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Tactics and strategies for the synthesis of iminosugar C-glycosides: a review

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ABSTRACT

Three decades after their first synthesis, iminosugar C-glycosides have become an important class of iminosugars with promising biological and therapeutic properties. The purpose of this review is to provide an overview of the versatile strategies that have been developed to synthesize this family of stable imino-analogues of glycosides and glycoconjugates. Some guidelines and predictive stereoselective models are presented to facilitate the design of synthetic strategies toward iminosugar C-glycosides of defined configuration.

Contents

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1. Introduction

1.1. Biological and therapeutic interest of iminosugars

It is difficult to imagine that the researchers who isolated or synthesized the first examples of iminosugars in 1960s, could have anticipated their therapeutic potential.[1] Since the commercialization of the first iminosugar-based drug in 1996 **1** (Glyset™), the rate of discoveries in the field of sugar mimetics with nitrogen replacing the ring oxygen (Fig. 1) has increased dramatically.[2] As a consequence of their inhibitory activity against a number of enzymes of medicinal interest including glycosidases,[3] glycosyltransferases,[4] metalloproteinases,[5] or nucleoside-processing enzymes,[6] iminosugars constitute leads for the development of new therapeutic agents in a wide range of diseases. Various structures have been, or are currently involved in, clinical trials for the treatment of diabetes,[7] cancers,[8] viral infections,[9] and rare genetic diseases (lysosomal storage disorders[10] and cystic fibrosis[11]).[2]

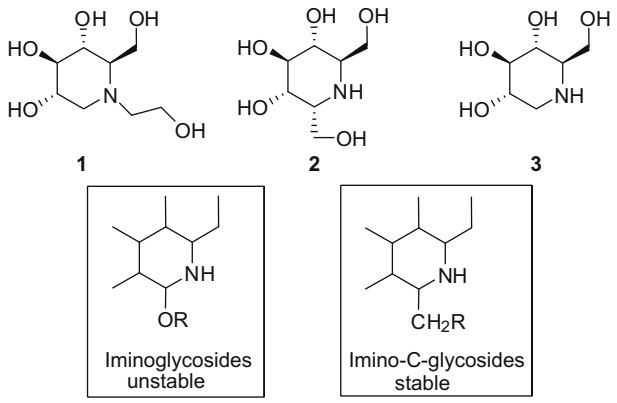


Figure 1.

1.2. Iminosugar C-glycosides

One of the major drawbacks associated with imino-analogues of glycosides is their instability caused by the lability of the *N*,*O*-acetal function, which prevents their use as biological probes or drug candidates. By analogy with C-glycosides,[12,13] the replacement of the oxygen atom of the *N*,*O*-acetal function by a methylene group to form a stable C–C bond at C-1 has been a frequently used tactic to generate stable analogues of glycoconjugates. The first synthesis of iminosugar C-glycosides was performed by Bayer's chemists in the early 1980s,[14] almost 10 years before natural α-homonojirimycin **2**, one of the simplest examples of this class of compounds, was isolated for the first time.[15] Since this pioneering work, which was triggered by the therapeutic interest of iminosugars, many synthetic efforts have been devoted to developing efficient and stereocontrolled routes to iminosugar C-glycosides.[16,17]

1.3. Iminosugar C-glycosides versus N-substituted iminosugars

The synthetic strategies designed have allowed the biological evaluation of a wide range of iminosugar C-glycosides. This family of compounds, which now constitute an important class of iminosugars, is indeed well positioned as stable glycoconjugate or oligosaccharide mimetics of biological and therapeutic interest (Fig. 2). The advantages of iminosugar C-glycosides in terms of potency and selectivity compared to simpler iminoalditols, including N-substituted 1-deoxyiminosugars, have been highlighted in various studies.[26] It is important to note that the latter compounds are much more readily available and can be obtained in a few steps by reductive amination or alkylation reactions from commercially available 1-deoxyiminosugars such as DNJ **3**. It has been shown, however, that iminosugar C-glycosides offer distinct advantages in the field of antiviral agents[22] and for the discovery of selective inhibitors of therapeutically relevant carbohydrate-processing enzymes.[26] Various comparative studies on simple glycolipid analogues have demonstrated a marked dependence of the selectivity and/or potency of the inhibitors/ligands upon the position of the alkyl chain (1-*C*- or *N*-alkyl derivatives).[26] As regards glycosidase inhibitors, improved results obtained with iminosugar C-glycosides may be partly explained by the stronger influence on the piperidine ring conformation of substituent linked to the C-1 rather than to the endocyclic N-atom.[19] Another point is the more favorable interactions with enzyme putative lipophilic pocket that may be achieved with a better position of the alkyl chain.[19,20,27]

1.4. Strategies for the synthesis of iminosugar C-glycosides

The main challenge associated with this family of glycomimetics is the design of efficient and general synthetic routes and the generation of structural diversity from advanced precursors to accelerate the discovery of biologically relevant compounds. More precisely, the structure of iminosugar C-glycosides presents a number of challenges that have to be addressed: (a) at least four contiguous stereogenic centers must be obtained with high stereochemical control; (b) the piperidine or pyrrolidine ring must be generated efficiently; and (c) due to the high density of functional groups, protecting groups must be selected judiciously, especially one for the endocyclic amino group. Synthetic strategies reported in the literature may be divided into two general categories: (a) those which construct the C-glycosidic structure by way of intramolecular cyclization (C5/C4–N and/or C1–N key disconnection, Figs. 3 and 4); and (b) those which make use of an electrophilic iminosugar donor (C1–CH_2R key disconnection, Figs. 5 and 6). The latter intermolecular approach is inspired from well-documented strategies developed for the synthesis of classical C-glycosides[12,13] and has to date been less exploited than the intramolecular approach. Due to their availability and their structural relationship with iminosugars, carbohydrates have been largely used as starting materials and a few de novo syntheses have been reported.

1.5. Aims and scope

Since our goal is to present versatile synthetic strategies that may be useful to access iminosugar-based inhibitors or ligands exhibiting high selectivity, this review will focus on the synthesis of iminosugar C-glycosides having a functionalized or relatively complex aglycon part. Synthetic strategies toward the synthesis

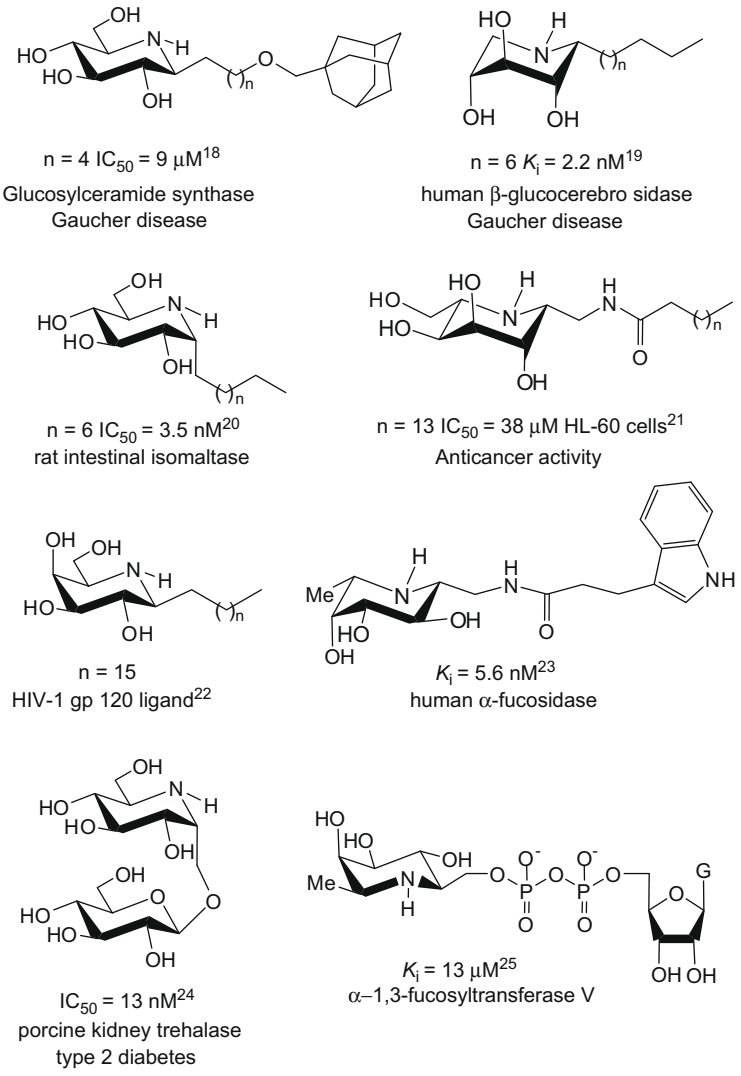


Figure 2. (See above-mentioned references for further information.)

of simple homoiminosugars, such as **2** will not be presented.[17] Some guidelines and predictive stereoselective models are presented at the end of this review to facilitate the design of synthetic strategies toward iminosugar C-glycosides of defined configuration.

2. Synthesis of iminosugar C-glycosides in the piperidine series

2.1. Intramolecular C–N bond formation (C5–N and/or C1–N key disconnection)

2.1.1. Reductive amination

The intrinsic reactivity of amines is always an issue that has to be considered in a synthetic scheme, and the choice of a suitable protecting group is often critical. In the case of iminosugars, chemists have taken advantage of the reactivity of amino groups to develop specific synthetic strategies that cannot be applicable to classical C-glycosides. Reductive amination has been the most popular reaction for the synthesis of iminosugar C-glycosides to date. This chemistry allows the formation of the C5–N and/or C1–N bond with the concomitant generation of one or two stereogenic centers. In addition, reductive amination is compatible with a broad array of functional groups. Double reductive amination of dicarbonyl sugars is theoretically the method of choice for the synthesis of iminosugar C-glycosides. In a single synthetic operation, C5–N and C1–N bonds can be stereoselectively formed to generate the piperidine ring[28] and intermolecular introduction of amine functionality allows a convergent access to a diversity of N-substituted iminosugar C-glycosides. However, examples reported in the literature so far have indicated that this strategy was suitable only for the synthesis of iminosugar β-C-glycosides; double reductive amination of 1,5-dicarbonyl sugars proceeded with complete β-selectivity in good yields. In 1996, Martin and Saavedra described the first synthesis of six-membered iminosugar C-glycosides by way of double reductive amination (Scheme 1).[29] Oxidation of diols **4**, obtained in two steps from tetra-*O*-benzyl-D-glucono-1,5-lactone, was achieved using DMSO–trifluoroacetic anhydride. To avoid the formation of undesired aldol products, diketone **5** was immediately submitted to reductive amination to afford iminosugar β-C-glycosides **6** using ammonium formate in the presence of $NaBH_3CN$ and molecular sieves. The use of strict anhydrous conditions was required for this reaction. The high stereocontrol observed is likely to exclude the amination of one of the carbonyl groups of the diketone in the open chain form. The 1,5- *cis*-stereoselectivity may be rationalized by the preferential axial addition of the hydride to a half-chair conformation of the cyclic iminium intermediates to minimize torsional strain.[30]

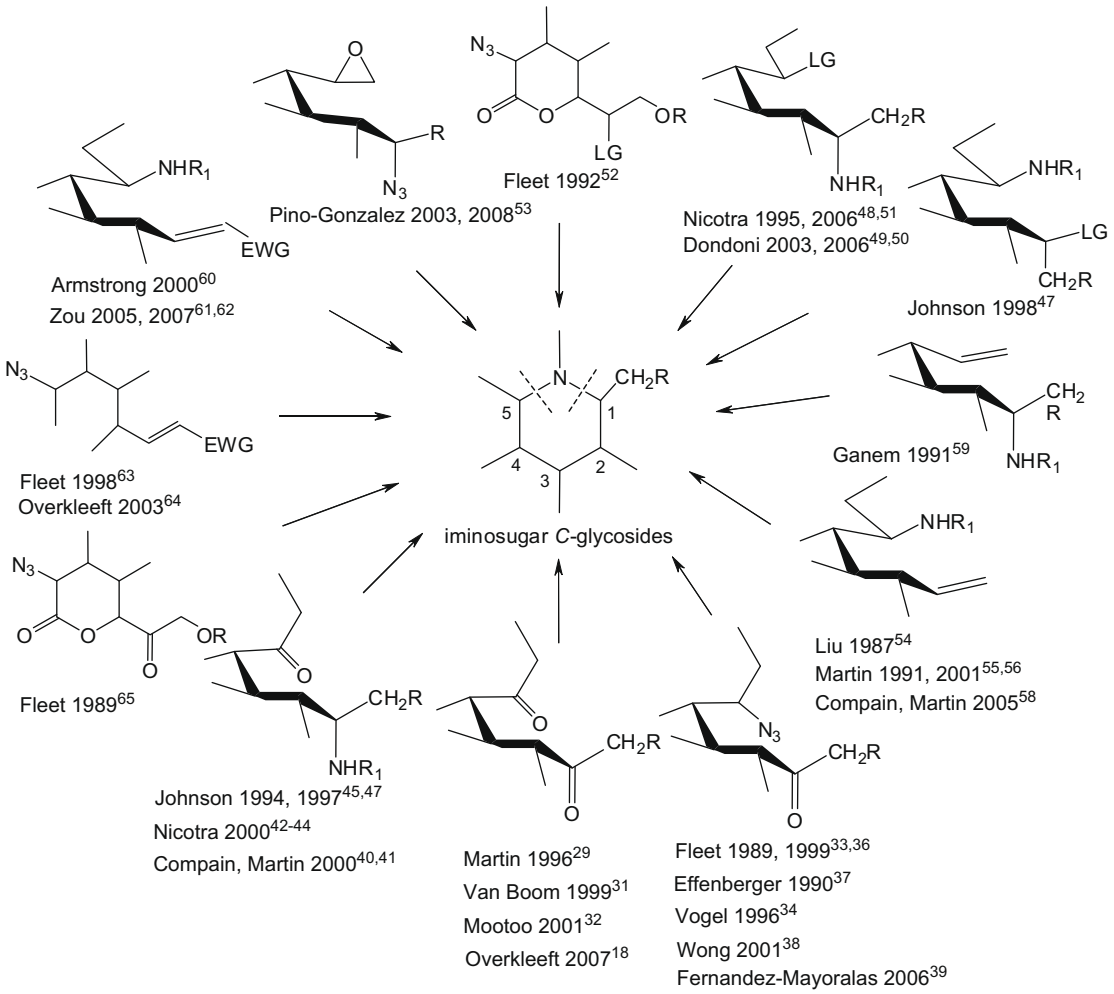


Figure 3. The intramolecular cyclization approach in the piperidine series.

Similar approaches from D-hexanolactone derivatives were described independently by van Boom et al.[31] (Scheme 2) and Mootoo et al.[32] (Scheme 3) for the synthesis of disaccharide mimetics. Interestingly, van Boom et al. performed the reductive amination with three diketone substrates obtained from tetra-*O*-benzyl D-hexanolactones in the D-*manno*, D-*gluco,* and D-*galacto* series. In all cases, the reaction led only to the β-(1→6)-*C*-disaccharide products indicating that the configuration at either C-2′ or C-4′ has no impact on the stereochemical outcome of the amination reaction (Scheme 2).[31] Complete β-selectivity was also observed from diketone derivatives protected with various protective groups[32] or from substrates with a lipophilic aglycon part.[18] These results further confirmed the generality of the double reductive amination strategy to obtain iminosugar β-C-glycosides in the piperidine series.

In 1989, Fleet, a pioneer in the field, reported the synthesis of 1-β-*C*-alkyl deoxymannojirimycin derivatives by way of hydrogenation of protected 6-azido-6-deoxy-hept-2-uloses.[33] In this strategy, the reduction of the azide and formation of the C1–N bond are performed in a single step to generate the piperidine ring with high diastereoselectivity in favor of the β-isomer (Scheme 4). The direction of the hydrogen addition to the cyclic imine intermediate **7** was determined by the protected hydroxymethyl substituent at C5 rather than by the isopropylidene group at C2–C3. The facial selectivity in the hydrogenation thus appears to be controlled solely by steric hindrance and not by chelation of any of the oxygen functions to the catalyst. A predictive model for the diastereoselective reductive amination of cyclic imine is presented (Fig. 7).

A similar result was obtained by Vogel et al. from the azido lactone **8** (Scheme 5).[34] Again, high stereoselectivities were obtained and, for steric reasons, *anti*-selectivity with respect to the group at C5 was observed for the hydrogenation of the cyclic imine intermediate **9**. Original 2,3,4,6-tetramethanol 5-hydroxypiperidine derivatives were prepared using the same chemistry.[35]

The azido lactol reduction strategy has also been applied to generate the piperidine ring by formation of the C5–N bond. However, results reported by Fleet et al.[36] and Effenberg[37] indicated that the reductive amination step occurs with a significant or complete loss of stereoselectivity. Azide reduction of azido lactol **10** and subsequent intramolecular reductive amination afforded an equimolar mixture of the pseudo α-D-*galacto* and β-L-*altro* products **11a** and **11b** (Scheme 6). A better selectivity in favor of the 1,5-*cis* product was reported from azido lactol **12**, the deprotected epimer of **10**. Interestingly azido lactol **12** was obtained by way of an aldolase-catalyzed C–C bond formation from readily available simple precursors (Scheme 7).

In 2001, Wong et al. described a related chemo-enzymatic synthesis of α- and β-1-phosphonomethyl iminosugars in the D-*galacto* and D-*manno* series by way of the hydrogenation of δ-azido ketones (Scheme 8).[38] Iminosugar phosphonates **13** and **14** were reported as the major products obtained after the hydrogenation step. The low yields observed and the absence of clear data regarding other

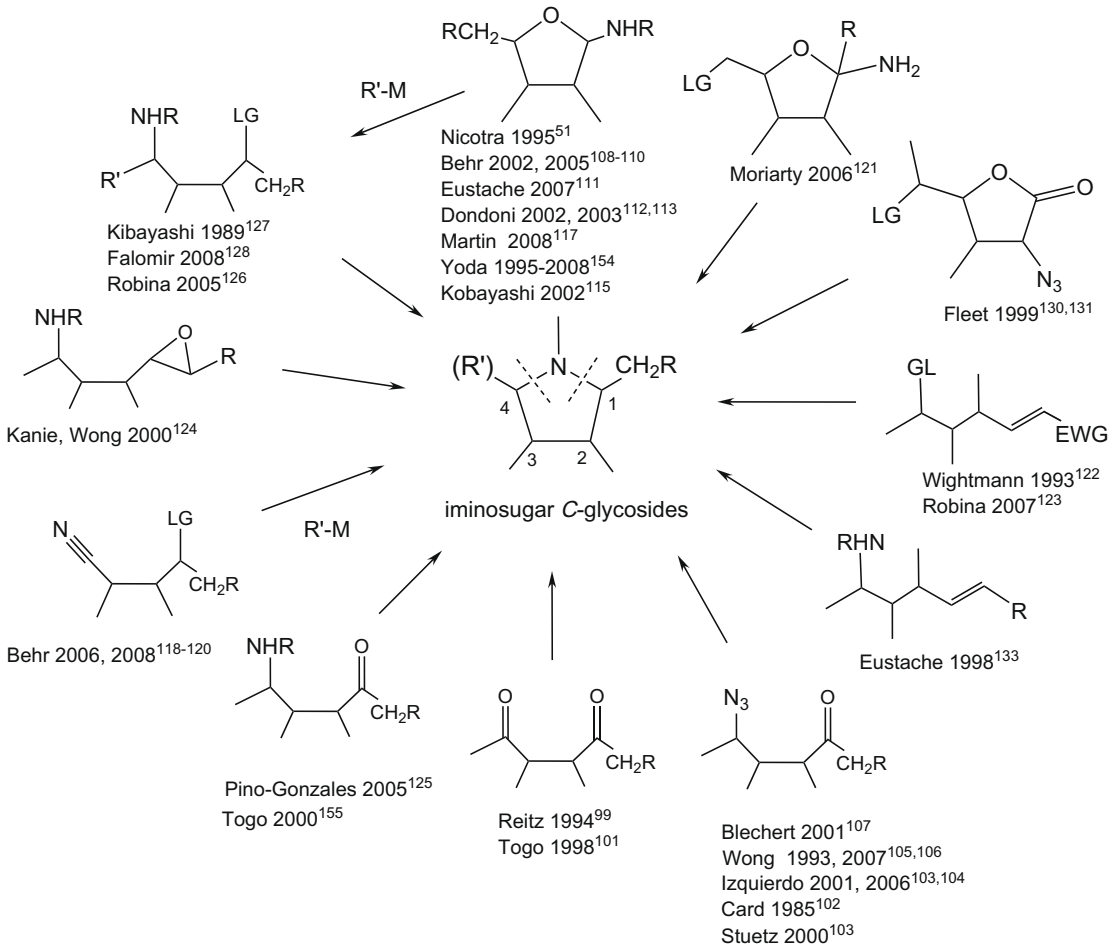


Figure 4. The intramolecular C–N cyclization approach in the pyrrolidine series.

possible by-products, prevent any reasonable rationalization of the diastereoselectivity reported.

Recently, Fernández-Mayoralas et al. reported a stereodivergent approach toward 1-*C*-alkyl iminosugars by way of a proline-catalyzed aldol condensation (Scheme 9).[39] Reaction of hydroxyacetone and aldehyde **15**, obtained in five steps from diethyl tartrate, catalyzed by L-proline afforded the *anti*-aldol product **16**. Hydrogenation of the δ azido ketone **16** in the presence of HCl provided the expected unprotected β-1-*C*-methyl 1-deoxymannojirimycin **17** as the major product with a good stereocontrol at C-5 (dr 6/1). The same reaction performed from **18**, the (3*R*,4*R*)-isomer of **16**, obtained by reaction of hydroxyacetone with aldehyde **15** catalyzed by D-proline, yielded unprotected 1-*C*-methyl 1-deoxyallojirimycin **19** with poor stereocontrol at C-5 (dr 1.4/1). No change in the diastereoselectivity was observed when the hydrogenation was performed in the absence of HCl to give the corresponding 4,6-*O*-benzylidene 1-deoxyiminosugar derivatives. However, hydrogenation of **20**, the acetylated analogue of **16** in the absence of HCl led only to β-1-*C*-methyl 1-deoxymannojirimycin (Scheme 10). Enantiomers of iminosugars **17** and **19** were obtained by applying the same chemistry on the (2*S*,3*S*)-isomer of **15**.

The synthesis of iminosugar C-glycosides by way of reductive amination of δ-amino ketones using hydride reagents has also been reported. A versatile strategy for the preparation of nojirimycin C-glycosides and related compounds from L-sorbose with full stereocontrol has recently been achieved (Scheme 11).[40] The first key step of the process is the highly diastereoselective chain extension of imine **21**, which controls the α- versus β-configuration at the pseudo-anomeric center in the final product. The stereoselectivity can be effectively inverted by adding an external monodentate Lewis acid (*si*-face addition). Structural diversity may be introduced at the 'anomeric' position by using the wide library of organometallic nucleophiles available.

Intramolecular reductive amination of the latent keto function of the amino-sorbofuranose derivatives **22a** proceeded with high diastereoselectivity in favor of the pseudo-α-D-*gluco* products. The facial selectivity of the reduction step may be explained by the addition of the hydride to a favorable half-chair conformation **A** of the cyclic iminium intermediate in which all substituents are in pseudo-equatorial position except for the R group (Scheme 12). Hydride delivery in the axial direction is sterically unhindered and minimizes torsional strain during the transition to the final chair conformation of the piperidine ring.[30] Under the same conditions, the reductive amination of the (6*S*)-epimers **22b** afforded an equimolar mixture of the pseudo-β-D-*gluco* and pseudo-α-L-*ido* products. The complete loss of stereoselectivity at C5 may be rationalized by the partial destabilization of the cyclic iminium ion in conformation **A**: in this conformer, all the substituents are in a pseudo-equatorial position, which generates $A_{1,2}$ strain between the C1 substituent and the *N*-benzyl group (Scheme 12). Hydride addition may thus also occur in the axial direction on the alternate half-chair conformation **B** of the iminium ion, and thus lead to a substantial proportion of pseudo-α-L-*ido* product. Removal of the *N*-benzyl group prior to internal reductive amination was indeed shown to suppress $A_{1,2}$ strain effects and to increase the stereoselectivity of the reduction toward the desired D-configuration. Removal of the benzyl protecting groups of the amino-sorbofuranose derivatives **22b** by hydrogenolysis, cleavage of the isopropyl-

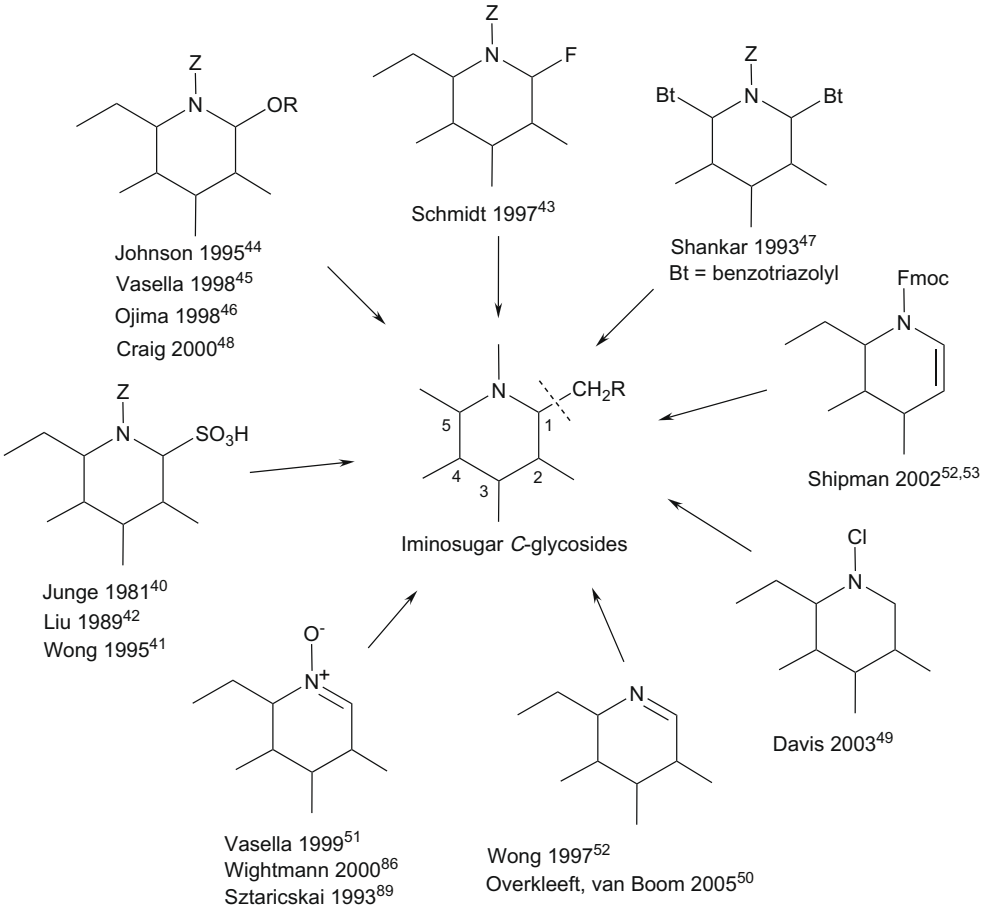


Figure 5. The electrophilic iminosugar donor approach in the piperidine series.

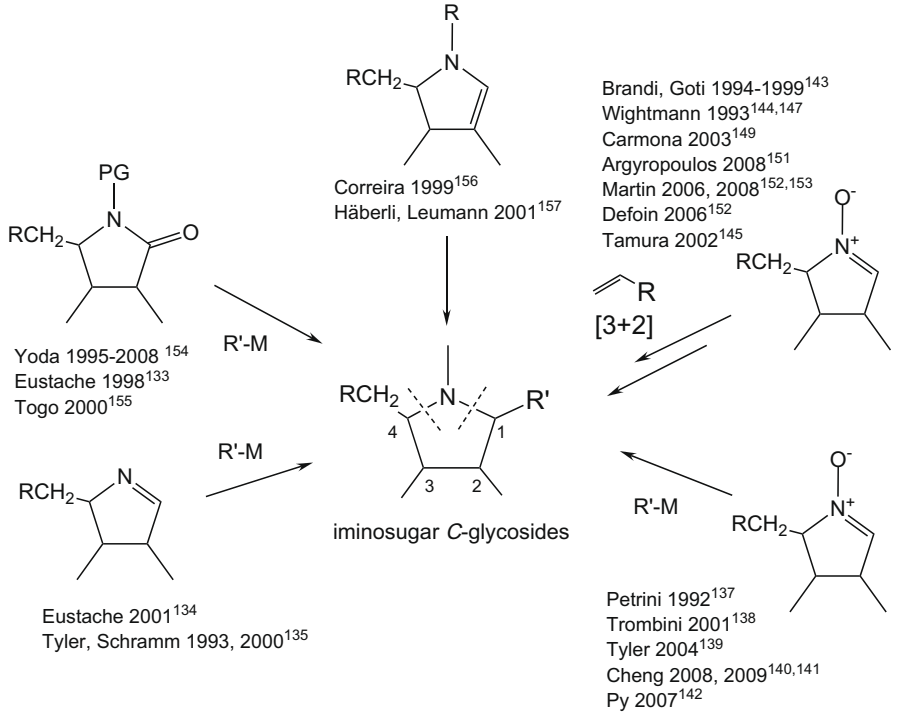
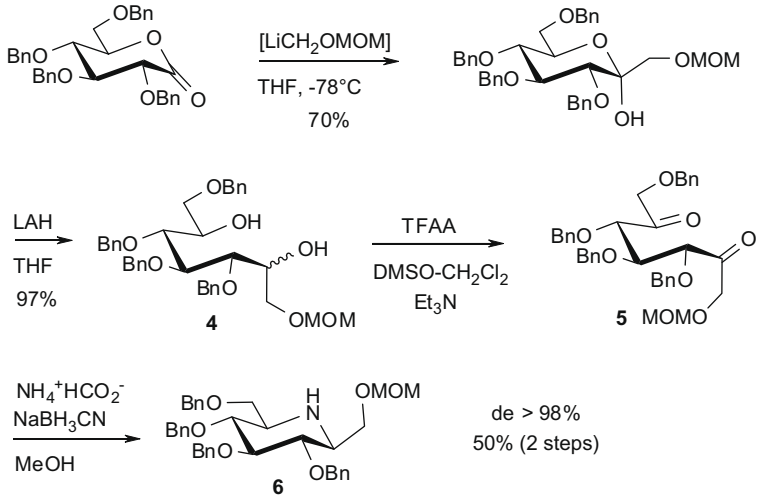
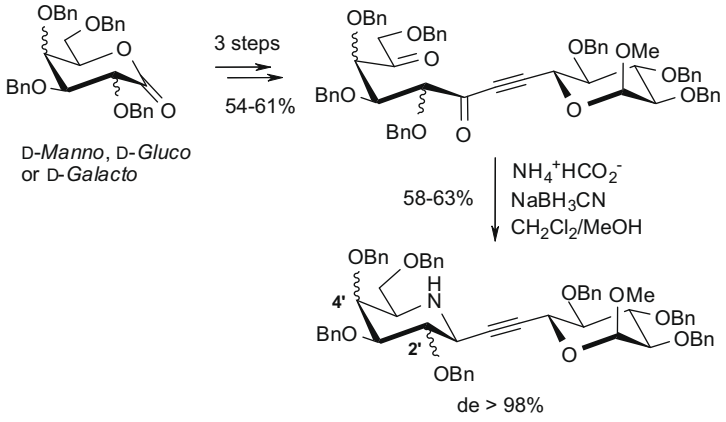


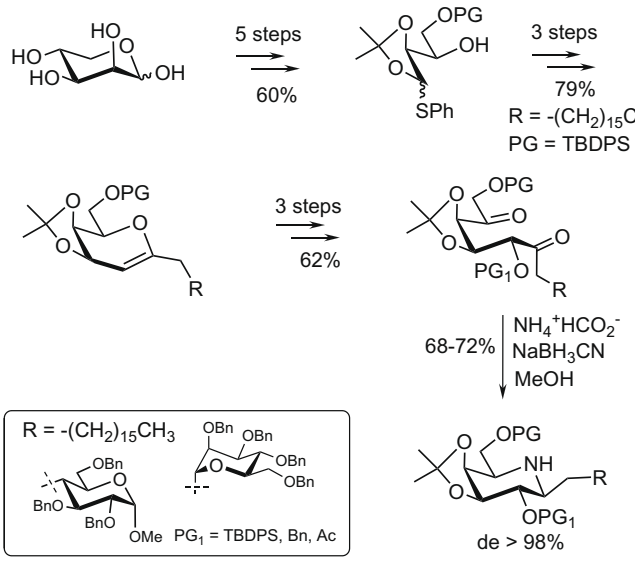
Figure 6. The electrophilic iminosugar donor approach in the pyrrolidine series.



Scheme 1.



Scheme 2.

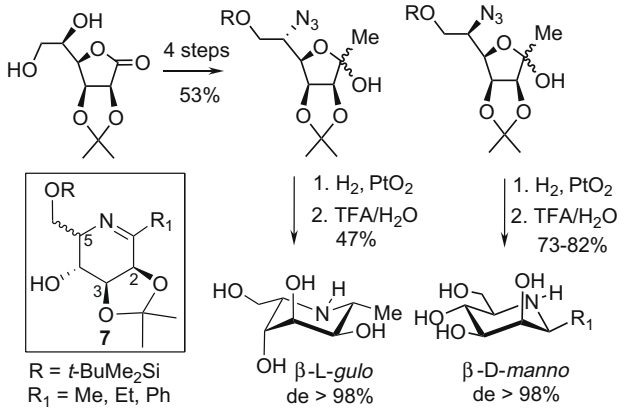


Scheme 3.

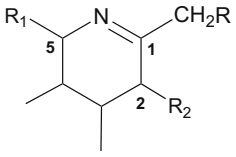
idene group, and reductive amination under classical conditions, provided the expected β-1-*C*-alkyl-1-deoxynojirimycin **23** in good overall yields. No trace of the other epimer was detected. A variation of this strategy using *N*-NAP or *N*-allyl protecting group has been developed to gain access to β-C-glycosides derivatives with an unsaturated R group such as **24** (Scheme 13).[41]

Access to α-1-*C*-alkenyl 1-deoxynojirimycin derivatives **26** by way of intramolecular reductive amination with $NaBH(OAc)_3$ has been reported by Nicotra et al. (Scheme 14).[42] The amino group was introduced by reaction of tetra-*O*-benzyl-D-glucose with benzylamine in the presence of *p*-toluenesulfonic acid. The reaction with organomagnesium reagents provided the open chain amino alcohol **25** after protection of the amino group with modest to good diastereoselectivity. Oxidation of the free hydroxyl group and removal of the Fmoc group followed by subsequent reductive amination afforded C-glycosides **26** with complete stereocontrol at C-5. Chemical manipulations of the alkenyl appendage have been also performed.[42,43]

The same group reported an access to different 1-*C*-carboxymethyl iminosugar derivatives **29** having both α and β structures and both D- and L-stereochemistries (Scheme 15).[44] The amino group was introduced by way of Michael addition performed on esters **27** with low diastereoselectivity. Reductive amination of stereoisomers **28** using $NaBH(OAc)_3$, afforded the expected iminosugar C-glycosides with generally good stereocontrol at C-5 in favor of the *trans*-epimers. These compounds were used as scaffolds to generate a library of potential glycosidase inhibitors.[44]

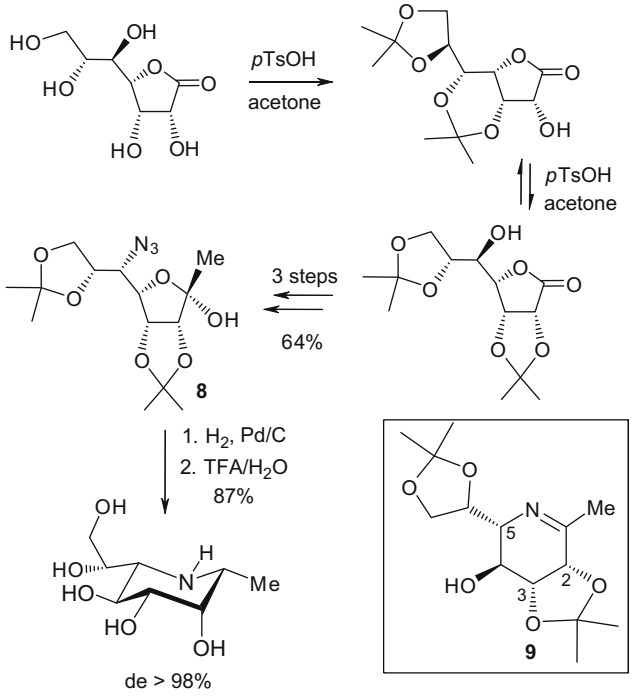


Scheme 4.



R_1	Stereoselectivity of the reductive amination	Sources
Medium or Large (alkyl, CH_2OR)	1,5-*cis* in all cases*	schemes 4,5,10,11
Small (Me) or CH_2OH	1,5-*cis* if R_1/R_2 *cis* low de if R_1/R_2 *trans*	schemes 7, 9, 16,17,18,19

Figure 7. Predictive model for the diastereoselective reductive amination of cyclic imine intermediates. This model cannot be applied to the pyrrolidine series (see for example Schemes 64 and 65). * With the exception of Scheme 48.



Scheme 5.

The synthesis of imino-*C*-disaccharides was reported by Johnson by way of an ozonolysis followed by reductive amination of the generated δ-keto amine (Scheme 16).[45] This approach is a rare example of de novo synthesis of iminosugar C-glycosides which does not adopt carbohydrates as the starting materials. The key intermediate **32** was obtained by coupling of vinyl bromide **30** with the borane obtained from **31** under standard conditions. Endocyclic alkene **32** was subjected to ozonolysis followed by DMS work-up to provide a keto-aldehyde which was reduced chemoselectively with $NaBH_3CN$ to produce a keto alcohol. Intramolecular amination yielded the expected β-(1→6)-aza-*C*-disaccharide **33** as a single diastereoisomer. The fully deprotected disaccharide mimetic was obtained in one step upon acidic treatment (6 M HCl, MeOH) in good yield. Similar results were obtained when the strategy was applied to the 2,3,4-tri-*O*-methoxymethyl analogue of **32** in the D-*gluco* series.[45]

The same group also synthesized β-(1→4) and β-(1→1) linked disaccharide mimics from endocyclic alkenes **34** and **35** following the same strategy. Intramolecular amination again led to protected 1,5-*cis*-piperidinol derivatives with a high level of diastereoselectivity (Scheme 17).[45]

Johnson et al. also applied the ozonolysis and selective reduction protocole to access β-1-C-aryl-1-deoxymannojirimycin analogues (Scheme 18).[46]

An elegant synthesis of β/β tethered polyhydroxylated ring systems (bis-imino-C-glycosides) has also been reported and further highlights the versatility of Johnson's strategy (Scheme 19).[47]

The double reductive amination of the bis-keto amine obtained after the reduction of the ozonolysis product afforded the expected β/β C_8 linked bis-iminosugar **37** as a single diastereoisomer in good yield from **36** (Scheme 19). However, the efficient ozonolysis and selective reduction protocols proved to be difficult for the synthesis of bis-iminosugar with a more complex linker. Consequently the authors developed an alternative strategy by way of an intramolecular S_N2 reaction, as shown in the next paragraph.[47]

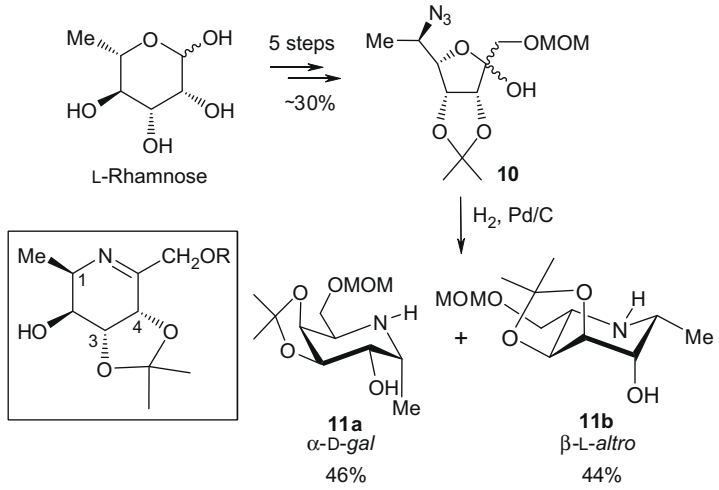
2.1.2. Intramolecular S_N2 reaction

Piperidine ring formation by displacement of a leaving group or ring-opening of an epoxide by an amino function is also a classical strategy to access to iminosugar C-glycosides. However, when this strategy is applied to readily available D-sugar precursors to generate the C5–N bond, inversion of configuration at C-5 (due to the displacement of a leaving group) leads to the formation of an iminosugar in the L-series. As a consequence, the intramolecular S_N2 reaction appears to be the method of choice to access mimetics of L-sugars, the appearance of which is very rare in Nature. Thus, all the examples reported in this section will concern L-iminosugars.

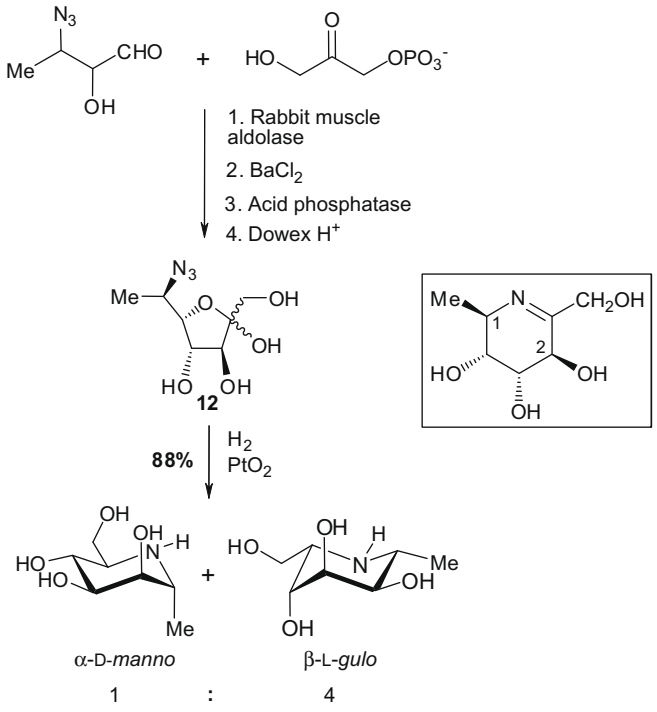
The α/α C_8-linked bis-iminosugar **38** was synthesized by Johns and Johnson by intramolecular nucleophilic displacement of a mesylate to form the key C1–N bond of the piperidine rings (Scheme 20).[47] The mesylate ring closing sequence started from the same alkene precursor **36** that was used for the synthesis of the β/β C_8-linked bis-iminosugars (Schemes 16–19) by way of reductive amination.

A variant of this approach using a more direct Mitsunobu strategy was successfully applied to the preparation of bis-iminosugar **39** linked with more complex linkers (Scheme 21).[47] It is noteworthy that the Mitsunobu approach required fewer chromatographic purifications than the mesylate protocol described above. Best yields were achieved for the synthesis of the pseudo-disaccharide with an amino linker.

Another Mitsunobu approach to iminosugar C-glycosides was described by Nicotra et al. to gain access to α-1-phosphonomethyl-1-deoxy-L-idonojirimycin derivatives from tetra-*O*-benzyl-D-glucose (Scheme 22).[48] The amino group was introduced with



Scheme 6.



Scheme 7.

inversion of configuration at C-5 by way of a first Mitsunobu reaction leading to carbohydrate derivatives in the L-ido series. A second Mitsunobu reaction allowed the formation of the piperidine ring by intramolecular displacement of the phosphonium intermediate. After the deprotection steps, the α-1-phosphonomethyl-1-deoxy-L-idonojirimycin **40** was obtained in 15 steps and in 9% overall yield.

In 2003, Dondoni et al. reported the preparation of iminosugar C-glycosides from tetra-*O*-benzyl-D-glucose and tetra-*O*-benzyl-D-galactose (Scheme 23).[49] The synthetic plan was based on the stereoselective addition of organometallic reagents onto *N*-benzyl-*N*-glycosylhydroxylamines **41** followed by the intramolecular displacement of a mesylate group by the amino group. The latter step, which involves an inversion of configuration at C-5, afforded the fully protected iminosugar C-glycosides with a pseudo L-*ido* or L-*altro* configuration. A similar strategy was reported by the same group to access six-membered homoiminosugars in the L-*ido* series by way of thiazole-based aminohomologation of *N*-benzyl-*N*-glycosylhydroxylamines **41**.[50]

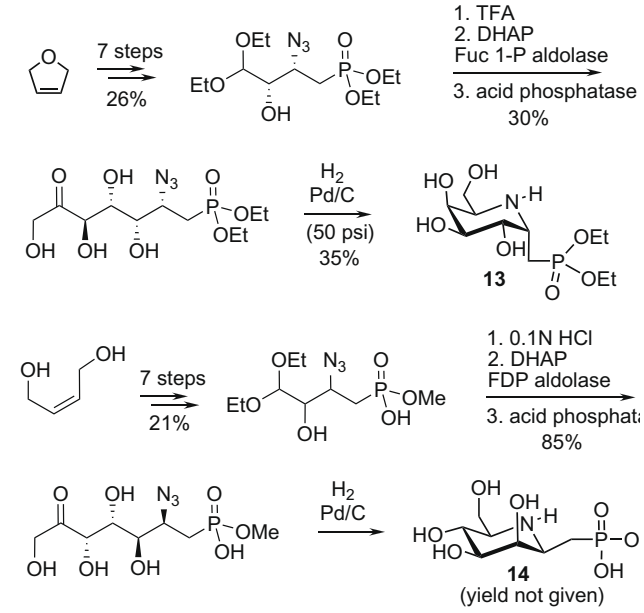
A related approach based on the stereoselective addition of organometallic reagents onto *N*-benzyl-*N*-glycosylamines followed by intramolecular displacement of a triflate group by the amino group was reported by Nicotra et al. (Schemes 24 and 25).[51] In sharp contrast to the results obtained by Dondoni with *N*-glycosylhydroxylamines (Scheme 23), the addition of organomagnesium reagents to imines afforded the *syn* adducts with high selectivity. The *anti* selectivity observed by Dondoni may be rationalized by a preferential conformation of the chelated open-chain nitrone intermediate due to magnesium coordination to the nitrone oxygen atom and the free hydroxyl group.

In 1992, Fleet et al. reported the synthesis of 1-carboxy 1-deoxyiminosugars by way of an azide reduction followed by an intramolecular S_N2 reaction.[52] The amino group was introduced at the beginning of the synthetic scheme after a cyanide chain extension of diacetone D-mannose and conversion of the remaining hydroxyl group into the corresponding azide via the S_N2 type reaction followed by epimerization (Scheme 26). The desired iminosugar **43** was obtained by hydrogenation of the azidomesylate **42**, followed by removal of the protecting groups and ring opening of the lactone under acidic conditions.

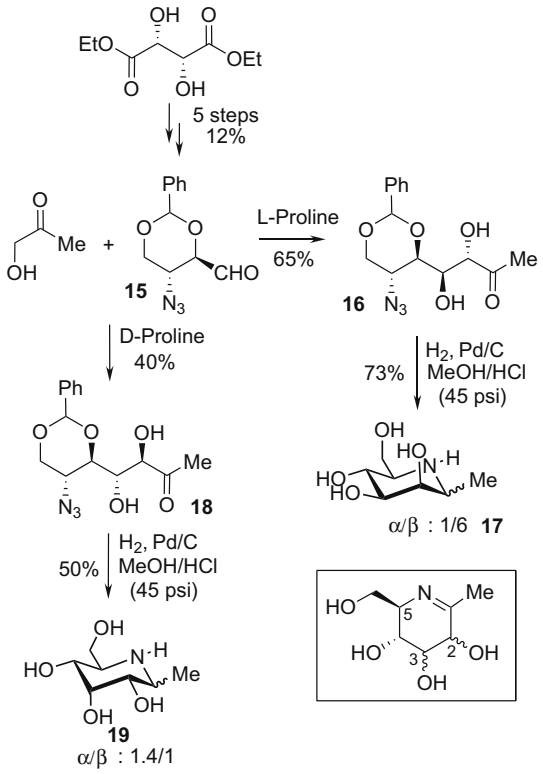
Stereodivergent access to 1-carbamoyl 1-deoxyiminosugars in the D- or L- series by way of α,β-epoxyamides and azidomesylate intermediates was described by Pino-González et al.[53] In this process, the amino group is introduced by regioselective ring opening of epoxyamide **44** obtained in three steps from D-ribose. Displacement of a mesylate group at C-6 by the amino group with inversion of configuration at C-2 provided the expected iminosugar C-glycoside **46** in the L-series (Scheme 27). A variant of this strategy was reported by the same group using a chloromesyl leaving group and an unprecedented azido group reduction with NaI in DMSO. Treatment of the chloromesylated derivative **47** under these conditions yielded the desired piperidine **48** in one step (Scheme 28).[53b] Access to the D-series was performed by way of a double inversion of configuration at C6 via terminal epoxide **49** obtained from the TIPS-protected analogue of **45** (Scheme 29). The intramolecular ring opening of the oxirane led to a mixture of the 6-*exo* product **50** and 7-*endo* product, the piperidine being the major product obtained.[53]

2.1.3. Electrophile-induced cyclization of aminoalkenes

The main advantage of synthetic strategies based on electrophile-induced cyclization of aminoalkenes is to form, in one step, a piperidine ring and an organomercurial or iodo derivative that



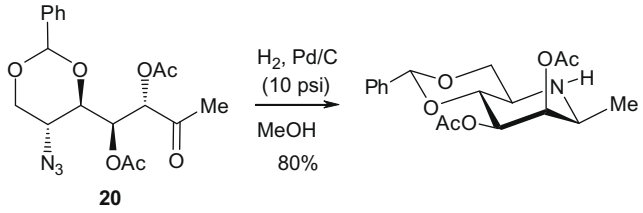
Scheme 8.



Scheme 9.

may be further functionalized. In addition, the reaction generally proceeds in good yield and with high diastereoselectivity. Cyclization of unsaturated amido- or aminoalditols has been usually promoted by mercury(II) salts or NIS as the source of electrophile. A pioneering example of such a strategy was performed by Liu in the 1980s to obtain homoimino disaccharides (Scheme 30).[54]

Liu's work and other studies indicated that the electrophile-induced cyclization of D-*gluco*, L-*altro*, D-*galacto* amino-, or



Scheme 10.

amidoheptenitol always afforded the corresponding iminosugar C-glycoside with a 2,3-*cis* configuration as dictated by the configuration at C3 (allylic carbon) of the starting material (Scheme 31).[54–56] The high diastereoselectivity observed may be rationalized by a key chelation effect of mercury cation with the vicinal C-3 benzyloxy group, preferential addition of the amido or amino group from the opposite site of the olefin affording the 2,3-*cis* epimer. Attractive interactions between iodine and oxygen atoms of the benzyloxy group may be explained in the same way the high diastereoselectivity observed for cyclization promoted by NIS.[57]

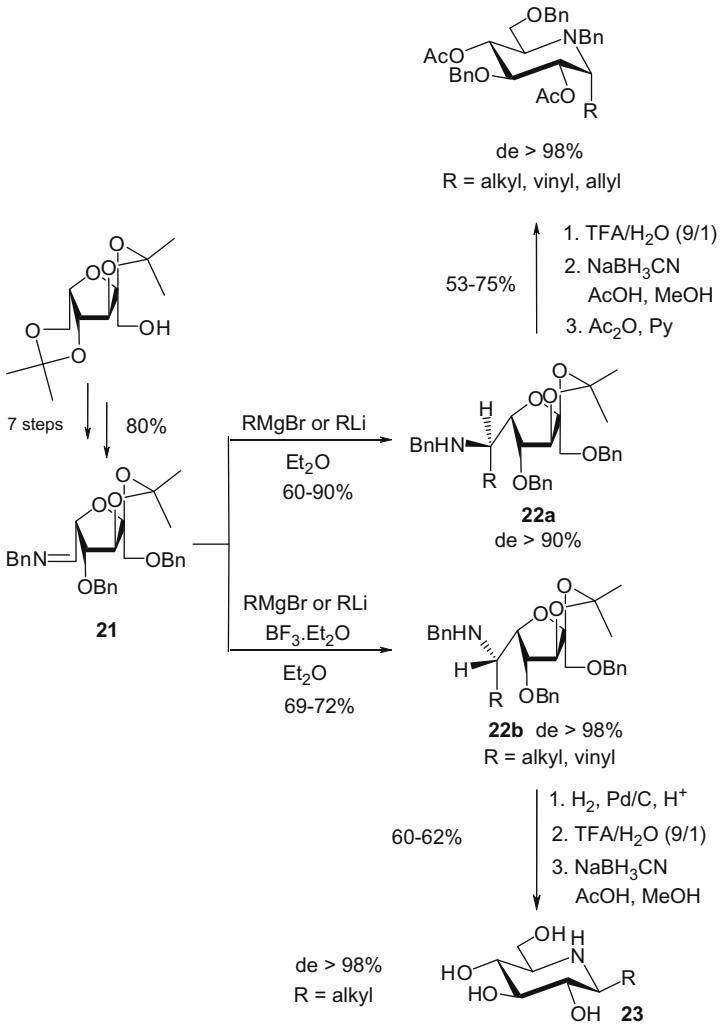
As an exception, the reaction performed from L-*ido* aminoheptenitol **51** leads to 2,3-*trans* epimer **52**, because of steric interactions between *syn*-diaxial substituents which probably destabilize the intermediate leading to the 2,3-*cis* isomer (Scheme 32).[55] A loss of diastereoselectivity is observed in the absence of an alkoxy group at C-3, as judged by the cyclization of 3-deoxy heptenitol **53** (Scheme 32).[58]

Ganem et al. utilized a cyclization promoted by mercury(II) salts to form the C5–N bond in iminosugar C-glycosides **55** and **57** (Scheme 33).[59] In this case, the degree of stereoselectivity was found to be strongly dependent on the configuration at C-1 of the starting material. The reaction is controlled efficiently by the incipient axial hexenyl side chain, so that only the equatorial organomercurial **57** was obtained from **56**. This result may be explained by unfavorable pseudo 1,3-diaxial interactions between the hexenyl side chain at C-1 and the terminal CH_2 group of the olefin in chair conformer **58b** (Scheme 34). In contrast, cyclization performed from **54**, the C-1-epimer of **56**, bearing an equatorial hexenyl side chain, afforded a 1:1 mixture of axial and equatorial organomercurials **55**. In this case, as previously shown (Scheme 31), the formation of the 4,5-*cis* epimer, with an axial mercurymethyl group, may be favored by chelation effect of mercury with the vicinal C-4 benzyloxy group, resulting in the addition of the amino group from the opposite site of the olefin.

2.1.4. Miscellaneous reactions

2.1.4.1. Hetero-Michael reaction. Intramolecular hetero-Michael reaction has been used as a valuable tool to form the C1–N bond of iminosugar C-glycosides. The diastereoselectivity of the Michael addition was found to be highly dependent on the structure of the starting material. Over the course of the synthesis of tricyclic guanidium model of cylindrospermopsin, Armstrong and McAlpine reported the synthesis of **60** as a single diastereoisomer by treatment of **59** with a catalytic amount of pTsOH and subsequent hydrogenation (Scheme 35).[60] The high diastereoselectivity observed may be explained by the favorable $^4\mathbf{C_1}$ conformation of the putative transition state **61**, in which all the substituents are equatorial except for the bulky silyl ether group.

The Zou's group described another approach in which 5-azido-5-deoxy-glycofuranosides were used as latent substrates for intramolecular Michael addition (Scheme 36).[61] The absence of diastereoselectivity observed for the conversion of **62** into iminosugar **63** is difficult to rationalize. Steric repulsion resulting from metal ion (Na^+) chelation or hydrogen bonding between the 4-axial OH group and the amino group may destabilize the favorable $^4C_1$



Scheme 11.

conformation of the putative transition state in which all the substituents are equatorial except the OH group at C-4.[62] It is noteworthy that in the strategy reported by Zou, the imino-C-glycosides are synthesized via a C-glycoside intermediate. Access to polyhydroxylated quinolizidines following a similar approach as well as access to pyrrolidine C-glycosides was also reported by the same group,[62] (Section 3.1.4., Scheme 88).

2.1.4.2. Intramolecular 1,3-dipolar cycloaddition. Thermally induced intramolecular 1,3-dipolar cycloaddition of open-chain azido-enoates was also used as a key step to generate the piperidine ring and stereoselectively form the key C1–N bond of iminosugar C-glycosides. In this process, the triazolines initially obtained may fragment to give β-amino-α-diazoesters which can further lose nitrogen to provide the corresponding methylene piperidines (Schemes 37 and 38). Fleet et al**.** reported the synthesis of 1-deoxymannojirimycin homologues following this strategy (Scheme 37).[63] The bicyclic aminolactone **65** was obtained from ***E***-enoate **64a** and ***Z***-enoate **64b** in 64% and 45% yields, respectively, under thermal conditions. Hydride reduction of the double bond, followed by reduction of the ester groups and subsequent removal of the isopropylidene protective groups afforded the iminosugar C-glycoside **66**.

A related strategy was reported by Overkleeft et al. *exo*-Iminoglycals as potential precursors of iminosugar C-glycosides were obtained by way of a tandem retro-Michael-[2+3] cycloaddition (Scheme 38).[64]

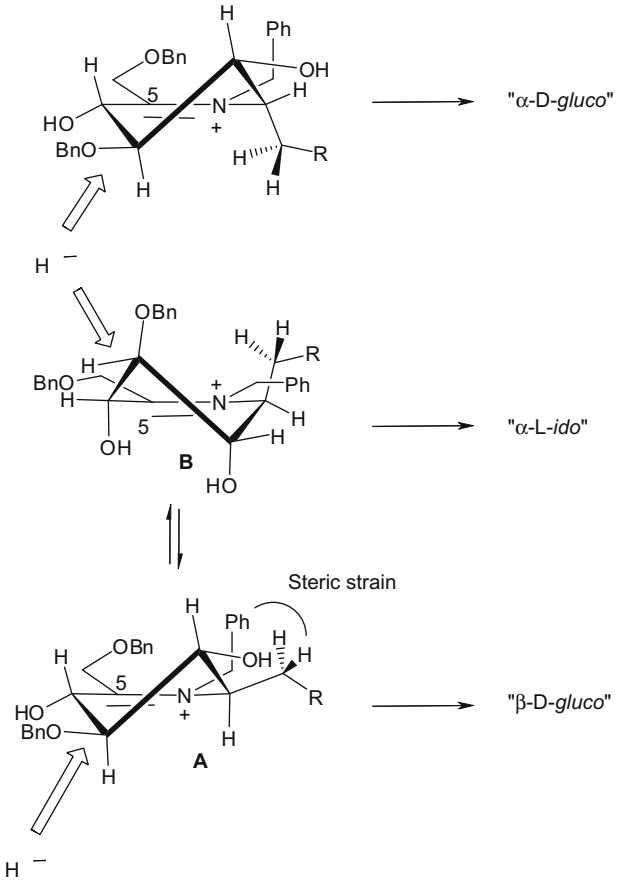
2.1.4.3. Intramolecular aza-Wittig. Fleet et al**.** also reported synthetic strategies which make use of intramolecular aza-Wittig reaction of ketoazides as the key step (Scheme 39).[65] The reduction of **67** proceeded in modest yield but with good diastereoselectivity (de 90%) to give, as the major product, α-D-manno homoiminosugar **68** corresponding to the hydride addition from the less hindred face of the imine.

2.2. Electrophilic iminosugar donors (C1–CH_2R key disconnection)

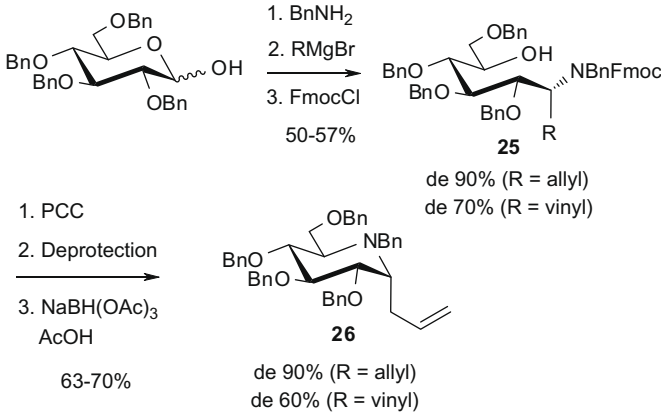
In this part, the C1–CH_2R key disconnection will be described. Almost all these methodologies involve an imine, an iminium, or *N*-acyliminium ion as reaction intermediates. The favored '*H*' conformations of these unsaturated piperidine systems, coupled with stereoelectronic effects[66] and steric interactions will directly influence the stereochemistry of the addition leading to α or β-anomers as shown in Scheme 40.

2.2.1. Nucleophilic substitution

One of the most widely used methods for the synthesis of classical C-glycosides involves Lewis acid catalyzed reactions of



Scheme 12.



Scheme 14.

carbon nucleophiles (including Lewis acid catalyzed reactions) with activated sugar donors bearing a leaving group at the anomeric position.[12,13] For iminosugars, the direct application of this strategy is not obvious because of the relative instability of the corresponding iminosugar donors. However, several examples of such methodologies have been published in the literature. The first general access to iminosugar C-glycosides reported in 1981 was based on sulfonate/cyanide and cyanide/alkyl group exchange reactions (Scheme 41).[14] The process afforded 1-α-*C*-substituted-1-deoxynojirimycin derivatives with modest to good stereoselectivities as judged from the diastereomeric excess reported. The sulfonate/cyanide exchange reaction was also applied to synthesize α-homoiminosugars.[67–69] The latter method involving the bisulfite adduct of nojirimicin has the advantage of being applicable to unprotected piperidinose derivatives.

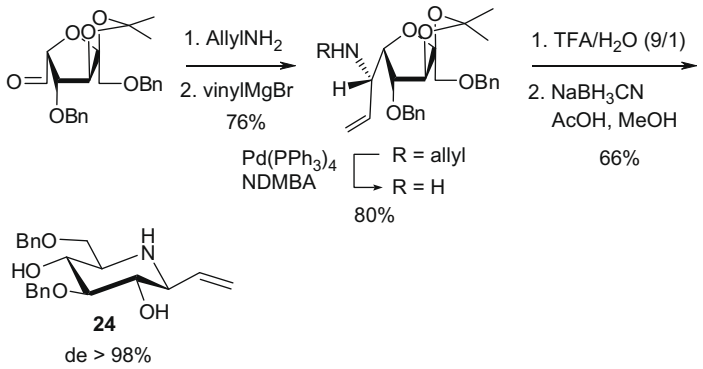
Johnson et al., Schmidt et al., and Vasella et al. reported that *N*-alkoxycarbonyl-protected piperidinosyl donors could be key intermediates in the synthesis of iminosugar C-glycosides.[69–71] Reaction of iminoglycosyl fluoride **69** with various silylated carbon nucleophiles in the presence of $BF_3{\cdot}OEt_2$ proceeded in good yields and with modest to high diastereoselectivity in favor of the α-epimer (Scheme 42).[69] The best stereoselectivity was achieved with allyl- and propynyltrimethylsilane. The direct conversion of the 1-methoxy derivative into fluoride **69** has not been mentioned in the literature, despite investigations by the authors.[69]

The phenyl 1-thioglycoside **70** can be converted into a nojirimycin derivative by treatment with NIS in wet CH_2CL_2 and then into an iminoglycal system via a trichloroacetimidate (Scheme 43). This intermediate is quite sensitive to hydrolysis and excess base.

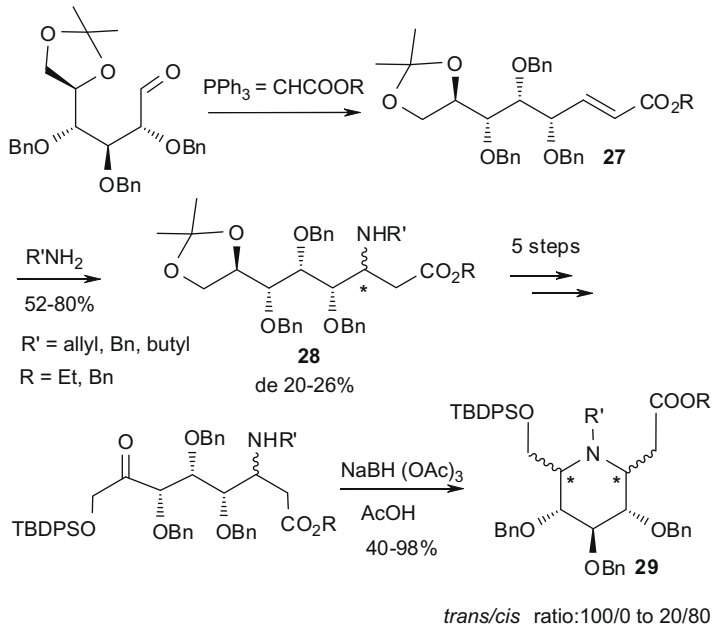
A related iminoglycal system was studied by Désiré and Shipman who demonstrated the possibility to carry out cyclopropanations (Scheme 44).[72b]

Exchange of pseudo anomeric alkoxy groups has also been performed by way of piperidinose-derived *N*-acyliminium intermediates. Reactions with TMSCN (Scheme 45)[70] or allyltrimethylsilane (Scheme 46) afforded the expected iminosugar C-glycosides with complete diastereoselectivity in low to very good yield.[70–72a]

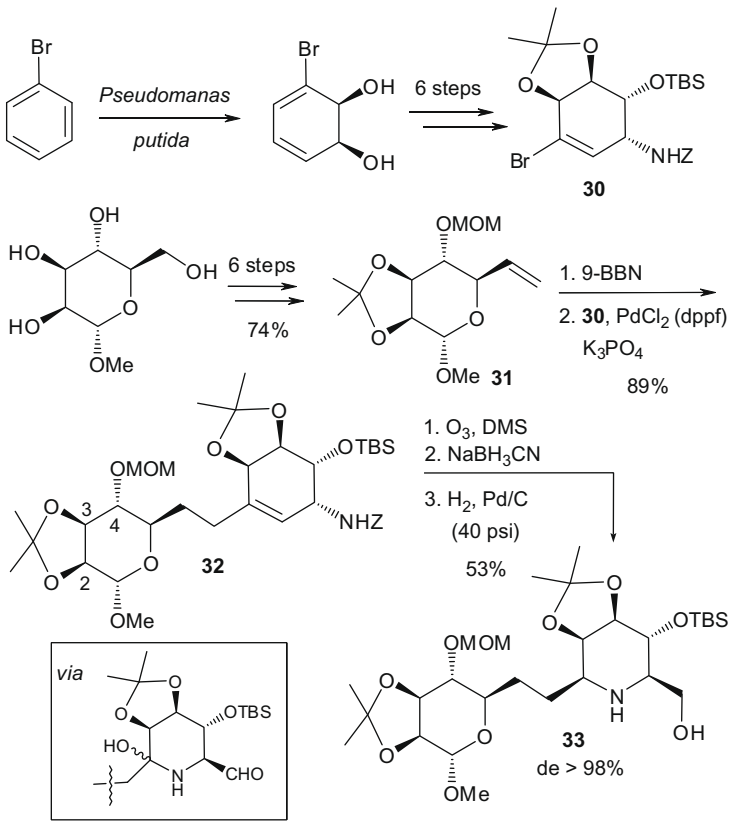
A mixture of anomers **73** (2:1) was treated directly with excess Me_3SiCN and $BF_3{\cdot}Et_2O$, leading diastereoselectively to the equatorial aminonitrile in 55% yield (Scheme 45). The unexpected monodebenzylation occurring for the *per*benzylated derivatives **71** is probably due to an intramolecular attack by the oxygen atom in position 6 to the *N*-acyliminium cation formed during the reaction,



Scheme 13.



Scheme 15.

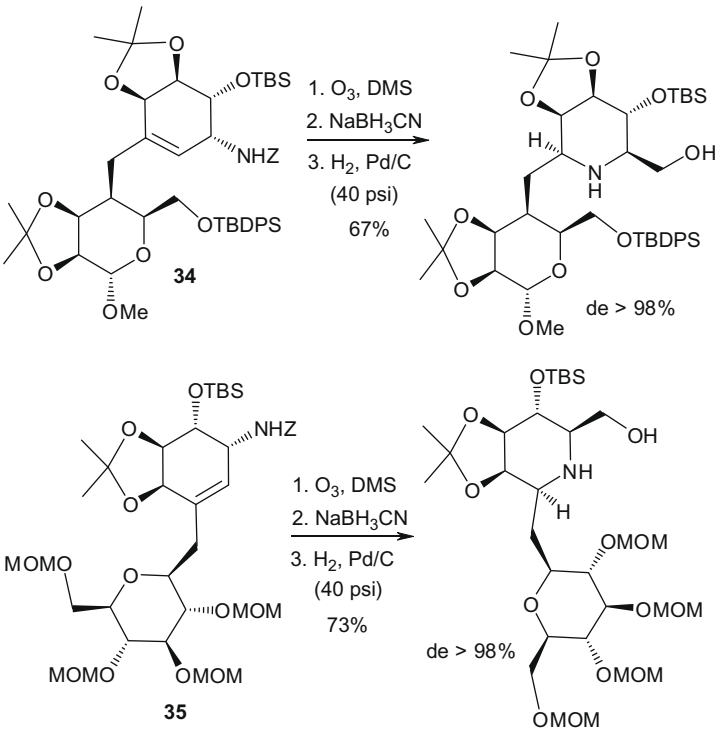


Scheme 16.

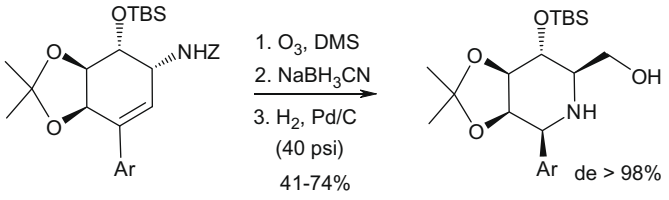
leading to a *N,O*-acetal intermediate. The neighboring-group participation of the acetamido group at C-2 is believed to control the stereochemistry of the bond forming step to generate 1-β-cyano-1-deoxynojirimycin **74** derivative.[71a]

In Scheme 46, the high diastereoselectivity and high yield of the methoxy/allyl exchange reaction highlights the potential of such *N*-alkoxycarbonyl-protected piperidinosyl donors.

Shankar et al. reported a related strategy from polyhydroxylated 2,6-bis(benzotriazolyl) piperidines which allows the one-step formation of two key C–C bonds at C-1 and C-5 (Scheme 47).[73a] The principal advantage of this straightforward approach is that no hydroxyl protection is required and that the displacement reaction can be performed without Lewis acid. However, the double benzotriazolyl/carbon nucleophile exchange, which provides the



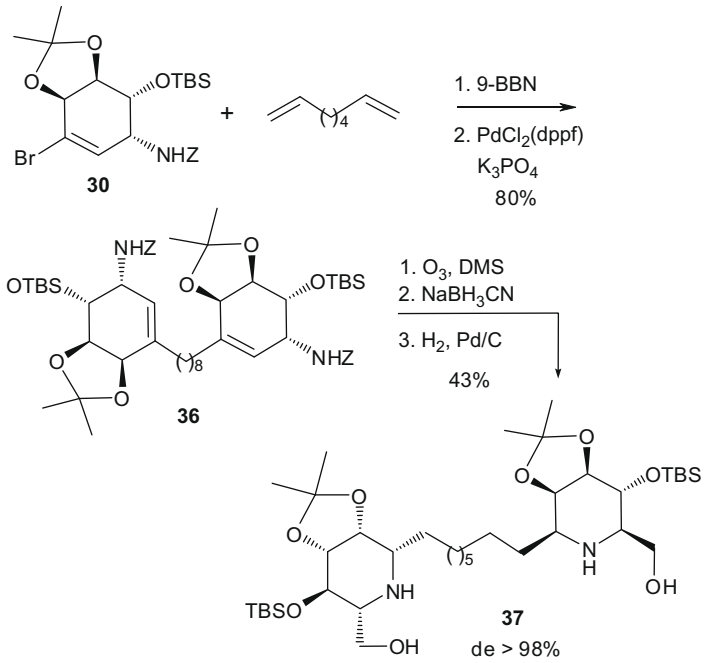
Scheme 17.



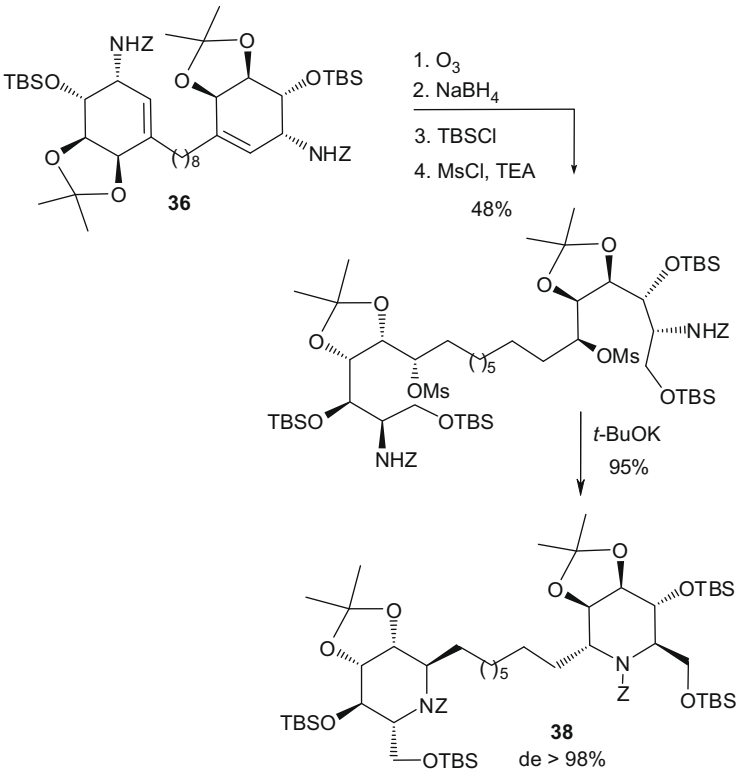
Scheme 18.

1,5-*trans* isomer as the major product, proceeds with modest diastereoselectivity.

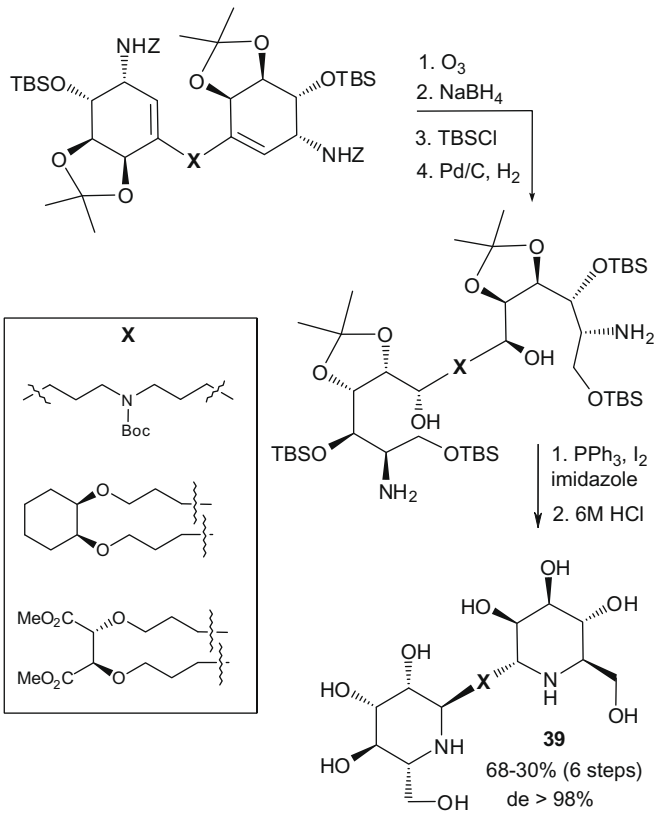
Another major inconvenience of this synthetic pathway is the lack of flexibility to prepare a diverse set of derivatives, with various protecting groups on the amino group or the OH groups. In this process, the key 2,6-bis(benzotriazolyl) piperidine intermediate should indeed be purified by careful crystallization, the product being unstable under silica gel chromatography conditions.[73b]



Scheme 19.



Scheme 20.



Scheme 21.

2.2.2. Addition to endocyclic C=N bond

In 2003, Davis et al. reported the synthesis of adenophorine **75** by way of nucleophilic addition to cyclic imines.[77] Starting from 1-deoxy-L-idonojirimycin derivative **76**, the internal aldimine **77** was obtained by treatment with *N*-chlorosuccinimide followed by subsequent regioselective elimination of HCl (Scheme 48). Addition of EtMgBr afforded protected 1-*epi*-adenophorine **78** as a single diastereoisomer. Epimerization at C-1 was performed using a similar strategy: regioselective formation of ketimine **79** followed by LAH reduction to give adenophorine after deprotection.

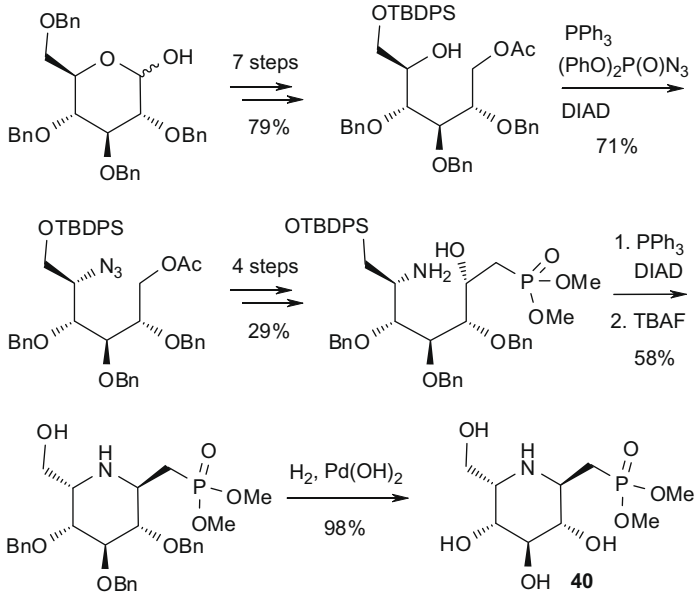
Furthermore, the highly functionalized *N*-chloroamine intermediate can undergo regioselective elimination toward C-1 or C-5 according to the given conditions (Scheme 49). The authors have demonstrated that this is a general process that may be applied with high regioselectivity to several pyrrolidine aldimines.

A small library of iminosugar C-glycosides was obtained by combining the Staudinger-aza-Wittig mediated synthesis of cyclic imine with the Ugi reaction (Scheme 50).[78] The overall process was found to be highly diastereoselective.

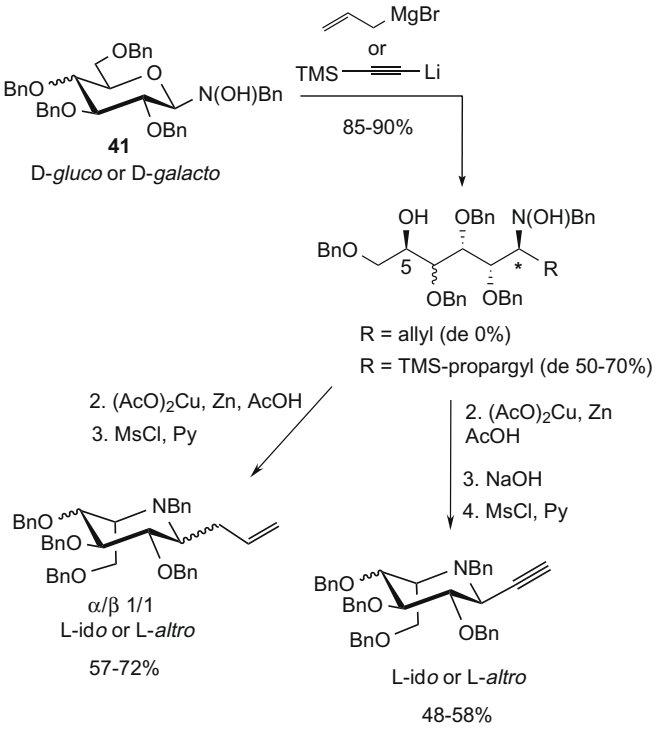
The diastereoselective addition of trimethylsilyl cyanide to a cyclic iminosugar-derived nitrone was reported by Vasella et al. (Scheme 51).[79] This approach has found limited applications to access imino-C-glycosides.

2.2.3. Iminoglucals

By analogy with classical glycal chemistry, Shipman et al. have shown that imino glucal **80**, obtained in 11 steps from D-glucal, could undergo Lewis-acid-mediated carbon–carbon bond forming reactions by allylic displacement of the C-3 acetate group.[82,83] The reaction favored the formation of the β-anomer in high yields but with modest diastereoselectivity (Scheme 52). The stereospecific dihydroxylation of the resulting endocyclic double bond



Scheme 22.



Scheme 23.

afforded the more highly oxygenated iminosugar C-glycoside **82** having a pseudo D-*allo* configuration. Interestingly, this diastereoselective facial addition to the *N*-acyliminium cation is not in agreement with what is observed when the same nucleophiles are added to tri-*O*-acetyl D-glucal under comparable conditions.[84]

Two conformations of the *N*-acyliminium ion exist in solution (Scheme 53).[83] Steric repulsions between the Fmoc protecting group and the acetoxymethyl substituent at C-5 disfavors conformer **A** compared to conformer **B** because of **A**[1,3] allylic strain. The observed major product is then in agreement with a stereoelectronically controlled *pseudo*axial approach of nucleophiles, to conformer **B**.

This product-dependent selectivity can be modified to a substrate-dependent one as shown by the P. Crotty's group.[85] Whilst β-C-Glycosides are obtained using iminoglucal **80**, compounds **83** and **84** are able to produce *pseudo*axial or *pseudo*equatorial *O*-glycosides, depending on the configuration of epoxides **85** and **86** (Scheme 54). It would be interesting to study the reactivity of such iminoglycal derivatives **85** and **86** upon nucleophile addition.

2.3. Miscellaneous reactions

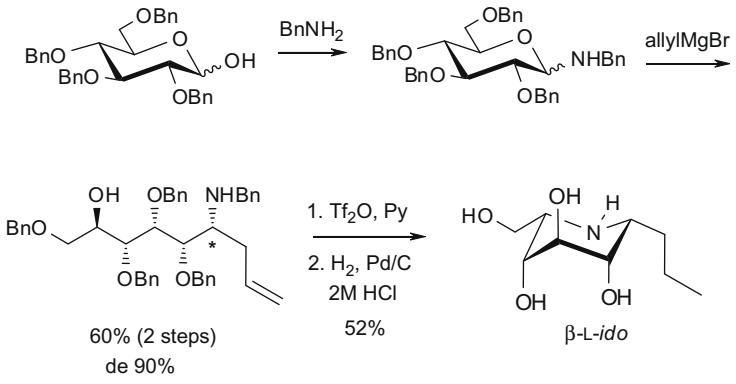
2.3.1. The cycloaddition approach

Wightman and Vasella have independently reported 1,3-dipolar cycloaddition reactions between cyclic iminosugar-derived nitrones and methyl acrylate[79] or sugar alkenes.[86] An aza-Diels–Alder reaction was also used as a key step to provide polysubstituted piperidines from non-carbohydrate starting precursors (Schemes 55 and 56).[87,88]

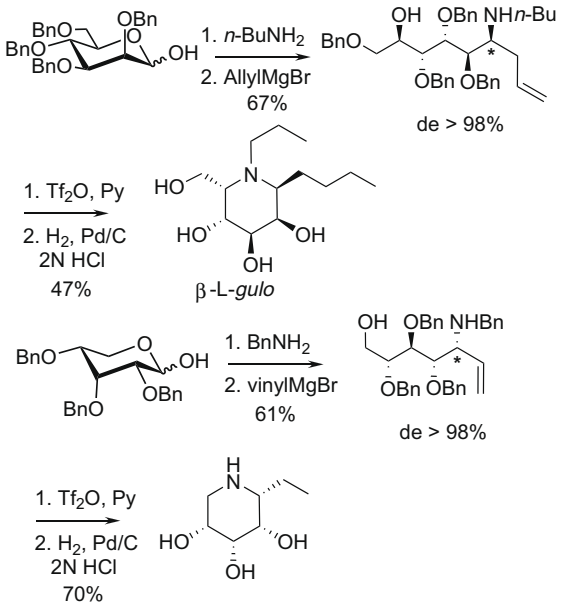
A highly stereocontrolled tandem aza[4+2]/allylboration process has recently been developed by Hall and Tailor.[87] An asymmetric version of this multicomponent reaction has been achieved using a chiral auxiliary approach (Scheme 55).

More recently, Afarinkia et al. reported the synthesis of adenophorine and related iminosugars (Scheme 57).[16e] Diels-Alder cycloaddition of 5-chloro-3-methoxy-6-methyl-1-4-oxazin-2-one with benzylvinyl ether afforded a mixture of cycloadducts in a *ratio* of 2:1:1 and in a modest yield. A reduction of these azabicyclic derivatives with lithium aluminum hydride led to benzyl protected 1,2-dideoxyazasugars in 55% yield and with low diastereoselectivity (1.5:1).

Moreover, 1,3-dipolar cycloaddition reactions of cyclic nitrones are very useful approaches toward the synthesis of imino-C-glycosides. Due to their regio- and stereoselectivity, these nitrones seem to be especially attractive for the construction of nitrogen-containing cycles. Sztaricskai et al. have used this interesting strategy for the synthesis of polyhydroxylated indolizidines, analogues of biologically active natural products such as swainsonine and castanospermine (Scheme 58).[89]



Scheme 24.



Scheme 25.

The cycloaddition leads to the formation of the *anti-exo* cycloadduct and this point has been illustrated by Wightmann et al.[86] in a synthesis of imino-*C*-disaccharides. In that case, the steric hindrance on the dipolarophile leads to an excellent diastereoisomeric excess (Scheme 59).

2.3.2. Ring closing metathesis

Iminosugars are usually synthesized using carbohydrates as chiral pool starting materials. However, a few examples have described the total synthesis of the piperidine moiety using ring closing metathesis to form the C_3–C_4 bond.[90–92] Thus, Lebreton et al. were able to obtain (+)-adenophorine starting from Garner's aldehyde (Scheme 60).[90] The three hydroxyl groups were introduced and their configuration controlled by regioselective opening of an epoxide ring with a 'selenium–boron complex'.

It should be noted that in nearly all situations, the nitrogen atom must be deactivated as an amide or a carbamate for RCM to be successful in such N-containing substrates.[92]

2.3.3. Aza-silyl-Prins reaction

The Aza-silyl-Prins reaction was used by Dobbs et al. to produce alkyl and trifluoroalkyl unsaturated piperidines.[112] Hydroxylation of these intermediates led to imino-C-glycoside precursors (Scheme 61).

The adaptation of the 'selenium–boron complex' method, used by Lebreton et al. to introduce hydroxyl groups at C-2, C-3, and C-4 (Scheme 60), would probably lead to new 1-*C*-trifluoromethyl imino-C-glycosides.

2.4. Iminosugar C-glycoside building blocks

Iminosugar C-glycosides bearing key structural functionalities have been used as advanced intermediates for the convergent synthesis of imino-C-glycosides with a great degree of structural diversity in the aglycone. In 2003, it was demonstrated that cross-metathesis was the method of choice to access in one step various glycoconjugate mimic precursors (Scheme 62).[41] The reaction proceeded with excellent *E*/*Z* selectivity and good to excellent yields. In 2005, Dondoni et al. used the same chemistry for the synthesis of iminosugar-containing *C*-glycopeptides.[93]

Iminosugar-based aziridine **88** was found to be a versatile intermediate for the synthesis of fagomine C-glycoside derivatives.[58] The ring-opening of bicyclic aziridine **88** with various heteroatomic nucleophiles including thiols, amines, alcohols, carboxylates, and phosphates occurred in modest to very good yields and was found to be completely regioselective (Scheme 63).

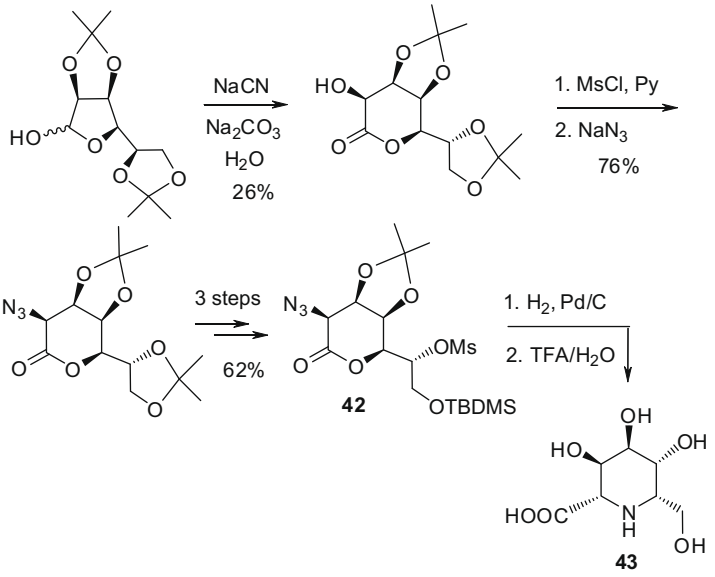
In addition, Zhou and Murphy described a similar procedure starting from bicyclic aziridines obtained by thermally promoted cycloaddition (Scheme 64).[94] The nucleophilic substitution has been carried out using alcohols, thiols. and sodium azide, leading to six-membered substituted iminosugars.

Aziridine intermediates produced as shown in Schemes 63 and 64 are interesting imino-C-glycoside precursors and it would be of interest to further study their reactivity with organometallic reagents.[58]

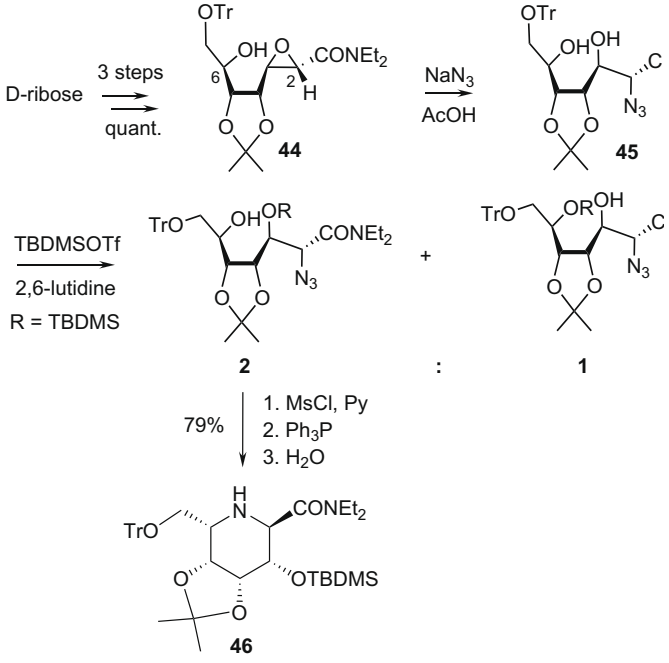
3. Synthesis of iminosugar C-glycosides in the pyrrolidine series

The synthetic strategies that have been developed to access pyrrolidine imino-C-glycosides largely follow those that have been presented in the previous section on piperidine systems, with some significant differences, however:

- Simple homoiminosugars in the pyrrolidine series, such as DMDP, can be reached directly from hexoses without a chain-extension step, which considerably simplifies the synthesis; as a rule, access to this type of compound will not be included in this review.



Scheme 26.



Scheme 27.

– Some methods have been used much more frequently to access pyrrolidine imino-*C*-glycosyl compounds than piperidine derivatives, in particular the cycloaddition reactions of five-membered cyclic nitrones. On the other hand, some methods have rarely been applied to pyrrolidine systems: this is the case, for example, of the direct C-glycosylation process of iminosugars carrying a leaving group at C-1.

Naturally occurring pyrrolidine alkaloids derived from DMDP and carrying a long, functionalized side-chain at C-1 have been isolated recently from *Broussonotia kajinoki* (broussonetines and broussonetinines)[95] and from *Scilla peruviana*;[96] such compounds are obvious targets for the methodologies described herein and first syntheses have already appeared.[97]

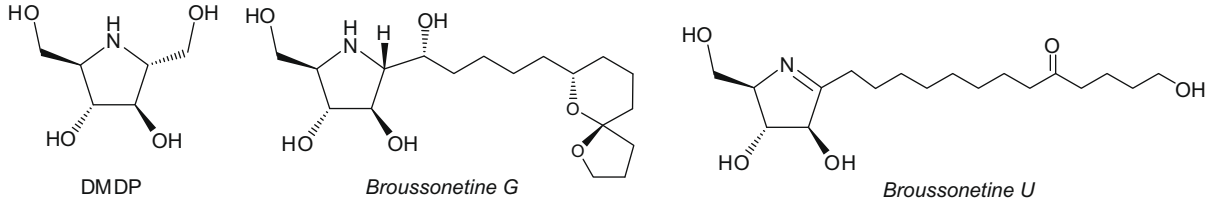
The general methodologies for the synthesis of 2,5-disubstituted pyrrolidines, either by creation of the five-membered ring or by elaboration of azacyclopentane derivatives have been described exhaustively in the excellent review by Pichon and Figadère.[98]

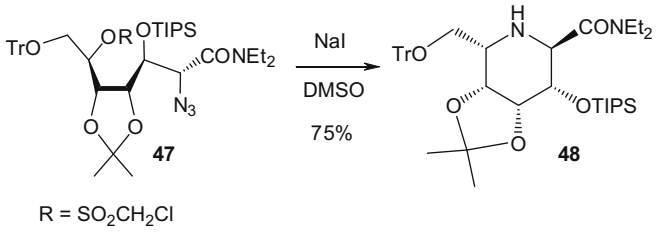
3.1. Intramolecular C–N bond formation (C_4–N and/or C_1–N key disconnection)

The different approaches to imino-*C*-glycosyl compounds in the pyrrolidine series by a cyclization process in which the C_1–N bond or the C_4–N bond is formed are outlined in Figure 4. Most syntheses arise from a carbohydrate precursor.

3.1.1. Reductive amination

Although the chain extension of a tri-*O*-benzylated pentofuranose, followed by a double oxidation and a double reductive amination with a primary amine would provide a short access to the target compounds, this sequence and its stereochemistry have





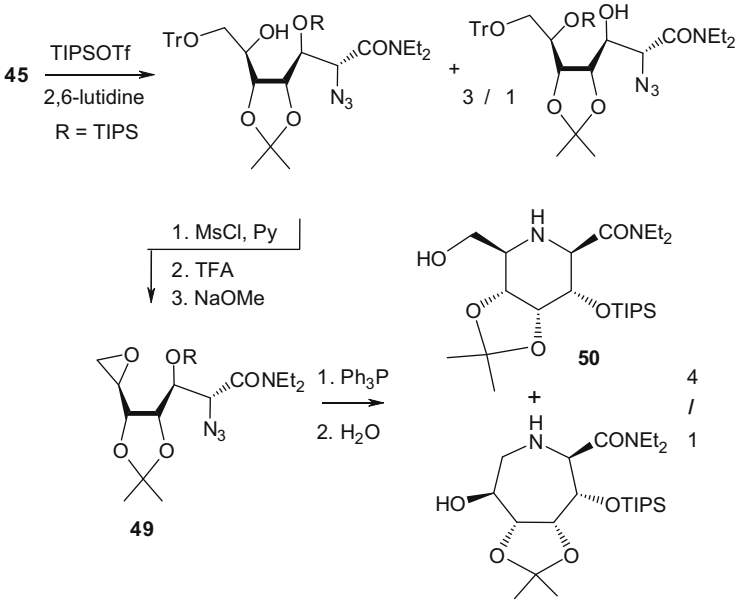
Scheme 28.

not been studied, except for the formation of homoiminosugars in the pyrrolidine series and for the synthesis of imino-*C*-nucleosides. For example, the double reductive amination of the di-ulose **89** afforded the corresponding pyrrolidines in various ratios and yields, according to the amine used (Scheme 65a).[99]

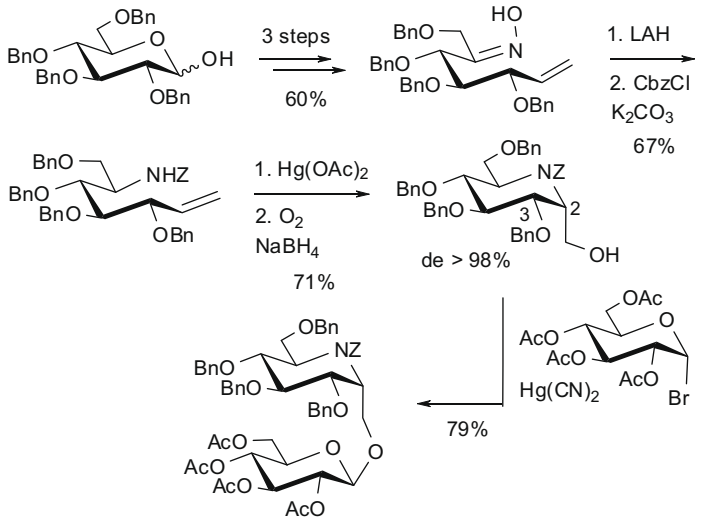
The addition of an aryllithium to a protected D-ribofuranose derivative followed by the double oxidation of the resulting diol and a double reductive amination provides a short and highly stereoselective approach to imino-*C*-nucleosides; initially reported as having a β-D-ribo-furanosyl configuration,[100] these nucleoside analogues were subsequently shown to have the β-L-*lyxo* stereochemistry, (Scheme 65b).[101]

The stepwise introduction of nitrogen (as an amine or an azido group) followed by an intramolecular reductive amination, has been extensively used for the synthesis of both DMDP-type compounds and for chain-extended systems. In the 6-carbon framework, from 5-azido-5-deoxy-ketoses, for example,[102–104] the stereoselectivity of the hydrogenation step was observed to be high (Scheme 66) and appears to be mainly controlled by the configuration at C-3 in the intermediate imine.

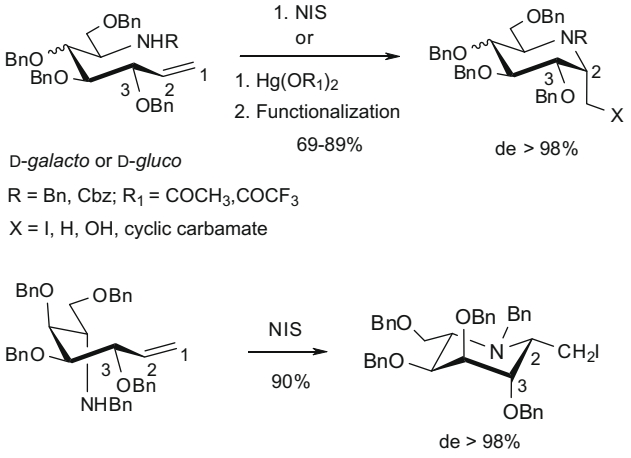
The intramolecular reductive amination of azido ketose derivatives was also the key step in the chemoenzymatic synthesis of pyrroline iminosugars by Wong et al.,[80] for example, using RAMA[105] or the remarkable aldolase FSA which does not require DHAP (Scheme 67),[106] and by Blechert (Scheme 68).[107]



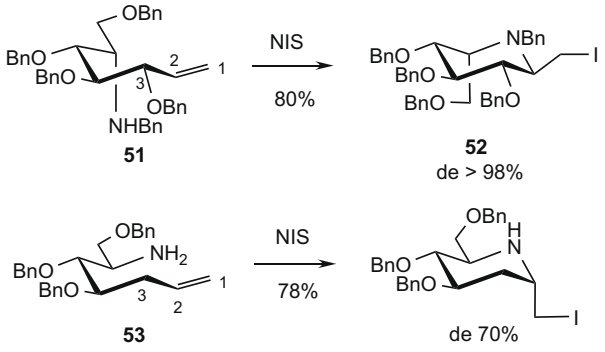
Scheme 29.



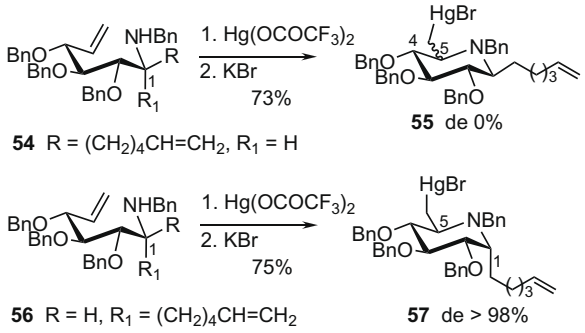
Scheme 30.



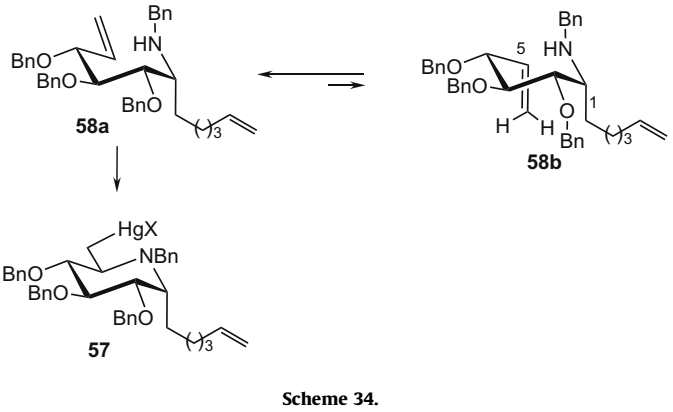
Scheme 31.



Scheme 32.



Scheme 33.



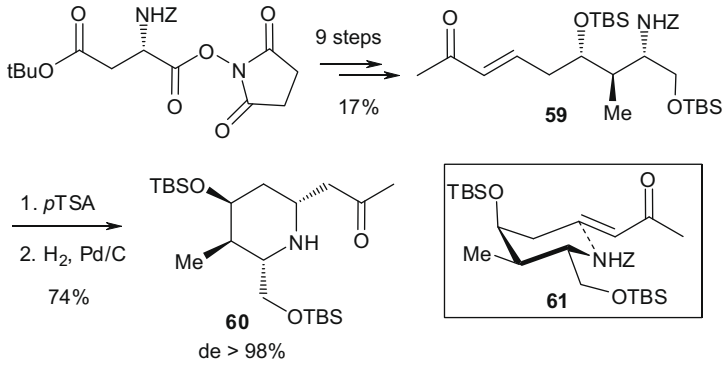
Scheme 34.

3.1.2. Addition to glycosylamines followed by internal S_N

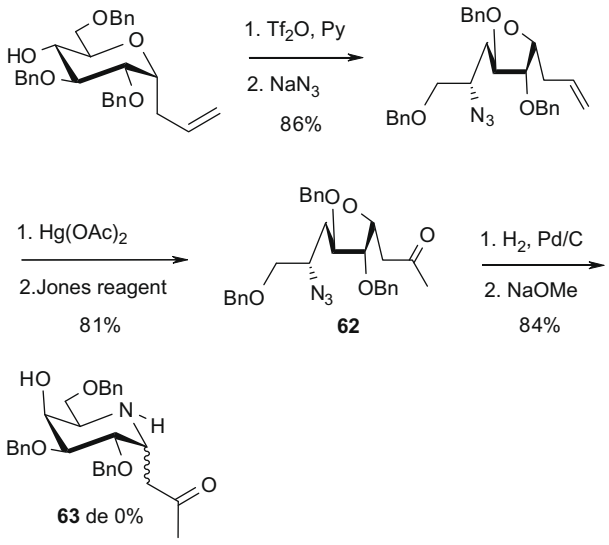
One of the most frequently used approaches to pyrrolidine imino-*C*-glycosyl compounds is the combination of the nucleophilic addition of an organometallic species to a glycosylamine, followed by the activation of the OH group thus freed and cyclization by internal S_N, according to the following scheme (see Scheme 69).

This approach is convenient and very efficient in that the introduction of nitrogen is facile, it generates a glycosylamine that exists as in equilibrium with the corresponding open-chain imine, this latent imine is able to react with a diversity of organometallic reagents. The addition generally occurs stereoselectively to give the *syn* addition product by a chelation-controlled process, and the cyclization leads to a substituted pyrrolidine in which substituents at C-1 and C-2 are *cis* related.

This process was pioneered by Nicotra et al.,[51] who showed that the chain extension of the *N*-benzyl arabinofuranosylamine **90** with vinylmagnesium bromide occurred with a de = 88%, whereas the addition of octylmagnesium to the corresponding *N*-hexyl glycosyl-amine was completely stereoselective, giving only the *syn* (D-*gluco*) open-chain amine (see Scheme 70). The same process was applied by Behr et al. to prepare such compounds as 6-deoxy-homoDMDP **91**,[108] compound **92**,[109] and the analogues **93** and **94**[110] as precursors of various pyrrolizidines (Scheme 71). It should be noted that, unlike the preceding examples, the addition of allylmagnesium bromide to the L-xylose-derived glycofuranosylamine is much less stereoselective (de 20% approx). Eustache et al.[111] have also taken advantage of this sequence to prepare interesting mimics of β-D-arabinofuranosyl-1-monophosphoryl decaprenol based on pyrrolidine C-glycoside **95** (Scheme 72). These compounds were found to exhibit promising activities as antimycobacterial agents.



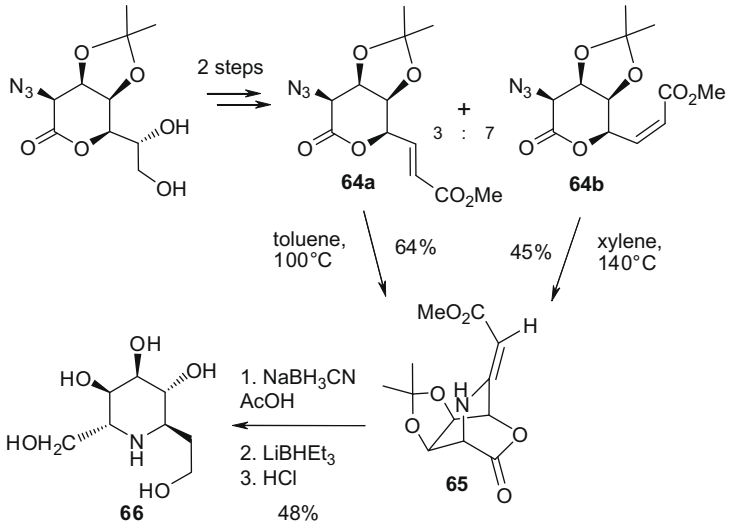
Scheme 35.



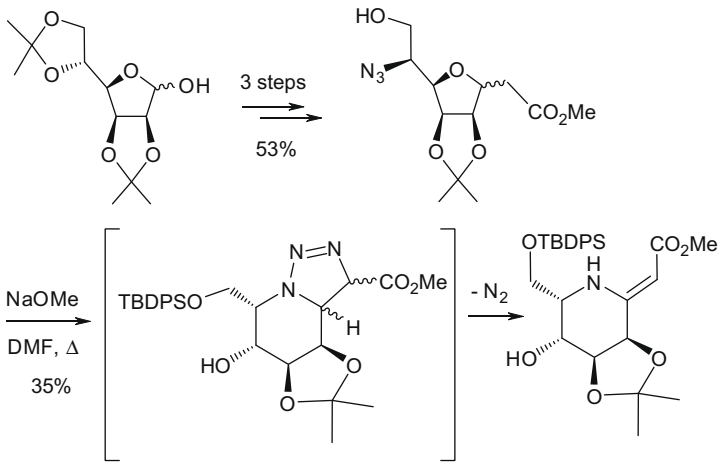
Scheme 36.

In a closely related approach, Dondoni et al.[49] have prepared a number of imino-*C*-glycosyl compounds in the pyrrolidine and in the piperidine series by the addition of organometallic reagents to *N*-benzyl-*N*-glycosylhydroxylamines. The intermediate electrophilic species is here an open-chain nitrone, which has a stronger electrophilic character than the imine in the previous examples. Thus for example, the reaction of tri-*O*-benzyl-L-xylofuranose with *N*-benzylhydroxylamine provides the corresponding glycosylhydroxylamine in high yield. The addition of reagents such as 2-thiazolyllithium, trimethylsilylethynyllithium, and allylmagnesium bromide gave the corresponding chain-extended hydroxylamines in good yield and with *anti* stereoselectivity predominantly. The N–OH group was then cleaved reductively, and the cyclization was promoted by the activation of the free OH group as a leaving group (Scheme 73). The 2-thiazolyl-carrying compound is the precursor of the 1-*C*-formyl pyrrolidine **96**, an important intermediate for the synthesis of various glycomimetics such as imino-*C*-disaccharides (e.g., **97**[113]) and imino-*C*-glycosyl amino acid derivatives (e.g., **98**[114]), both of which incorporate a 1-*C*-substituted pyrrolidine as a furanoside mimic (see Scheme 74).

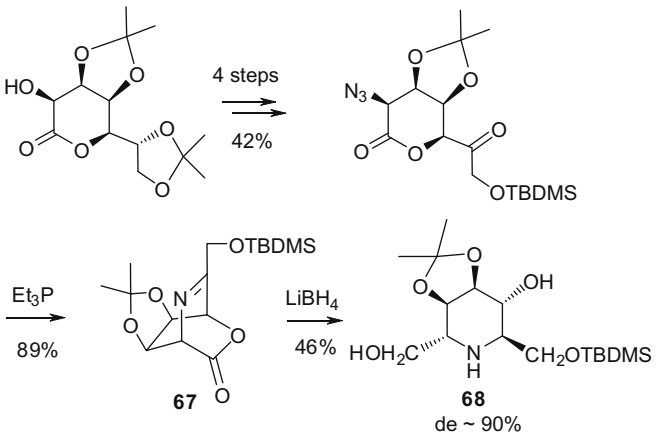
A further extension of this methodology has been proposed by Kobayashi et al.[115] The substrates are N-carbonylated glycosylam-



Scheme 37.



Scheme 38.



Scheme 39.

ines, which are more stable than free glycosylamines and can be reacted with various silylated *C*-nucleophiles under Lewis-acid catalysis (see Scheme 75).

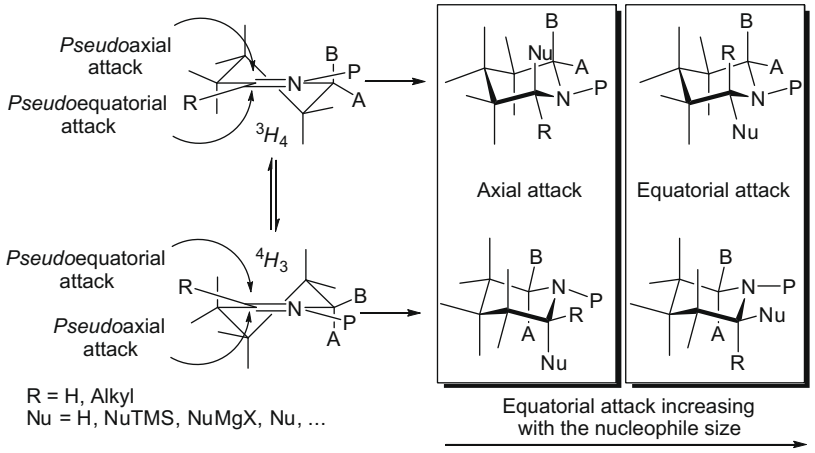
The N-protected glycosylamines are accessible by the reaction of glycosyl acetates (e.g., **99**) with benzyl carbamate in the presence of a Lewis acid, or even directly from the free hemiacetals, as shown recently by Martin,[116] and are reacted at low temperature with silyl enol ethers or allyltrimethylsilane in the presence of TMSOTf. The reaction is a highly *syn*-stereoselective addition to the corresponding open-chain N-acylated imine. Cyclization, after activation of the free OH group, requires the use of a strong base (*t*BuOK).

This sequence was developed by Martin et al.[117] into an efficient and general approach to 1-C-substituted 1,4-imino-galactitol derivatives as galactofuranose mimics (Scheme 76).

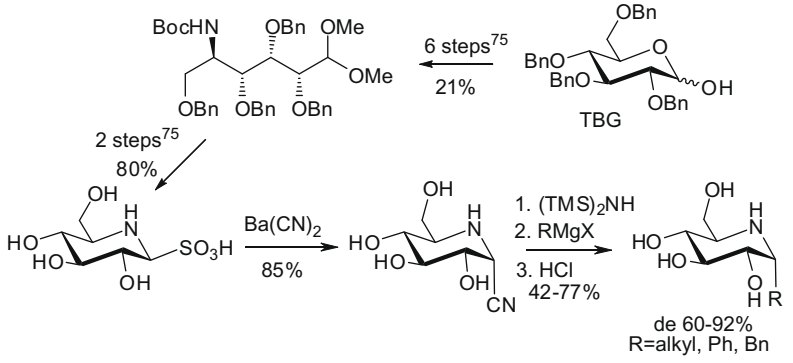
A chain extension of glucofuranosylamine **100** with a variety of silylated nucleophiles gave the corresponding open-chain products with *syn*-stereoselectivity, which upon activation and cyclization with inversion at C-4, provided the *galacto*-configured pyrrolidine imino-*C*-glycosyl compounds **101**. The 1-*C*-allyl derivative was used as the starting material for the synthesis of a diversity of galactofuranoside mimics such as imino-*C*-disaccharide **102** and the original UDP-Gal*f* mimics **103**, by way of sequences involving alkene homodimerization and alkene cross-metathesis reactions (Scheme 77).

3.1.3. Tandem addition to aldononitriles—internal S_N

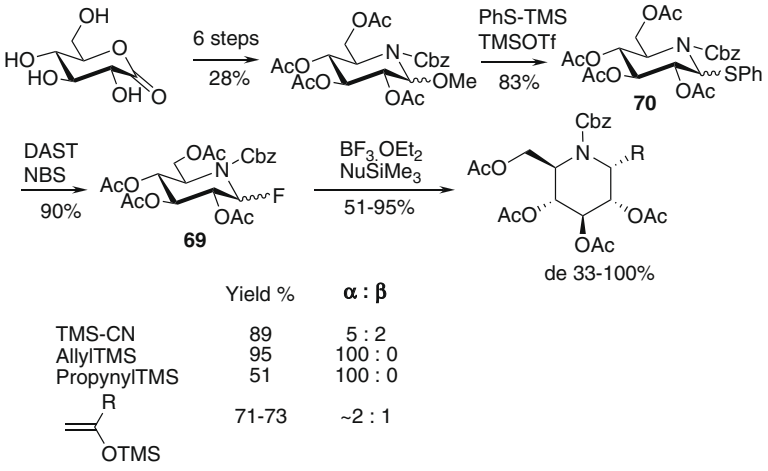
A useful sequence has recently been developed by Behr et al.[118,119] for the synthesis of 1-*C*-substituted pyrroline iminosugars (cyclic ketimines): the procedure consists of generating a glycononitrile from a protected pento- or hexo-furanose hemiacetal, mesylating the free γ-hydroxyl group and performing the addition of a Grignard-type organometallic reagent onto the nitrile function; the resulting anionic species promotes the subsequent cyclization to a pyrroline (Scheme 78). The process appears to be quite general and provides a good solution to the synthesis of such unsaturated iminosugars, which are found as constituents of natural products (e.g., *broussonetine U*).



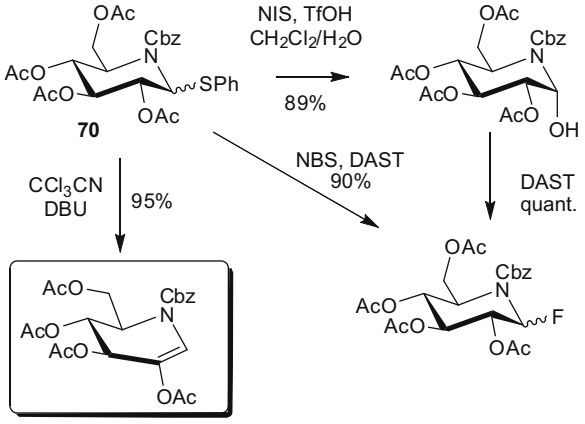
Scheme 40. (See Ref. 74)



Scheme 41. (See above-mentioned reference for further information.)

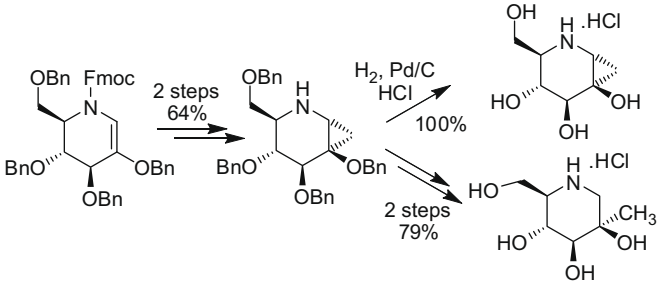


Scheme 42.



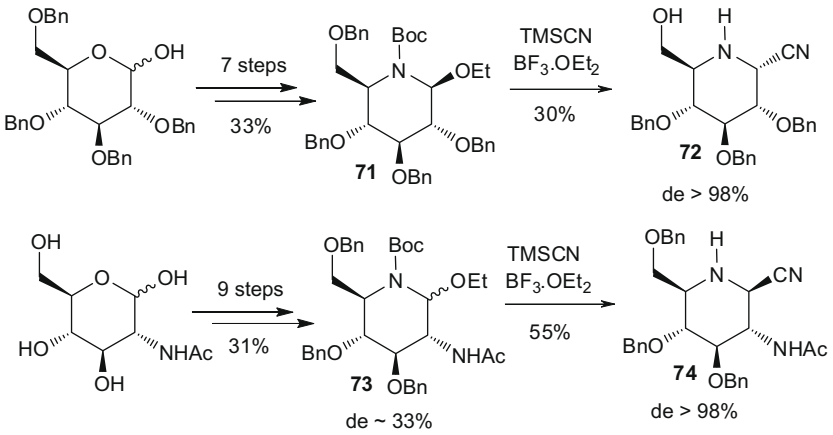
Scheme 43.

A related sequence, which makes use of the reaction of the nitrile with a titanacyclopropane generated in situ between titanium tetraisopropoxide and ethylmagnesium bromide, provides access to unprecedented spirocyclopropyl pyrrolidine derivatives (Scheme 79) such as **105**.[120] The iminosugar resulting from the deprotection of **105** was found to have significant activity as a L-fucosidase inhibitor.

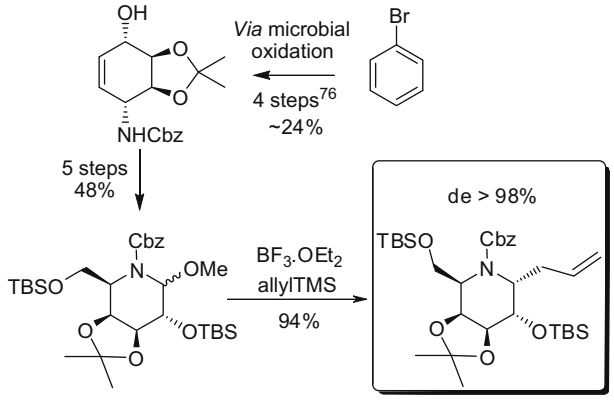


Scheme 44.

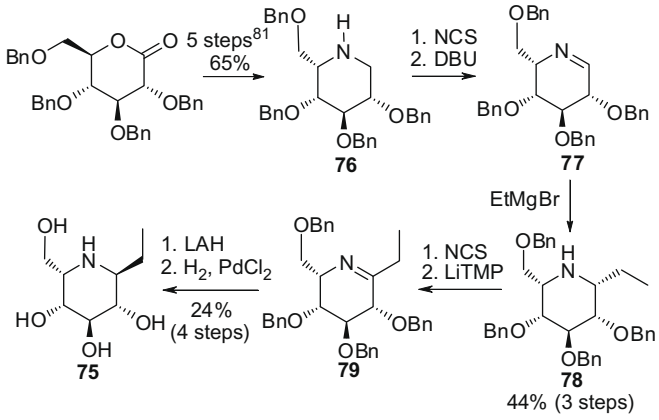
A unique synthetic sequence that is somewhat related to the one described by Behr (Scheme 78) has been reported by Moriarty et al.[121] as a means to generate pyrrolidine iminosugars carrying various alkyl chains at C-1. The sequence involves the low-temperature addition of a Grignard reagent to an aldono-1,4-lactone carrying a leaving group at the C-δ position, followed by the conversion of the resulting hemiketal into a glycosylamine (Scheme 80). The glycosylamine is not isolated: it rearranges directly into a pyrroline (e.g., **105**) by way of opening of the furanosylamine, which leads to the acyclic imine and promotes the formation of an epoxide, followed by ring closure at the C-δ position to the five-membered ring. The N, C-1-dialkylated species that



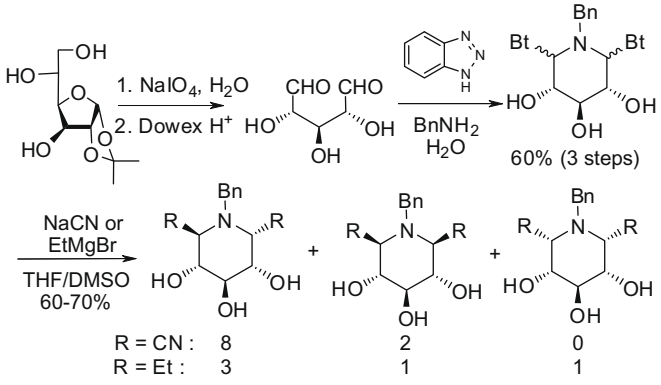
Scheme 45.



Scheme 46. (See above-mentioned reference for further information.)



Scheme 48. (See above-mentioned reference for further information.)



Scheme 47.

are accessible by this procedure have interesting antiviral activities.

3.1.4. Other cyclizations by internal S_N

Other sequences have been developed which provide a means of introducing nitrogen on a chain-extended product, followed by ring closure by an internal S_N:

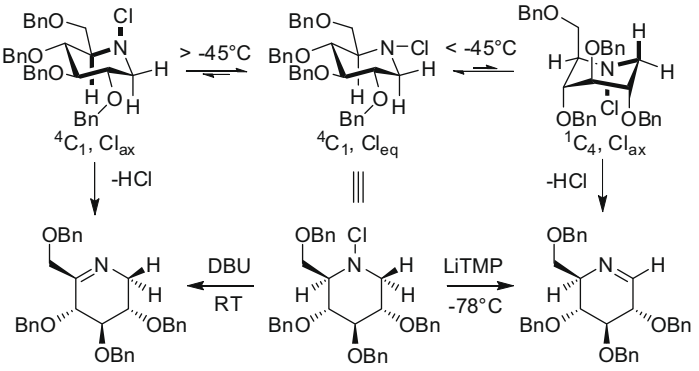
- Chain extension by a Wittig reaction, tandem 1,4-addition - internal S_N; this process was pioneered by Wightman (Scheme 81)[122] and applied to other substrates by Robina.[123]
- Chain-extension reaction by a Wittig reaction, epoxidation, S_N, and internal S_N (Scheme 82).[124]
- Chain-extension with a sulfur ylid, oxidation, tandem epoxide-ring opening, and internal reductive amination (Scheme 83).[125]
- Chain extension by nucleophilic addition, S_N followed by internal S_N (see Scheme 84).[126]

A related sequence was used by Perlmutter[97b] to achieve a synthesis of *broussonetine C*.

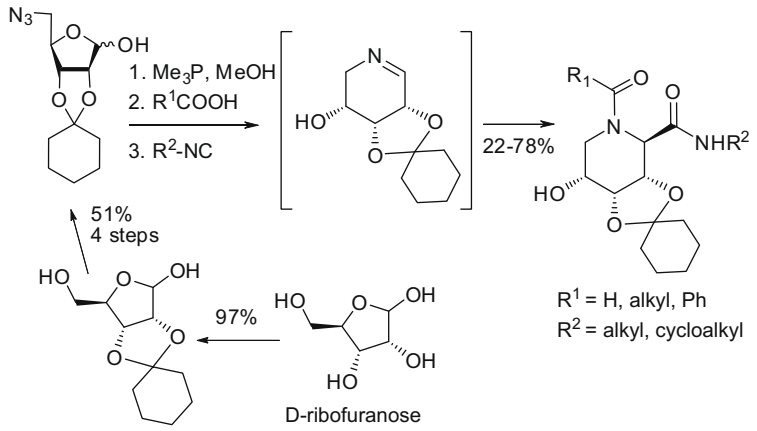
- The amino ketone **106** was obtained from L-tartaric acid by a lengthy procedure. It was converted to the pyrrolidine **107** by an internal S_N process en route to indolizidine alkaloids (see Scheme 85);[127] a similar process was developed to achieve the synthesis of *radicamine B*.[128]

The synthesis of the remarkable 5,8-dideoxy-5,8-imino-nononic acid component of the acaricide *gualamycin* was prepared by a related cyclization process.[129] Precursor **109**, obtained in 15 steps from 2-azido-2-deoxy-L-mannopyranoside **108**, was submitted to an internal Mitsunobu reaction to form the required pyrrolidine derivative **110** with the appropriate configuration (Scheme 86). Further elaboration of **110** and glycosylation with a disaccharide completed the first synthesis of *gualamycin*.

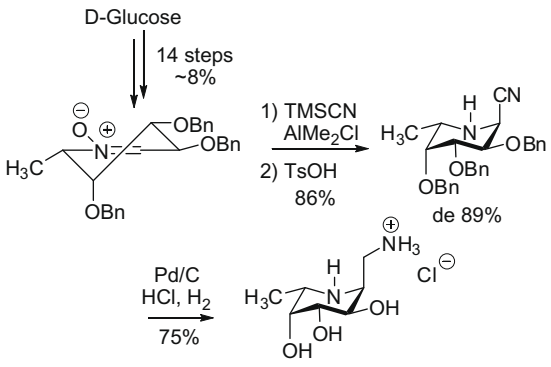
The first synthesis of imino-galactofuranose C-glycosides was reported by Fleet and co-workers.[130,131] The key step in their approach is the intramolecular S_N of a 2-amino-2-deoxy-heptono-1,4-lactone carrying a leaving group at position 5 (e.g., **112**). The cyclization is promoted by the opening of the lactone with an alcohol, to give 2,5-imino-aldonates such as **113** or with an amine to give 2,5-imino-aldonamides such as **114** (Scheme 87).



Scheme 49.

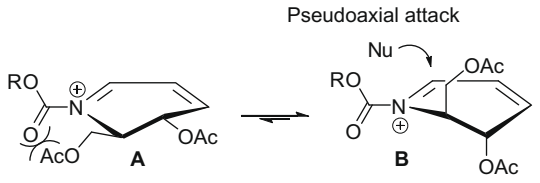


Scheme 50.

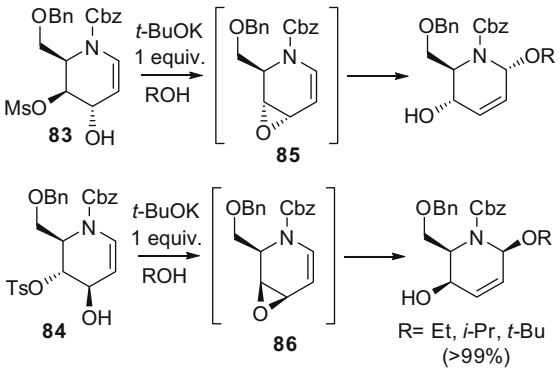


Scheme 51.

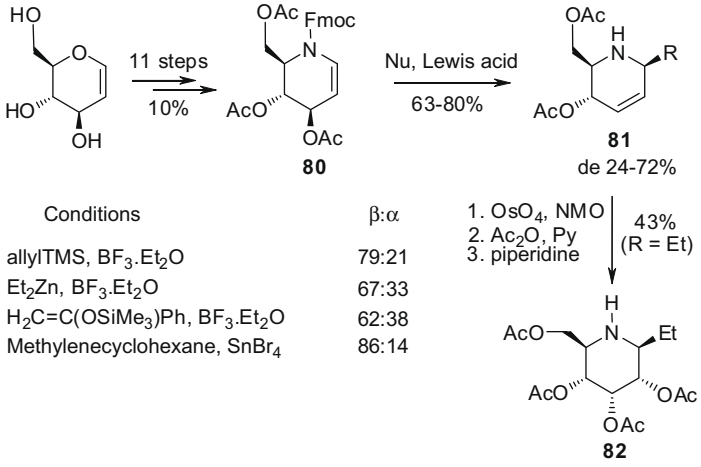
Another approach to imino-galactofuranose C-glycosides was recently described by Zou et al.[132] The synthesis starts with an α-1-*C*-allyl D-galactopyranose derivative carrying an azido group at C-4; oxidation of the allyl group to a 2-oxopropyl group leads to a system that can undergo ring opening to an unsaturated ketone by β-elimination under basic conditions. Hydrogenolysis of the azido group followed by treatment of the resulting amine with LiOH promotes this β-elimination and subsequent cyclization by conjugate addition to a pyrrolidine as a mixture of C-1 isomers (Scheme 88; see also Section 2.1.4, Scheme 36).



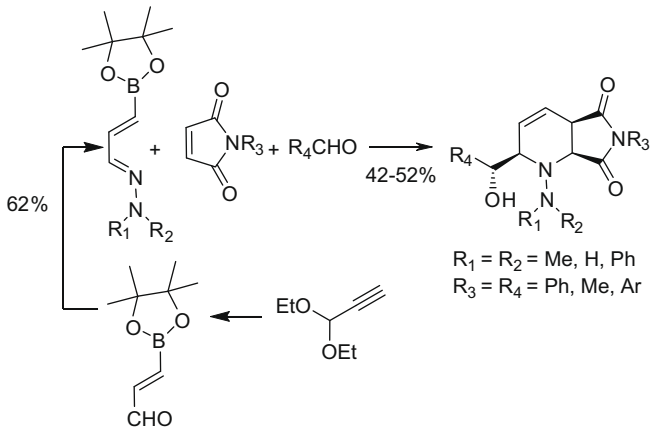
Scheme 53.



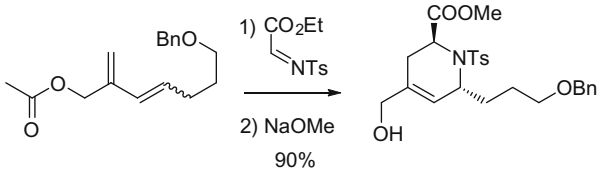
Scheme 54.



Scheme 52.



Scheme 55.

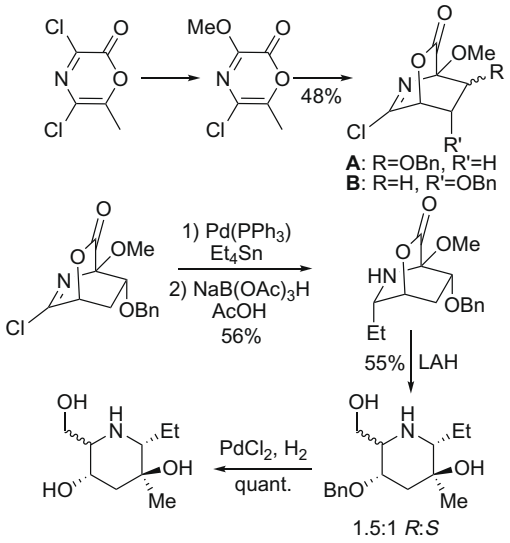


Scheme 56.

3.1.5. Electrophile-mediated cyclization

While the synthesis of 2,5-dialkylpyrrolidines by the electrophile-mediated cyclization of unsaturated amines has been studied by several groups,[98] this process has found limited application in the preparation of polyhydroxylated analogues. One example is the synthesis by Eustache et al.[133] of arabinofuranose-1-phosphate mimics as potential inhibitors of D-arabinosyltransferases, enzymes that play a key role in the biosynthesis of the mycobacterial cell wall glycans. The synthesis (Scheme 89) starts from tri-*O*-benzyl-D-arabinose and involves a Wittig chain extension, substitution of the free OH group by a protected amino group with retention of the configuration at C-5, and NBS, or NIS-mediated cyclization.

The ring closure was completely stereoselective and led to the corresponding 1,2-*trans* disubstituted pyrrolidine. The cyclization was followed by an Arbuzov reaction and deprotection using BCl_3 to afford the imino-*C*-glycosyl analogue of diethyl α-D-arabinofuranosyl phosphate **111**. The corresponding 'β-anomer' was obtained by a different procedure (from a lactam, see below).



Scheme 57.

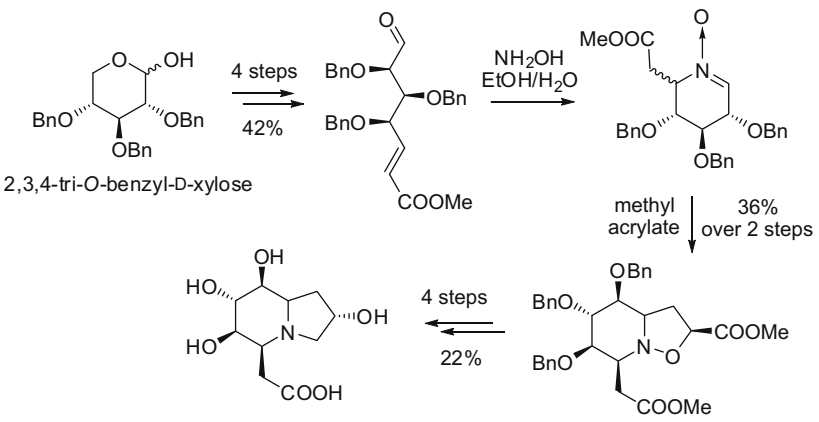
3.2. Electrophilic iminosugar donors (C_1–R′ key disconnection)

The different approaches to imino-*C*-glycosyl compounds in the pyrrolidine series starting from a preformed pyrrolidine are outlined in Figure 6. Most syntheses arise from a carbohydrate precursor and involve an electrophilic pyrrolidine derivative (lactone, imine, and nitrone).

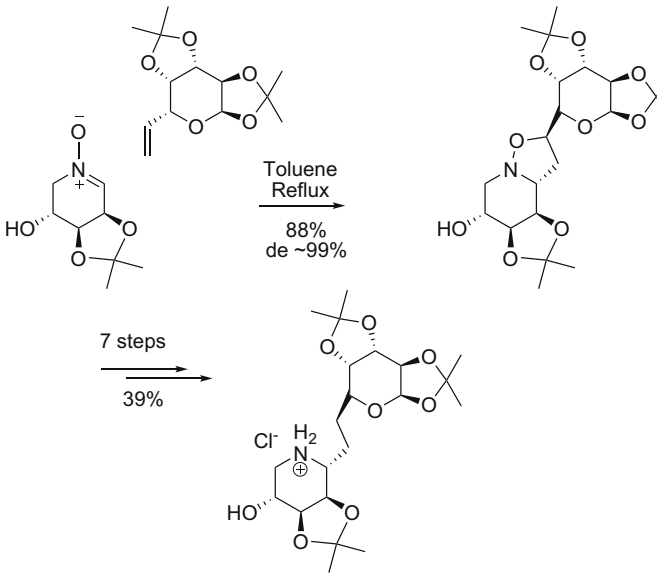
3.2.1. Nucleophilic addition to cyclic imines

Eustache et al.[134] have used this approach to generate the same type of arabinofuranosyl-phosphate mimics as described in (Section 3.1.2). The imine was prepared from the 5-trifluoroacetamido-5-deoxy-D-arabinofuranose hemiaminal **112** by cleavage of the trifluoroacetyl group (Scheme 90) and was reacted with lithiated dimethylmethanephosphonate, to afford highly stereoselectively the 'α'-linked imino-*C*-glycosyl compound **113** in modest yield. This compound was converted in six steps into the α-D-arabinofuranosyl eicosanoyl phosphate mimic **114**, a significant analogue of glycosyl donors involved in arabinofuranosyltransferase-mediated processes.

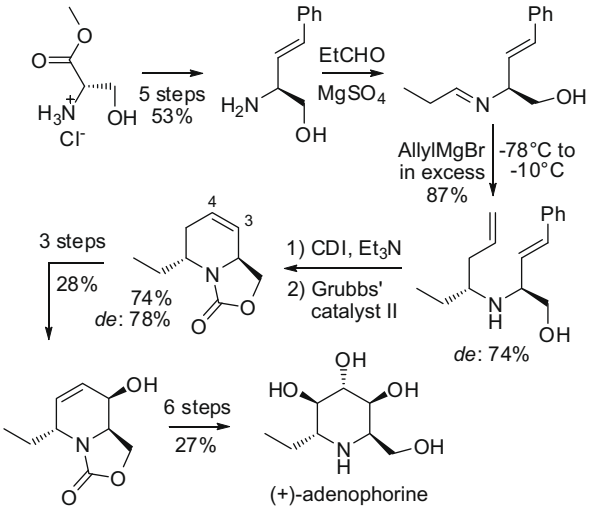
Most of the work involving the addition of organometallic reagents onto sugar-derived pyrrolines (cyclic imines) was however reported by Furneaux, Tyler, Schramm, and co-workers as the key step of their synthesis of nucleoside analogues.[135] The starting



Scheme 58.

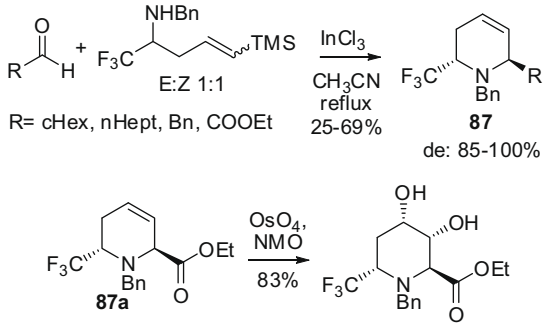


Scheme 59.



Scheme 60.

material, imino-ribitol **116**, which is obtained in nine steps from L-gulonolactone derivative **115**, is converted into the corresponding pyrroline by N-chlorination using NCS immediately followed by a regioselective dehydro-chlorination using LiTMP. The imine thus formed is engaged without isolation in the next step. A wide variety of organometallic reagents were added to this imine, leading highly stereoselectively to 'β'-linked iminoribitols carrying at C-1 substituents such as phenyl, substituted phenyl and naphthyl, 3-pyridyl, 2-pyridylmethyl, 1,3-dithian-2-yl, cyanomethyl (see Scheme 91).



Scheme 61.

These studies were prompted by the remarkable biological activity of imino-*C*-nucleosides related to guanosine and inosine, known as *immucillins H* and *G*, which are extremely potent inhibitors of human purine nucleoside phosphorylase and related enzymes (see Scheme 92).

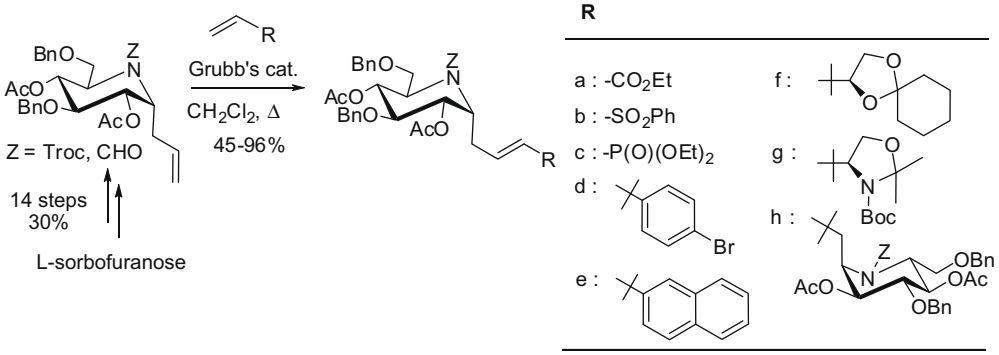
The first syntheses of these compounds involved the lengthy construction of the deazapurine from a cyanomethyl group. Eventually the authors found conditions for the direct addition of a 9-deazapurine derivative to the cyclic imine **117**, thus providing a considerably shorter synthesis of these imino-*C*-nucleosides.

3.2.2. Nucleophilic addition to cyclic nitrone

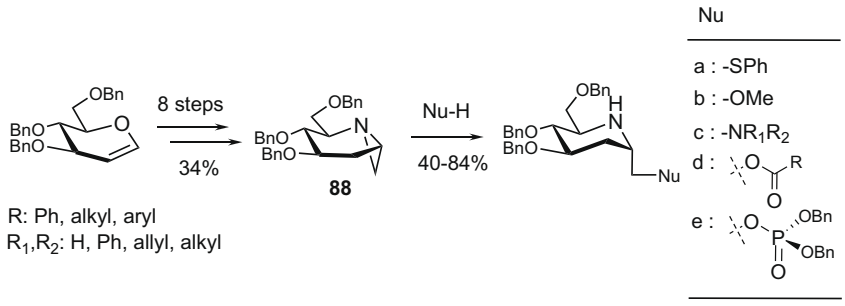
Several studies have been devoted over the past decade to the use of nitrones in nucleophilic addition reactions to give *N*,*N*-disubstituted hydroxylamines.[136] This functional group acts as an additional chelating center and strongly enhances the electrophilicity of the C=N double bond. Moreover, this carbon–carbon bond formation seems to be highly diastereoselective, favoring the 1,2-*trans* epimer (Scheme 93).

In 1992, Petrini[137] et al. described the addition of the Grignard reagent 4-methoxybenzylmagnesium chloride to a diMOM pyrroline N-oxide. The diastereoselectivity reported (40% in favor of the *cis*-diastereoisomer) was rectified in 2001 by Trombini et al.,[138] confirming the *trans*-stereoselectivity preference of the nucleophilic addition (Scheme 94).

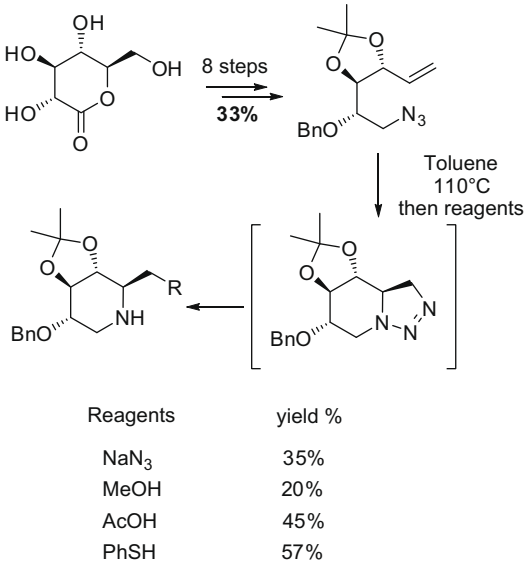
It is interesting to note that the facial stereopreference could be reversed (**118**:**119** = 7:3) in the presence of a nitrone complexing



Scheme 62.



Scheme 63.



Reagents	yield %
NaN_3	35%
MeOH	20%
AcOH	45%
PhSH	57%

Scheme 64.

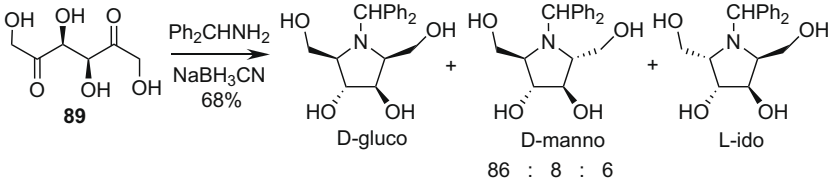
agent, $MgBr_2$·etherate in dichloromethane. However, without Lewis acids or complexing agents the *trans*-stereoselectivity is favored. Other investigations described different carbon–carbon disconnections of hydroxylated five-membered cyclic nitrones using organolithium or organomagnesium reagents with generally a high diastereoselectivity (Scheme 95).[139–141]

Whatever are the substituents and configurations at C-3 and C-4, the stereoselectivity is controlled by the configuration at C-2.

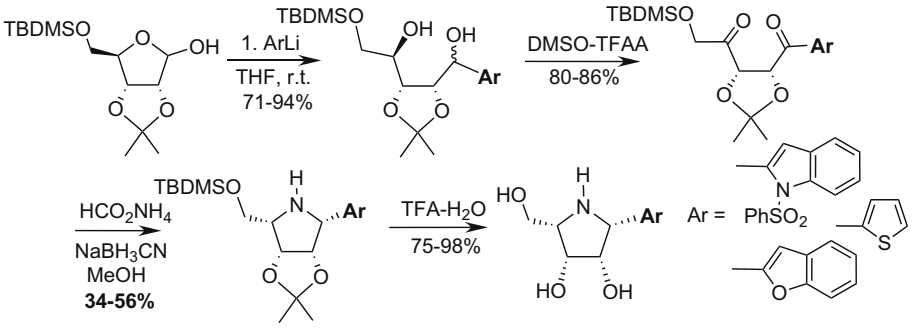
Another interesting methodology confirms the high potential of such nitrones.[142] The α-amino radical species generated by SmI_2 was trapped in situ with ethyl acrylate. The reaction proceeded in good yield (68%) and, remarkably, the diastereoselectivity of the reaction was excellent as the minor isomer could not be detected from NMR analysis of the crude material (Scheme 96).

3.2.3. Cycloaddition to cyclic nitrones

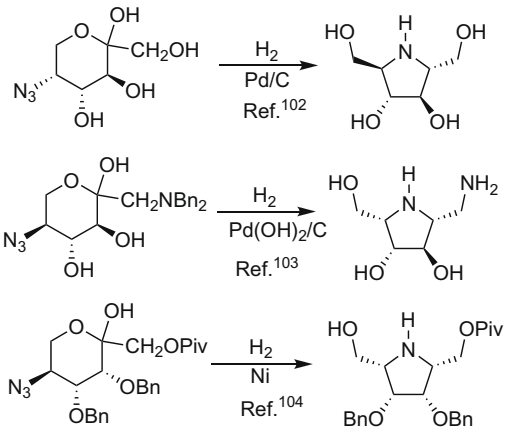
As excellent dipolarophiles, cyclic nitrones have frequently been used for the creation of a C–C bond at C-1 of pyrrolidine iminosugars. Following model studies by Goti, Brandi, and co-workers[143], Wightman[144], and others[145], the cycloaddition approach has been used extensively for the synthesis of pyrrolizidine alkaloids such as lentiginosine,[146] alexines,[147] and related pyrrolizidine alkaloids.[148] For example, the cyclic nitrone **118**, prepared



Scheme 65a.



Scheme 65b.

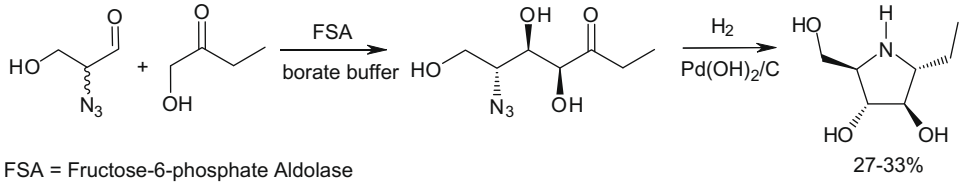


Scheme 66.

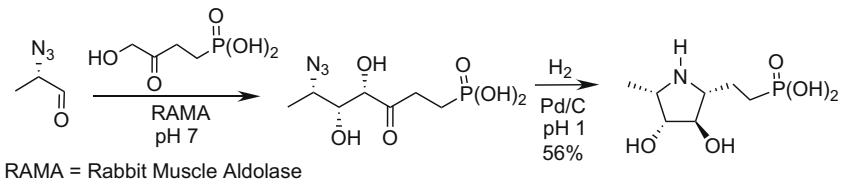
from tri-*O*-benzyl-D-arabinofuranose, reacts stereoselectively with allyl alcohol to give the bicyclic adducts **119** and **120** resulting from *exo-anti* and *endo-anti* cycloaddition modes, in a ratio of ~4:1 (Scheme 97). The major isomer was converted in three steps into 7-deoxycasuarin **121**.[149]

As a rule, the stereoselectivity of these cycloadditions is efficiently controlled by the configuration at C-2 of the nitrone, giving the *anti* adduct (highly stereoselectively), and the product arising from an *exo* addition mode is generally predominant (see Scheme 93).

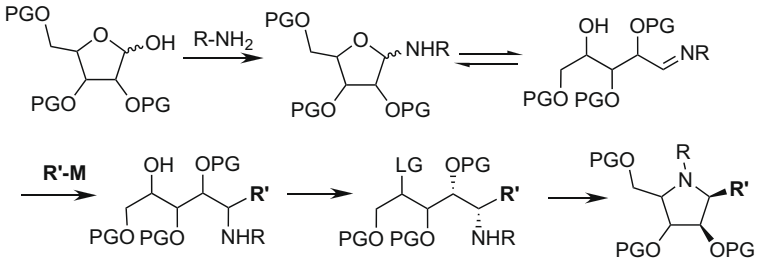
This method of C–C bond formation was also applied to the coupling of sugars, for example, the reaction of monosaccharide derivatives carrying a vinyl group with galactofuranose-derived nitrone **122**, led to a single stereoadduct, **123**, which was converted into an imino-*C*-disaccharide mimicking Gal*f*-β-(1-6)-Gal*f* **124** (Scheme 98).[150] The disaccharide analogues **125** and **126** (Scheme 99) were obtained by a similar procedure.[151]



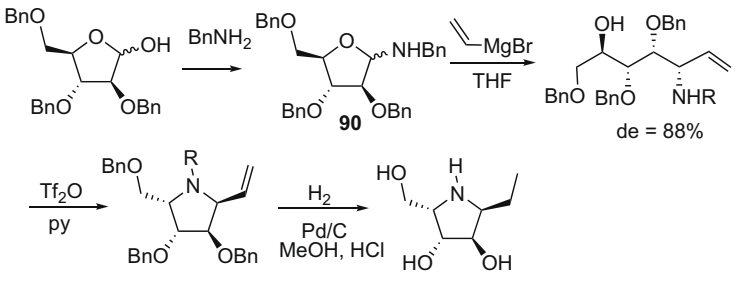
Scheme 67.



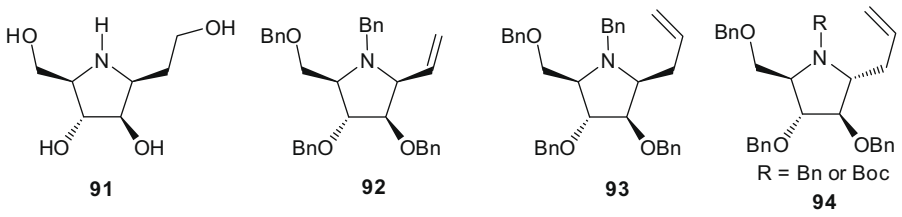
Scheme 68.



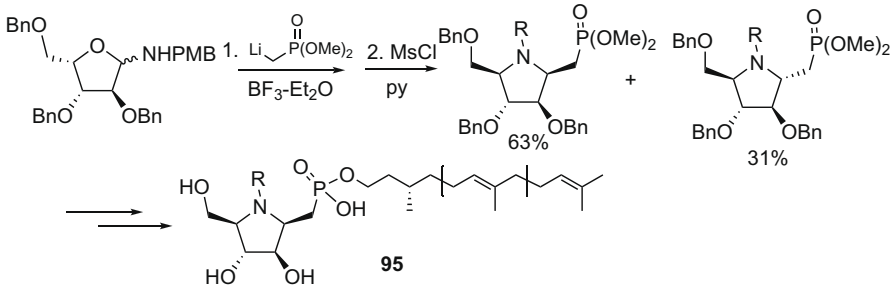
Scheme 69.



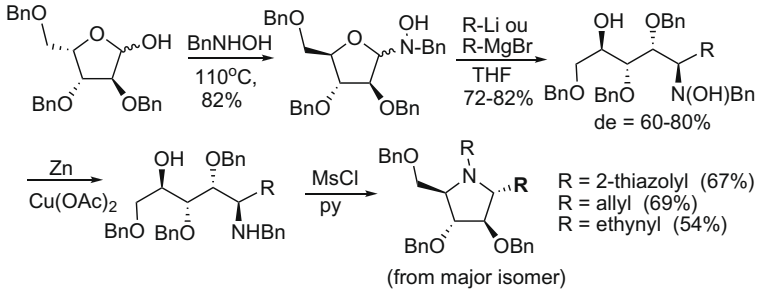
Scheme 70.



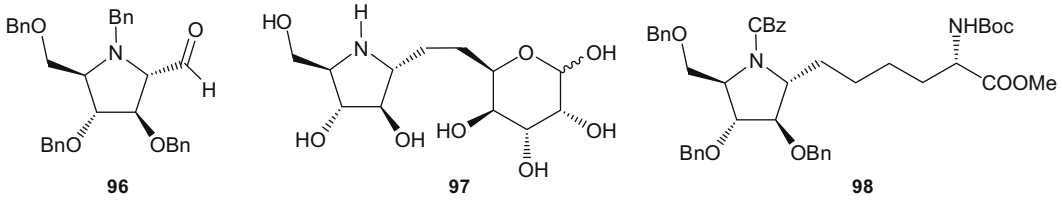
Scheme 71.



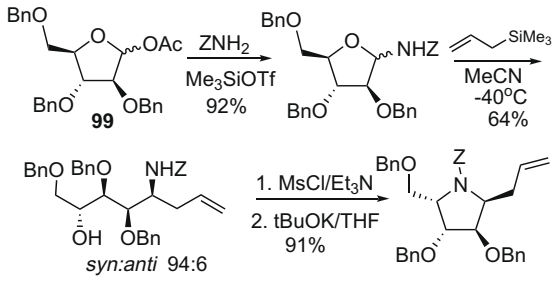
Scheme 72.



Scheme 73.



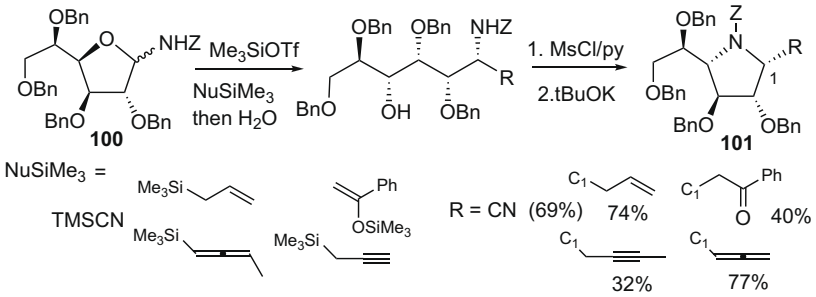
Scheme 74.



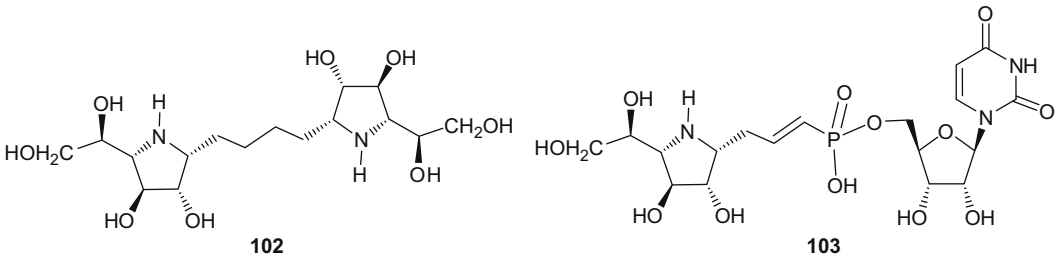
Scheme 75.

The method was also applied to the synthesis of molecules mimicking sugar phosphates and sugar nucleotides. The cycloaddition of diethyl vinylphosphonate with nitrone **127** in tetrachloroethylene proceeded with a lower degree of stereo- and regioselectivity than the previous reactions, as four *anti*-products were identified in a ratio of 30:52:13:6 (*exo*-5P: *endo*-5P:*exo*-4P:*endo*-4P). The major isomer (*endo*-5P) was converted in six steps into phosphonate **128** (see Scheme 100).[152]

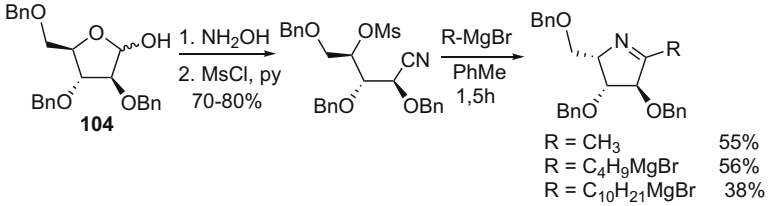
By contrast, the cycloaddition of nitrone **122** with diethyl allylphosphonate was completely regio- and stereoselective, leading to the *exo-anti* cycloadduct **129a**. The reaction was also successful with an ethyl uridin-5-yl allylphosphonate; the resulting cycloadduct **129b** was elaborated into an analogue of UDP-galactofuranose in which the Gal*f* unit is replaced by an iminogalactitol and the



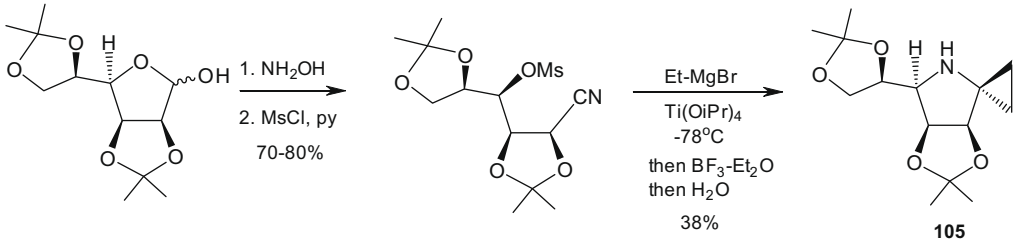
Scheme 76.



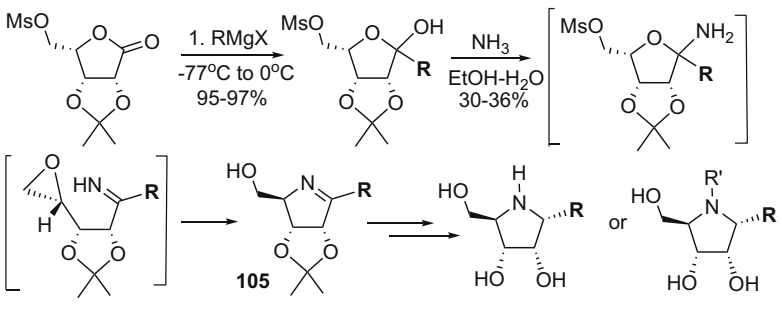
Scheme 77.



Scheme 78.

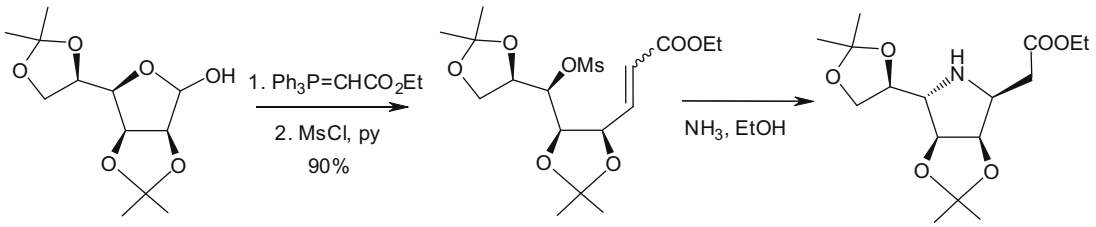


Scheme 79.

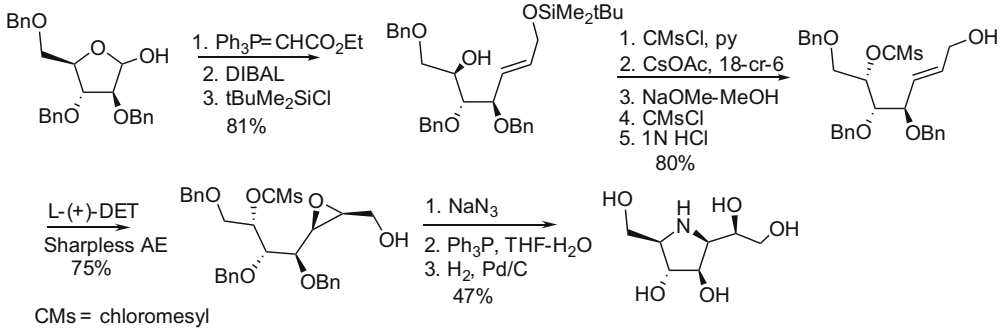


R = CH_3, C_4H_9, C_8H_{17}, C_9H_{19}

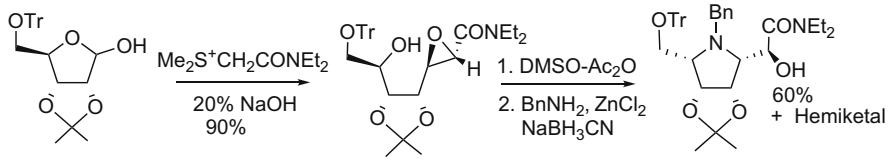
Scheme 80.



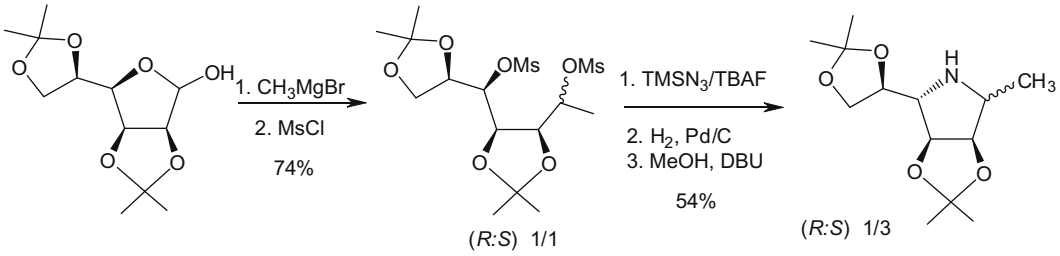
Scheme 81.



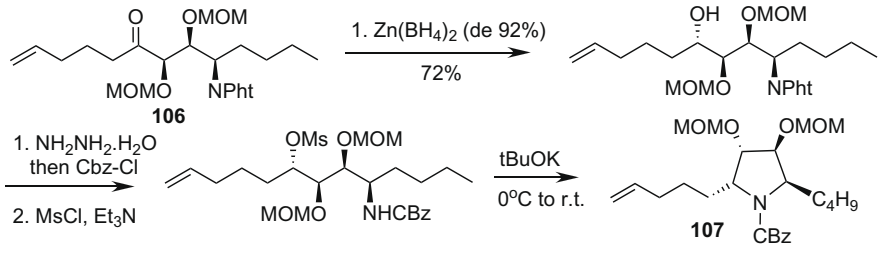
Scheme 82.



Scheme 83.



Scheme 84.

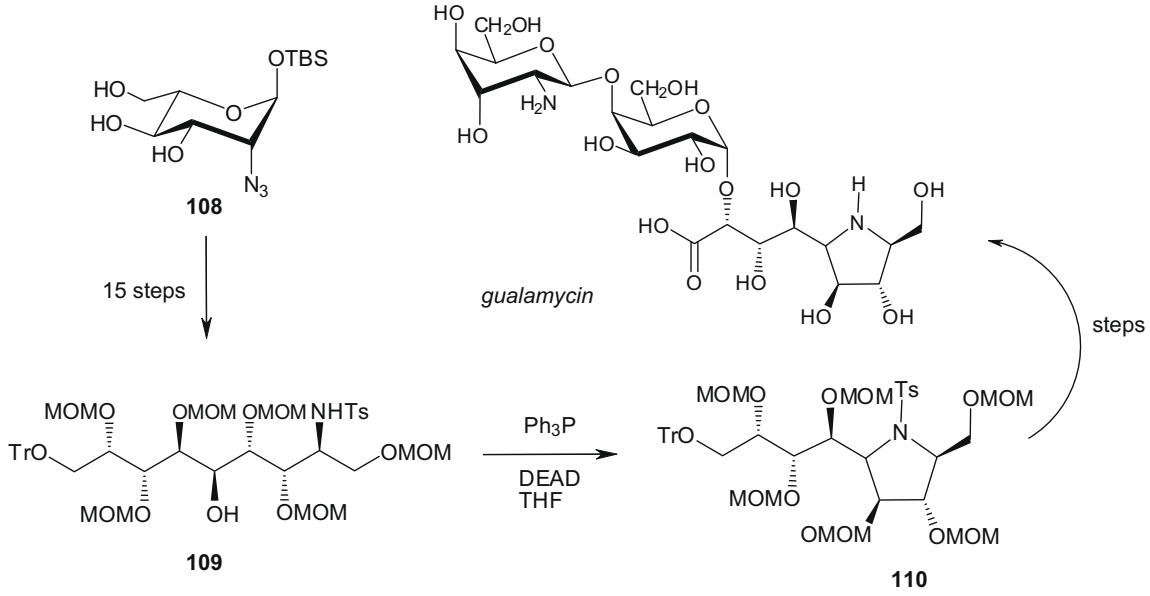


Scheme 85.

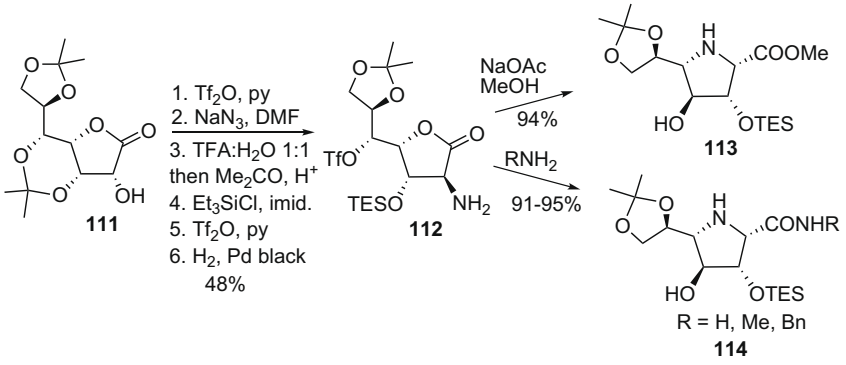
β-phosphate by a 2-hydroxypropyl group **130**.[153] The N–O bond was cleaved reductively and the cycloadduct could be efficiently *O*-debenzylated using BCl_3 in CH_2Cl_2 (see Scheme 101). Analogues of UDP-Galf such as **130** are potential inhibitors of mycobacterial enzymes such as UDP-Gal mutase and Gal*f*-transferases.

3.2.4. Nucleophilic addition to lactams

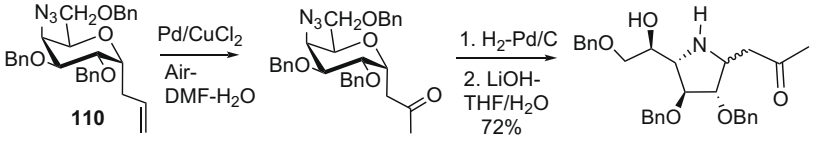
Nucleophilic addition to lactams has been used much less frequently for the synthesis of imino-C-glycosides than the addition to lactones to access normal C-glycosides. Yoda et al.[154a] have designed an interesting approach to 2,5-disubstituted



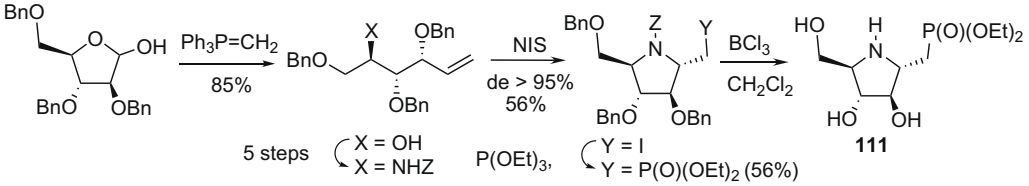
Scheme 86.



Scheme 87.

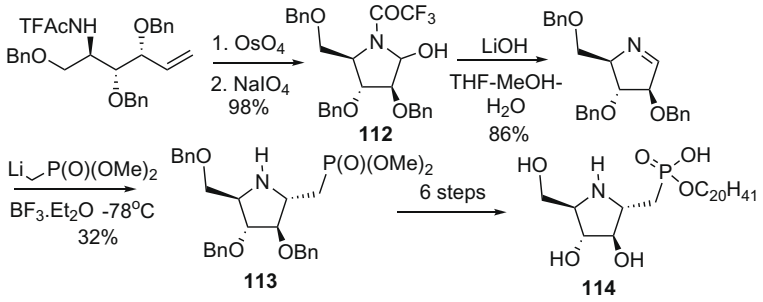


Scheme 88.

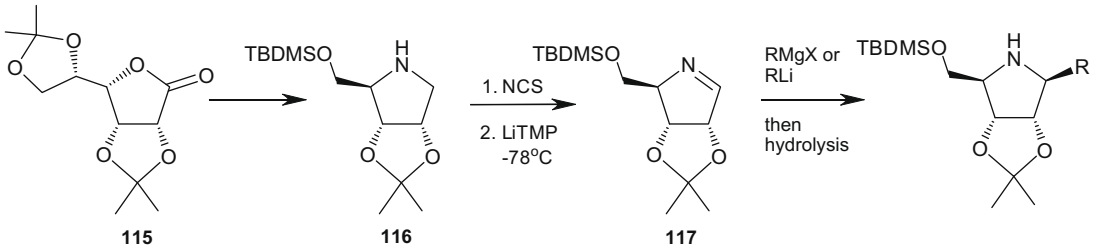


Scheme 89.

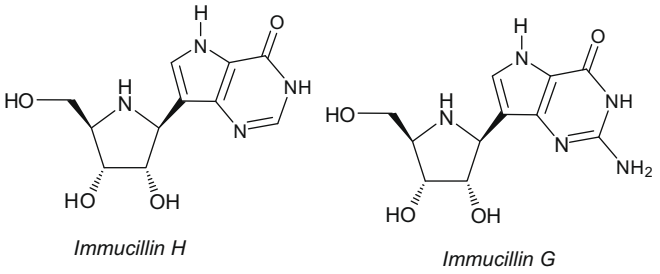
3,4-dihydroxy-pyrrolidines that provides diversity at both positions: the first R^1 group (Scheme 102) is introduced by nucleophilic addition of a Grignard reagent to a pentofuranosylamine, the resulting open-chain amino alditol is oxidatively degraded to a carboxylic acid that cyclizes to a lactam, the lactam is then activated and reacted with a second organometallic reagent to introduce the R^2 group. The reduction of the latent aminoketone **131** thus formed with $NaBH_4$ followed by mesylation and cyclization provides the pyrrolidine derivative **132** with essentially no stereoselectivity at C-4. However, reduction of the hemiaminal **131** with Et_3SiH/BF_3



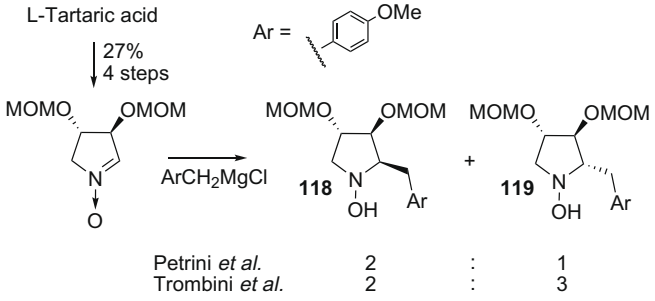
Scheme 90.



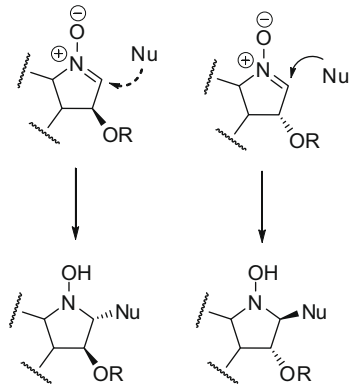
Scheme 91.



Scheme 92.



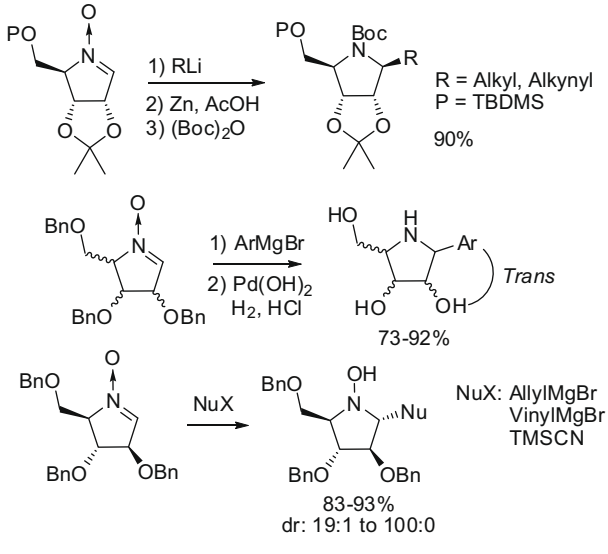
Scheme 94.



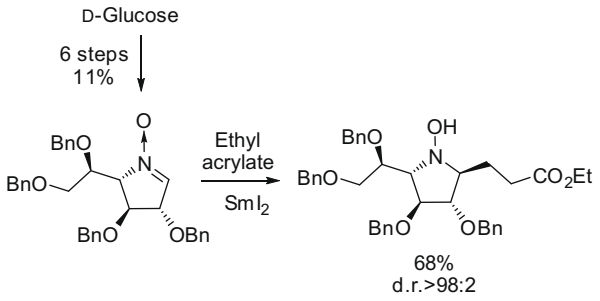
Scheme 93.

provided the 2,5-*cis* disubstituted pyrrolidine with excellent stereoselectivity.

This process was applied to a variety of organometallic reagents and was used for the synthesis of a diversity of natural products such as (+)-preussin,[154b] (+)-lentiginosine,[154c] (+)-alexine,[154d] and hyacinthacines.[154e]



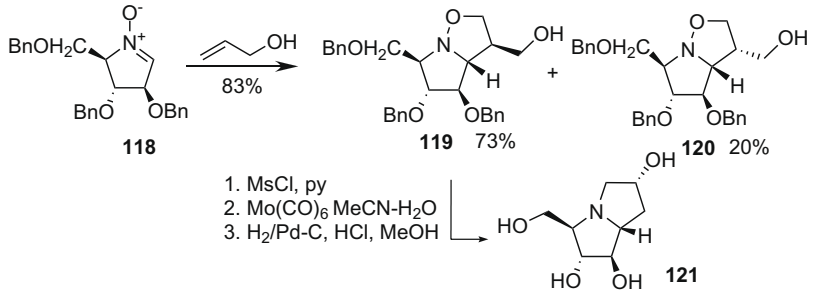
Scheme 95.



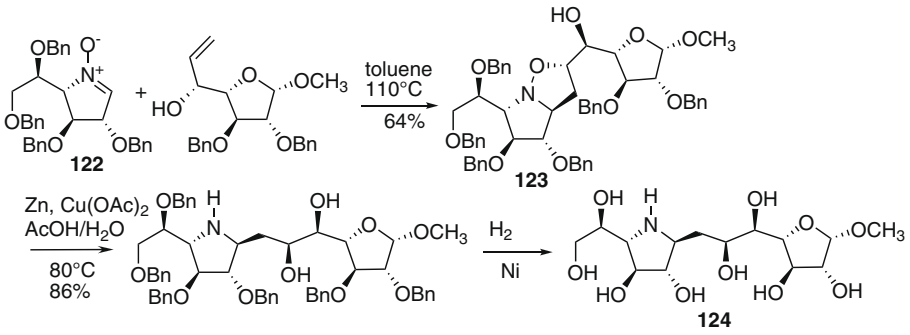
Scheme 96.

Togo et al. have developed a related procedure, which leads to imino-*C*-nucleosides such as the analogue of 5-β-D-ribofuranosyluracil (Scheme 103).[155] While the internal reductive amination procedure gave only the α-linked nucleoside analogue, the reduction of the open-chain ketone with $NaBH_4$ followed by cyclization by internal S_N provided the β-linked nucleoside with good stereoselectivity.

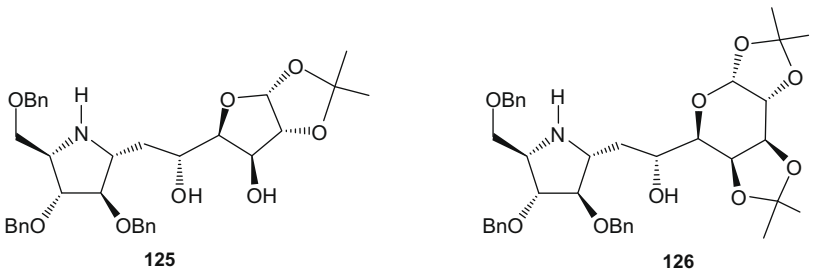
The procedure was applied to other nucleophiles: as shown by Eustache et al.,[133] iminosugars substituted by a phosphonomethyl group could be obtained by way of the addition of lithiated diethyl methanephosphonate to a lactam (Scheme 104).



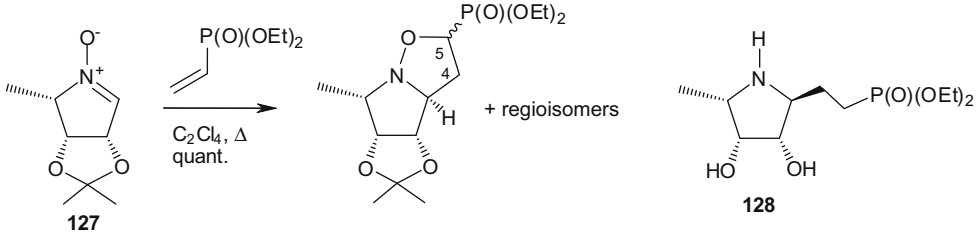
Scheme 97.



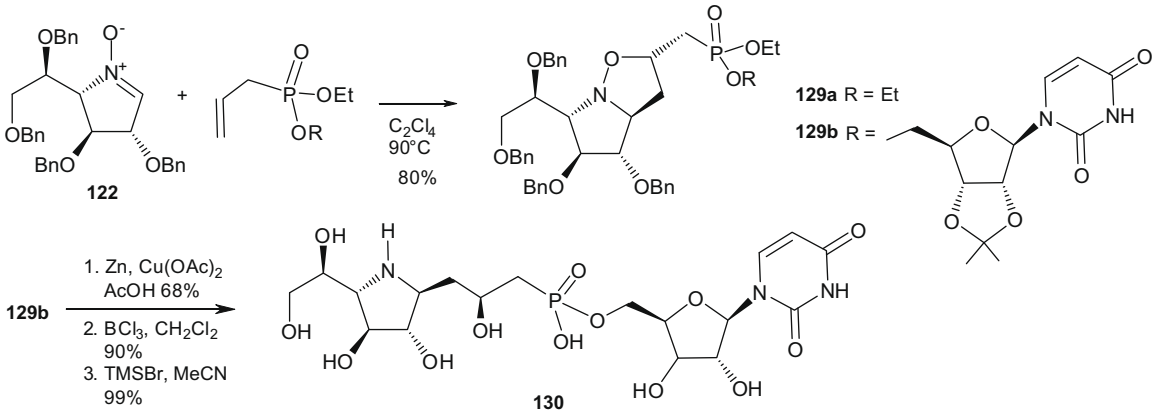
Scheme 98.



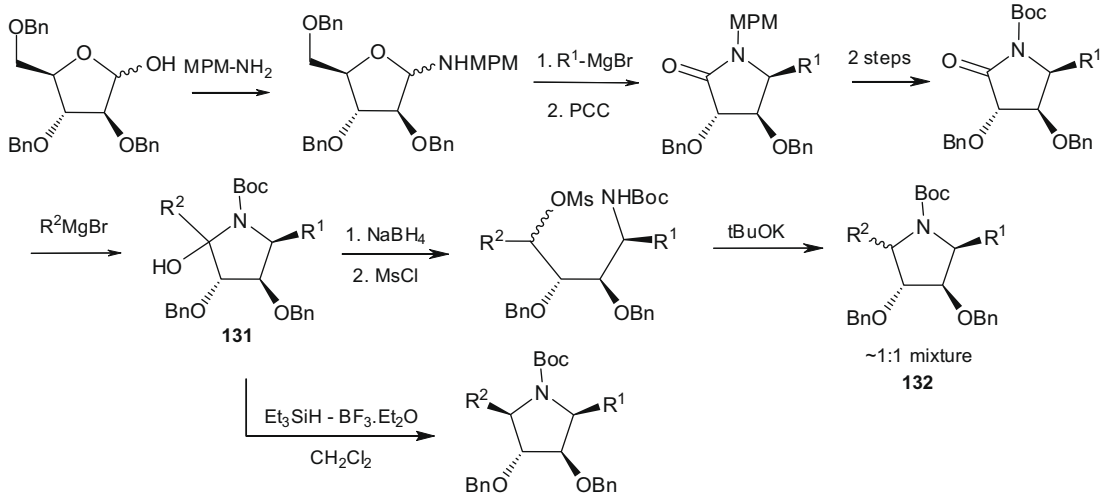
Scheme 99.



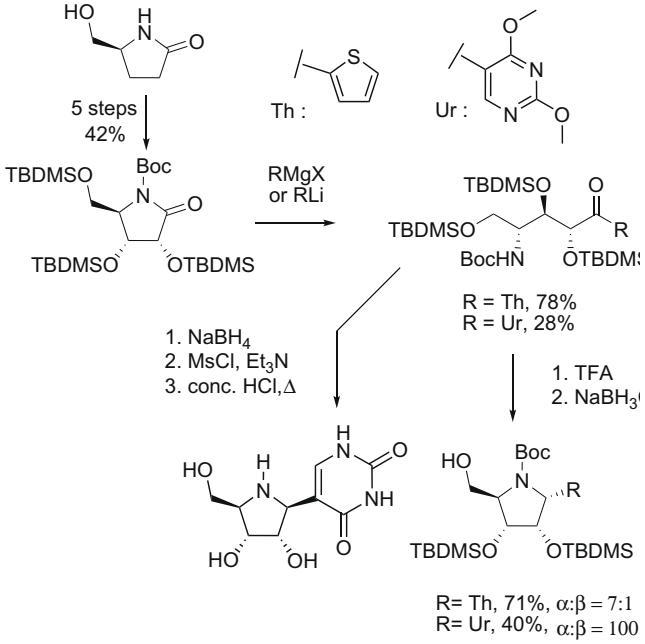
Scheme 100.



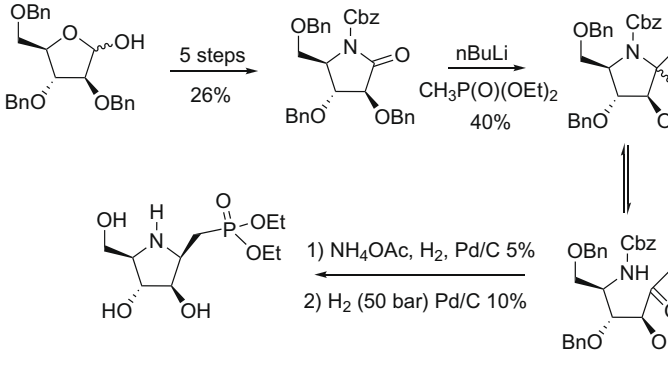
Scheme 101.



Scheme 102.



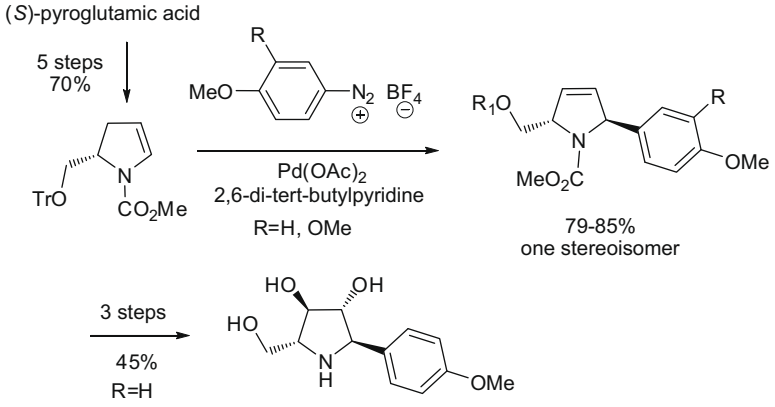
Scheme 103.



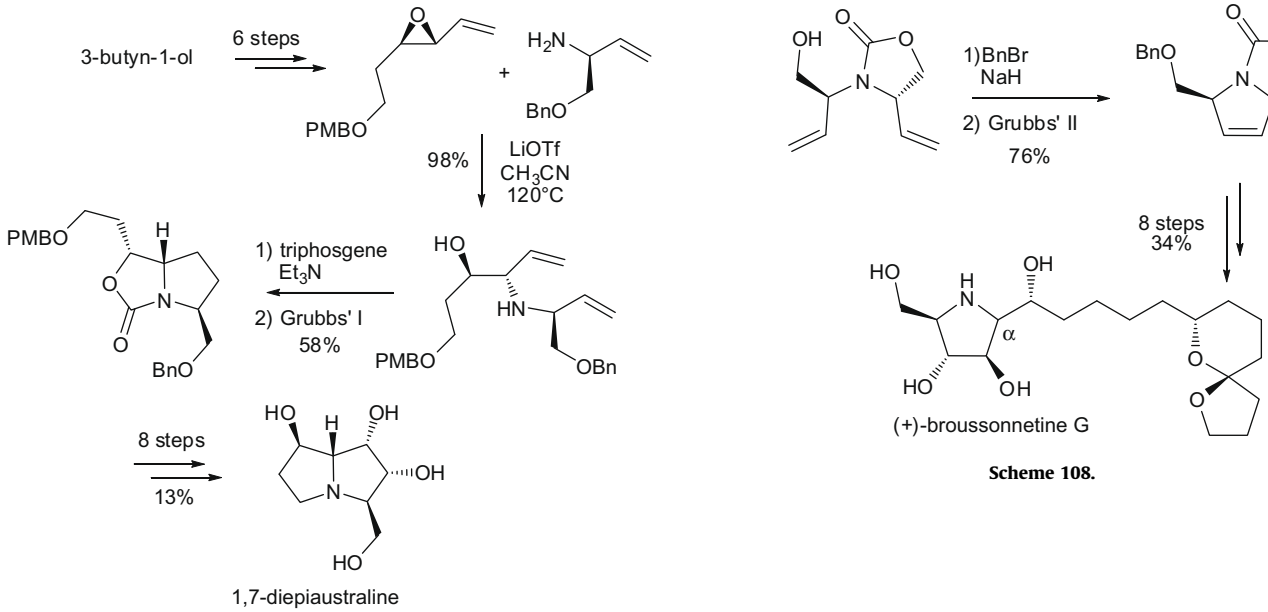
Scheme 104.

3.2.5. The Heck reaction

The Heck reaction constitutes a powerful methodology in organic synthesis for the controlled construction of C–C bonds. Correira et al. have focused their attention on the synthesis of iminosugars in the pyrrolidine series using this technique.[156] By applying standard Heck arylating conditions on enantiomerically pure endocyclic enecarbamates, they were able to obtain different iminosugar precursors with modest to high yield and with high diastereoselectivity (Scheme 105).



Scheme 105.

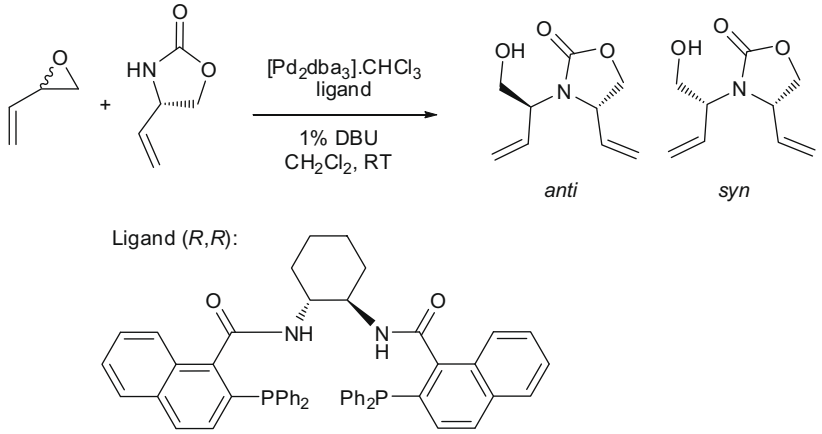


Scheme 106.

Leumann and Häberli described a similar procedure to produce the imino-analogue of 2′-deoxy-pseudouridine with modest yields but with high stereoselectivity.[157]

3.3. De novo synthesis

As we saw in Section 2.3.2., the ring closing metathesis is an important tool for the synthesis of imino-C-glycosides. This methodology has been extended to the pyrrolidine series by the Pyne's



Scheme 107.

Table 1
General guidelines to access iminosugar *C*-glycosides with a definite configuration

Series	Strategy	Glycon	Aglycon	Stereoselectivity	Sources
Piperidine	Double reductive amination	D-Gluco, D-manno, D-galacto	Sugar, alkyl	Always β-selectivity(1,5-*cis* disubstituted piperidine)	Part 2.1.1.
Piperidine	Electrophile-induced cyclization	D-Gluco, D-galacto, L-altro	-	C1–N bond formation 2,3-*cis* stereoselectivity observed except in the L-ido series	Part 2.1.3.
Piperidine	Reduction of cyclic imines	D-Gluco, D-manno, L-gulo, L-manno, D-allo	Alkyl, aryl, sugar	See Figure 7	See Figure 7
Pyrrolidine	Nucleophilic addition to cyclic nitrones	—	Aryl, alkyl, alkynyl	See Figure 8	See Figure 8

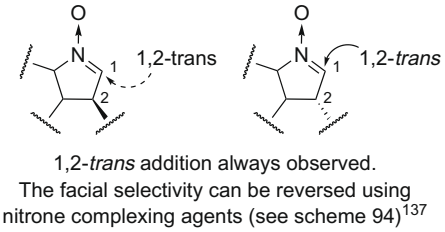


Figure 8. Diastereoselective model for the addition to cyclic nitrones in pyrrolidine series.

group in 2003.[158] They reported the syntheses of analogues of natural product *australine* (Scheme 106).

The starting vinyl epoxide was prepared from the corresponding Sharpless epoxy alcohol via Swern oxidation and Wittig-olefination reaction. The ring closing reaction was reported to be very slow with Grubbs catalyst I but the reaction could proceed in good yield after 48 h of heating at reflux.

Another procedure has been used by Trost et al. which allowed the preparation of enantiomerically pure starting material in fewer steps.[97] Asymmetric allylic alkylation (AAA) reactions utilizing palladium have proven to be extremely useful and versatile synthetic transformations. This procedure allows the transformation of racemic compound into a single enantiomer. This deracemization constitutes a dynamic kinetic asymmetric transformation (DYKAT). Thus, as an example, Scheme 107 describes the synthesis of imino-C-glycoside precursors.

Using the (*R*,*R*) ligand the *anti* product is obtained with a very good diastereoselectivity (de 86%). The reversed stereoselectivity can be observed using the (*S*,*S*) ligand (de 82%). Having this RCM precursors in hand, Trost et al. have proceeded to the cyclization and, by way of an epoxidation and a hydrolysis, were able to produce (+)-broussonetine G, a recently discovered glycosidase inhibitor (Scheme 108).

4. Conclusion

Three decades after the first synthesis of iminosugar C-glycosides, a myriad of synthetic strategies has been developed to prepare this important class of glycomimetics of biological interest. However, much remain to be done. Indeed, nearly no examples of amino iminosugar C-glycosides have been reported in the literature to date,[71a] despite the tremendous importance of aminosugars as structural elements of glycoconjugates and natural products. In such systems, the presence of a neighboring reactive amino group brings additional difficulties and is expected to be incompatible with most C-glycosylation strategies reported. In the future, the main challenges will still be to access efficiently enantiomerically pure iminosugar C-glycosides of predictable configuration. Based on the results presented in this review, some guidelines may be formulated to predict the stereoselectivity of certain synthetic strategies in the piperidine series shown in (Fig. 7 and Table 1). Except for cyclic nitrones (Fig. 8), such predictive models are much more elusive in the pyrrolidines series mainly because of the greater conformational flexibility of the five-membered ring. Future studies in the field of iminosugar C-glycosides will certainly focus on better efficiency, structural diversity, and higher stereocontrol.

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