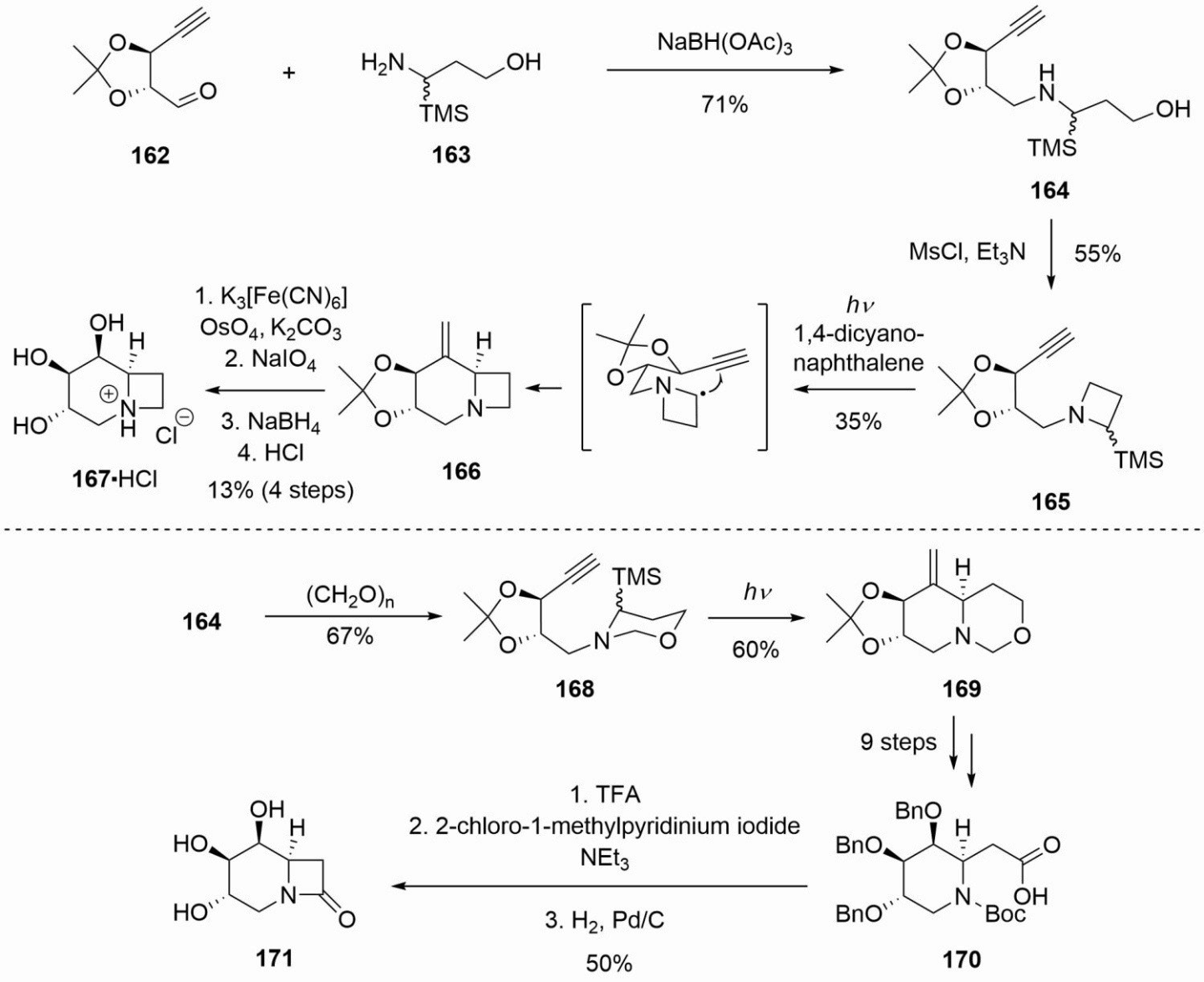

Scheme 27. Photochemical synthesis of trihydroxyconidine derivatives **167** and **171.**

Following their work on carbapenems (Scheme 20),[77] Alcaide *et al.* extended the scope of their efforts to the synthesis of carbacepham derivatives such as **175** (Scheme 28).[96,97] The *cis*-β-lactam **172**, prepared *via* enantioselective Staudinger cycloaddition,[96] was engaged in a deacetalization-silylation-oxidation sequence which afforded aldehyde **174**. In order to avoid loss of material during purification process, crude **174** was directly treated with $BF_3{\cdot}Et_2O$, leading to the formation of cycloadduct **175** through ene cyclization (36% yield from **173**). The authors proposed a six-membered, cyclic chair-like transition-state model to explain the stereochemical outcome of this reaction. The use of a more resistant silyl ether protecting group (TBS instead of TMS) considerably improved the cyclization yield by preventing desilylation to occur, however this was shown to reduce the diastereoselectivity of the reaction as illustrated with the conversion of **176** to **177** and **178**.

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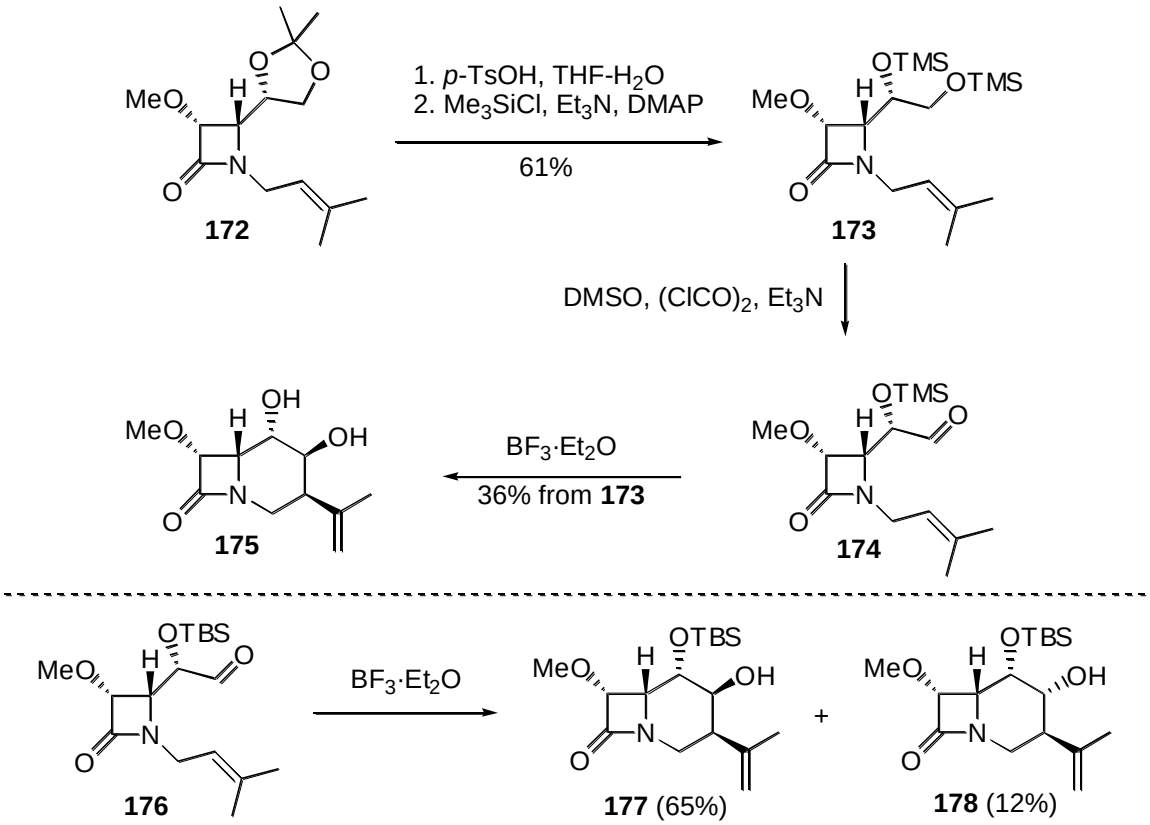

Scheme 28. Synthesis of carbacepham derivatives *via* ene cyclization.

The group of Grande also synthesized carbacepham derivatives from stereoselective Staudinger cycloaddition products (Scheme 29).[98] The *cis*-2-azetidinone **179** and its diastereoisomer were readily prepared by reaction of methoxyacetyl chloride with a D-glucosamine-derived imine. Compound **179** was submitted to dithioacetal deprotection conditions to afford the corresponding aldehyde which was directly engaged in a Wittig reaction. Using this sequence, acrylate ester **180** was obtained in high yields. Regioselective epoxidation of the more electron-rich alkene provided compound **181** with low diastereoselectivity. Efficient ozonolysis of the remaining double bond yielded epoxyaldehyde **182** in quantitative yield. Treatment by *in situ* generated $TiCp_2Cl$ induced homolytic cleavage of the epoxide, triggering a radical cyclization that ultimately delivered the carbacepham derivative **183** in moderate yield (pathway *a*, Scheme 29). Same reaction was performed on the more sterically hindered epoxyester **181** and expected bicyclic compound **184** was obtained in 52% yield. This cyclization was found to compete with β-elimination of the titanium-coordinated oxygen (pathway *b*, Scheme 29), hence the reversion to diene **180**. It is noteworthy that, in the case of the C5,C6 diastereoisomer of **181**, no cyclization product was observed and only the diene **180** was isolated.

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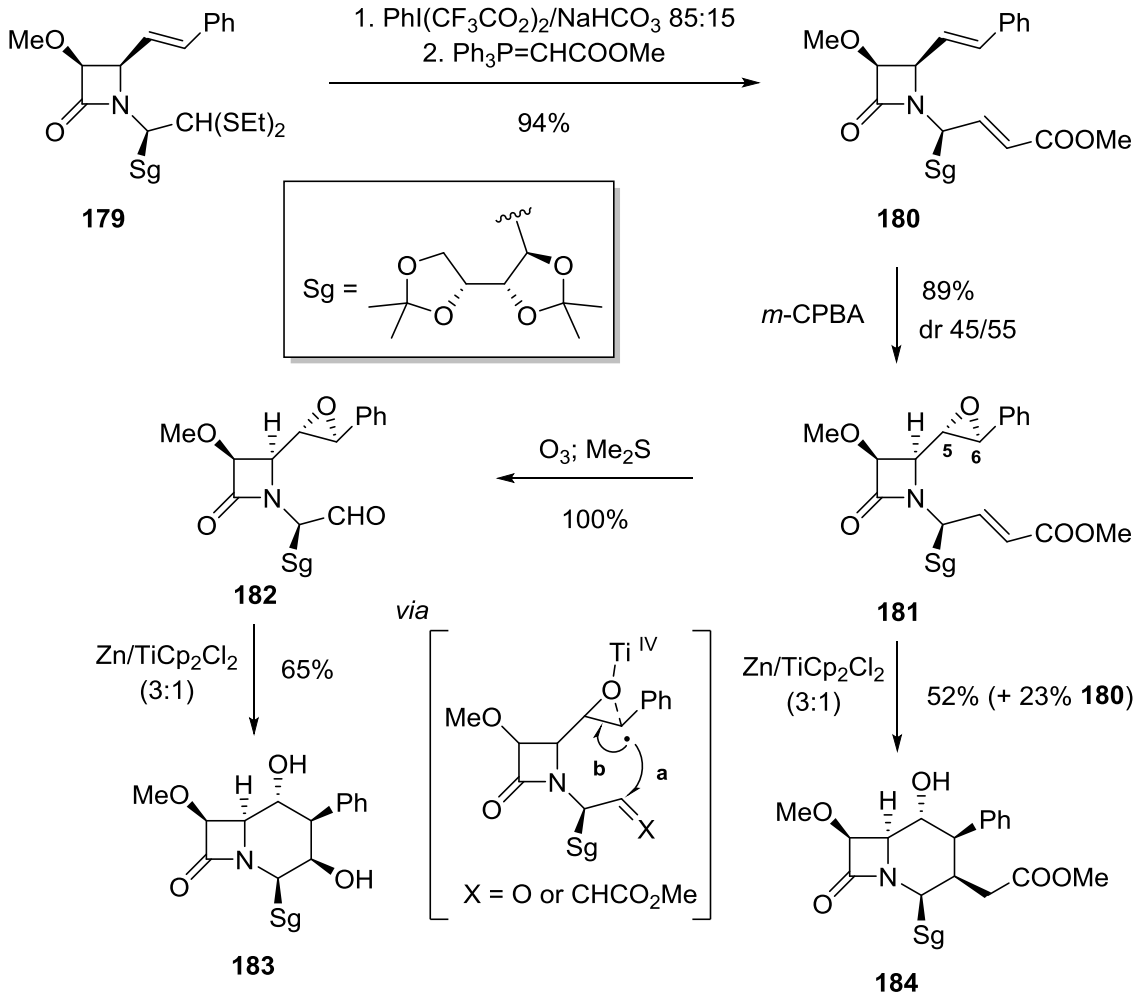

Scheme 29. Synthesis of carbacepham derivatives **183** and **184** *via* radical cyclization.

Madsen *et al.* reported a unique example of a bicyclic iminosugar featuring an azepane ring, as a byproduct *en route* to the synthesis of castanospermine **6** (Figure 1).[99] Conversion of methyl α-D-glucopyranoside **95** to the corresponding 6-iodopyranoside followed by perbenzylation and zinc-mediated fragmentation efficiently provided enal **185** (Scheme 30). In order to avoid epimerization upon standing, the crude **185** was directly submitted to reductive amination, leading to homoallylamine **186** in 89% yield. After treatment with trifluoroacetic anhydride, the resulting diene **187** was engaged in a ring-closing metathesis reaction which required extensive optimization to favor the desired product **189** over byproducts such as **190** or the homodimer of **187**. The use of Grubbs catalyst **188** and its dropwise addition over 20 h allowed the formation of the nine-membered *N*-heterocycle **189** in 78% yield along with 7% of its eight-membered counterpart **190**. Subsequent epoxidation by the *in situ* generated dioxirane of 1,1,1-trifluoroacetone followed by base-mediated *N*-deprotection/transannular cyclization delivered both tribenzylated castanospermine **191** and the bicyclic azepane derivative **192** in 44% and 15% yield, respectively. This constitutes an interesting example of a skeleton-diversity-oriented reaction.

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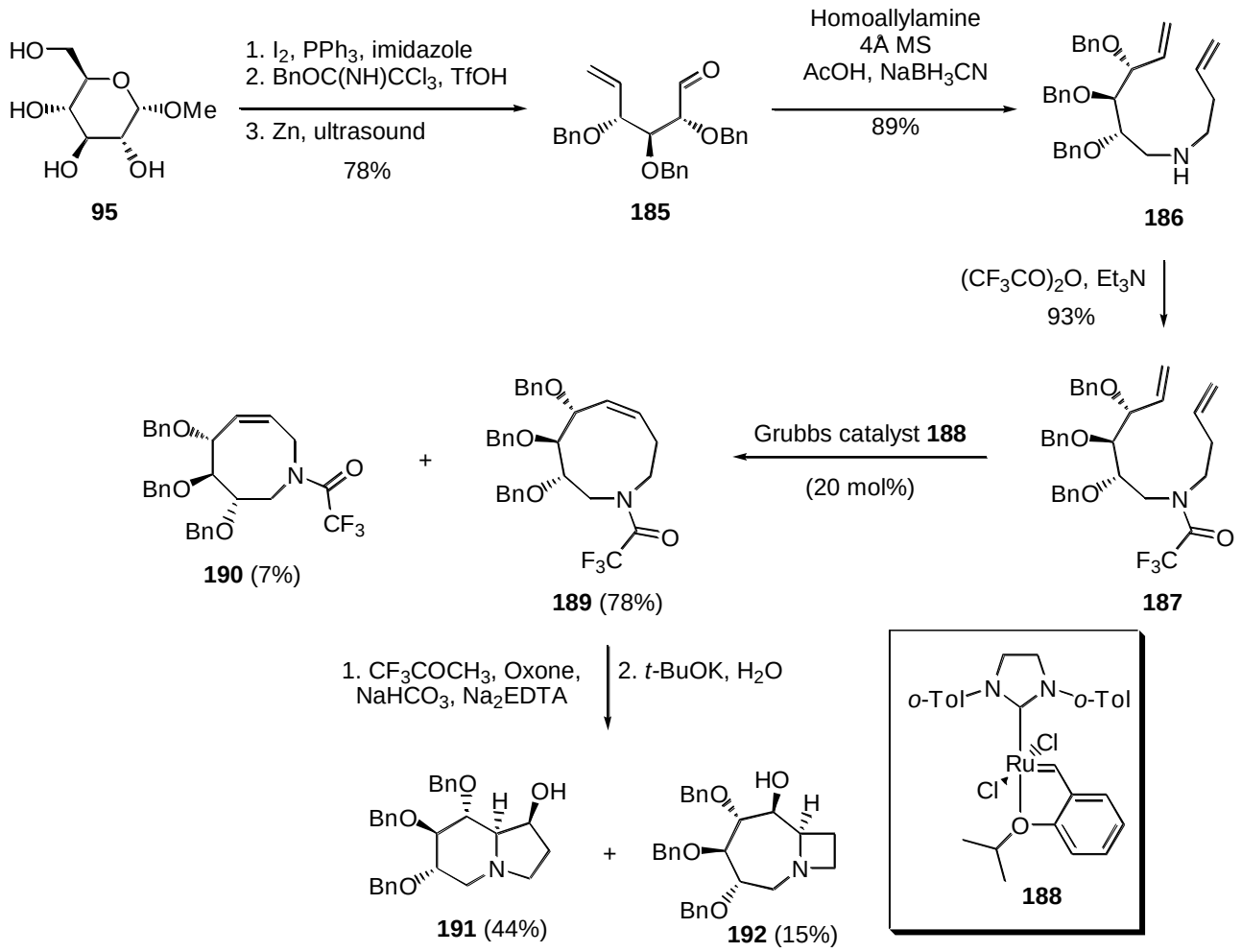

Scheme 30. Divergent synthesis of bicyclic iminosugars **191** and **192.**

3.2 Bicyclic systems with nitrogen not at the ring junction

There are few examples of fused bicyclic iminosugars for which the nitrogen atom is not part of the ring junction. Recently, the group of Compain reported the synthesis of such compounds, based on a 6-aza-bicyclo[3.2.0]heptane skeleton (Schemes 31-32).[100] When treated with TMSOTf and Et_3N, β-lactam diester **193**, readily prepared from L-glutamic acid,[101] underwent a cationic Dieckmann-type cyclisation[102] leading, after desilylation, to the desired bicyclic intermediate **194** in 81% yield on a gram-scale. In order to reach analogues bearing three hydroxyl groups on the cyclopentane ring, ketone **194** was converted to enone **195** in 70% yield *via* IBX-mediated desaturation. Unreactive towards both dihydroxylation and epoxidation, this key intermediate **195** underwent efficient chemo- and diastereoselective Luche's reduction into allylic alcohol **196** with good diastereoselectivity (5/1 dr). The major diastereoisomer **196** was in turn converted in two steps to the advanced intermediate **197**, which proved to be a suitable substrate for further functionalization. Diastereoselective dihydroxylation of **197** under Upjohn's conditions indeed led to **198** as the sole diastereoisomer, in 80% yield. Sequential benzylation, reduction and debenzylation afforded in good overall yield bicyclic amino-tetrol **199** (racemic) which may be seen as an analog of Galafold™. *N*-butyl derivative **200** was then obtained through reductive amination (Scheme 31).[100]

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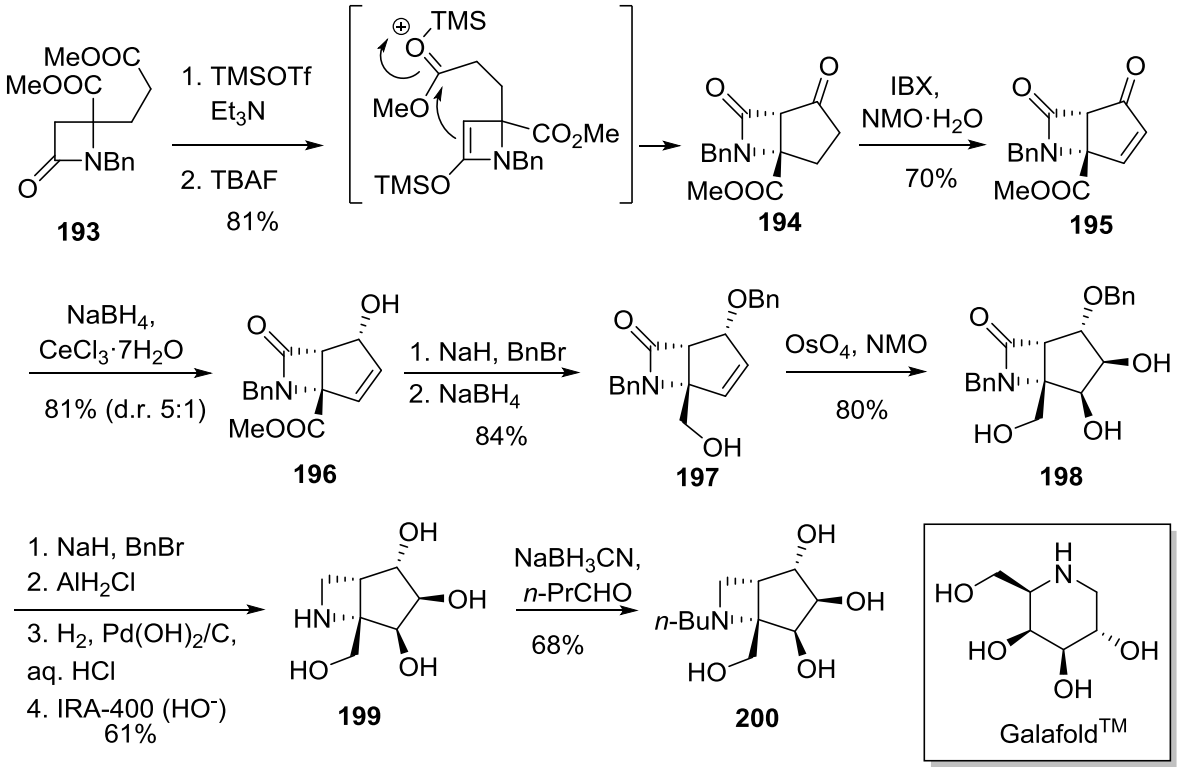

Scheme 31. Synthesis of constrained bicyclic iminosugars *via* cationic Dieckmann-type cyclisation.

The same authors reported the synthesis of diastereoisomers of **199** and **200** *via* the *m*-CPBA oxidation of alkene **197** which provided epoxide **201** as a single diastereoisomer in 88% yield (Scheme 32).[100] After benzylation of the hydroxymethyl group, epoxide-ring opening could be efficiently achieved, with complete regioselectivity, using catalytic sulfuric acid in acetic acid. Applying the same end game sequence used for the preparation of compounds **199-200** yielded 1-deoxygulonojirimycin bicyclic analogue **203** as well as its *N*-butyl derivative **204** (racemic form). Unfortunately, none of the four amino-tetrols **199**, **200**, **203** and **204** were potent inhibitors of any glycosidase among the test panel (*Saccharomyces cerevisiae* α-glucosidase, almond β-glucosidase, green coffee beans α-galactosidase, *E. coli* β-galactosidase and Jack bean α-mannosidase).[100]

In the course of their work towards the 6-azabicyclo[3.2.1]octane ring system, Grainger *et al.* synthesized the bicyclic β-lactam diols **210** and **211** as well as triol **212** (Scheme 33).[103] Starting from compound **205**, carbamoyl diethyldithiocarbamate **206** was readily prepared in two steps. The bicyclic skeleton was then formed in 84% yield by way of photo-induced 4-*exo*-*trig* radical cyclisation, with the dithiocarbamate moiety being transferred to the less hindered face of the resulting β-lactam **207** – obtained as the sole isolated product. Regioselectivity of the following dithiocarbamate elimination was found to be dependent on the methodology used: α,β-unsaturated β-lactam **208** was thus formed almost quantitatively through base mediation, whereas thermal reaction led to its β,γ-unsaturated counterpart **209** in 80% yield. Dihydroxylation of lactam **208** afforded *syn*-diol **210** in good yield. In the other hand, β-lactam **211** was obtained following a two-step sequence; the *trans* relationship was achieved through epoxidation of lactam **208** followed by regioselective opening. Three hydroxyl groups could be introduced elegantly into β,γ-unsaturated β-lactam **209**. Regioselective base-mediated ring-opening of the epoxide generated from **209** afforded an allylic alcohol intermediate which was subjected to dihydroxylation reaction after protection as a benzoate ester to give β-lactam **212** in good overall yield (56% from **209**).

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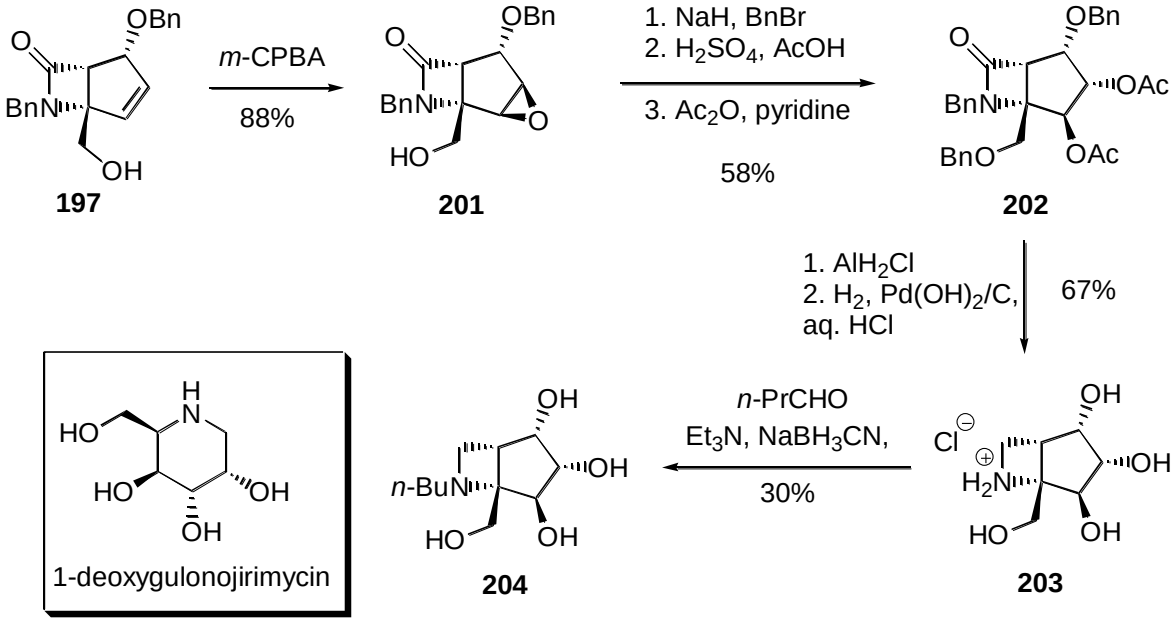
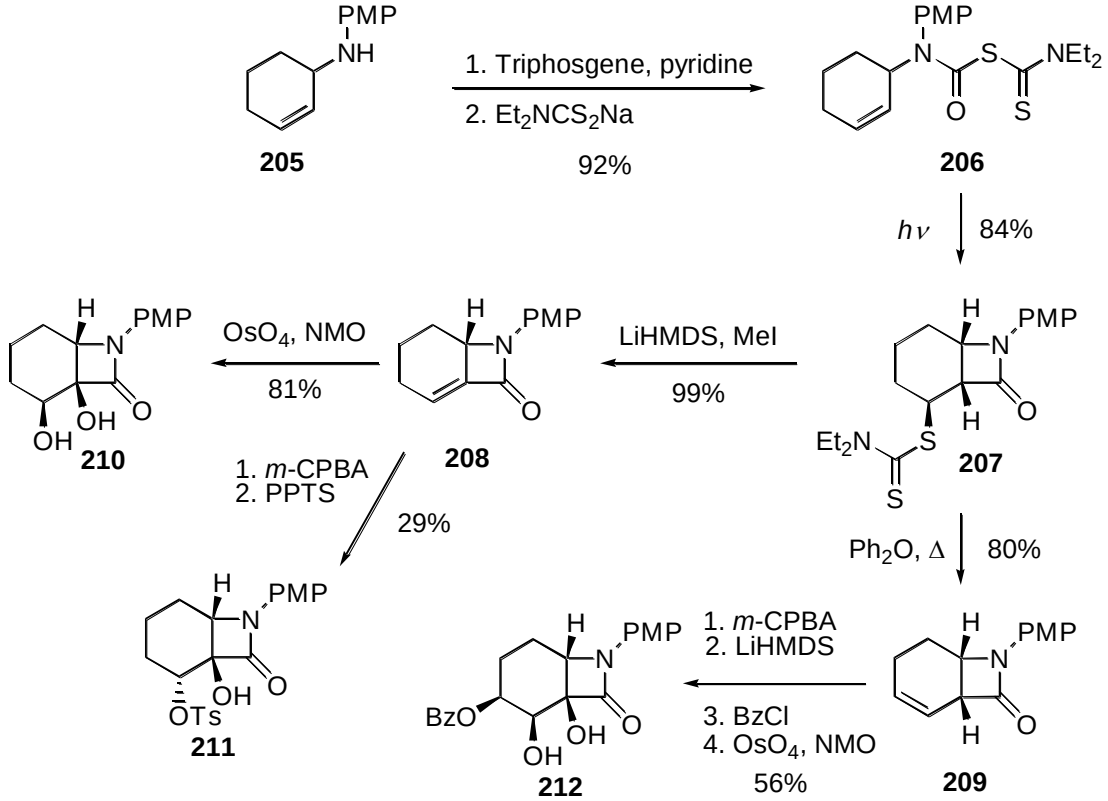


Scheme 32. Synthesis of bicyclic 1-deoxygulonojirimycin analogs **203** and **204.**



Scheme 33. Synthesis of bicyclic β-lactam *via* photo-induced 4-*exo*-*trig* radical cyclisation.

3.3 Bicyclic systems having an additional ring heteroatom

Few examples of constrained bicylic iminosugars containing an additional endocyclic heteroatom have been described. β,δ-Dilactam **217** was obtained as an intermediate in the synthesis of carbacephem precursors developed by the group of Saito (Scheme 34).[104] Starting from enantiopure aldehyde **213**, the β-lactam ring

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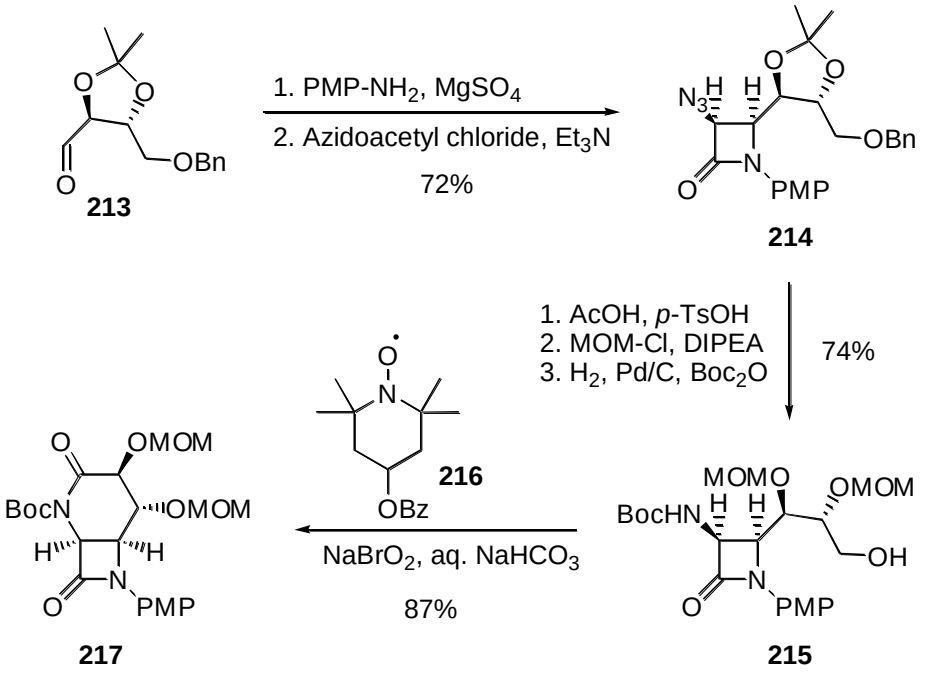
was formed by way of Staudinger cycloaddition using *in situ* generated azidoketene, leading to the *cis*-β-lactam **214** as a single diastereoisomer. After protecting group manipulation, the one-pot debenzylation / azido reduction and Boc-protection of the resulting amine efficiently afforded **215**. TEMPO-like oxidation of the free primary alcohol using **216** triggered the formation of a hemiaminal intermediate which was further oxidized to a δ-lactam, thus providing bicyclic dilactam **217** in 87% yield.



Scheme 34. Synthesis of the bicyclic β,δ-dilactam **217**.

Rai *et al.* reported an original synthesis of fused iminosugar β-lactams **219** by way of iodine/ionic liquid-catalyzed [1C+2C+1N] three-components one-pot coupling (Scheme 35).[105] Unprotected carbohydrates, 2-phenyl-2-oxazolan-5-one **218**, and aromatic amines were used as one carbon, two carbons and nitrogen sources, respectively. In this process, imidazolium hydroxide-mediated deprotonation of **218** is expected to trigger a Mannich-type reaction affording adducts **221**. The β-lactam ring is then formed upon activation of the carbonyl moiety by iodine, leading to **219** through intermediate **222**. This methodology was applied to D-glucose and D-xylose in the presence of aniline derivatives. All resulting fused iminosugar β-lactams **219** were obtained in good yields and with a high *cis* diastereoselectivity.

While working on the synthesis of polyhydroxylated azetidines, the group of Dhavale obtained unprecedented furan-based bicyclic iminosugars **231** and **232** (Scheme 36).[106] D-Glucose derivative **223**[107] was engaged in a Corey-Link and Jocic-Reeve-type protocol, affording **225** through azidation of an *in situ* generated chlorooxirane intermediate. Compound **225** was then converted in three steps to the key intermediate **226**. Oxidative cleavage of the free diol followed by reduction and activation of the resulting primary alcohol led to tosylate **227**. Subsequent reduction of the azide to amine function triggered the azetidine ring closure, providing fused sugar azetidine **228** in 79% yield. Compound **226** could also undergo selective benzylation of its primary alcohol. In this case, straightforward activation of the remaining free hydroxyl group followed by azide to amine reduction did not allow the formation of the expected bicyclic product. Instead, the azido group had to be reduced first and the resulting amine protected as a carbamate before performing an alcohol mesylation in order to reach the actual cyclisation precursor **229**. Fused sugar azetidine **230** was obtained in

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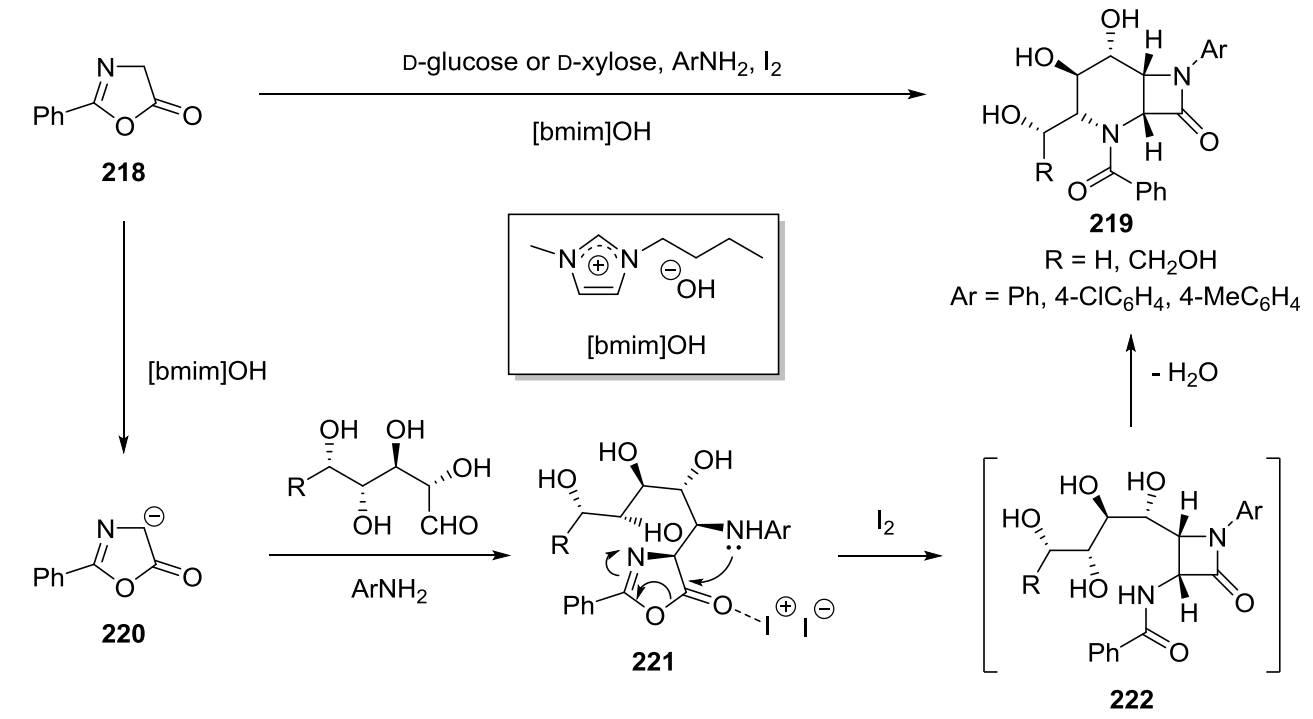
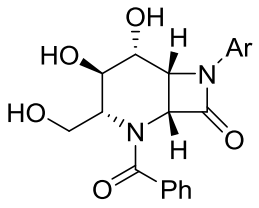
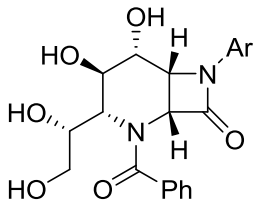
95% yield by treatment of mesylate **229** with potassium carbonate. Interestingly, hydrogenolysis of **230** led to the corresponding *N*-COOH derivative **231**. The key role of the 5-CH_2OBn moiety in **228** in the outcome of this final deprotection step is illustrated by the synthesis of free bicyclic azetidine **232** obtained after full cleavage of both benzyl and carbamate protecting groups. Fused furanose azetidines **231** and **232** were found to be moderate inhibitors of *Aspergillus niger* amyloglucosidase. Diol **231** is also a moderate inhibitor of coffee bean α-galactosidase as well as a weak inhibitor of rat intestinal β-glucosidase.[106]





219a, Ar = Ph (94%, *cis*/*trans* 97:3)
219b, Ar = 4-ClC_6H_4 (90%, *cis*/*trans* 99:1)
219c, Ar = 4-MeC_6H_4 (87%, *cis*/*trans* 96:4)



219d, Ar = Ph (91%, *cis*/*trans* 98:2)
219e, Ar = 4-ClC_6H_4 (86%, *cis*/*trans* 99:1)
219f, Ar = 4-MeC_6H_4 (92%, *cis*/*trans* 95:5)

Scheme 35. Synthesis of fused iminosugar β-lactams **219** *via* iodine/ionic liquid-catalyzed [1C+2C+1N] three-components one-pot coupling.

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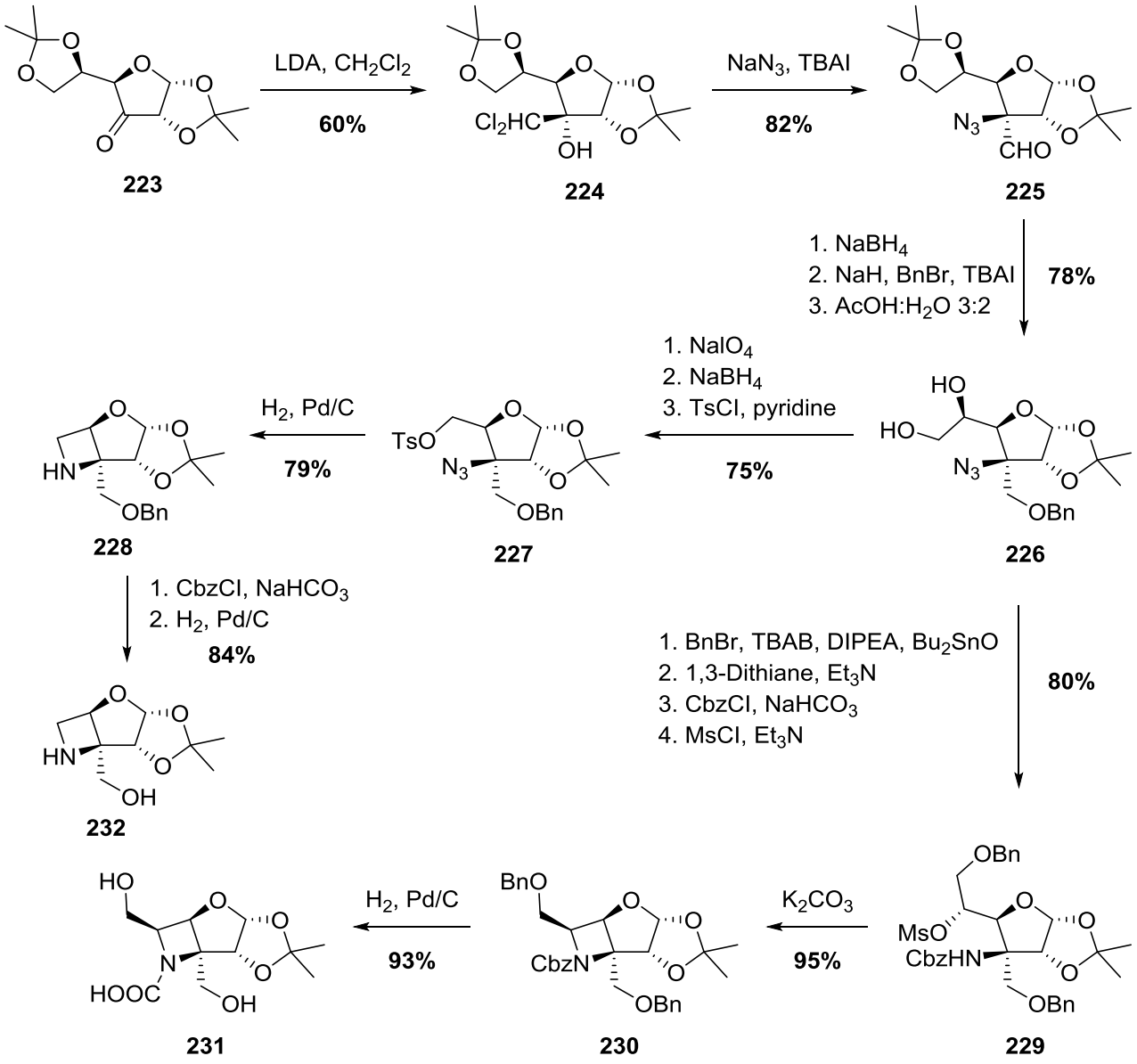

Scheme 36. Synthesis of fused sugar azetidines **231** and **232.**

4. Conclusions

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

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bicyclic iminosugars is still to be explored. The field is thus wide open for exciting discoveries and organic chemistry has an important role in designing and synthesizing promising molecules.

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Pr Philippe Compain gained his Engineer degree at CPE Lyon. In 1998, he was awarded the Dina Surdin Prize from French Chemical Society for his PhD research on alkaloid synthesis (Group of Prof. J. Goré, Lyon). After a postdoctoral stay at Montreal with Prof. S. Hanessian, he was appointed *Chargé de Recherche* at CNRS (Group of Prof. O. R. Martin, ICOA, Orléans). In 2008, he accepted a full professorship at the University of Strasbourg. He is now Professor of Organic Chemistry in this University and at the European Engineering School of Chemistry, Polymers and Material Science (ECPM) where he heads the research group "Organic Synthesis and Bioactive Compounds" (SYBIO). His research interests span from synthetic methodologies to glycomimetics, from square sugars to multivalent sweet giants. He is co-editor of a book untitled Iminosugars: from synthesis to therapeutic applications (Wiley-VCH). In 2010, Pr. Compain has been made Junior Member of the Institut Universitaire de France (IUF) and elected Fellow of the Royal Society of Chemistry in 2016. He is currently Vice-President of the "Groupe Français des Glycosciences" (the French network in Glycosciences).

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Dr Damien Hazelard obtained his PhD in 2005 under the supervision of Dr A. Fadel (Paris-Sud University). In 2006, he performed a post-doctoral training in the field of organocatalysis in the group of Pr Y. Hayashi at the Tokyo University of Science. Then he joined the group of Pr F. Colobert to work on total synthesis at the University of Strasbourg. He was appointed in 2010 as assistant professor at the same university in the group of Pr. P. Compain. His current research interests deal with the development of new synthetic methodologies for the synthesis of nitrogen heterocycles related to glycomimetics.

Dr Raphaël Hensienne performed his doctoral research under the supervision of Pr P. Compain and Dr D. Hazelard at the University of Strasbourg, where he worked on the synthesis of bicyclic iminosugars. Having successfully defended his PhD in 2016, he is currently a postdoctoral researcher in the group of Pr S. Hanessian at the University of Montreal. At the core of his research interests lies the synthesis of challenging molecules with potential biological activity and therapeutic applications through the development of innovative methodologies.

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