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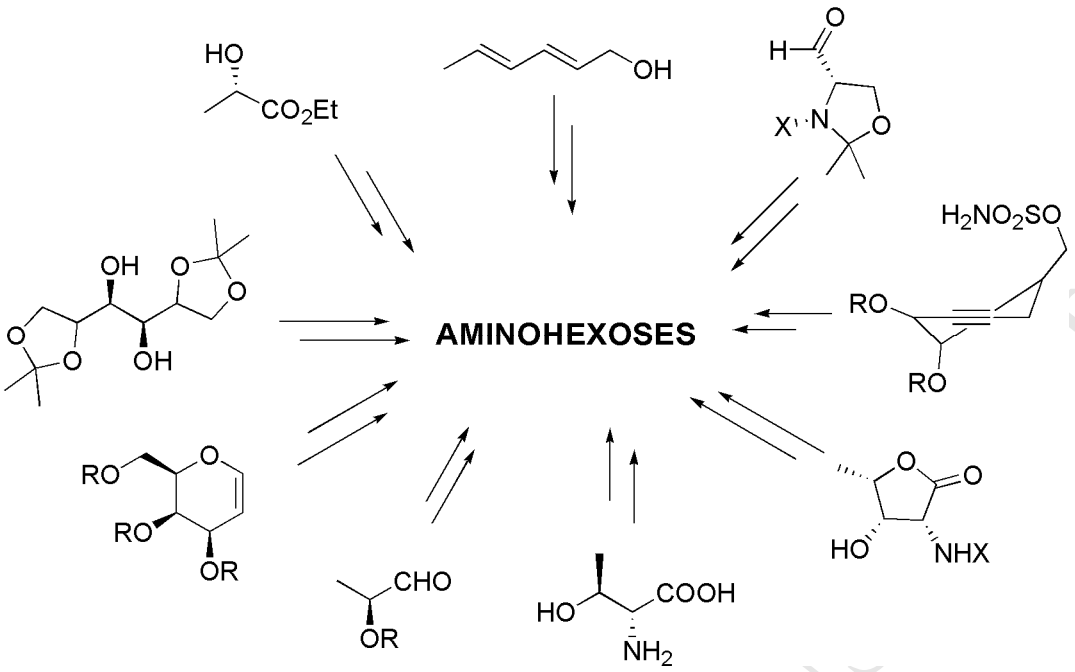

Biosynthetic and synthetic access to amino sugars

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ABSTRACT

Amino sugars are important constituents of a number of biomacromolecules and products of microbial secondary metabolism, including antibiotics. For most of them, the amino group is located at the positions C1, C2 or C3 of the hexose or pentose ring. In biological systems, amino sugars are formed due to the catalytic activity of specific aminotransferases or amidotransferases by introducing an amino functionality derived from L-glutamate or L-glutamine to the keto forms of sugar phosphates or sugar nucleotides. The synthetic introduction of amino functionalities in a regio- and stereoselective manner onto sugar scaffolds represents a substantial challenge. Most of the modern methods of for the preparation of 1-, 2- and 3-amino sugars are those starting from “an active ester” of carbohydrate derivatives, glycals, alcohols, carbonyl compounds and amino acids. A substantial progress in the development of region- and stereoselective methods of amino sugar synthesis has been made in the recent years, due to the application of metal-based catalysts and tethered approaches. A comprehensive review on the current state of knowledge on biosynthesis and chemical synthesis of amino sugars is presented.

Keywords

Amino sugars; biosynthesis; aminohydroxylation; tethered synthesis; regio/diastereoselectivity

1. Introduction

Amino sugars are sugar derivatives in which at least one of the hydroxyl functionalities is substituted with an amino group. Introduction of an amino group into hexose or pentose structures significantly changes physicochemical properties of these molecules and in consequence, may also strongly affect their biological activity. Amino sugars can be obtained by a total synthesis or from sugars by site-specific introduction of the amino functionality. Some of these aspects were addressed in reviews published in the 1963-2010 period.[1-5] Other review publications, aimed at the biochemistry of amino sugars and their derivatives, were presented in the previous century.[6,7] In this work, we summarize the present knowledge on chemistry and biochemistry of amino sugars.

2. Amino sugars of natural origin – structures and functions

A number of amino sugars are components of the living matter. More than 60 have been described and the most important ones are listed in Table 1. The only amino sugar of natural origin synthesized in an intact, unbound form is an antibiotic kanosamine, *i.e.* 3-amino-3-deoxy-D-glucose, although it is also a constituent of another antibiotic, kanamycin A. The majority of amino sugars are the components of more complex molecules, mainly antibiotics or biomacromolecules such as chitin, glycoproteins, lipopolysaccharides, or mucopolysaccharides.

[Table 1]

The most abundant amino sugars which are the products of a primary metabolism, are D-glucosamine (GlcN), D-mannosamine (ManN), D-galactosamine (GalN) and their *N*-acetyl derivatives, GlcNAc, GalNAc and ManNAc. Chitin, the second most abundant polysaccharide after cellulose, is a β-1,4-linked homopolymer of GlcNAc. Specific rheological properties of glycosaminoglycans (mucopolysaccharides) and proteoglycans are

in part due to the presence of amino sugar derivatives, GlcNAc or GalNAc.[8,9] GlcNAc, GalNAc and ManNAc are components of numerous glycoproteins and structural polysaccharides present in the microbial cell walls, such as peptidoglycan and lipopolysaccharides in bacteria and chitin and mannoproteins in fungi. Other amino sugars of natural origin are most often constituents of different products of secondary metabolism, including antibiotics. Mycosamine is present in polyene macrolide antifungal antibiotics, amphotericin B and nystatin.[10,11] Ribosamine is a component of puromycin, desosamine is present in erythromycin, daunosamine occurs in the anticancer anthracycline daunomycin and different amino sugars and its derivatives are found in aminoglycoside antibacterial antibiotics. In each case, the amino sugar moiety is important for biological activity of these antimicrobials.[12]

3. Methods of amino sugar synthesis

A number of amino sugars are derived from biosynthesis, where the conversion of a monosaccharide, usually in the form of sugar phosphate or sugar nucleotide, to the corresponding amino sugar derivative is catalyzed by a specific aminotransferase or an amidotransferase. On the other hand, the chemical preparation of amino sugars is possible by a total synthesis from precursors, such as alcohols, aldehydes, carboxylic acids, esters and lactones or amino acids or by the regio- and stereospecific introduction of an amino functionality into appropriate sugar or sugar-derived substrate by nucleophilic substitution or addition.

3.1. Amino sugar biosynthesis

3.1.1. Amino sugars derived from primary metabolism

A biosynthetic route from sugar to amino sugar involves transfer of the amino group from an amino acid donor (usually L-glutamate or L-glutamine) to the keto function of a ketose derivative in the open form or to the keto carbon atom generated in the preceding reaction

upon oxidation of a C-OH of the closed form of an aldose derivative. The amino transfer is catalyzed by the specific enzyme, namely either a PLP-dependent aminotransferase or a PLP-independent amidotransferase, in a stereospecific manner. The acceptor substrate is usually a sugar phosphate or a sugar nucleotide. The only reaction of this type in the primary metabolism gives rise to D-glucosamine-6-phosphate formed from D-fructose-6-phosphate and L-glutamine. The reaction is catalyzed by L-glutamine: D-fructose-6-phosphate amidotransferase (hexose isomerizing), EC. 2.6.1.16, known under a trivial name of glucosamine-6-phosphate (GlcN-6-P) synthase. The enzyme is widely distributed in Nature and is present in almost all living organisms. One of the very few exceptions to this rule is the protozoan *Giardia lamblia*, lacking GlcN-6-P synthase, where GlcN-6-P is formed from Fru-6-P and ammonia in the reaction catalyzed by GlcN-6-P deaminase,[46] a catabolic enzyme in all other organisms.

GlcN-6-P synthase does not require any coenzyme and catalyzes a complex, irreversible reaction that involves transfer from the amide group of L-glutamine to D-Fru-6-P and subsequent ketose-aldose isomerization of the fructoseimine intermediate as shown in Scheme 1. More information about the enzyme may be found in the review papers.[47,48]

[Scheme 1]

GlcN-6-P formed in the reaction catalyzed by GlcN-6-P synthase is subsequently converted into UDP-GlcNAc in a series of the three consecutive reactions, known as the Leloir pathway.[49,50] This sugar nucleotide serves as a GlcNAc donor in biosynthesis of structural polysaccharides, such as chitin, peptidoglycan, glycosaminoglycans and glycoproteins. UDP-GlcNAc gives also rise to the respective sugar nucleotides of ManNAc and GalNAc formed in the reaction catalyzed by uridine diphosphate-*N*-acetylglucosamine-2-epimerase and uridine diphosphate-*N*-acetylglucosamine-4-epimerase, respectively.[51,52] ManNAc is a precursor of sialic (neuraminic) acid (Neu5Ac), formed upon aldolase-catalyzed condensation

of ManNAc and pyruvate (Scheme 2). Neu5Ac is in turn an important common component of glycoproteins involved in intercellular communication and recognition. Chemistry and biochemistry of Neu5Ac and its derivatives that is outside the scope of this review, have been extensively studied and the reader is referred to the recent reviews on this subject.[53,54] *N*-Acetyl-L-fucosamine present in lipolysaccharides of some bacteria, including *Pseudomonas aeruginosa* is derived from UDP-GlcNAc,[55] while origin of D-fucosamine participating in formation of teichuronic acids of *Bacilli* is unknown.

[Scheme 2]

3.1.2. Amino sugars derived from secondary metabolism

[Figure 1]

Biosynthesis of amino sugars deriving from the secondary metabolism routes (Table 1 and Figure 1) involves introduction of the amino functionality by a PLP-dependent aminotransferase. The best characterized is the enzyme participating in the biosynthesis of 3-amino-3-deoxy-D-glucose (kanosamine). The biosynthetic pathway leading from glucose-6-phosphate to kanosamine in *Bacillus subtillis*[56] is shown in Scheme 3. Amination of 3-oxo-D-glucose-6-phosphate in this pathway is catalyzed by the *Ntd*A aminotransferase. This enzyme was isolated and its structure was determined.[57]

[Scheme 3]

Kanosamine is produced by *Bacillus subtilis*, *Bacillus circulans* and *Bacillus aminoglucosidicus* and exhibits growth inhibitory effect against some bacteria, including *S. aureus* and *K. pneumonia*,[58] and yeasts, *S. cerevisiae* and *C. albicans*.[59] Mechanism of its antimicrobial action involves transport by the hexose permease, phosphorylation to kanosamine-6-phosphate (K6P) and inhibition of GlcN-6-P synthase by K6P.[59,60] Another biosynthetic route for kanosamine formation operates occurs in *Streptomyces* spp. producing kanamycin A, in which kanosamine is one of the components. Kanosamine and UDP-

kanosamine are also the specific intermediates in the biosynthesis of 3-amino-5-hydroxybenzoate, a precursor of the mitomycin and ansamycin antibiotics, including rifamycin B.[61] Biosynthesis of kanosamine in *Streptomyces* involves phosphorylation of glucose to glucose-1-phosphate, followed by pyrophosphorylation to UDP-glucose. The sugar nucleotide is subsequently oxidized to UDP-3-oxo-D-glucose. Transamination of UDP-3-oxo-D-glucose yields UDP-kanosamine, which is finally hydrolyzed to form kanosamine.[62-64]

Other amino sugars derived from microbial secondary metabolism are components of more complex molecules, mostly antibiotics. Desosamine, 3-(dimethylamino)-3,4,6-trideoxy-D-glucose present in erythromycin is formed from glucose in a six-step pathway involving amination of TDP-3-oxo-6-deoxy-D-glucose by *Des*V aminotransferase[65] followed by dimethylation catalyzed by *N,N*-dimethyltransferase *Des*VI.[66] Perosamine (4-amino-4,6-dideoxy-D-mannose) in *Vibrio cholerae* is formed as a GDP-linked derivative from GDP-4-keto-6-deoxy-D-mannose, in reaction catalyzed by perosamine synthase.[67] Amination of GDP-3-keto-6-deoxy-D-mannose by GDP-3-keto-6-deoxy-D-mannose 3-aminotransferase *Nys*DII affords GDP-mycosamine (GDP-3-amino-3,6-dideoxy-D-mannose), a precursor of the D-mycosamine moiety, present in an antifungal antibiotic nystatin produced by *Streptomyces noursei*.[68] TDP-daunosamine, a precursor of the daunosamine moiety in an anticancer antibiotic daunorubicin, is derived from 3,4-diketo-2-deoxy-D-rhamnose, which is aminated at C3 by the product of the *dnm*J gene.[69] Other 3-amino-2,3,6-trideoxy-hexoses present in anthracyclines or vancomycins, including L-ristosamine, L-acosamine and L-vancosamine, are formed from respective 3-keto-2,6-dideoxy-hexoses in a similar manner.[70] D-Gulosamine (2-amino-2-deoxy-D-gulose) present in atypical aminoglycosides, comes from the epimerization and deacetylation of *N*-acetyl-D-galactosamine.[71] UDP-*N*-methyl-D-glucosamine-6-phosphate was identified as a precursor for biosynthesis of *N*-methyl-L-glucosamine, a component of streptomycin.[72]

3.2. Synthesis of aminosaccharides

Synthetic strategies that have been employed in the synthesis of amino sugars include substitution reaction on various carbon atoms in the sugar core, cleavage of an epoxide ring with amines, reduction of oxime and azide derivatives, addition to double bonds in glycal substrates, asymmetric and total synthesis.

3.2.1. Methods involving the S_N2 reaction

Some aminosaccharides are easily accessible from monosaccharides through the bimolecular nucleophilic substitution (S_N2). The most common strategy involves the formation of an "active ester" sugar derivative, followed by replacement of the -OX leaving group by ammonia, hydrazine or an azide anion, in the classical S_N2 reaction. The hydrazides and azides thus obtained are finally reduced with hydrogen to give the expected amino sugars (Scheme 4).

[Scheme 4]

The sugar derivatives most often used are sulfonate esters, namely tosyl,[73] mesyl,[74] trifluoromethane[75] or imidazolyl sulfonate.[76] Such derivatives are easily formed upon treatment of an appropriately protected sugar with sulfonyl chlorides or anhydrides. This method was used for the synthesis of several amino sugars, including amino derivatives of glucose,[75,77] ribose,[78,79] galactose[50] and allose[80] and in the synthesis of perosamine.[37,81] The choice of an aminating reagent in this reaction is not obvious. Although liquid ammonia is a reactive nucleophile and a good solvent, its application not always leads to the expected products. While in the reaction with 2,3- and 4,5-diisopropylidene 1-tosyl-L-sorbofuranose **1** as a substrate, a dimeric product **2** was obtained, presence of sodium amide led to the unequivocal formation of the expected amino sugar derivative **3**. A dimeric product was not formed in the reaction of 2,3-isopropylidene 1-tosyl-L-sorbofuranose (**4**, R_1=OH) and a 1,6-

diamino derivative was obtained with 2,3-isopropylidene 1,6-ditosyl-L-sorbofuranose (**4**, R_1=OTs) (Scheme 5).[82]

[Scheme 5]

Undoubtedly, use of azides or hydrazine leads to more unequivocal results. However, one must bear in mind that aminations involving azides call for longer reaction times and higher temperatures. Sodium azide is the most often used aminating reagent in these reactions and a number of amino sugar derivatives were obtained by nucleophilic substitution and subsequent reduction (Scheme 6) but use of trimethylsilyl azide instead of NaN_3 may result in higher reaction yields (Scheme 7).

[Scheme 6]

Using this method, 3-amino-3-deoxy-D-xylose,[12,83] 3-amino-3-deoxy-D-glucopyranose derivatives,[12,83,84] perosamine,[83,85] D-fucosamine,[84,86] amino derivatives of ribose,[78] D-daunosamine,[87,88] methyl-3-amino-4,6-*O*-benzylidene-2,3-dideoxy-α-L-*arabino*-hexapyranoside and methyl-3-amino-4,6-*O*-benzylidene-2,3-dideoxy-α-L-*ribo*-hexapyranoside,[89] 3-amino-3-deoxy-D-allose,[90] benzyl 2,4-diacetamido-3-*O*-acetyl-2,4,6-trideoxy-α-D-glucopyranoside,[91] 2,4-diacetamido-2,4,6-trideoxy-D-galactose,[91] methyl 2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranoside,[92] 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-L-talopyranoside,[93] D-mannosamine,[94-96] D-gulosamine[97] derivatives and 2-acetamido-4,5,6-tri-*O*-acetyl-3-(*tert*-butoxycarbonyl)amino-2,3-dideoxy-D-mannopyranose[98] were obtained. Derivatives of 4-azido-4-deoxy-L-arabinose,[99] 3-azido-α-D-glucopyranose, 3-azido-α-D-mannopyranose,[100] 2-azido-α-D-mannopyranose,[101] 5-azido-5,6-dideoxy- and 2,3-*O*-isopropylidene-α-L-talofuranoside,[102] as convenient substrates to obtain aminosaccharides, were also synthesized in the same manner.

[Scheme 7]

Another leaving group in the nucleophilic substitution can be a halogen atom. Using this strategy derivatives of 2-amino-2-deoxy,[103] 3-amino-3-deoxy,[103] 6-amino-6-deoxy-D-glucopyranose,[104] 2-azido-D-altropyranose and 3-azido-D-*arabino*-hexapyranose[103] were obtained.

Wolfrom and collaborators compared application of azide and hydrazine in the displacement reaction of secondary *O*-tosyl groups in different sugar rings. [105,106] The reactions with an azide ion afforded lower yields compared to those obtained with hydrazine, especially if the leaving group was located in the more hindered vicinity. The authors explained this phenomenon by an electrostatic repulsion between a negatively charged azide anion and electron pairs present on the oxygen atom connected to the C1 or C2 atoms in the sugar molecule. On the contrary, hydrazine bears no negative charge and exhibits comparable strong nucleophilic properties. The hydrazine and azide derivatives can be reduced with hydrogen to the desired amino derivatives. 5-Amino-3,6-anhydro-5-deoxy-1,2-*O*-izopropylideno-β-L-idofuranose (**6**) was obtained from the respective 5-*O*-tosyl substrate **5** treated with hydrazine and after subsequent reduction of the hydrazine formed. 3,5-Diamino-3,5-dideoxy-1,2-*O*-izopropylideno-α-D-ribofuranose (**8**) was synthesized in course of the reduction of a dihydrazine derivative **7** to diaminosacharide (Scheme 8).[104,106]

[Scheme 8]

Obviously, any amination according to the S_N2 mechanism results in inversion of configuration of an asymmetric carbon atom, so any application of this approach in synthesis of amino sugar derivatives is limited by availability of appropriate sugar substrates in which the configuration of the secondary C-OX reaction center is opposite to that required.

3.2.2. Synthesis *via* epoxide intermediates

Another synthetic strategy used in the preparation of amino sugars is ring opening in epoxysaccharides upon attack of ammonia or an amine. In this approach, there is no need for

the creation of an intermediate with a good leaving group but formation of a mixture of products should be expected, as a consequence of two possible directions of the nucleophilic attack. Relative ratio of these products depends on the stereo structure of an epoxy substrate. For example treatment of methyl 4,6-dimethyl-2,3-anhydro-β-mannoside **9** with ammonia leads to the formation of methyl 3-amino-3-deoxy-β-altroside **10** and methyl 2-amino-2-deoxy-β-glucoside **11**, with 9:1 ratio (Scheme 9).[107,108] Ammonolysis of 2,3-anhydro ring of allose, mannose and gulose derivatives leads to two *trans* isomers.[109] By using this strategy, the amino derivatives of hexoses, such as glucosamine,[107,109,110] altrosamine,[107,109] galactosamine,[107,109] mannosamine,[111] idosamine,[107,109,112-115] perosamine[116,117] and pentoses, such as xylosamine and arabinosamine[118] were obtained. A modification of this reaction was the use of an azide for the epoxide ring opening. In this way, D-daunosamine,[119] and methyl 2-acetamido-4-amino-2,4,6-trideoxy-α-D-gulopyranoside[92] were obtained and derivatives of 4-azido-D-glucose[120], 3-azido-D-mannose,[121] 3-azido-D-altrose,[121] 3-azido-D-idose,[121] 3-azido-D-glucose[120,121] and 2-azido-D-altrose[121,122] were synthesized, as convenient substrates for the subsequent reduction leading to amino sugars. Application of diethylamine as a nucleophilic agent allowed to obtain mycaminose, *i.e.* 3,6-dideoxy-3-(dimethylamino)-β-D-glucopyranose.[85]

[Scheme 9]

The epoxy derivatives can be used for the synthesis of amino dideoxysugars (Scheme 10). Reduction of the epoxide ring in **12** with lithium aluminum hydride leads to derivative **13**. Further oxidation of the hydroxyl group, oxime **15** formation and its subsequent reduction results in formation of a mannosamine derivative **16** (Scheme 10). The advantages of this strategy are mild reaction conditions and inexpensive, easily available starting materials. Based on the oxime formation a number of derivatives have been obtained including methyl 2-amino-2,3-dideoxy-α-D-mannopyranoside (**16**) (Scheme 10).[123] Modifications of this

method were applied for the synthesis of other dideoxysugars. After reduction of the epoxide ring with LAH, respective azidohexose derivatives were obtained, including those of D-acosamine and D-daunosamine.[70] *N*-Acetyl-L-ristosamine was prepared using a 2,3-*O*-benzylidene ring as an intermediate to form the respective ketone.[124]

[Scheme 10]

3.2.3. Synthesis *via* oximino intermediates

This synthetic strategy involves the stereoselective oxidation of a hydroxyl group to carbonyl functionality which is then converted into an oximino intermediate and subsequently stereoselectively reduced to obtain an amino group (Scheme 11). A disadvantage of this method is the formation of a mixture of products composition of which depends on a type of reducing agent and sugar derivative used. This method allows to introduce an amino group at appropriately selected carbon atom.[125] The following amino sugars have been prepared in this way: 5-amino-5-deoxy-D-glucose, 4-amino-4-deoxy-D-galactose, 4-amino-4-deoxy-L-arabinose,[125] 3-amino-3-deoxy-D-allose,[125-127] D-glucosamine,[128] 3-amino-3-deoxy-D-xylose,[125] D-galactosamine,[125,128-130] 2-amino-2-deoxy-D-mannose,[125,128,129] 2-amino-2-deoxy-D-talose,[129-131] kanosamine,[125,132] L-vancosamine,[133,134] L-fucosamine,[135] L-acosamine,[136,137] L-daunosamine,[137] 2-amino-2,6-dideoxy-L-talose.[135]

[Scheme 11]

The oxime intermediates can be also formed from carbohydrate halides **17** *via* the cobaloxime salts **18** subjected to photolysis in the presence of nitrous oxide to form an oxime **19** which can be easily reduced to amine (Scheme 12). Using this strategy a derivative of 2-amino-2-deoxy-D-mannopyranose **20** was obtained.[138]

[Scheme 12]

3.2.4. Addition to the double bond

Substrates used in these reactions are appropriately protected glycals,[139-143] *i.e.* sugar analogs containing an internal double bond. Addition of appropriate reagent(s) to this bond should result finally in the formation creation of C-NH_2 and C-OH bonds at the two neighboring carbon atoms, originally connected by a double bond.

3.2.4.1. Azide addition

The crucial point of this strategy is the addition of an azide to the double bond present in the *O*-protected glycal substrates. This method can be preferentially used for the preparation of 2-amino-2-deoxy derivatives but also allows attachment of an amino group to other carbon atoms. An exemplary synthesis of L-acosamine is shown in Scheme 13. Heating of L-rhamnal **21** in the presence of water gave hex-2-enopyranose **22,** which treated with sodium azide afforded **23**. Refluxing of the **23** intermediate with an inexpensive catalyst (K_{10} montmorillonite) led to the methyl acosaminide derivative **24**. Transformation of the 4-*O*-acetyl-3-azido-2,3,6-trideoxy-α-L-*arabino*-hexapyranosides (**24**) into the methyl acosaminide (**26**) was achieved in nearly quantitative yield in two steps, by transesterification of **24** with MeONa/MeOH giving **25**, followed by the catalytic hydrogenation in MeOH in the presence of 10% palladium-charcoal and triethylamine.[144] L-*arabino*-, L-*lyxo*- and L-*ribo*-hexapyranoside[145] derivatives and daunosamine[85,146] were obtained using this approach. Use of nitro glycals as substrates gives rise to diamino derivatives. 2,3-Diamino-2,3-dideoxy-D-glucose was synthesized using this methodology.[147]

[Scheme 13]

In the method described by Bovin and coworkers the addition of chloroazide to tri-*O*-acetyl-D-glucal was promoted by UV irradiation, to give the epimeric mixture of 1-chloro-2-azidoderivatives, which treated with glacial acetic acid and mercuric acetate afforded mixture of tetra-*O*-acetyl-2-azido-2-deoxy-D-glucose and tetra-*O*-acetyl-2-azido-2-deoxy-D-mannose (molar ratio 71:11) that could be easily converted into D-glucosamine and D-mannosamine.[148]

An alternative method of formation of chloroazide derivatives from glycals by addition of sodium azide in the presence of ferric chloride hexahydrate and hydrogen peroxide has been proposed more recently. This method was used for preparation of 2-azido-2-deoxy derivatives of D-glucose and D-galactose and in consequence D-glucosamine and D-galactosamine, respectively.[149]

Lemieux and Ratcliffe reported the synthesis of 2-amino-2-deoxy-D-galactose **28** from D-galactose, where the crucial step was azidonitration of the glycal intermediate **27** with sodium azide and $(NH_4)_2Ce(NO_3)_6$ (Scheme 14).[150] By using the analogous azidonitration, D-glucosamine,[151] D-fucosamine[152] and L-fucosamine[153,154] derivatives were also obtained.

[Scheme 14]

3.2.4.2. Photoinduced aziridination

A convenient method for the preparation of amino dideoxysugars is a photoinduced aziridination. Synthetic route leading to L-daunosamine involving this method is shown in Scheme 15. As a starting material for this synthesis, L-*threo*-hex-2-enopyranoside **29** was used. The acyl azide intermediate **30** upon irradiation with UV light was converted into aziridine derivative **31**.The regioselective aziridine ring opening upon hydrogenation over Pd/C catalyst, followed by treatment with barium hydroxide afforded L-daunosamine **32**. L-Ristosamine was obtained using the same method.[155]

[Scheme 15]

3.2.4.3. [3,3]-Sigmatropic rearrangement

Another method applying glycals as starting substrates is the [3,3]-sigmatropic rearrangement. A key step in this approach is the formation of 2-enopyranoside with trichloroacetimidyloxy group in an allylic position. The imine group in compound **33**, upon heating in xylene, attacks the C2 atom, forming a cyclic intermediate (not shown), which is subsequently opened, towards formation of **34**. Despite the possibility of attack on the double

bond from the bottom side of the ring an alternative product is not formed. Stereoselectivity of this reaction is probably due to the steric hindrance at C1. Using this method, derivatives of mannosamine **35**,[156] idosamine,[156] altrosamine[156,157] and talosamine[156,157] were obtained.

[Scheme 16]

3.2.4.4. [4+2] Cycloaddition

[4+2] Cycloaddition of azodicarboxylates **37** to glycols **36** affords the dihydrooxadiazine ring, which can be opened with methanol, and subsequent catalytic hydrogenation gives the amino sugar derivative **38** (Scheme 17). Methyl tetra-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranoside, methyl *N*-acetyl-*O*-trisilyl-D-glucopyranoside,[158] methyl 2-amino-2-deoxy-α-D-idofuranoside[159] and derivatives of 2-amino-2-deoxy-β-D-galactopyranoside and 2-amino-2-deoksy-β-L-glucopyranoside[160,161] were obtained using this approach.

[Scheme 17]

3.2.4.5. [1,3]-Dipolar cycloaddition

An example of this method for the preparation of amino sugars is shown in Scheme 18. Treatment of glycals **39** with benzyl azides in triethylorthoformate as a solvent gives rise to the formation of triazoline intermediates **40**, which upon irradiation form the *N*-benzyl aziridine rings (**41**). Further treatment with a strong base affords an aminoglycoside derivative. Such dipolar cycloaddition can be used to obtain 2-amino-2-deoxyglycosides **42**.[162,163]

[Scheme 18]

3.2.4.6. Tethered aminohydroxylation

Another method of introduction of an amino functionality to glycals is the osmium-catalyzed tethered aminohydroxylation. Oxazolidinones formed as intermediates are subsequently hydrolyzed in an aqueous solution of lithium hydroxide. Preparation of methyl 3-amino-3-deoxy-α-D-talopyranoside **43** involving this method is shown in Scheme 19.[164] An

alternative catalyst for tethered aminohydroxylation is rhodium(II).[165-167] The use of manganese nitrido complex facilitated synthesis of derivatives of the following amino sugars: D-glucosamine, 6-deoxy-D-glucosamine, D-galactosamine, 2-amino-2-deoxy-D-altrose.[161,168] Application of the iodo-oxazoline intermediate allowed to obtain L-daunosamine and related amino sugars, including L-risostamine.[169]

[Scheme 19]

3.2.4.7. Sulfonamidoglycosylation

In this reaction, iodine and sulfonamide are added to the two neighboring carbon atoms connected by a double bond in the glycal substrate. Subsequent formation of the aziridine intermediate, followed by hydrolysis, results in an eventual shift of the sulfonamide functionality to the carbon atom originally connected with iodine, with concomitant inversion of configuration (Scheme 20). The reaction with triethylamine in H_2O/THF results in migration of nitrogen from C1 to C2 and introduction of a hydroxyl group at the anomeric position in **45**. The *N*-sulfonated derivatives of D-mannose and D-glucose (82% yield) were obtained in this way.[170-172] An inspiration for this synthesis was a previously described method based on the treatment of glycal **44** with iodine azide (N_3I) and trimethylphosphite. That reaction was not stereoselective and led to the formation of two stereoisomers.[173,174]

[Scheme 20]

3.2.4.8. Acetamidoglycosylation

Acetamidoglycosylation of glycals **46** as shown in Scheme 21 results in an oxazoline intermediate **47**, giving rise to an amino sugar derivative **48**.[175] The reaction proceedes with good stereoselectivity in 45-73% yield. Replacement of the sulfoxide reagent with dibenzothiophene-5-oxide (DBTO) or its 2,8-dimethyl derivative (DMDBTO) further improves the diastereoselectivity of this reaction from gluco- to mannopyranoside.[176]

[Scheme 21]

3.2.4.9. Selective tandem hydroamination

This stereospecific synthesis allows to obtain aminoglycosides or aminosaccharides in one-pot reaction. An appropriately protected glycal is treated with O and N nucleophiles in the presence of $BF_3 \cdot Et_2O$ (Scheme 22). Tertiary, secondary or primary alcohols are used as *O*-nucleophilic reagents. The best yields (~80%) were obtained using sterically non-hindered alcohols. The *N*-nucleophile has been usually an aromatic or aliphatic sulfonamide. This methodology was used for the preparation of L-ristosamine and L-*epi*-daunosamine derivatives.[177]

[Scheme 22]

3.2.4.10. Epoxidation and aziridination

Sugai and coworkers proposed a method of D-mannosamine formation, in which two intermediates containing three-membered rings, epoxide **50** and aziridine **52**, were formed, as shown in Scheme 23. The starting substrate, hex-2-enopyranoside **49**, was oxidized with UHP to the epoxide derivative **50**, as the *syn*/*anti*- mixture (molar ratio 87:13). The *syn*-**50** isomer was subsequently opened with sodium azide, to give the mixture of regioisomeric azide derivatives **51ab** (molar ratio 74:28), which were converted under Staudinger conditions to aziridine and acetylated to give **52**. Treatment of aziridine **52** with sodium azide resulted in opening of the three-membered ring and in consequence of the intramolecular substitution, formation of an oxazoline **53**. Hydrolysis and subsequent deprotection afforded the 2-amino-2-deoxy sugar with *manno* configuration.[178]

[Scheme 23]

3.2.5. Addition to the carbonyl group

Addition of a nitrile group to the carbonyl moiety, followed by nitrile reduction may result in formation of spiro-aziridines intermediates. Subsequent catalytic hydrogenation in the

presence of Raney nickel leads to formation of amino sugars (Scheme 24). Using this reaction, derivatives of vancosamine[179,180] and glucosamine[181] were obtained**.**

[Scheme 24]

3.2.6. Synthesis of aminohexoses from pentoses

The amino group can be introduced into a sugar core in course of a sequence of reactions leading from pentose to 2-aminohexose. Nitromethane is used in this scheme for chain elongation and an amino group derived from ammonia is introduced at C2 upon addition to the double bond, present in the unsaturated nitro derivative. The route from D-arabinose **55** to D-mannosamine **56** is shown in Scheme 25.[169,182] D-Gulosamine was obtained from D-xylose in similar reactions.[170,183] In this way, desosamine[85,184] acosamine[185], methyl 3-amino-3-deoxy-α-D-mannopyranoside,[186] 3-amino-3,6-dideoxy-L-glucose and 3-amino-3,6-dideoxy-L-talose[187] were obtained.

[Scheme 25]

3.2.7. *De novo* synthesis of amino sugars

The stereoselective synthesis is an important objective in preparative chemistry of amino carbohydrates. Amino sugars are also interesting target molecules for the total synthesis. The main problem in this strategy is to plan the most convenient route for the synthesis of structurally complex aminosaccharides from commercial non-sugar sources.

3.2.7.1. From alcohols

Unsaturated alcohols are convenient substrates for the total synthesis of amino trideoxycarbohydrates. Stereoselective syntheses of *N*-trichloroacetyl derivatives of racemic 3-amino-2,3,6-trideoxyhexoses, namely daunosamine, ristosamine and vancosamine, from unsaturated alcohols were proposed by Hauser *et al*.[188] Daunosamine was obtained from a sorbyl alcohol **57** in a sequence of reactions shown in Scheme 26. In the first step, an amino group was introduced into the hydrocarbon chain by the Overman reaction, with a good yield.

The aldehyde functionality was generated from acetoxysulfide in water in the presence of $CuCl_2$. Hydroxylation of the olefinic moiety with a catalytic amount of osmium tetraoxide and TMNO finally gave a mixture of two products: a daunosamine derivative (**58a**) and its *xylo* isomer (**58b**) in 6:4 ratio.

[Scheme 26]

The vancosamine derivative was obtained as one of the components necessary for the total synthesis of vancomycin, with appropriately protected unsaturated amino alcohol as a starting substrate, as shown in Scheme 27.[189] For the purpose of incorporation into the vancomycin core, the 1-*O*-acetyl residue was substituted with fluorine.

[Scheme 27]

Commercially available mannitol derivative **59** was used as a substrate for the total synthesis of kanosamine **64**, as shown in Scheme 28.[183] This substrate was converted into an appropriately protected glyceraldehyde **60**, which was subsequently subjected to the cross-aldol condensation with an amino ketone **61** in the presence of the $Sn(OTf)_2$ catalyst. Subsequently, a stereoselective reduction of the ketone functionality in **62** with the borane:dimethylsulfide complex afforded intermediate **63**. The use of cerium(IV) ammonium nitrate (CAN) allowed release of a diene from the metal complex. Ozonolysis, aldehyde reduction with dimethylsulfide and deprotection led to the final formation of kanosamine **64**. A similar approach was used for the synthesis of 3-amino-3,6-dideoxyglucose and mycosamine.[190] Acosamine and ristosamine were obtained by the Henry reaction of 2-benzyloxypropanal with 1,2-*O*-isopropylidene-4-nitro-1,2-butanediol.[191] Kanosamine and 3-amino-3-deoxy-D-altrose were prepared by the cross-aldol condensation of the multiprotected D-glyceraldehyde obtained from mannitol and the divalent tin enol ether of racemic *N*-Boc-α-aminodienonetricarbonyl iron complex.[192]

[Scheme 28]

An enantioselective preparation of the diastereomeric 3-amino-2,3,6-trideoxy-hexoses was proposed by Ginesta *et al*.[193] The starting substrate, (2*E*)-hexa-2,5-dien-1-ol, was subjected to Sharpless catalytic asymmetric epoxidation. The regioselective ring opening with titanium diazidodiisopropoxide, followed by convenient functional group transformations, afforded the key aldehydes *cis*- or *trans*-**66** in any configuration. The diastereoselective addition of methylmetal reagents to these aldehydes followed by ozonolysis, gave access to derivatives of *epi*-daunosamine, acosamine, daunosamine and ristosamine, in a completely stereocontrolled manner. A route leading to D-daunosamine **67** is shown in Scheme 29.

[Scheme 29]

A vinyl epoxide **68** was used by Trost *et al*. as a starting substrate in the total synthesis of branched amino sugars, as shown in Scheme 30.[194] In the first step, the epoxide ring was opened with *p*-methoxybenzylamine in the palladium-catalyzed regio- and enantioselective ring opening reaction, in the presence of a chiral ligand **L1**. Oxidation with osmium tetraoxide afforded a mixture of diasteroisomeric triols **69** that were separated by column chromatography. The isolated proper diastereoisomer **70** was oxidized to aldehyde **71**with Dess-Martin periodinane. A vancosamine derivative **72** was obtained as the final product. The *ep*i-vancosamine may be obtained in the same way, when another diastereoisomer is isolated and subjected to the Dess-Martin oxidation.

[Scheme 30]

Weinstein *et al*. described synthesis of (-)-acosamine in which a detachable, tethered nitrogen nucleophile was used to generate the 1,2-aminooxygenation pattern from the bromovinyl alcohol **73** by the palladium-catalyzed aza-Wacker cyclization, resulting in the formation of the five-membered oxazolidine product **74**, with a high level of diastereoselectivity. In the final step, the oxazolidine ring was opened under acidic conditions with concomitant formation of the methyl-protected cyclic acetal **75** (Scheme 31).[195]

[Scheme 31]

3.2.7.2. From aldehydes or ketones

Aldehydes and ketones, especially α-hydroxyaldehydes, are convenient substrates for *de novo* synthesis of amino sugars. The amino group is usually introduced as a component of one of the substrates condensed with another aldehyde/ketone substrate. *N*-Acetyl-L-acosamine and *N*-benzoyl-L-ristostamine were obtained starting from coupling of the *O*-protected L-lactaldehyde **76** with methyl propiolate in the presence of LDA. The resulting alkyne **77** underwent reaction with chlorosulfonyl isocyanate, followed by hydrogenation in the presence of the Lindlar catalyst. The olefin **78** thus formed, was cyclized to oxazolidinone. Hydrolysis of both the carbamate and the ester groups, evaporation of the volatiles, and lactonization with acetic anhydride, followed by reduction with an excess of DIBAL-H afforded the amino sugar derivative. The route leading to *N*-acetyl-L-acosamine **79** is shown in Scheme 32.[196]

[Scheme 32]

The α,β-unsaturated ketones can undergo a hetero Diels-Alder reaction with an activated alkene, as shown in Scheme 33. Heating an enone **80** with activated alkene **81** in toluene gave two different glycals in ratio 1:9 (**82a**:**b**). Desosamine **83** was obtained from the glycal intermediate **82b**.[197]

[Scheme 33]

The α,β-unsaturated aldehyde was used as a starting substrate in the L-acosamine synthesis described by Menzel and others.[198] The key point in this strategy as shown in Scheme 34, is the Henry reaction of a nitroaldol **86** obtained from acrylaldehyde **85** with the *O*-protected α-hydroxyaldehyde **84**.

[Scheme 34]

Ermolenko and coworkers proposed an universal methodology for an asymmetric synthesis of 2-amino-2-deoxy sugars, starting from readily available chiral building blocks, 2,3-*O*-isopropylidene-glyceraldehyde and dilithiate, *via* the Julia olefination and subsequent dihydroxylation as the key steps. This method was used for the preparation of L-glucosamine, L-mannosamine and L-talosamine derivatives.[199,200] The pathway leading to L-mannosamine is shown in Scheme 35.

[Scheme 35]

Iodoxybenzoic acid (IBX) was proposed as a convenient reaction mediator in a synthetic pathway leading to L-vancosamine **89** as shown in Scheme 36. The first step in this pathway was an intermolecular Kishi-Nozaki coupling of vinyl iodide **87** and lactaldehyde **88**. IBX acted at subsequent steps as an oxidative reagent and a cyclization inducer.[201]

[Scheme 36]

Another example of a total synthesis starting from an aldehyde substrate is a two-step synthesis of D-mannosamine shown in Scheme 37. Enantioselective dimerization of *O*-TIPS α-hydroxyacetaldehyde **90** afforded a product **91** that was condensed with appropriately protected enamine **92** in the presence of Lewis - $TiCl_4$, to give a mixture of derivatives of D-mannosamine **93** and D-allosamine (10:1 ratio).[202]

[Scheme 37]

In a similar approach applied for the synthesis of desosamine (Scheme 38), coupling of α-hydroxyaldehyde **94** with an alkyne derivative was catalyzed by $Zn(OTf)_2$. The tungsten-catalyzed alkynol cycloisomerization led to a glycal **95** which was subsequently dihydroxylated, to give the final product.[203]

[Scheme 38]

Aldehydes can also undergo condensation with nitroalkenes which are useful reagents in *de novo* synthesis of aminosaccharides, due to their high reactivity with different nucleophiles.

An exemplary synthesis of the D-glucosamine derivative is shown in Scheme 39. An important advantage of such approach is that this route does not require isolation and purification of intermediates after each reaction step.[4,5,204]

[Scheme 39]

Seeberger and Leonori described a total synthesis of several amino sugars using a commercially available L-Garner aldehyde **96** as a starting substrate.[205] This compound was transformed into intermediate **97**. Dihydroxylation of aldehyde **97** under Upjohn conditions gave, after peracetylation with acetic anhydride, a derivative of D-fucosamine **98** in 81% yield, with 5:1 diastereoselectivity (C3–C4 *anti/syn*). Dihydroxylation of aldehyde **97** and further selective anomeric acetylation, gave intermediate **99**. After activation of the C4 hydroxyl group, compound **99** was finally converted to precursor of D-bacillosamine **100** (Scheme 40).[205,206] The 2,4-diacetamido-2,4,6-trideoxy-D-galactose was synthesized using a similar protocol, in which the Garner aldehyde was prepared from L-threonine.[207]

[Scheme 40]

A method of synthesis of 3-amino-3,6-dideoxyamino sugars starting from highly stereoselective titanium-mediated aldol addition of a chiral α-bromo ketone **101** to crotonaldehyde was presented by Nebot et al.[208] Further transformations of functional groups including a regioselective Staudinger–aza-Wittig reaction of an azidodiacetate, afford in a few steps and high yield the desired carbohydrates as advanced intermediates capable of participating in subsequent glycosylation reactions. The route leading to the ultimate formation of *N*-benzyloxycarbonyl-L-mycosamine **102** is shown in Scheme 41.

[Scheme 41]

3.2.7.3. From acids, esters or lactones

Carboxylic acids, their esters and lactones have been used as starting substrates in several methods of amino sugar synthesis. Racemic desosamine was prepared from methyl hexa-2,5-

dienoate **103**, which treated with polyphosphoric acid underwent cyclization to the parasorbic acid lactone **104**. Epoxidation, treatment of the epoxide with dimethylamine and the final reduction of the lactone **105** with DIBAL-H afforded the *rac*-desosamine **106** (Scheme 42).[209]

[Scheme 42]

The stereoselective synthesis of L-daunosamine was accomplished from diethyl L-(+)-tartrate **107** as a starting substrate, as shown in Scheme 43.[210] The key step in the total sequence was a stereoselective addition of α-lithio *N*,*N*-dimethylacetamide to the imine of 2,3-*O*-cyclohexylidene-4-deoxy-L-threose **108**, in the presence of zinc halide.

[Scheme 43]

Reaction of (*S*)-lactate **109** with vinyl ether and subsequent reactions of selective reduction and oxidation gave an intermediate **110** which was involved in the nitrile-acetate coupling reaction. In consequence of the condensation of **111** with the Grignard reagent, the derivative **112** was formed. The reduction of a double bond and subsequent acidic hydrolysis, afforded a lactone derivative **113**, which was finally reduced to the L-acosamine derivative **114** (Scheme 44).[211]

[Scheme 44]

An appropriately protected amino lactone **115**, obtained from L-lactate, was a starting substrate for the stereoselective synthesis of L-vancosamine (Scheme 45). Methylation of a carboanion prepared from the substrate **115** proceeded with high stereoselectivity. The Wittig reaction afforded an unstable methylene enol **116** which under acidic conditions cyclized to the vancosamine derivative **117**.[212]

[Scheme 45]

Another method of a total synthesis of L-daunosamine was proposed by Jurczak *et al*. The whole sequence of reactions is shown in Scheme 46.[213] The β-aminolactone **118** obtained from L-aspartic acid was converted into *N*,*O*-dibenzyl-*N*-*tert*-butoxycarbonyl-L-homoserinal

119. Reaction of this compound with vinylmagnesium chloride was highly stereoselective. Subsequent epoxidation, reductive ring opening and cyclization resulted in the formation of the L-daunosamine derivative **120**.

[Scheme 46]

In another method of synthesis of 3-amino-2,3,6-trideoxyhexoses, starting from ethyl sorbate **121**, the *cis*- or *trans*-oxazoline intermediates were assembled by an intramolecular conjugate addition of γ-trichloroacetimidoyloxy-α,β-unsaturated esters in an acyclic system.[214] A route leading to D-daunosamine and 3-*epi*-D-daunosamine is shown in Scheme 47.

[Scheme 47]

In another method of L-acosamine synthesis, sorbic acid 1**22** was converted in the first step to methyl ester and next treated with lithium *R*-*N*-benzyl-*N*-(α-methylbenzyl)amide. The single diastereoisomer of a β-aminoester **123** was formed in 72% yield. Oxidation of this intermediate allowed to obtain an unstable epoxide **124** that was immediately converted into lactone **125**. A sequence of four subsequent reactions led to the L-acosamine derivative **126**, as shown in Scheme 48.[215]

[Scheme 48]

3.2.7.4. From amino acids

The use of amino acids as starting substrates for *de novo* synthesis of amino sugars is advantageous because of the possible choice of a suitable, optically active compound. Several amino acids, including alanine, serine, threonine and aspartic acid, have been used for this purpose.

L-Alanine **127** was a starting material for the total synthesis of *N*,*N*-dimethyl-L-mycosamine, as shown in Scheme 49.[216] The initial deamination afforded 2-acetoxypropionic acid, with 96% retention of configuration. An anomeric mixture of methyl 2,3,6-trideoxy-α-L- and β-L-

hex-2-enopyranosid-4-uloses **128** obtained could be separated by column chromatography. Reduction of the keto group, followed by epoxidation and ring opening with dimethyl amine, gave the expected L-mycosamine derivative **129**.

[Scheme 49]

N-Benzoyl-L-daunosamine can be obtained from D-threonine D-**130** in a sequence of reactions shown in Scheme 50.[217] The amino acid after deamination was converted into a dioxolane aldehyde derivative **131** which was then subjected to the reaction with a Grignard reagent, leading to the inseparable mixture of epimeric alcohols, converted subsequently into azide derivatives **132**. The five further reactions afforded finally the L-daunosamine derivative **133**.

[Scheme 50]

N-Benzoyl-3-D-*epi*-daunosamine was synthesized by the reactions shown in Scheme 51.[218] *N*-Benzyloxycarbonyl-L-aspartic acid **134**, used as an initial substrate, was converted into lactone **135**. Reduction of the lactone **135** with DIBAL-H led to a lactol which was opened with 1,2-ethanethiol in acidic medium to give a hydroxythiolane. Oxidation with SO_3 afforded a protected α-aminoaldehyde **136**. The key step of this pathway was a cross-pinacol coupling of α-aminoaldehyde **136** with an excess of acetaldehyde, in the presence of a vanadium reagent. The *syn*,*syn*-3-amino-1,2-diol derivative **137** obtained as the major isomer was subsequently converted into a D-3-*epi*-daunosamine derivative **138**.

[Scheme 51]

N-Methyl-D-fucosamine was synthesized from L-serine **139** (Scheme 52).[219] The amino acid was first converted into the corresponding Schiff base **140**, with an appropriate protection of hydroxyl and carboxyl groups. After catalytic reduction of the ester functionality to aldehyde, addition of an alkenyllithium compound afforded the enol derivative **141**, with high diastereoselectivity (>20:1). The osmium-catalyzed dihydroxylation led to a mixture of

aminotriols which was resolved by column chromatography. The isolated proper isomer **142** was subjected to several further reactions, with the eventual formation of *N*-methyl-D-fucosamine **143** in 13% overall yield.

[Scheme 52]

Three amino acids were used in the total synthesis of L-fucosamine as shown in Scheme 53. L-Threonine L-**130** was converted into (4*S*)-*trans*-2,2,5-trimethyl-1,3-dioxolane-4-carboxaldehyde **144**,[220] while L-valine **145** and glycine **146** were used for preparation of (3*S*)-2,5-diethoxy-3-isopropyl-3,6-dihydropyrazine **147**.[221] Reaction of these two cyclic substrates gave the key intermediate **148**. After a selective hydrolysis of the pyrazine moiety and cyclization in acidic media, the fully protected lactone **149** was formed. Its reduction and deprotection led to D-fucosamine **150**.[222] Intermediate **147** was used also for the synthesis *N*-methyl-D-fucosamine[223] and D-galactosamine derivatives.[223,224]

[Scheme 53]

Another amino acid-based total synthesis of an amino sugar used L-threonine L-**130** as a starting substrate. The amino acid was first fully protected and subsequently reduced to aldehyde. The aldehyde was converted into enoate **151** under Horner-Wadsworth-Emmons type olefination reaction. Under conditions indicated in Scheme 54 the Z/E ratio of the products was 17:1. The aminal deprotection was selectively performed in neat acetic acid with concomitant lactonization. Oxidation with osmium tetroxide produced stereoselectively the diol lactone **152**. The 4-amino-4,6-dideoxygulose derivative **153** was finally formed after reduction with DIBAL-H followed by acidic methanolysis.[225] Using a similar strategy, a D-*epi*-daunosamine derivative was obtained.[226]

[Scheme 54]

3.2.7.5. From other substrates

Acosamine and ristosamine derivatives were prepared *via* stereoselective reductive cleavage reactions of a benzylidenated dihydroisoxazolyl diol **156**. The diol was prepared from 3-nitro-4,5-dihydroisoxazole **154** *via* sequential propynylation, Lindlar reduction and catalytic hydroxylation as shown in Scheme 55. Reaction of the nitrodihydrooxazole with excess of propynyllithium followed by alkyne hydrogenation led to the formation of an inseparable mixture of isomeric alkenes **155** (*Z/E* ratio 9:1). Subsequent conversions led to the ultimate formation of L-acosamine **157**.[227]

[Scheme 55]

2,3-*O*-isopropylidene-D-ribose mercaptal was a substrate for L-ristosamine (Scheme 56), L-acosamine and D,L-daunosamine synthesis. Oxidative cleavage of unprotected hydroxyl groups in the substrat **158** led to aldehyde which was subsequently subjected to chain elongation and azide addition. Separation of isomers was performed after formation of a dimethyl acetal intermediate **159**. The amino group was obtained in consequence of the azide reduction. Reductive desulfurization, deprotection and cyclization afforded finally L-ristosamine **160**.[228] In the same way, L-acosamine[228] and D,L-daunosamine derivatives[229] were obtained.

[Scheme 56]

An interesting approach seems to be the use of a oxazolidinone derivative **161** as a chiral auxiliary. The initial first deprotonation and attachment of the 3-carbomethoxypropionyl function derived from 3-carbomethoxypropionyl chloride allows to obtain **162** as a convenient substrate for aldol condensation. Application of LHMDS favors deprotonation of an α-carbon of the imide carbonyl instead of that of the ester **163**, thus ensuring high regioselectivity of reaction. After lactonization, an amino group was introduced to the lactone ring by DPPA. The carbamate formed was converted in a few simple steps into a ristosamine derivative **164**. Using this strategy, a daunosamine derivative was also obtained.[230]

[Scheme 57]

A total synthesis of *N*-acetylneuraminic acid **167** was accomplished with a sulfamate ester **165** as a substrate (Scheme 58). The initial reaction in the sequence leading to the formation of intermediate **166** was the C-C coupling in the sequential rhodium-catalyzed aziridination and the Barbier allylation at the anomeric position of D-glycal, catalyzed by trifluoroacetamide rhodium (II) (Rh_2[tfacam]$_4$) and the metal-allyl reagents. Among different metals tested in the Barbier allylation, the best results were obtained with indium, so that the optimal conditions for this reaction were In/KI/THF.[231] Recently, a similar synthesis was proposed by Murakami and co-workers, however the starting substrate was glucal, which in a single-step, namely a rhodium anion-catalyzed amidoglycosylation, was converted into D-glucosamine.[232]

[Scheme 58]

4. Protection of an amino group in amino sugars

Synthesis of amino sugar derivatives, particularly formation of amino sugar conjugates with other compounds, often calls for appropriate suitable protection of the amino functionality. A number of different protective groups have been employed for this purpose. Most of them are the same that are used for the protection of α-amino functionality in peptide chemistry but a few specific reagents providing amino protection in amino sugars are also known.

The “classical” protective groups are: acetyl (Ac), benzyloxycarbonyl (Z, Cbz) and fluorenylmethyloxycarbonyl (Fmoc) and examples of the respective *N*-protected amino sugar derivatives include *N*-acetyl-D-galactosamine,[233] *N*-acetyl, and *N*-benzyloxycarbonyl-D-glucosamine,[234] *N*-acetyl-D-kanosamine,[235] *N*-acetyl-D-fucosamine,[236] 3-acetamido-3-deoxy-D-allopyranose,[125] and *N*-acetyl-D-mannosamine,[237] *N*-Fmoc-D-galactosamine,[238] *N*-Fmoc-D-mannosamine,[238] *N*-Fmoc-D-glucosamine[238] and *N*-Fmoc-D-mycosamine.[239]

A list of other protective groups used in amino sugar chemistry, especially in the synthesis of glycosides is broad. These include: phthaloyl,[240] dichlorophthaloyl and tetrachlorophtaloyl,[241] allyloxycarbonyl,[242] dimethylpyrrole,[243] *N*,*N*-diacetyl,[244] dimethylmaleoyl,[245] 2,2,2-trichloroethoxycarbonyl,[246-248] mono-,[249] di-,[250,251] trichloro-,[252] trifluoroacetyl,[253,254] and dithiasuccinoyl[255] functionalities. The phtaloyl protection can be easily introduced but its removal is difficult. For this purpose, much more convenient are dichlorophthaloyl and tetrachlorophtaloyl functionalities that may be removed by the action of ethylenediamine under mild condition.[240,241]

One of the specific reagents for amino protection in amino sugars is 1,3-dimethyl-2,4,6-(1*H*,3*H*,5*H*)-trioxopyrimidine-5-ylidene)methyl (DTPM). The DTPM group is stable in an acidic environment and its removal is possible with hydrazine, primary amines and aqueous ammonia.[256-259]

A particular type of amino-protecting groups in amino sugars are those containing the photosensitive fragments. These are the nitro aromatic compounds containing benzylic hydrogens, ortho- to the nitro group. Such systems are light sensitive and their removal can be easily achieved by exposition to light. Examples of such protective groups include the 2-nitrobenzyloxycarbonyl and 6-nitroveratryloxycabonyl functionalities.[260]

An useful and convenient strategy for the simultaneous protection of C2 amino and C3 hydroxy group in 2-amino-2-deoxy sugars is formation of a cyclic carbamate. This strategy has been applied for the preparation of glucosamine, gulosamine, galactosamine and allosamine derivatives.[261-263]

5. Conclusions

The growing interest in synthesis and modifications of amino sugars is stimulated by the important role of some of these compounds as components of a number of biologically active substances, especially antibiotics. An amino sugar, if present in the antibiotic structure, is

usually important for activity and its removal or even slight modification may substantially alter biological properties of the drug. A good example is an antifungal antibiotic amphotericin B (AmB). Removal of the mycosamine residue from the AmB molecule makes the latter inactive as an antifungal agent,[264] while the 2'deoxy-AmB demonstrates substantially better selective toxicity than the mother antibiotic.[265] It is not surprising, therefore, that there is a constant need for convenient, inexpensive but efficient methods of amino sugar synthesis and/or conversion.

Obviously, there is no single, universal and simple method of amino sugar synthesis. Some of the reported strategies are complicated because of the inherent challenges associated with carbohydrate chemistry, especially stereochemistry. Many of these procedures do not provide access to amino sugars with complete regio- and stereoselectivity, thus difficult separations of the mixtures formed are required and in consequence the overall yields of final products are often low.

The earliest methods of amino sugar synthesis were based on easily available monosaccharides as precursors having defined stereogenic centres. This approach is still attractive but an unequivocal conversion of a hexose/pentose into particular amino sugar is in many cases impossible because of lack of the appropriate substrate or calls for a multi-step, laborious procedures. Most of the modern methods of preparation of 1-, 2- and 3-amino sugars are those starting from glycals, which are the relatively cheap and commercially available starting substrates. Presence of stereogenic centres on the glycal skeleton can be exploited to introduce new functionalities in a stereoselective manner.

A substantial progress has been made in the recent years due to the development of synthetic methodologies involving metal-based catalysts that promote the introduction of new functionalities with concomitant strict regio- and stereo control. On the other hand, the recent tethered approaches provide target compounds with complete stereo control proceeding

through the formation of *cis*-fused cyclic intermediates but usually require cumbersome procedures for the preparation of the starting substrates.

What may be expected is the future development of greener, metal-free and atom economical methods that maintain appropriate regio- and stereo control.

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Figure 1. Amino sugars derived from secondary metabolism.

Scheme 1. Mechanism of amino transfer and sugar phosphate isomerization catalyzed by *E. coli* GlcN-6-P synthase.[48] The *cis*-enamine intermediate is shown in parentheses.

Scheme 2. Biosynthesis of sialic acid (Neu5Ac).

Scheme 3. Biosynthesis of kanosamine in *Bacillus subtilis.*[56]

Scheme 4. Strategy for the formation of amino sugars in S_N2 reaction.

Scheme 5. Preparation of amino sugar derivatives using liquid ammonia.[82]

Scheme 6. A synthetic route to 6-amino-6-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose.

Scheme 7. Bimolecular nucleophilic substitution using trimethylsilylazide.[78]

Scheme 8. Synthesis of 5-amino-3,6-anhydro-5-deoxy-1,2-*O*-izopropylideno-β-L-idofuranose **6** and 3,5-diamino-3,5-dideoxy-1,2-*O*-izopropylideno-α-D-ribofuranose **8**.[105,106]

Scheme 9. Opening of the epoxide ring in an epoxysugar molecule with ammonia.

Scheme 10. Synthesis of methyl 2-amino-2,3-dideoxy-α-D-mannopyranoside (**16**), with oxime **15** reduction.[12]

Scheme 11. Formation of an oximino intermediate in mannosamine synthesis.[125]

Scheme 12. Cobalooxime intermediate as a convenient substrate to introduce an amino group.[138]

Scheme 13. Addition of an azide to the double bond in synthesis of L-acosamine.[144]

Scheme 14. Azidonitration in synthesis of 2-amino-2-deoxy-D-galactose **28** from D-galactose.[150]

Scheme 15. Synthesis of L-daunosamine involving formation of the aziridine ring.[155]

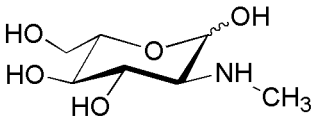
Scheme 16. [3,3]-Sigmatropic rearrangement in preparation of a mannosamine derivative **35**.

Scheme 17. Addition of an azodicarboxylate **37** to glycals.[160]

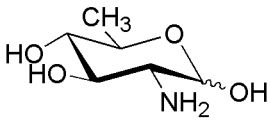
Table 1. Amino sugars of natural origin.

IUPAC name	Common name	Component of	Biosources
2-amino-2-deoxy-D-glucose	D-glucosamine	chitosan	*Mucor rouxii*[13,14]
2-methylamino-2-deoxy-L-glucose	*N*-methyl-L-glucosamine	streptomycin	*Actinomycetes*[15,16]
2-acetamido-2-deoxy-D-glucose	*N*-acetyl-D-glucosamine	chitin, murein, hialuronic acid, glycoproteins	crustaceans, insects, fungal and bacterial cell wall[17,18]
2-amino-2,6-dideoxy-D-glucose	D-quinovosamine	lipopolysaccharides	*Vibrio cholerae*[19]
4-acetamido-2-amino-2,4,6-trideoxy-D-glucose	*N*-acetyl-D-bacillosamine	polysaccharides	*Bacillus licheniformis*[20]
2,4-diacetamido-2,4,6-trideoxy-D-glucose	-	polysaccharides	*Bacillus licheniformis*[21]
3-amino-3-deoxy-D-glucose	kanosamine	unbound kanamycin A	*Streptomyces kanamyceticus*, *Bacillus spp.*[22,23]
6-amino-6-deoxy-D-glucose	-	kanamycin A	*Streptomyces kanamyceticus*[24]
3,6-dideoxy-3-dimethylamino-D-glucose	mycaminose	leucomycins, magnamycins	*Streptomyces kitasatoensis Hata*[25]
3-(dimethylamino)-3,4,6-trideoxy-D-glucose	desosamine	erythromycin	*Streptomyces erythreus*, *Streptomyces venezuleae*[26,27]
2-amino-2-deoxy-D-galactose	D-galactosamine	bacterial cell wall chondroitin sulfate	*Bacillus subtilis*, mammalian glycosaminoglycans[28]
2-amino-2,6-dideoxy-D-galactose	D-fucosamine	teichuronic acid (component of the cell wall)	*Bacillus subtilis*[29-31]
2-acetamido-2,6-dideoxy-L-galactose	*N*-acetyl-L-fucosamine	lipopolysaccharides	*Pseudomonas aeruginosa*[32]
2-amino-2-deoxy-D-mannose	D-mannosamine	*N*-acetylneuraminic acid sialic acids	human plasma[33]
3-amino-3,6-dideoxy-D-mannose	D-mycosamine	amphotericin B, nystatin, trichomycin A, pimaricin	*Streptomycetes*[34,35]
4-amino-4,6-dideoxy-D-mannose	perosamine	O-antigen, perimycin	*Vibrio cholerae*, *Streptomyces coelicolor*[36,37]
2-amino-2-deoxy-D-gulose	D-gulosamine	streptothricins	*Actinomycetes*[38,39]
2-amino-2-deoxy-D-talose	D-talosamine	chondroitin sulfate	sheep cartilage[40]
3-amino-3-deoxy-D-ribose	D-ribosamine	puromycin	*Streptomyces alboniger*[41,42]

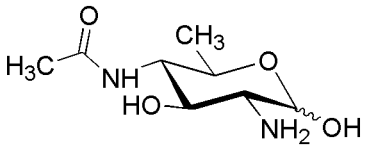
4-amino-4-deoxy-L-arabinose	-	lipopolysaccharides	*Salmonella minnesota*[43]
3-amino-2,3,6-trideoxy-L-*lyxo*-hexose	L-daunosamine	daunomycin	*Streptomyces spp.*[44]
3-amino-2,3,6-trideoxy-L-ribose	L-ristosamine		*Streptomyces spp.*
3-amino-2,3,6-trideoxy-L-arabinose	L-acosamine		*Streptomyces spp.*
2,3,4,6-tetra-deoxy-4-(methoxycarbonylamino)-3-C-methyl-3-nitro-D-*xylo*-hexapyranose	D-kijanose	kijanimicin A	*Actinomadura kijaniata*[45]



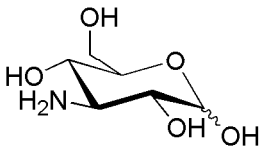
N-methyl-L-glucosamine



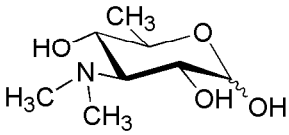
D-quinovosamine



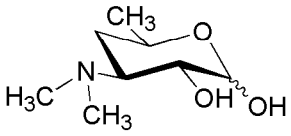
N-acetyl-D-bacillosamine



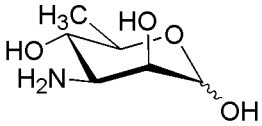
kanosamine



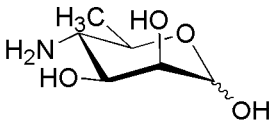
mycaminose



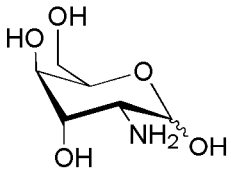
desosamine



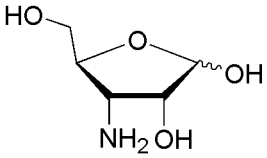
D-mycosamine



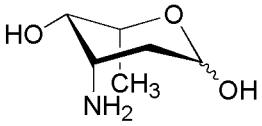
perosamine



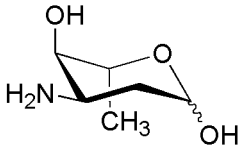
D-gulosamine



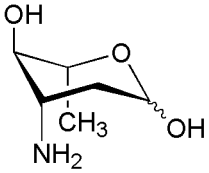
D-ribosamine



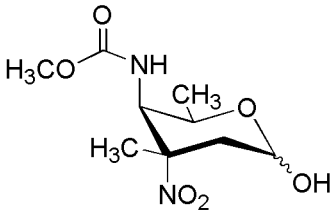
L-daunosamine



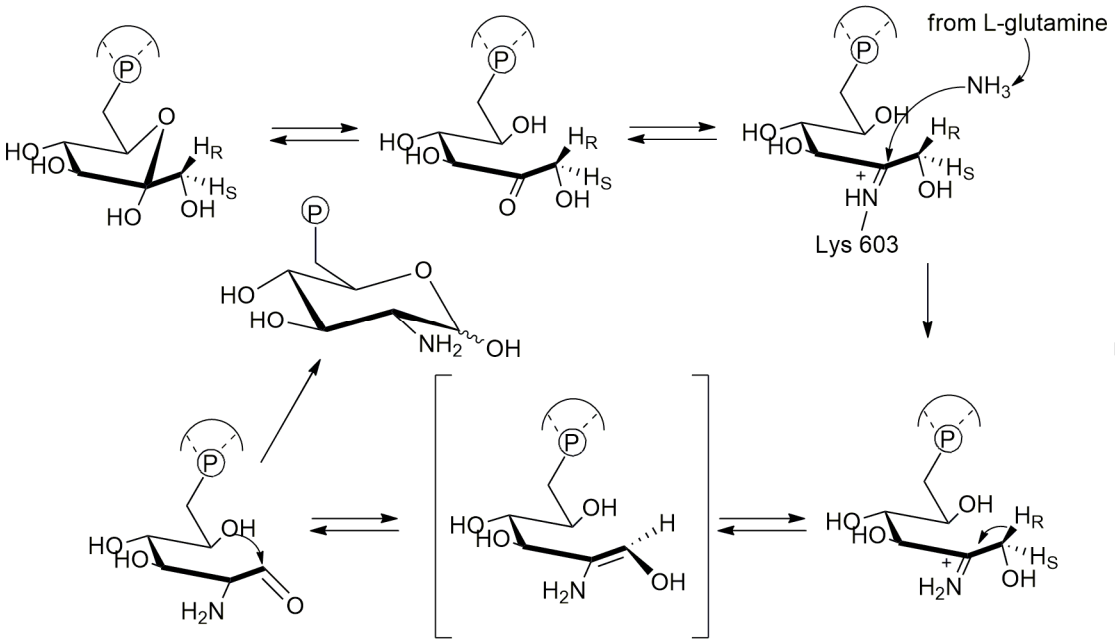
L-ristosamine

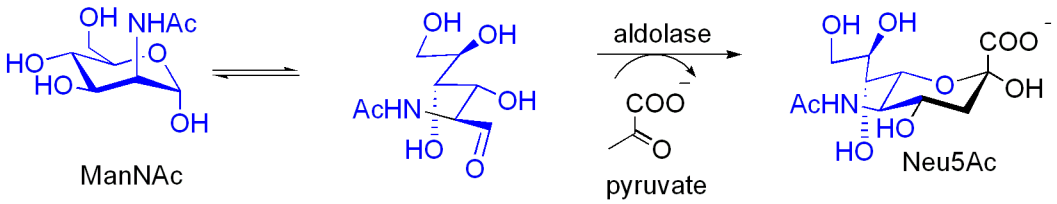


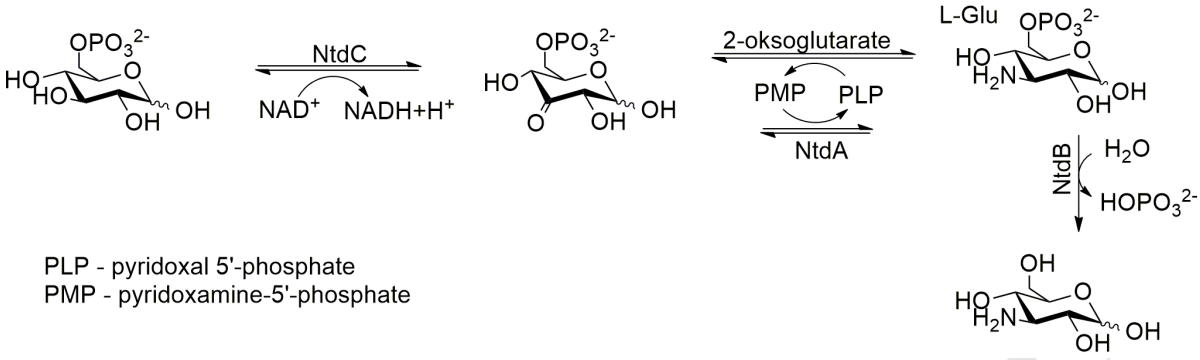
L-acosamine



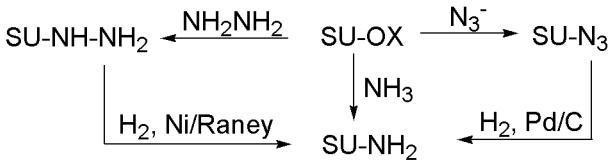
D-kijanose



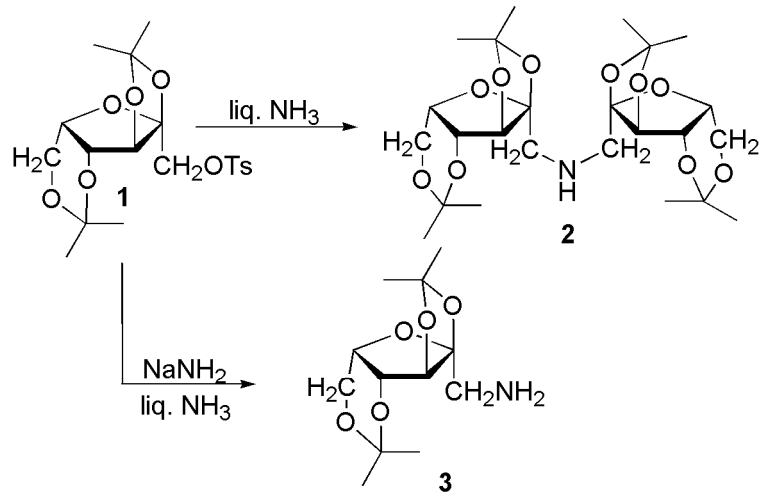


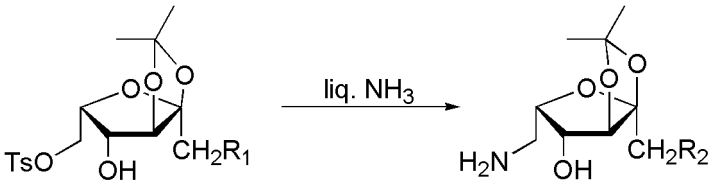


PLP - pyridoxal 5'-phosphate
PMP - pyridoxamine-5'-phosphate



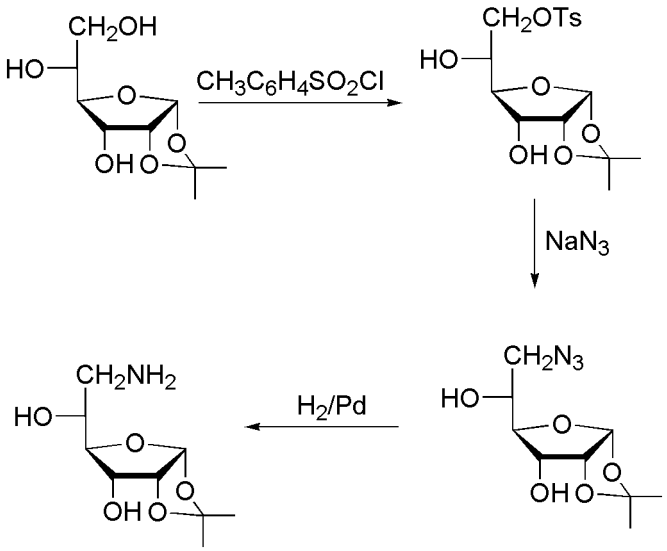
SU-sugar
X- Ms, Ts, Tf, Imd

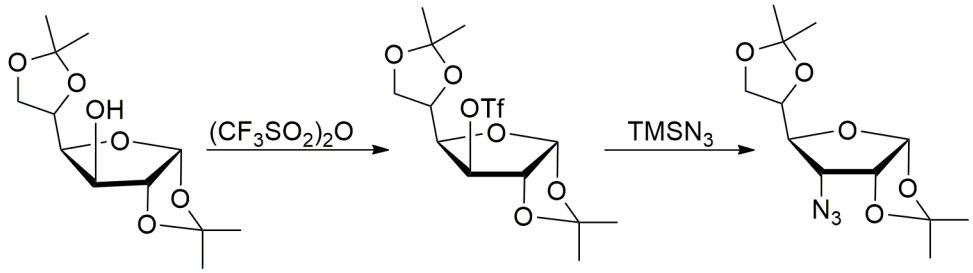


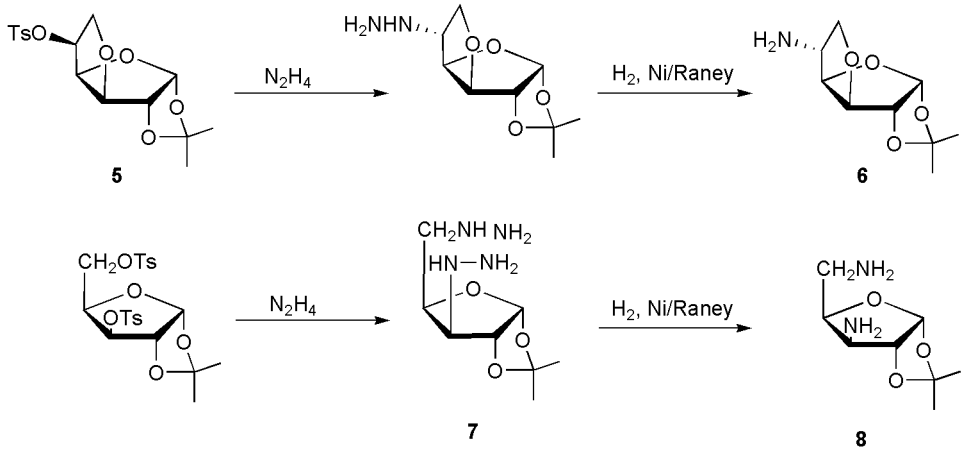


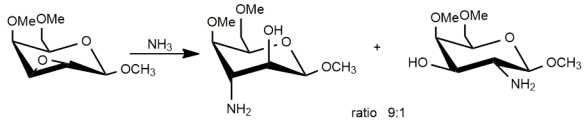
4, R_1: OH or OTs

R_2: OH or NH_2



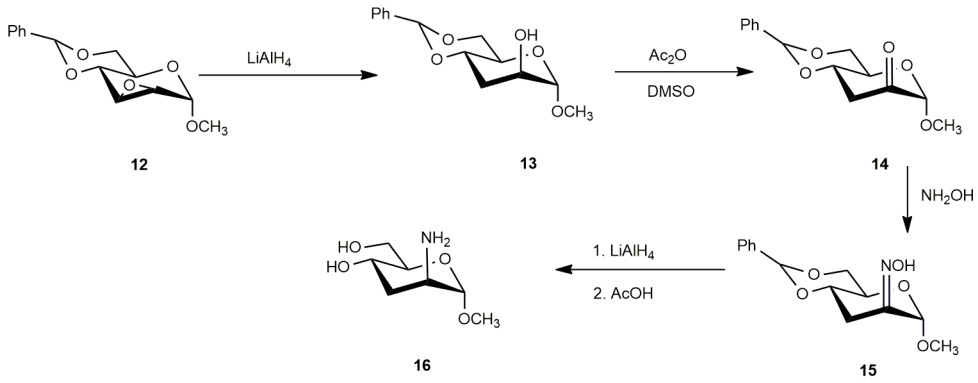




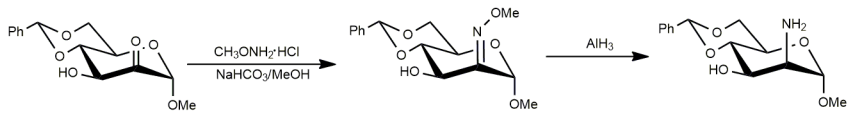


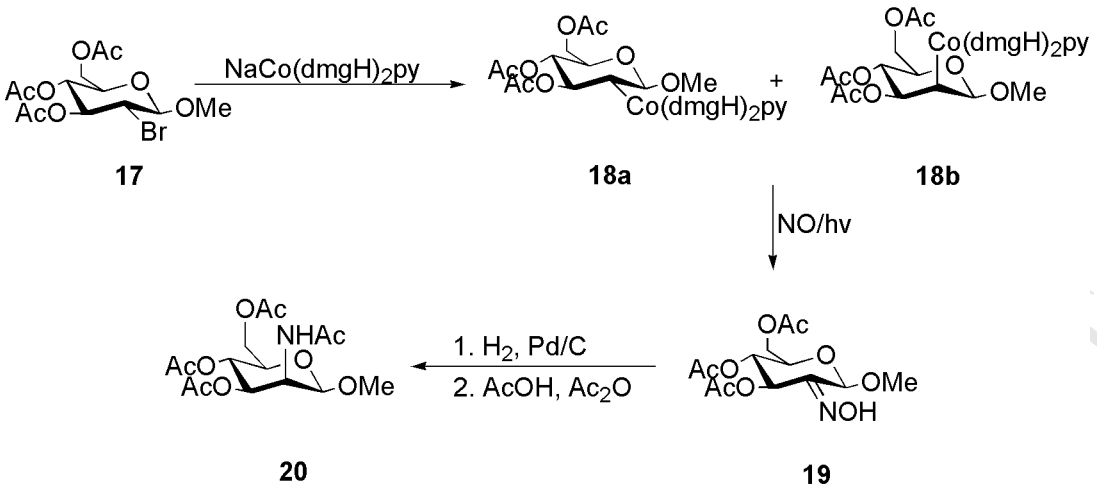
ratio 9:1

9 **10** **11**



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

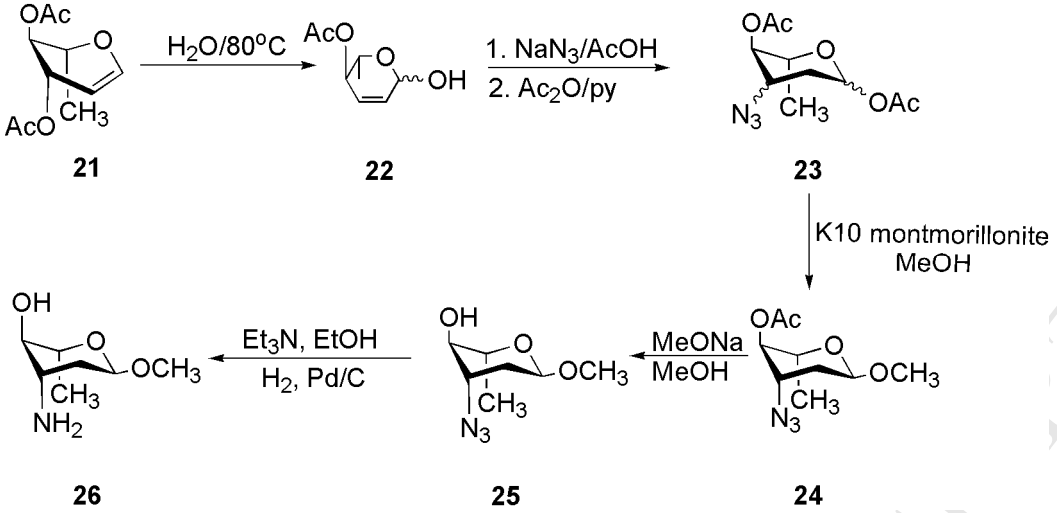


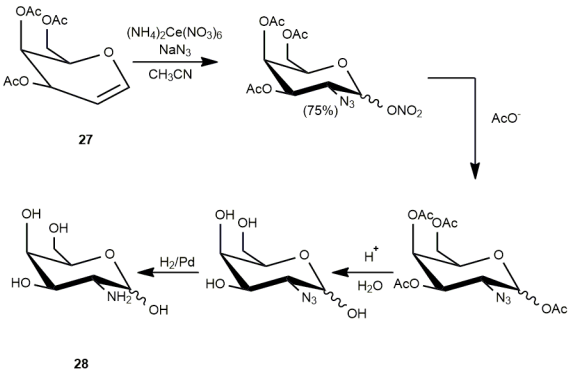


17 **18a** **18b**

20 **19**

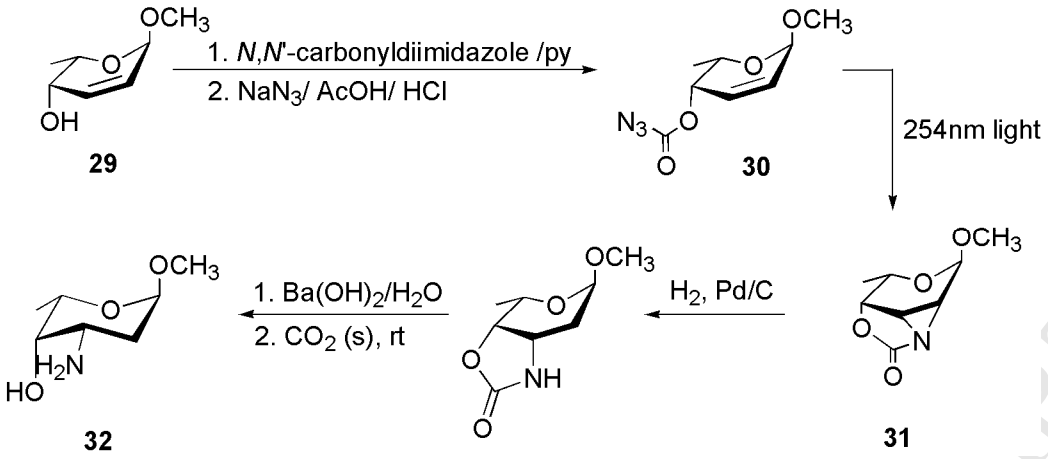
dmgH - dimethylglyoxime monoanion

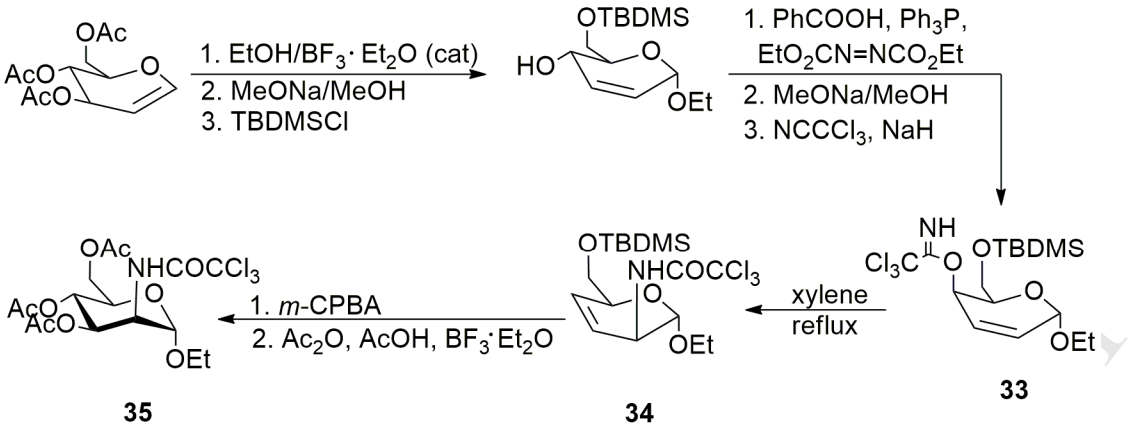




27

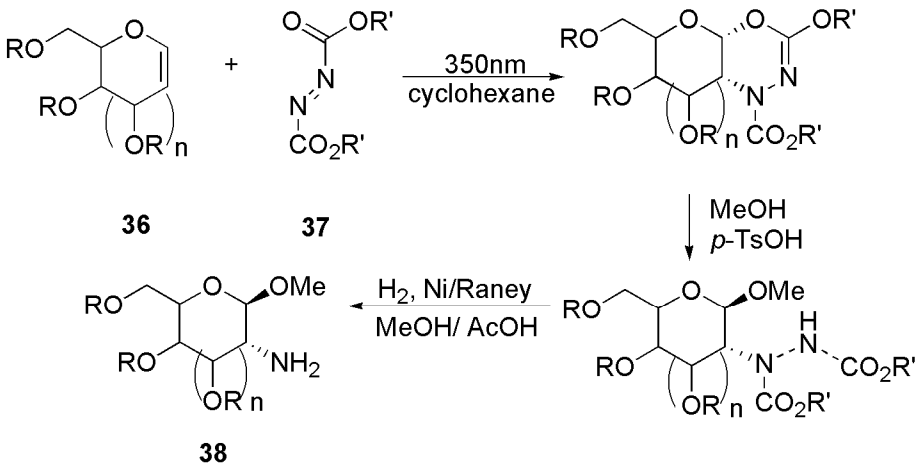
28





35 **34** **33**

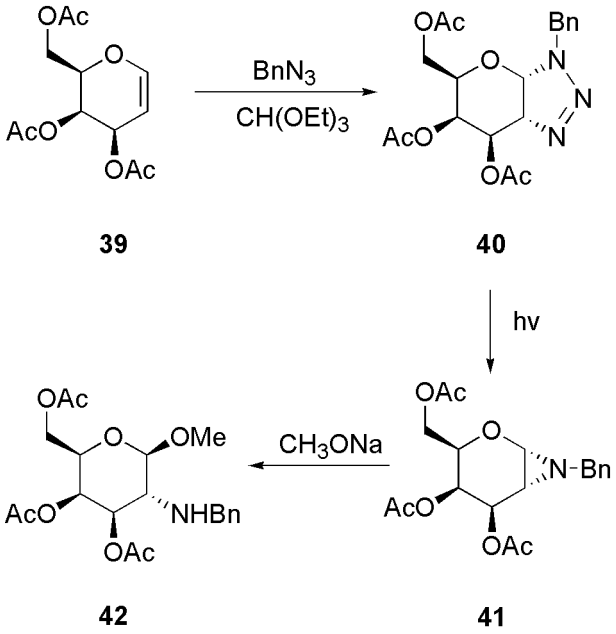
m-CPBA - *meta*-chloroperoxybenzoic acid



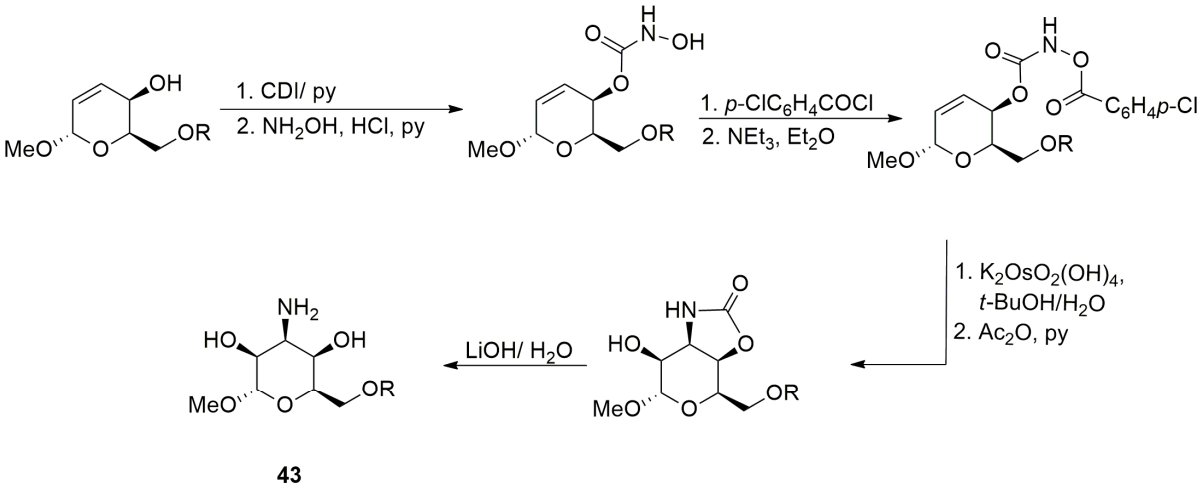
36 **37**

38

n = 0 or 1
R = *t*-$BuMe_2Si$
R'= $-CH_2Ph$, $-CH_2CCl_3$

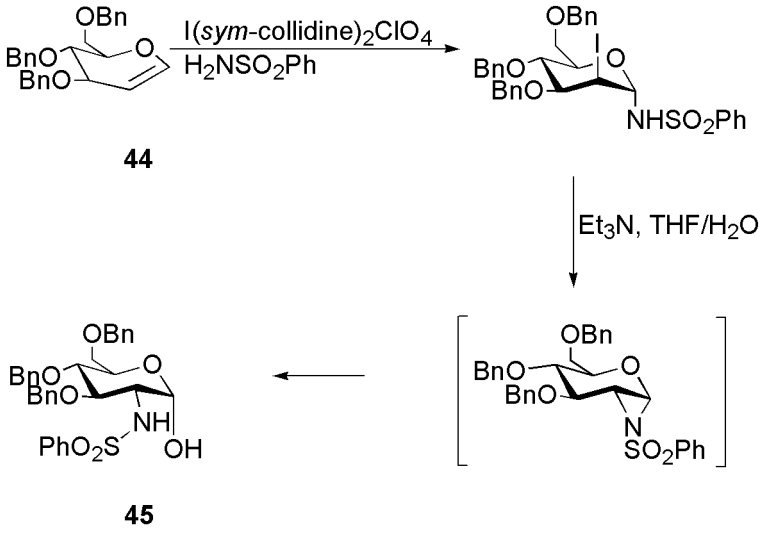


39 **40** **41** **42**



43

R - TBDMS
CDI - *N*,*N*'-carbonyldiimidazole



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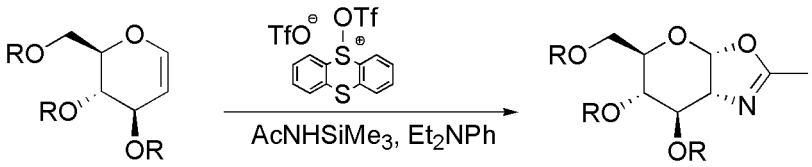
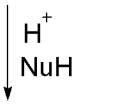
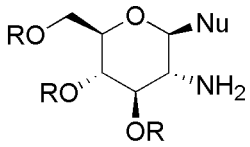
45

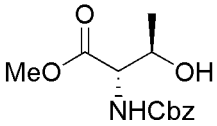


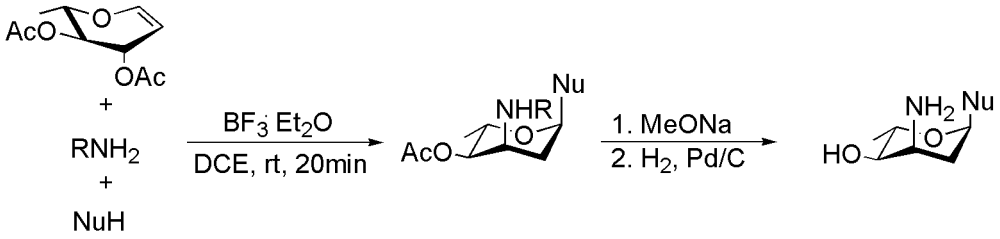
46 **47**





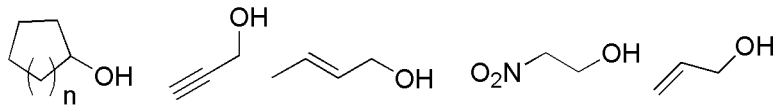
48

NuH: e.g. HN_3 $PhCH_2OH$  MeOH

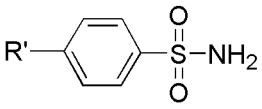


DCE - 1,2-dichloroethane

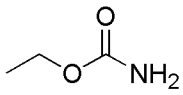
Nu: e.g.



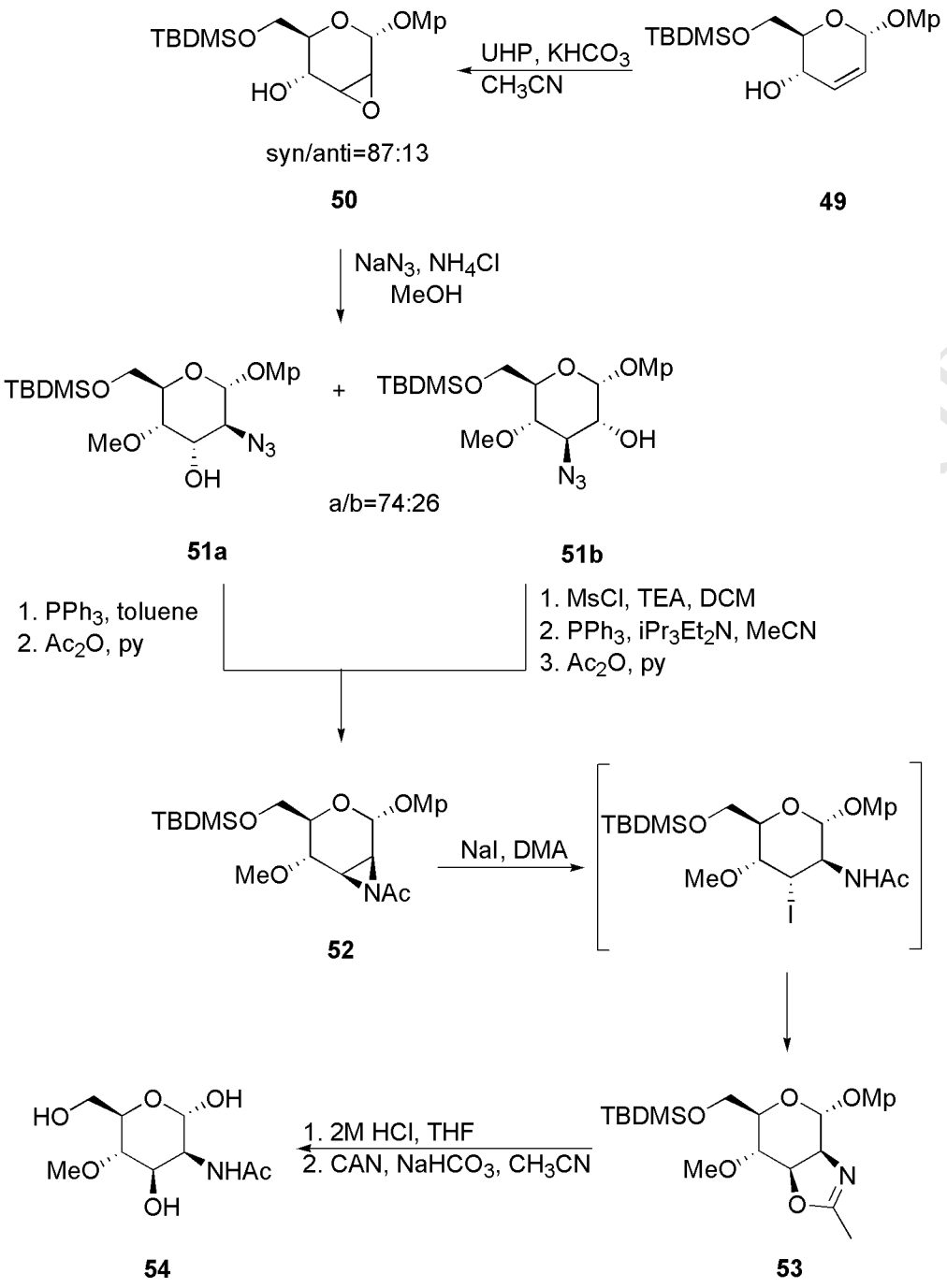
RNH_2: e.g.



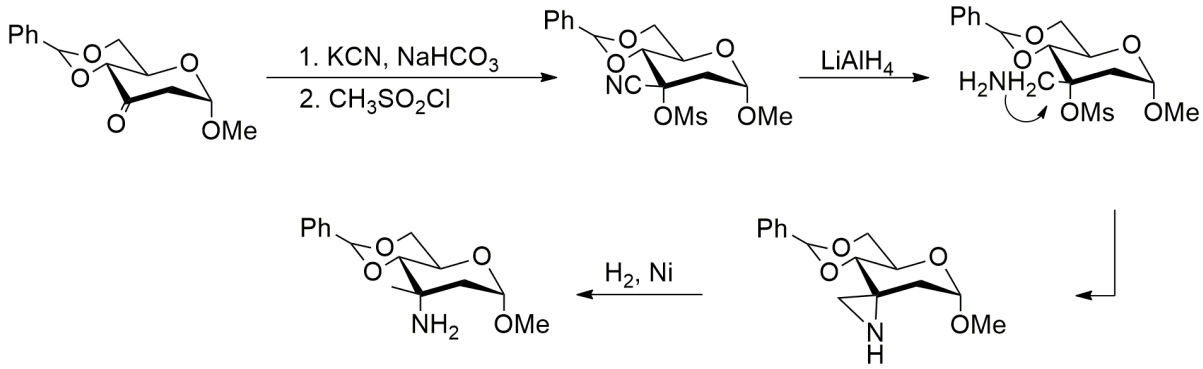
$MsNH_2$

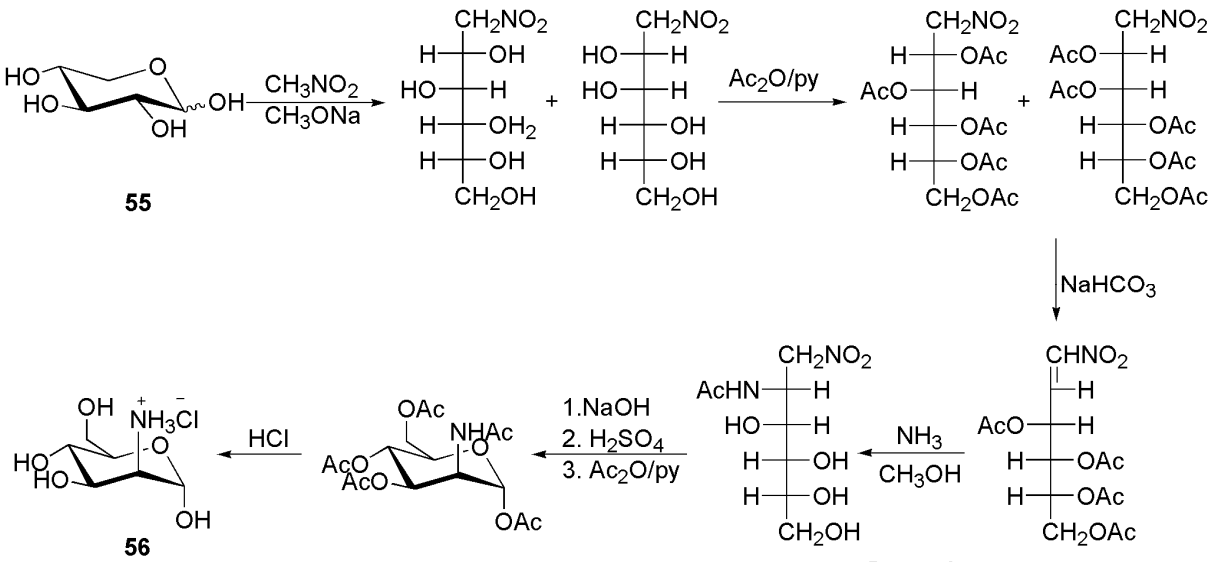


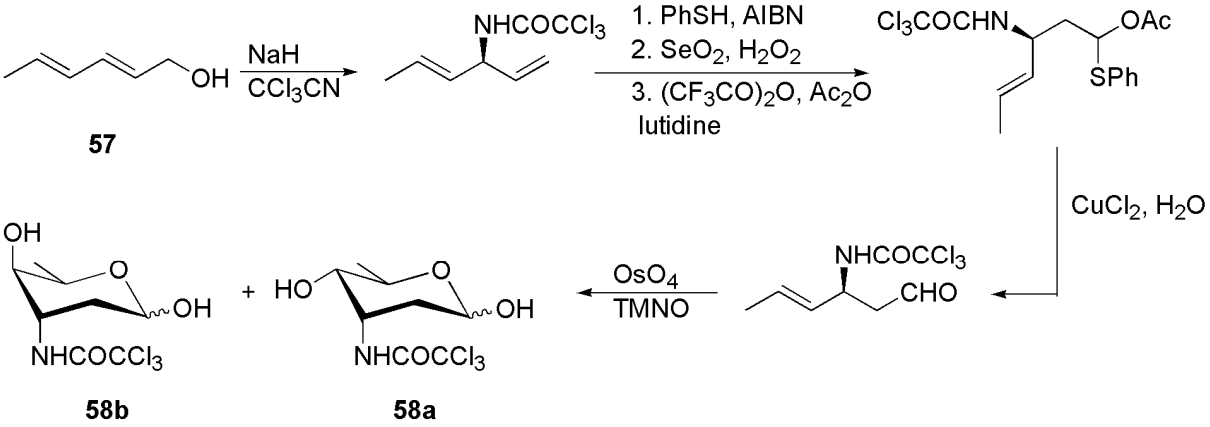
R' = F, H, Cl, NO_2, OCH_3, CH_3



UHP - urea-hydrogen peroxide complex
DMA - *N.N*-dimethylacetamide
MP - *p*-methoxyphenyl



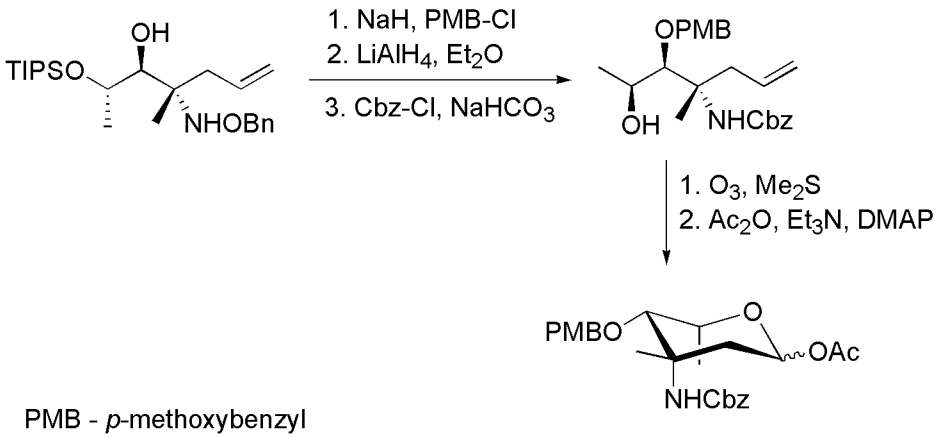




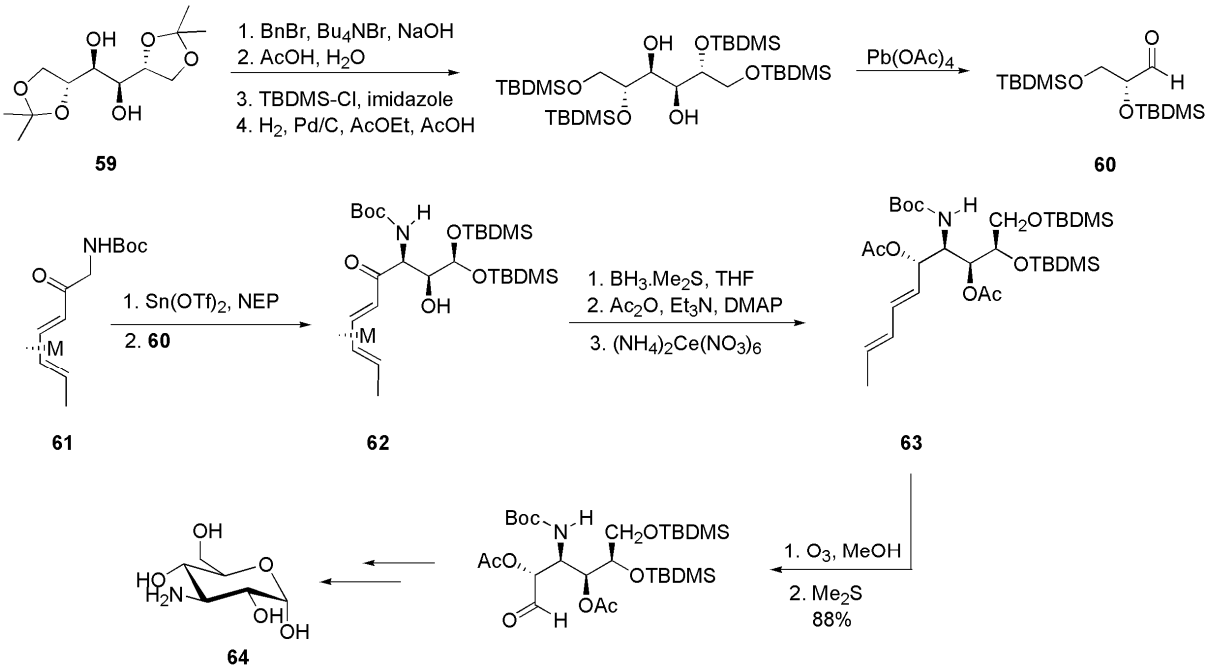
57

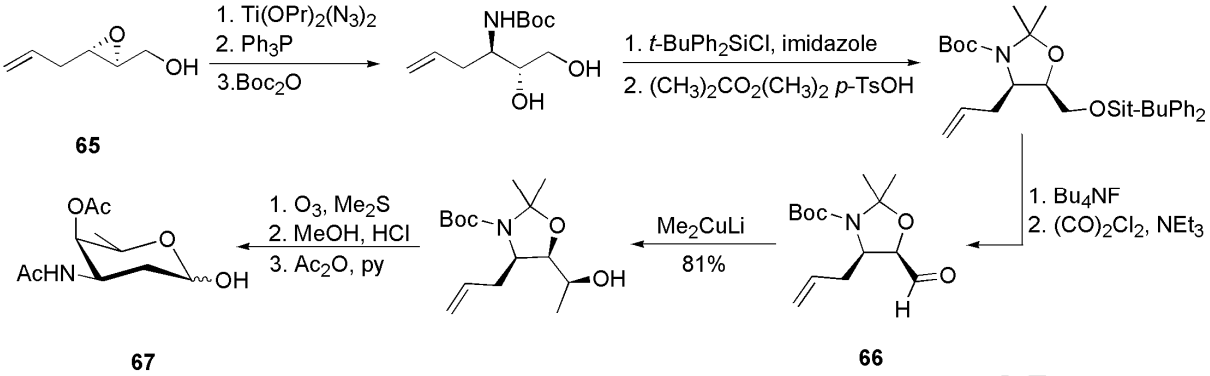
58b **58a**

TMNO - trimethylamine *N*-oxide
AIBN - azobisisobutyronitrile

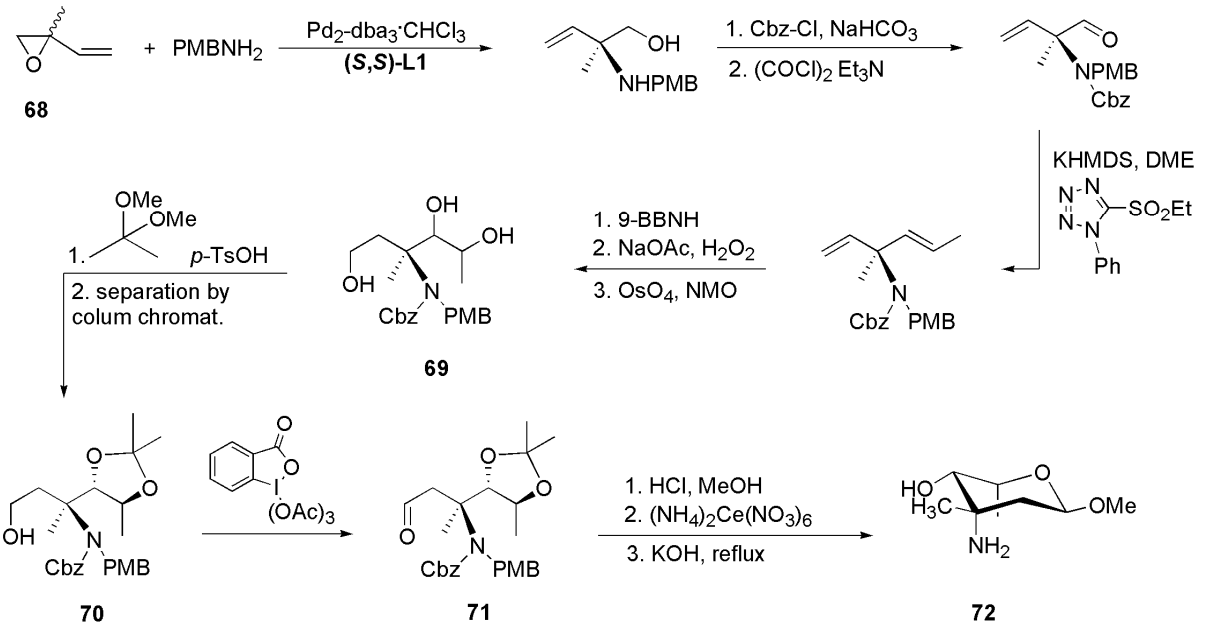


PMB - *p*-methoxybenzyl

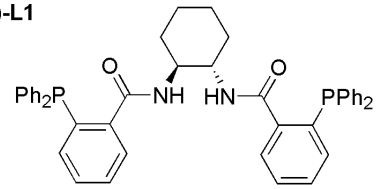




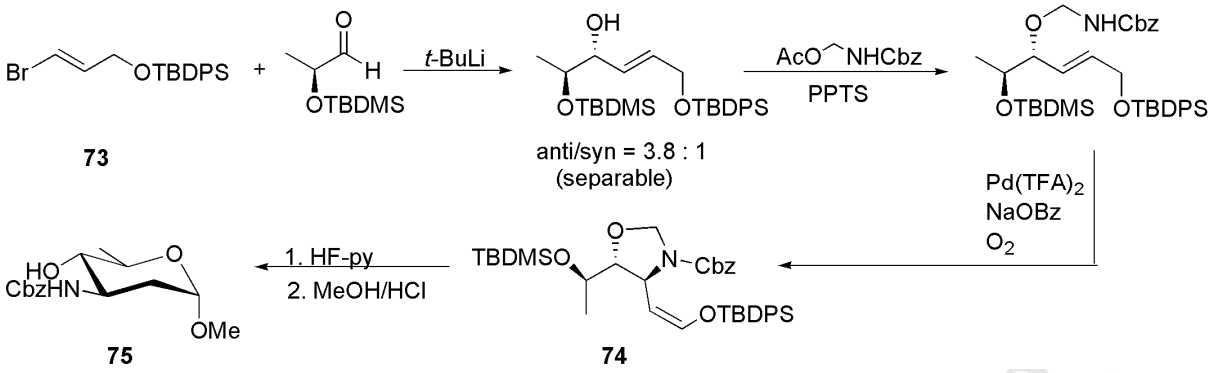
65 **66** **67**

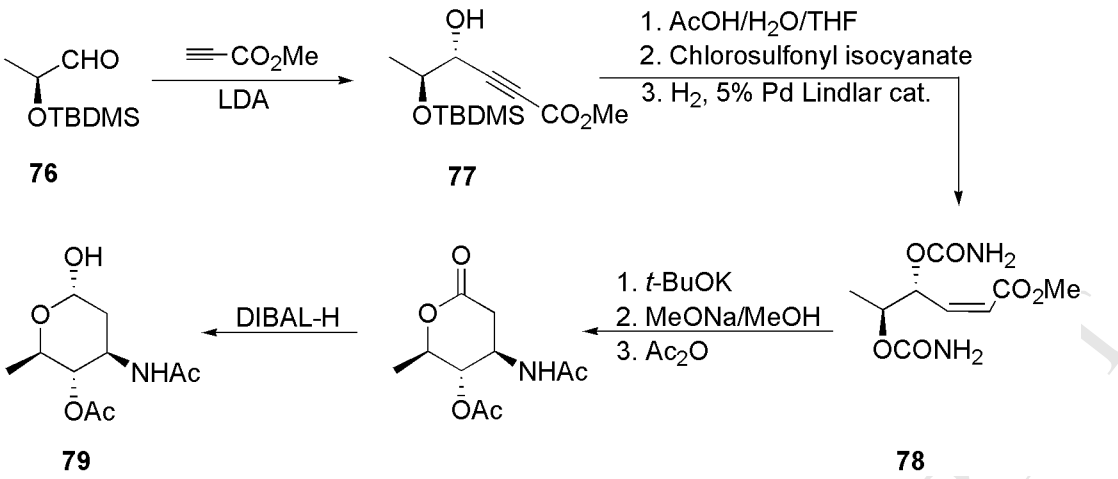


(*S*,*S*)-L1

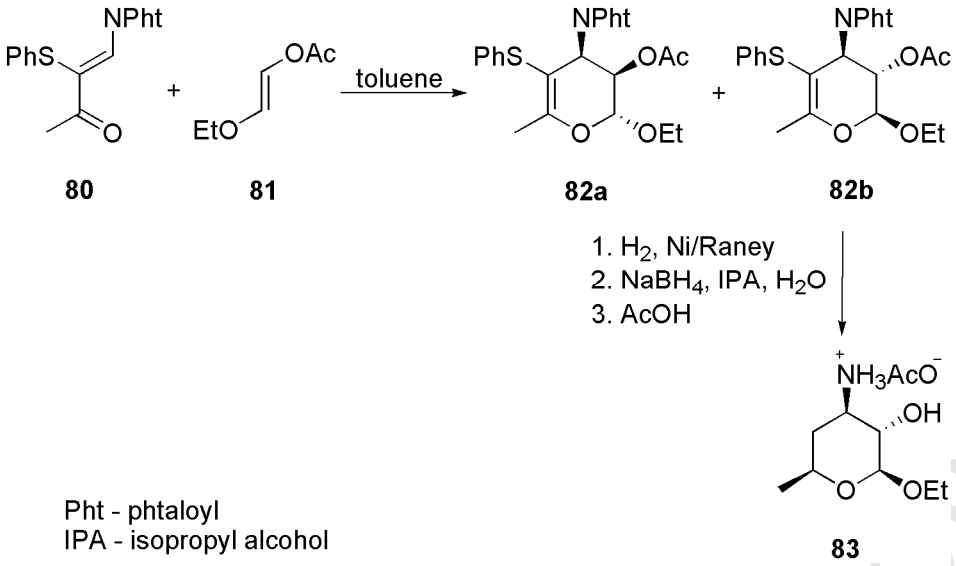


KHMDS - potassium bis(trimethylsilyl)amide
9-BBNH - 9-borabicyclo[3.3.1]nonane
Pd_2-dba_3· $CHCl_3$- dipalladium-tris(dibenzylideneacetone)chloroform complex



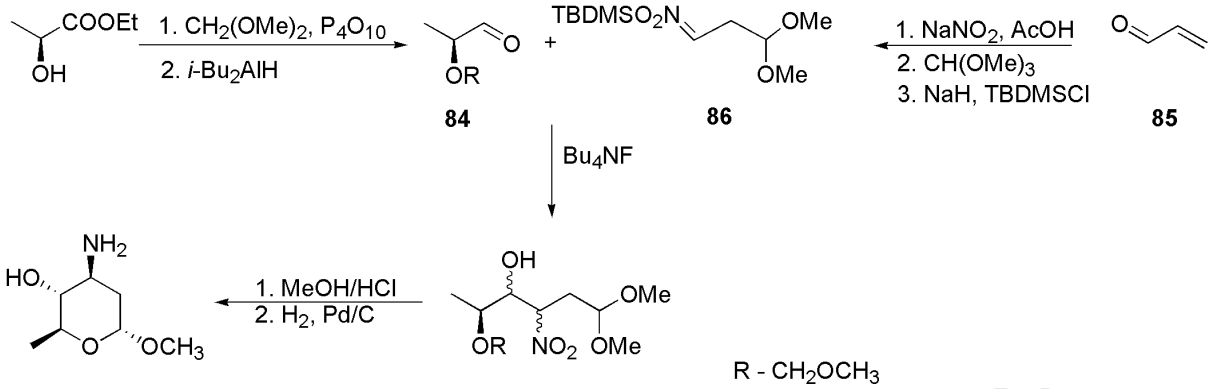


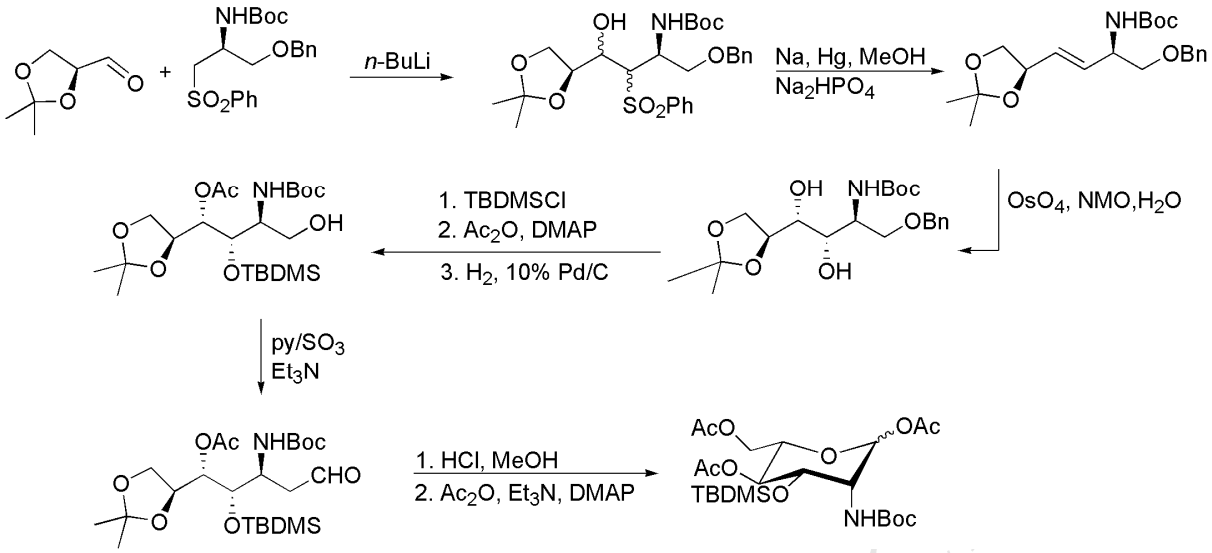
76 **77** **78** **79**

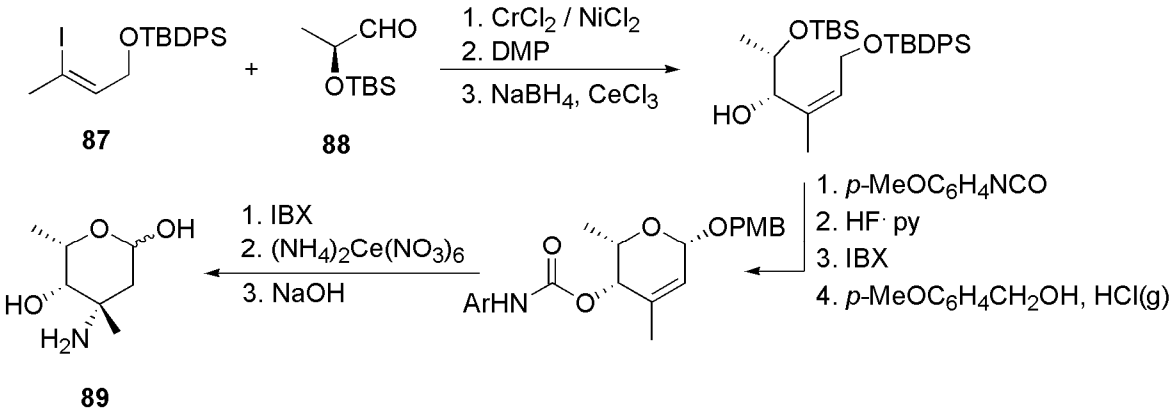


80 **81** **82a** **82b** **83**

Pht - phtaloyl
IPA - isopropyl alcohol

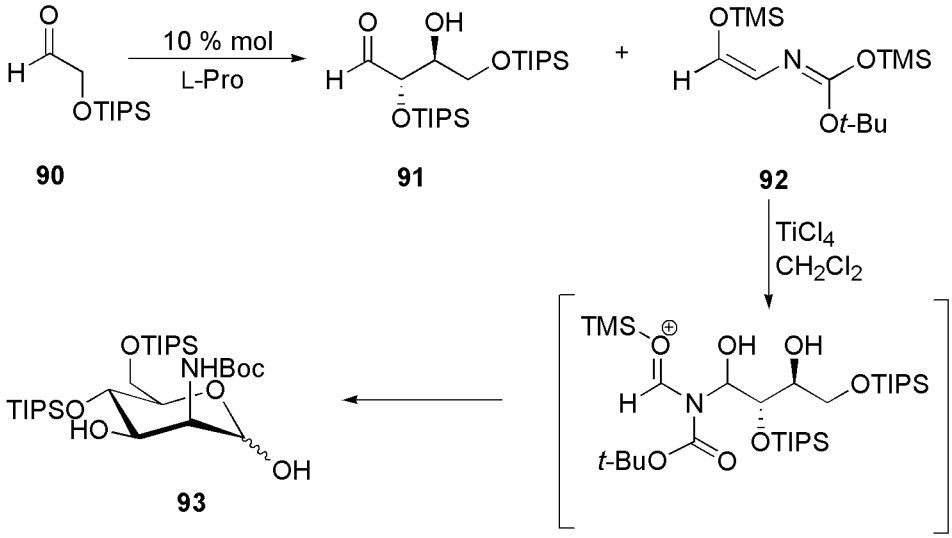






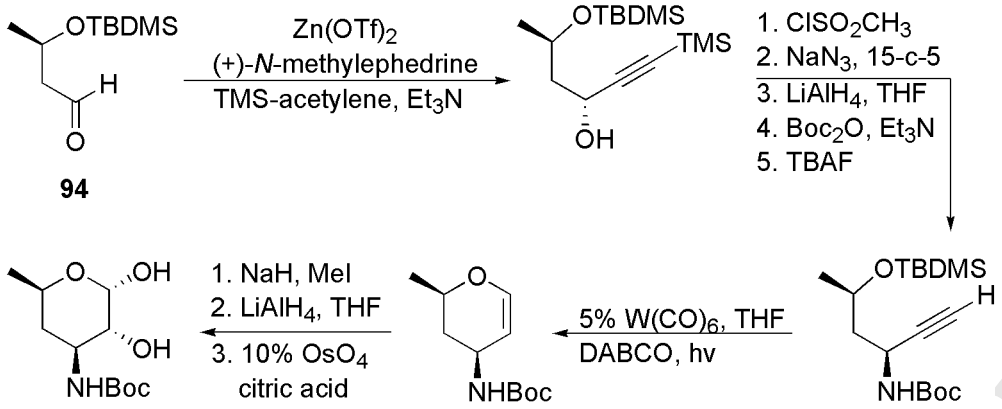
87 **88** **89**

DMP - Dess-Martin periodinane

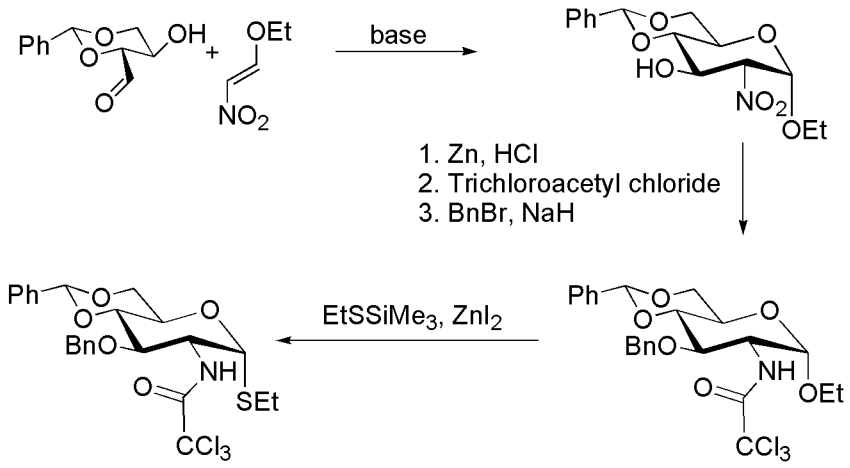


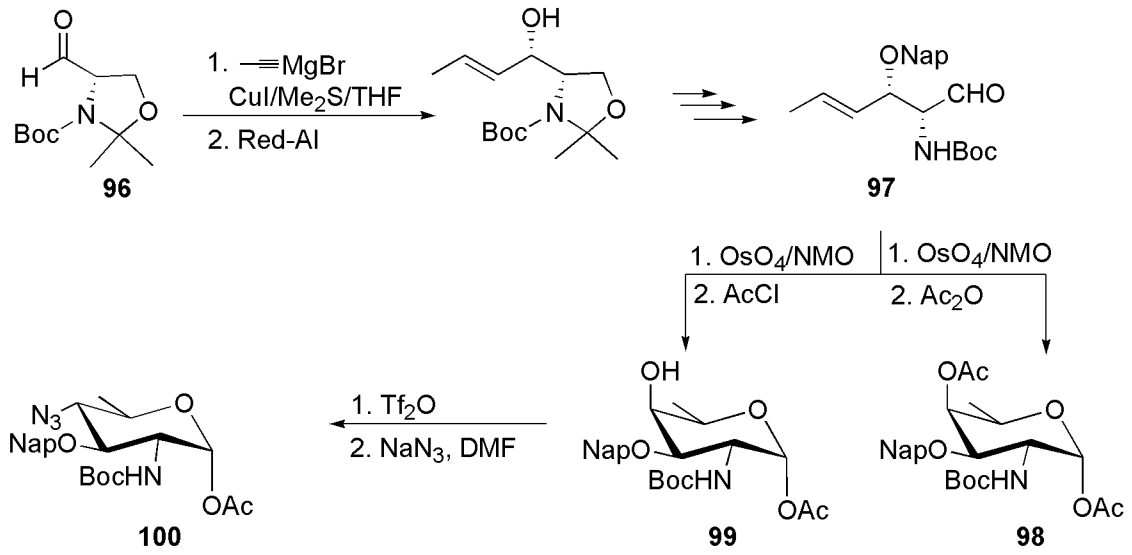
90 **91** **92** **93**

TIPS - triisopropylsilyl
TMS- trimethylsilyl

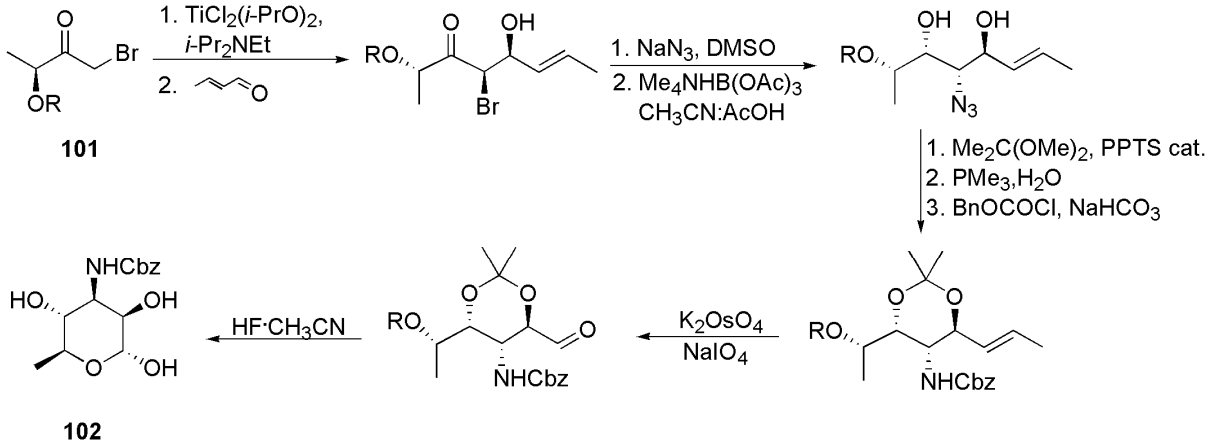


95





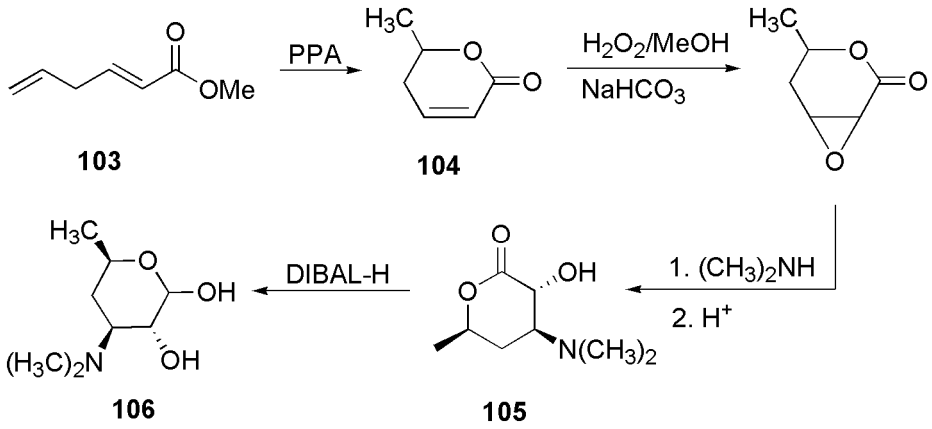
Nap - 2-naphthylmethyl ether
NMO - *N*-methyl morpholine-*N*-oxide



101

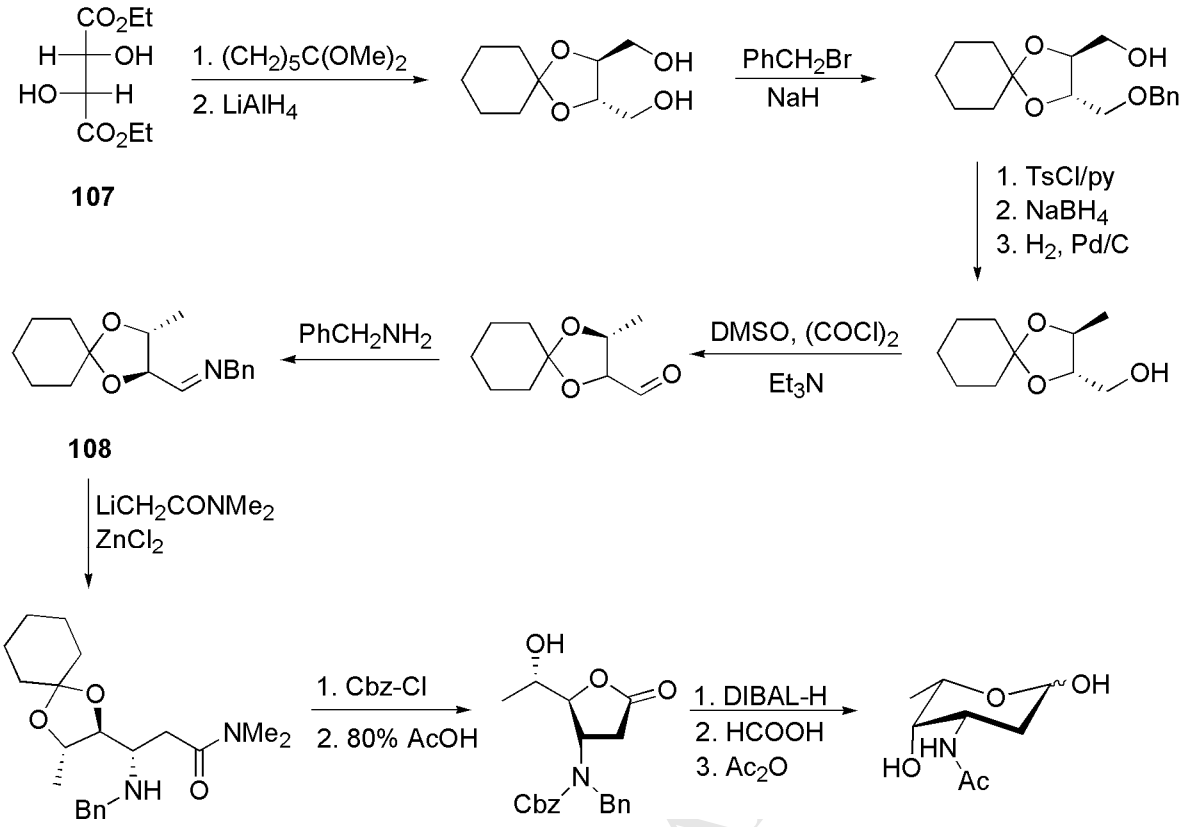
102

R = TBDMS
PPTS - pyridinium *p*-toluenesulfonate



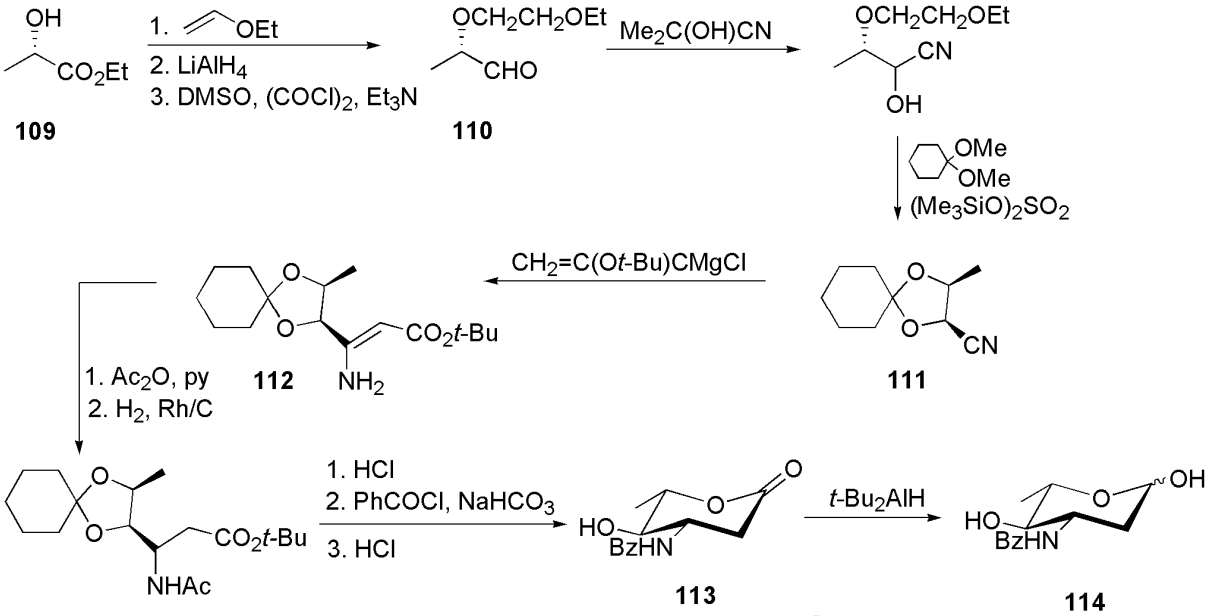
103 **104** **105** **106**

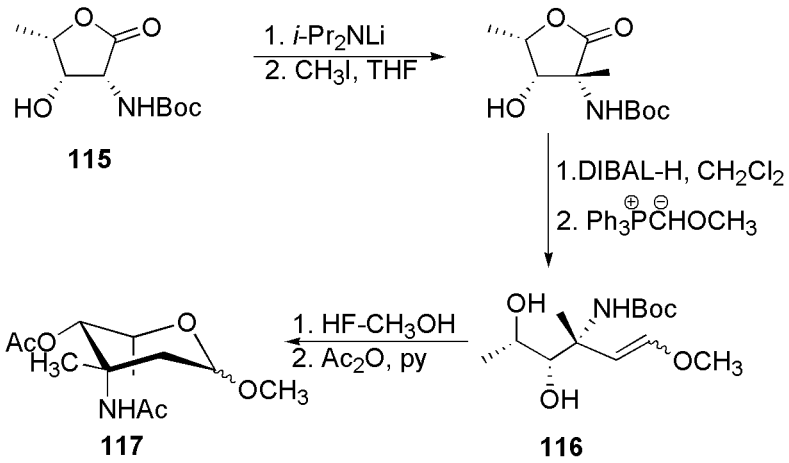
PPA - polyphosphoric acid

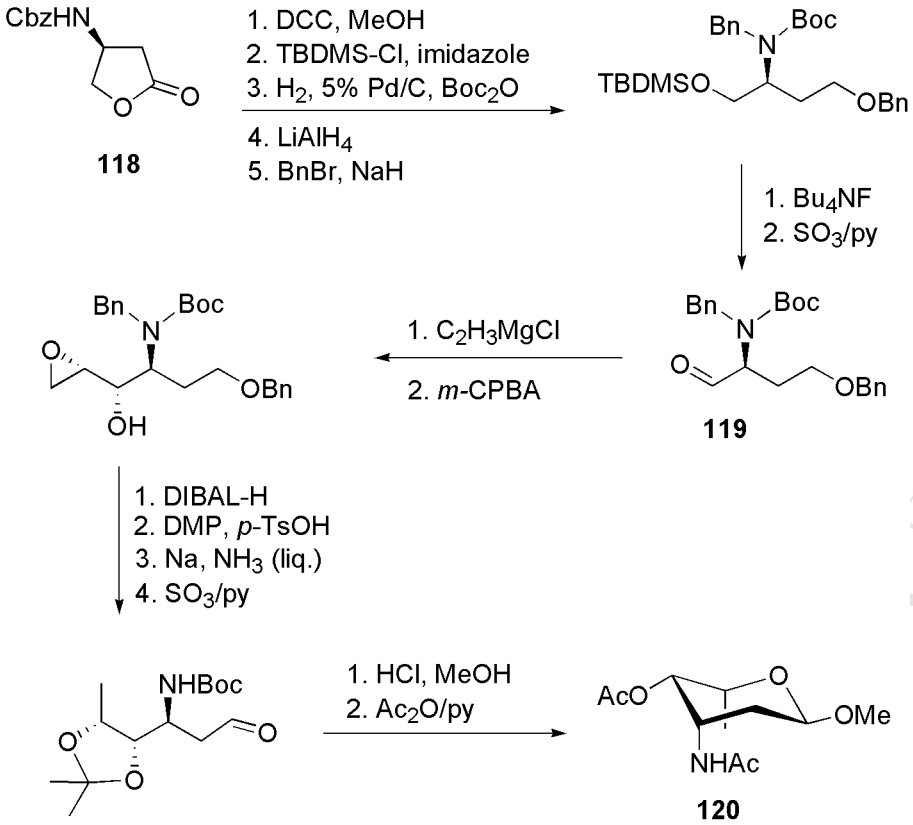


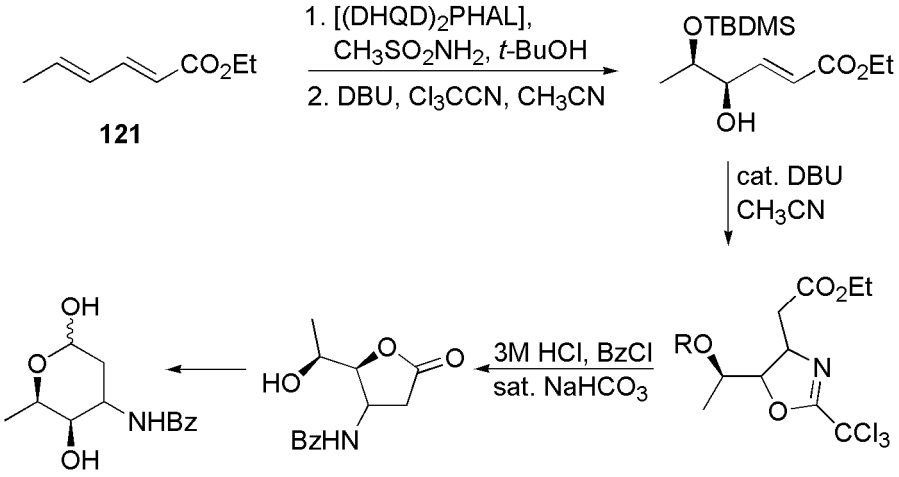
107

108

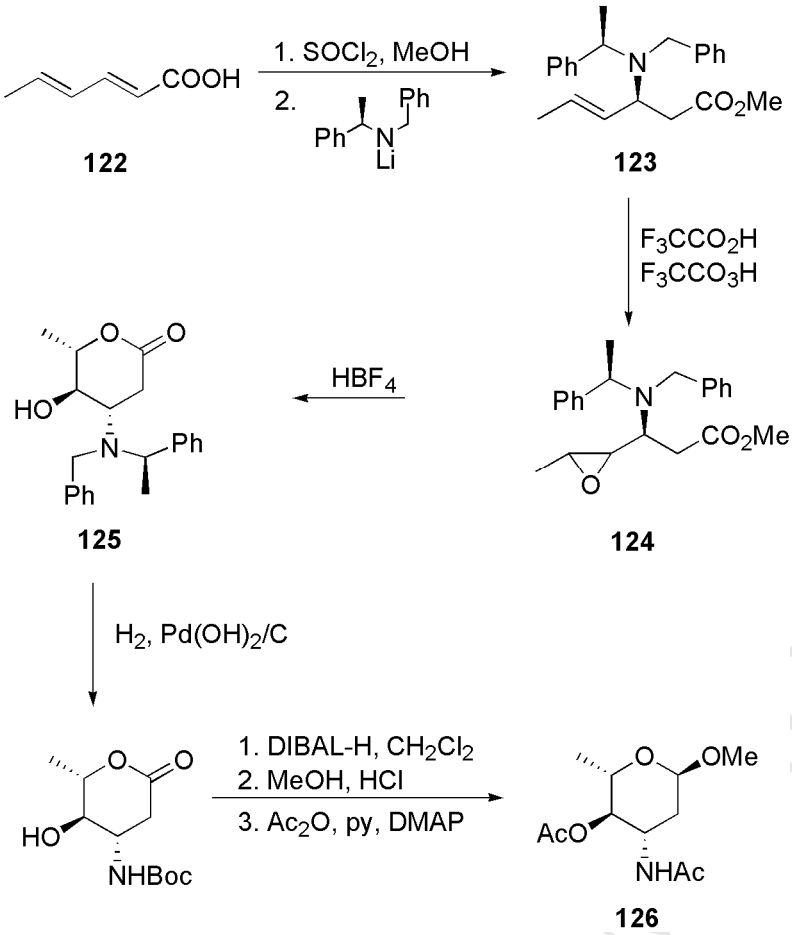




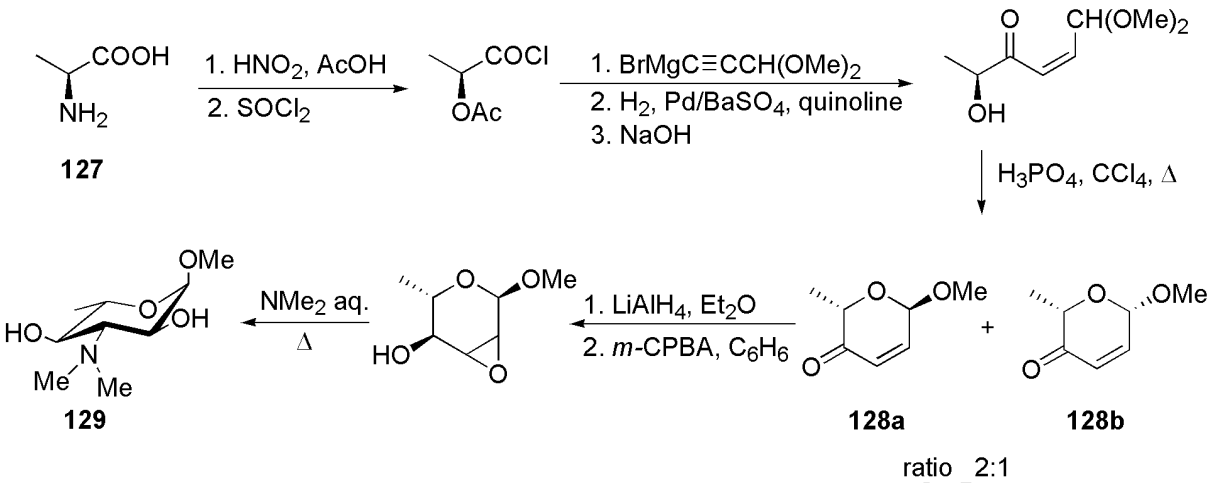




R= TBDMS
[(DHQD)$_2$PHAL] - dihydroquinidine phthaladine
DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene



122 **123** **124** **125** **126**



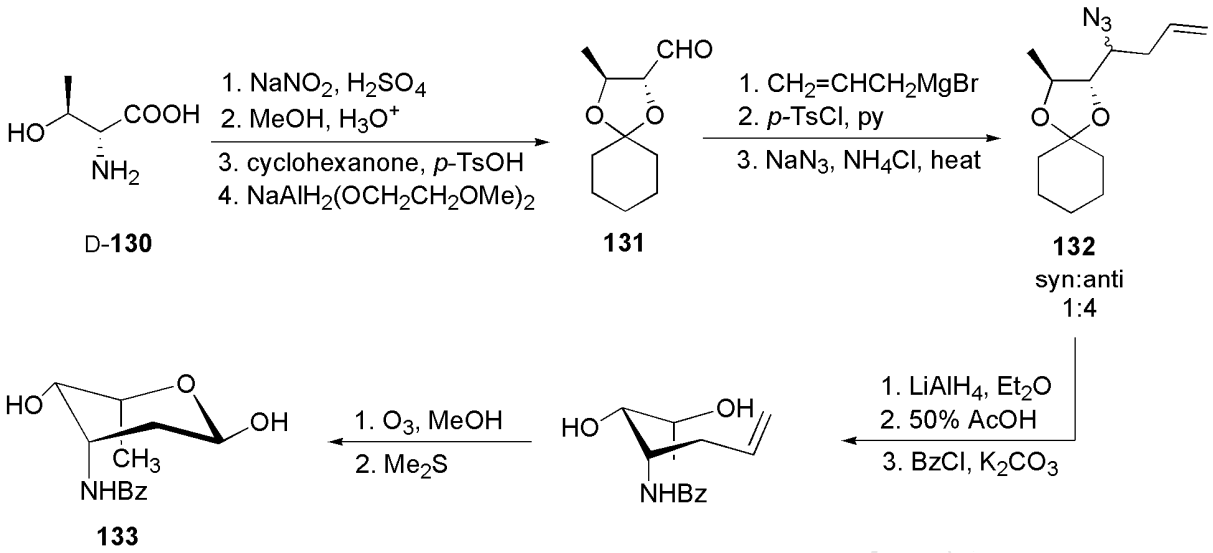
127

129

128a

128b

ratio 2:1

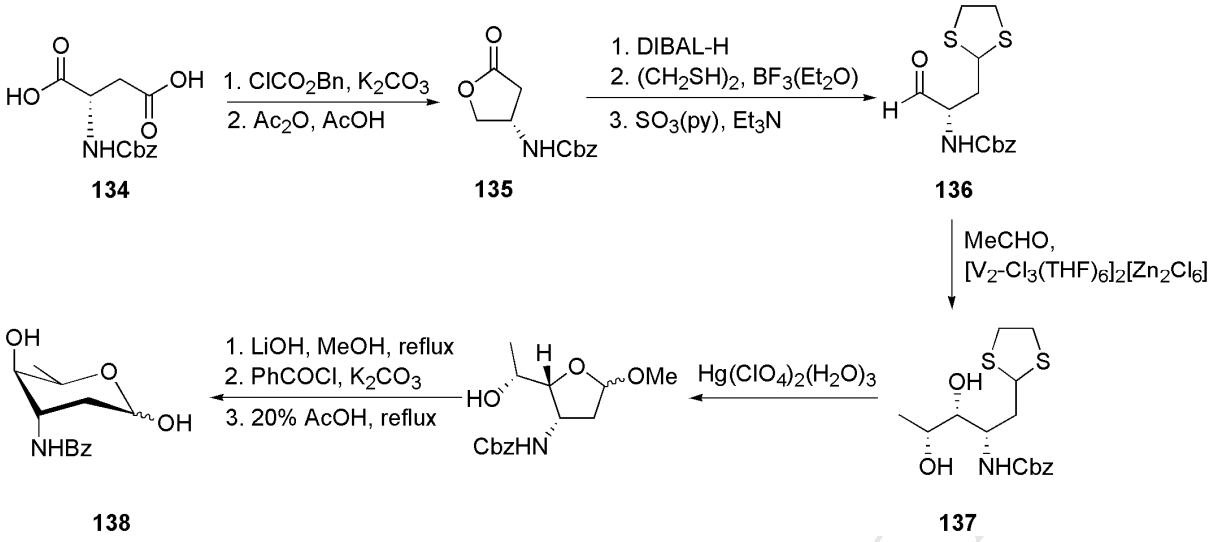


D-**130**

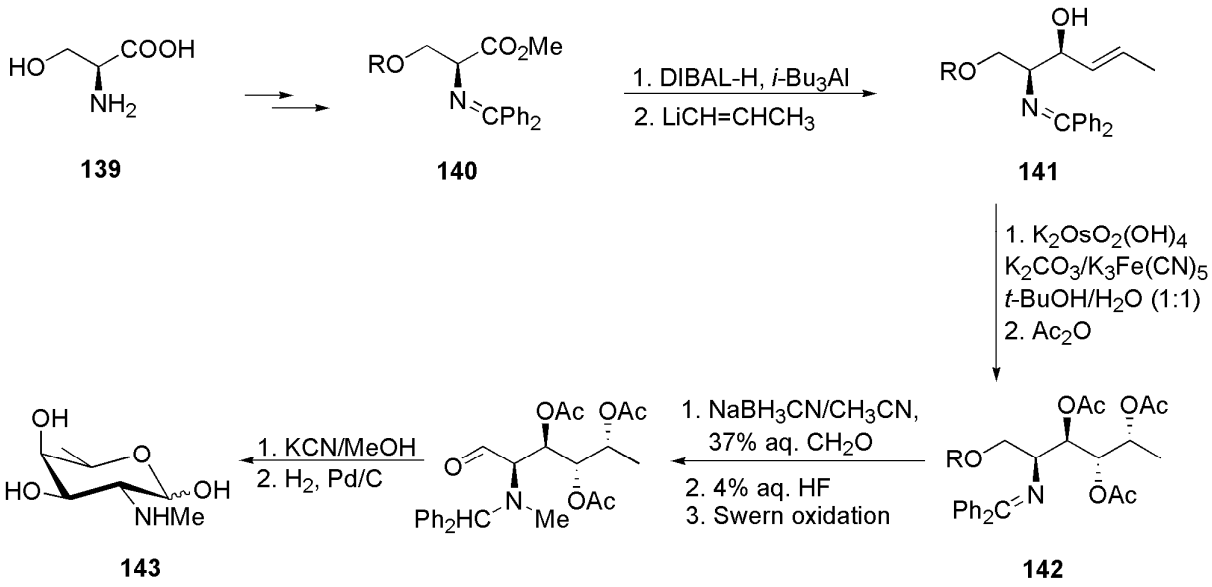
131

132
syn:anti
1:4

133

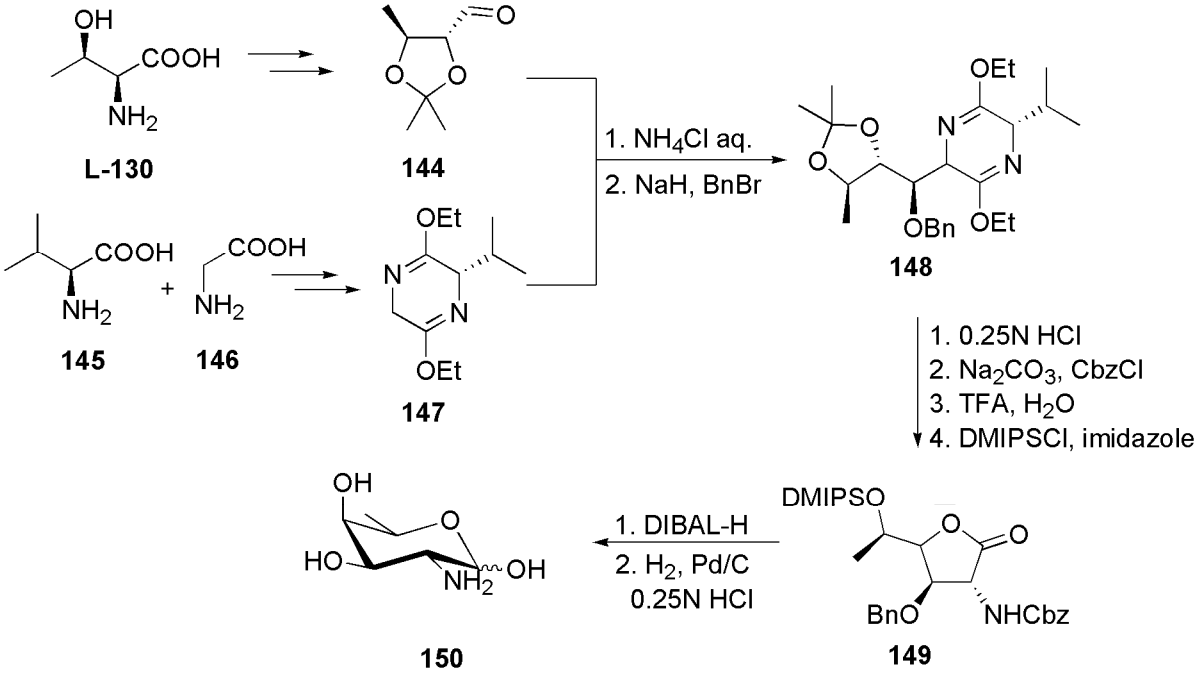


134 **135** **136** **137** **138**

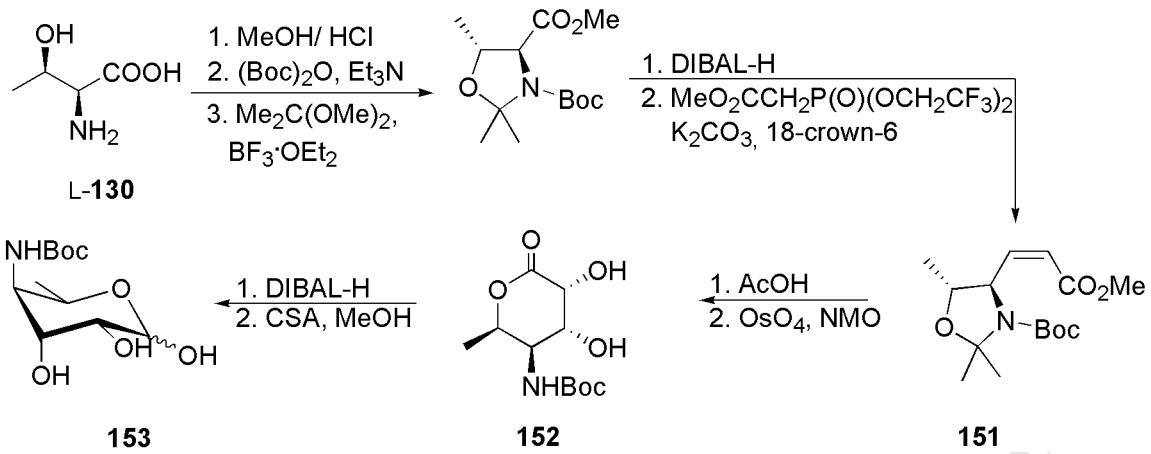


139 **140** **141** **142** **143**

R = TBDMS

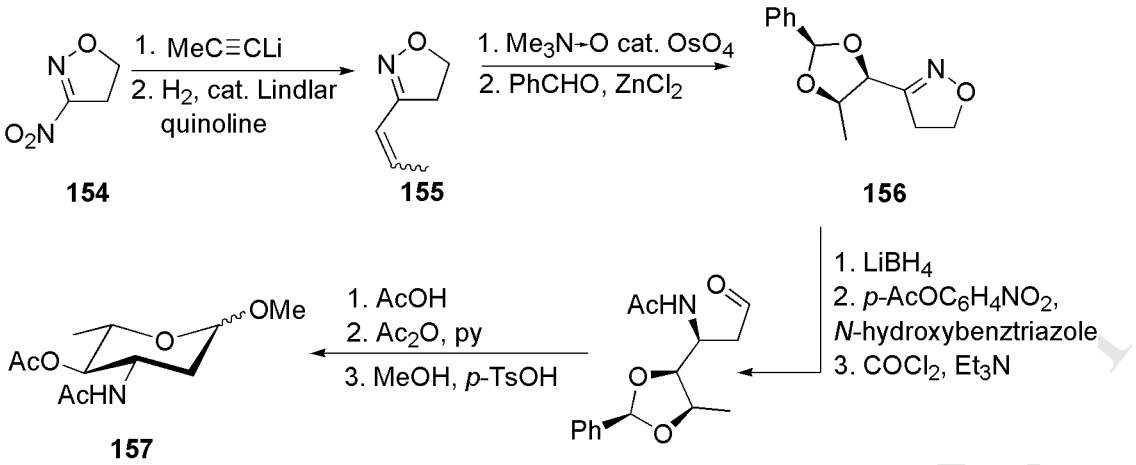


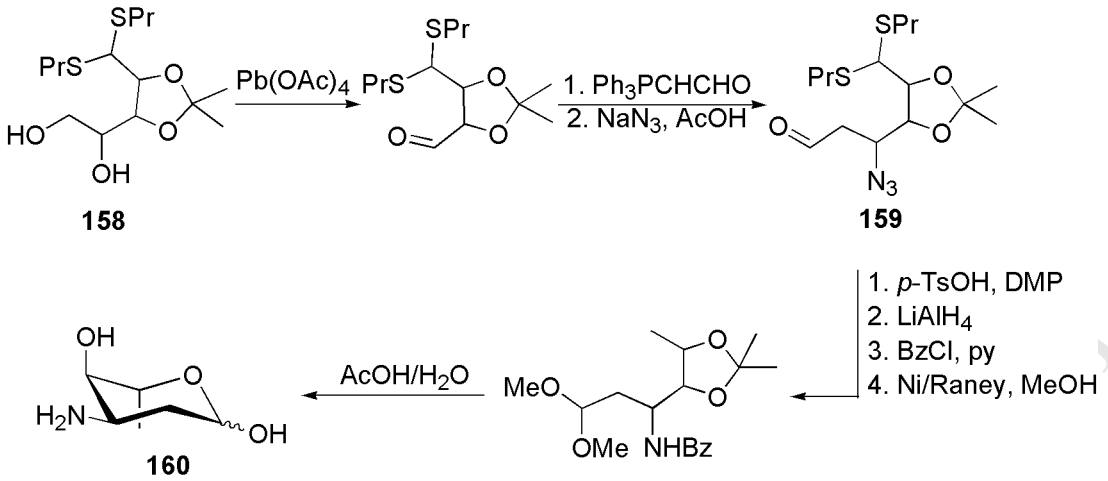
DMIPSCl - isopropyldimethylsilyl chloride



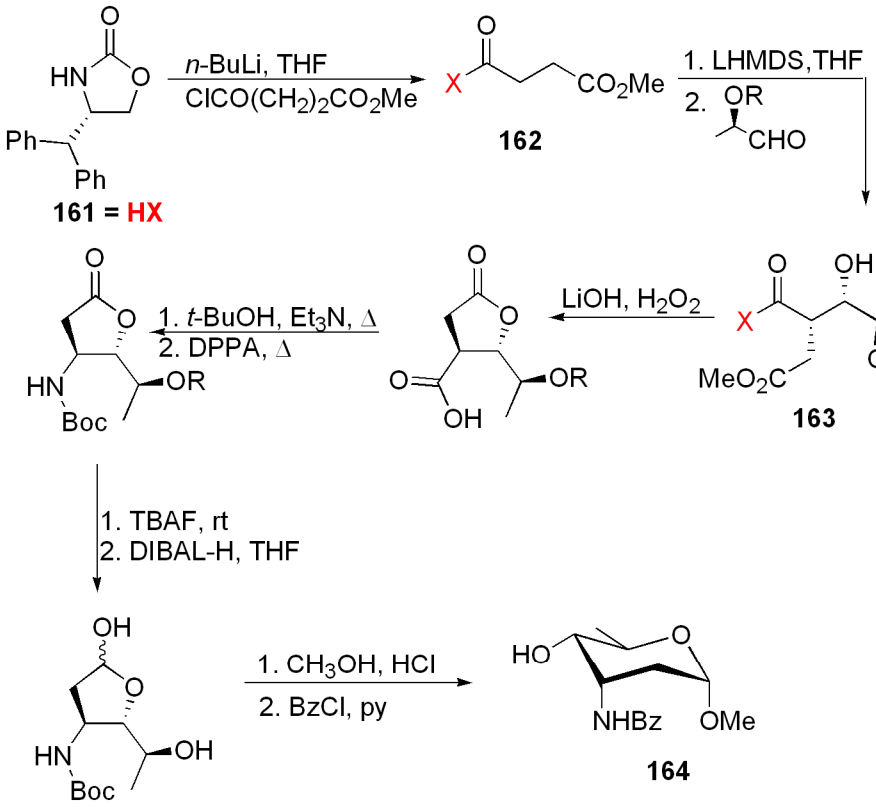
L-**130**

153 **152** **151**

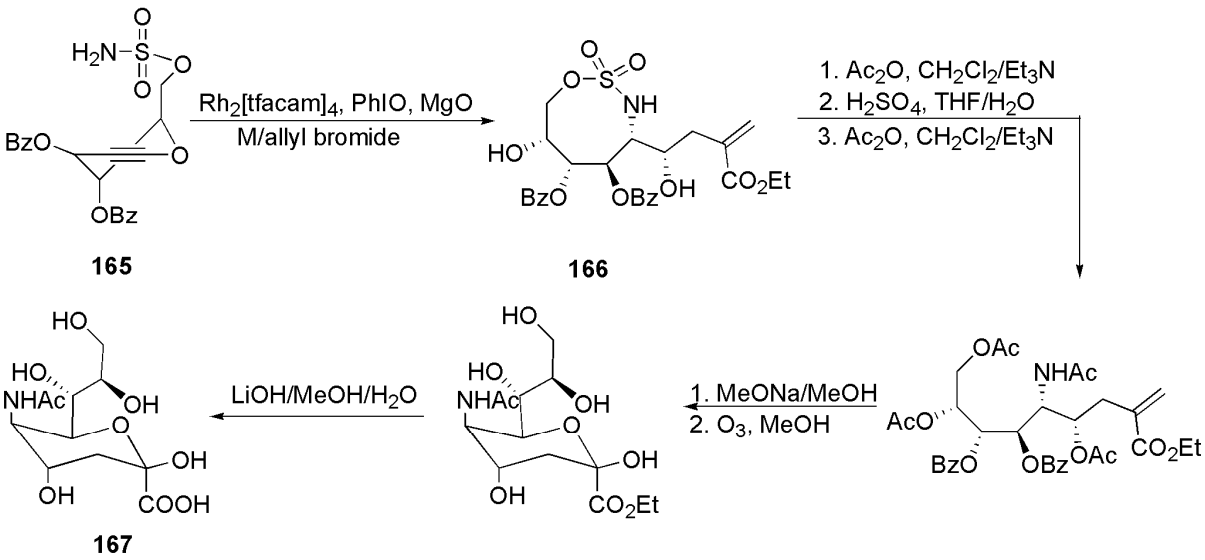




DMP -2,2-dimethoxypropane



R = TBDMS
LHMDS - lithium bis(trimethylsilyl)amide
DPPA - diphenylphosphoryl azide
TBAF - tetra-*n*-butylammonium fluoride



165 **166** **167**

$Rh_2[tfacam]_4$ - rhodium(II) trifluoroacetamide
M: Mg, In, Sn, Zn