Cyclisations and Strategies for Stereoselective Synthesis of Piperidine Iminosugars

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Selected reactions that have been used to form piperidine based iminosugars are shown
Abstract: This personal account focuses on synthesis of polyhydroxylated piperidines, a subset of compounds within the iminosugar family. Cyclisations to form the piperidine ring include reductive amination, substitution via amines, iminium ions and cyclic nitrones, transamidification (N-acyl transfer), addition to alkenes, ring contraction and expansion, photoinduced electron transfer, multicomponent Ugi reaction and ring closing metathesis. Enantiomerically pure piperidines are obtained from chiral pool precursors (e.g. sugars, amino acids, Garner’s aldehyde) or asymmetric reactions (e.g. epoxidation, dihydroxylation, aminohydroxylation, aldol, biotransformation). Our laboratory have contributed cascades based on reductive amination from glycosyl azide precursors as well as Huisgen azide-alkene cycloaddition. The latter’s combination with allylic azide rearrangement has given substituted piperidines, including those with quaternary centres adjacent to nitrogen.

Keywords: Iminosugars, Piperidine, Cyclisation, Deoxynojirimycin, Enantioselective synthesis.

1. Introduction

Iminosugars are polyhydroxylated cyclic amines where nitrogen replaces the ring oxygen of a monosaccharide (Figure 1). These glycomimetics have the unique structural characteristics of polyhydroxylated alkaloids and are potent inhibitors of glycosidases[1] and glycosyltransferases.[2] Whereas glycosidases hydrolyse glycoside bonds, the glycosyltransferases form them, giving oligosaccharides or other glycoconjugates from nucleotide sugar donors and an acceptor.[3] Iminosugars also act as chaperones,[4] where the active site inhibitor induces folding and conformational stabilization in mutated and improperly folded glycosidases, and thereby prevent their cellular degradation. The ring nitrogen is important as replacing it with carbon or sulfur can give rise to much weaker affinity.[5] This difference in affinity has been associated with the increased basicity of nitrogen and the possibility it is protonated when bound at receptor sites at physiological pH. However, such glycomimetics have also been observed bound in the neutral form (Figure 2).[1]

Their properties has led to their investigation as potential drugs for viral infection,[6] diabetes,[7] cancer,[8] cystic fibrosis,[9] & lysosomal storage disorders.[10] Miglitol (Figure 3), an \( \alpha \)-glucosidase inhibitor, commercialized in 1996 under the trade name Glyset,™ is used for the therapy of type-2 diabetes.[7b] Miglustat (Figure 3) is used clinically for Gaucher[11] & Niemann-Pick type C[12] (NPC) diseases. The galactose mimetic migalastat, developed for the treatment of Fabry disease,[13] is a chaperone that reversibly binds to the active site of the alpha-galactosidase A (alpha-Gal A). Several other
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Paul Murphy obtained his BSc (1990, NUI) and PhD (1994, NUI) at University College Galway (now NUI Galway). He was then awarded a Chiroscience postdoctoral fellowship at the University of York (1994–1996), where he worked on design and synthesis of sialyl Lewis' mimetics with Richard J. K. Taylor (synthesis) and Rod E. Hubbard (computational chemistry) and John G. Montana (Chiroscience Ltd, medicinal chemistry). He was appointed as a Lecturer in Organic Chemistry at University College Dublin in 1996 and in 2008 as the Established Professor of Chemistry in Galway. He has had research visits to the University of Pennsylvania (Amos B Smith, III), Universitaet Mainz (Horst Kunz) and Harvard Medical School (Jerome Groopman, Gabriel Birrane). His research interests are in design and synthesis of bioactive compounds based on carbohydrates.
iminosugars are undergoing clinical evaluation or have been evaluated previously in a clinical setting. These are for the treatment of various disease such as cancers, viral infections (Dengue, HIV), and cystic fibrosis. Iminosugars have also been investigated as immunomodulators, as activity based molecular probes, or in peptidomimetic research. Recently an argument was made for repurposing of miglitol, celgosivir and miglustat for the treatment of COVID-19.

Over 200 iminosugars, many with piperidine rings, have been isolated from plants, insects or bacteria (see Figure 1). Nojirimycin was first isolated from Streptomyces. Scilla sibirica is a rich source of pyrrolidine and piperidines based polyhydroxylated compounds. N-Methyl-1-deoxynojirimycin (N-Me-DNJ) was isolated from the leaves and roots of Mulberry trees. More than 10 calystegines have been isolated from the Calystegia sepium or Convolvulus arvensis. Nagstatin, isolated from a Streptomyces species was identified as a potent inhibitor of a glycosaminidase. There are various structural classes including polyhydroxylated piperidines, pyrrolidines, indolizidines, pyrrolizidines, azetidines and nortropanes. The content of iminosugars isolated is often low, with 1-deoxynojirimycin (DNJ) in mulberry leaves being ~ 0.1 % by weight. Enantiomers of the natural products have shown interesting properties. The lack of access to large quantities from natural sources as well as their interesting properties, including those of enantiomers, requires the development of synthetic routes to these compounds as part of medicinal chemistry programmes. Derivatives of natural iminosugars, for example, N-alkylated piperidines, fluorinated derivatives, as well as C-branched iminosugars have been prepared and found to be potent inhibitors of glycoprocessing enzymes.

The main purpose of this personal account is to document various cyclisation strategies employed for synthesis of piperidine iminosugars commencing with the pioneering early research work of Hans Paulsen, who is credited with the first syntheses of piperidine mimetics of pyranose sugars, and to highlight our laboratory’s contributions among selected exemplars. Versatile synthesis strategies have been developed by others also. The authors recognize that many cyclisation methods discussed here are relevant for synthesis of pyrrolidines and/or azepanes also. The concise nature of this account does not permit us detailing a more comprehensive account of all syntheses. A selection have been chosen. The review is organized around primarily cyclisation methods that have been used with some additional detail included. A comprehensive discussion of the isolation of iminosugar natural products or the biological properties of these compounds is beyond the scope of this account. These have been discussed in various reviews and publications which should be consulted for more detailed information on biological and pharmacological properties.

With regard to nomenclature, we do not use a prefix D- for iminosugars when it corresponds to the α-configuration for the parent sugar; thus DNJ 3 is 1-deoxynojirimycin, the 1-deoxymimetic of α-D-glucopyranose 1; DMJ 4 is 1-deoxymanno-jirimycin or mannino-DNJ and mimics D-mannopyranose. If referring to their enantiomers we will use L- as a prefix to denote configuration; thus L-DMJ is the enantiomer of DMJ 4 or the 1-deoxymimetic of L-mannopyranose.

2. Cyclisations for Iminosugar Synthesis

2.1. Nucleophilic Addition Giving Cyclic N,O-Hemiaminals or a Geminal Diamine Derivative

In 1966, Paulsen, in a seminal paper, reviewed properties of the cyclic hemiaminals derived from pyranoses. The formation of an N-acetylated piperidinose was observed after hydrolysis of xylose derivative; this led to a mixture of and 26 (1:2, Scheme 1), from which crystalline 26 was obtained as a single isomer. Formation of the piperidine occurs by nucleophilic addition by the acetamide nitrogen to the carbonyl group. Paulsen also reported that benzoxycarbonyl protection of the nitrogen led to increase in piperidinose to furanose ratio due to there being a more nucleophilic nitrogen atom in the urethane.

Nojirimycin 2, isolated in 1967 subsequent to Paulsen’s review, is formed from cyclisation from an amine (Scheme 2), rather than an amide/urethane, with an aldehyde and it also has an N,O-hemiaminal group. However, it is unstable, as observed for related compounds by Paulsen. The greater availability of the nitrogen lone pair due to absence of

Scheme 1. Paulsen’s formation of stable piperidinose 26, which was isolated by crystallization.
conjugation to a carbonyl group explains the observed decomposition via the Amadori rearrangement (Scheme 2).\[35\]

The synthesis of stable cyclic hemiaminals have contributed to strategies to prepare polyhydroxylated piperidines. O’Doherty and co-workers have synthesised manno-DNJ 4 and other analogues via a stable cyclic hemiaminal, where the piperidine nitrogen is conjugated to a Cbz group.\[36\] Thus the key intermediate 29 prepared in 3 steps from furfural 27 via 2-vinyl furan 28. Subsequent Sharpless asymmetric aminohydroxylation\[37\] of 28 gave 29. The reaction with mCPBA induced the aza-Achmatowicz rearrangement giving 30, via cyclisation like that observed by Paulsen, that was converted to the manno-DNJ salt 32 in five steps, including reductive elimination by hydrogenolysis via 31 (Scheme 3).\[38\] This approach provides ready access to both enantiomers.

Calystegines provide another example of stable cyclic N,O-hemiaminals. In this case, the presence of the bridgehead carbon, rather than conjugation, prevents formation of a planar imine required for decomposition by the Amadori rearrangement.\[35\] Madsen et al. synthesised calystegine B\[2\] 38 via 33–37 (Scheme 4). Steps included zinc-mediated tandem reaction from glucose derivative 33, a variation of a reaction reported earlier by Vasella and co-workers,\[40\] followed by ring closing metathesis and regioselective hydroboration with oxidative work-up giving 36 and 37. Piperidine 38 was formed after protecting group removal and nucleophile addition of the resulting amine to the ketone.

Yu et al. synthesised calystegine B\[3\] 42 from l-arabinopyranose using intramolecular Nozaki-Hiyama-Kishi coupling reaction in a key step, with a similar cyclisation to give the piperidine.\[41\] The l-arabinopyranose derivative 39 was converted to the cycloheptenol 40. Oxidation of 40 by Dess-Martin periodinane (DMP) gave 41 which after hydrogenolysis afforded the calystegine B\[3\] 42 (Scheme 5).\[41\] Changing the precursor 39 to 2,3,4-tri-O-benzyl-d-xylopyranose led to calystegine B\[2\] 38 (Scheme 4).

Pearson and co-workers synthesised kifunensine (Scheme 6) 11 from 43 and Kayakiri intermediate 44, which were obtained from l-ascorbic acid.\[42\] Thus oxidation of 44 to an unstable aldehyde may involve formation of a cyclic N,O-hemiaminal (structure not shown). Ammonification gives an imine, which may cyclise to geminal diamino derivative 45, which then gives 46 after transamidification. Removal of acetonides gave the mannosidase inhibitor 11.\[43\] Cyclisation

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**Scheme 2.** Formation and Amadori rearrangement of nojirimycin 2, a cyclic N,O-hemiaminal.

**Scheme 3.** Synthesis of DMJ salt 32 by O’Doherty and co-workers.

**Scheme 4.** Madsen groups’ synthesis of Calystegine B\[2\] 38.

**Scheme 5.** Synthesis of calystegine B\[3\] 42 by Yu and co-workers.
via a geminal diamino derivative was also used in a synthesis of siastatin B 12 by Nishimura and co-workers.\[44\]

### 2.2. Reductive Amination

#### 2.2.1. Chemical Approaches

Reductive amination strategies have proven popular for synthesis of iminosugars.\[45\] In 1967, Hans Paulsen and co-workers, employed the highly stereoselective reduction of cyclic imines generated via N,O-hemiaminals in the synthesis of DNJ 3 from \(\text{\textit{l}-sorbose}\).\[46\] Taking inspiration from this approach and developing an interest in using organic azides in synthesis, Elisa Danieli and Jérôme Lalot, in our own laboratory, prepared azide 47 from \(\text{\textit{l}-sorbose}\), and converted it, via 48 – 50, stereoselectively to benzylated piperidine 51. Hydrogenolytic removal of the benzyl group required addition of HCl in order to give DNJ (Scheme 7).\[47\] With this route we routinely have prepared gram quantities of DNJ. Incidentally it was investigating variations of this route that led us to identify potential to use Huisgen cycloaddition, discussed in more detail later in this account.

The availability of DNJ in our laboratory provided a basis for the synthesis of peptidomimetics (Figure 4) based on DNJ 3 and DMJ 4 as scaffolds\[48\] with contributions from Sebastien Gouin, Vincent Chagnault, Colin O’Brien, Ciaran O’Reilly, Stephen Barron, Arvind Negi and Jian Zhou. Biological findings showed that whereas glucopyranoside 52 and 53 (Figure 4) showed similar affinity for somatostatin receptors-4 (SSTR4, 4.4 μM) and 5 (SSTR5, 5.0 μM) the piperidine 54, synthesised by Vincent Chagnault, showed selectivity only for SSTR4 (3.2 μM; IC\(_{50}\) for SSTR5 = > 100 μM).\[49\] One of the attractive features of using the piperidine is the potential for protonation of peptidomimetics, although it is not known if it is important for recognition of 54. We also completed the synthesis and evaluation of hybrid bifunctional angiogenesis inhibitors by Ying Zhou and Yunxue Zhao\[18,47–49\]. The latter were designed to incorporate DNJ as well as a residue to inhibit methionine aminopeptidase II, a target for angiogenesis therapy. The hybrid compound and other related compounds inhibited capillary tube formation, a process similar to blood vessel formation in angiogenesis.\[50\]

Chemoenzymatic synthesis of DNJ 3 was reported almost five decades ago by Kinast and Schedel of Bayer AG\[51\] in a route involving reductive amination of \(\text{\textit{d}-glucopyranose}\) 1 to give 1-amino-1-deoxy-\(\text{\textit{d}-sorbitol}\) 55 (Scheme 8). Then the \(\text{\textit{l}-sorbose}\) derivative 56 is formed by biotransformation using a \textit{Gluconobacter} bacterium, which regioselectively oxidises the C-5 alcohol to a ketone. Finally use of Paulsen’s reductive amination gives DNJ 3. This

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**Scheme 6.** Pearson and co-workers’ synthesis of kifunensine 11.

**Scheme 7.** Synthesis of DNJ 3 via reductive amination via \(\text{\textit{l}-sorbose}\).

**Scheme 8.** Bayer AG’s chemoenzymatic synthesis of DNJ 3.

**Figure 4.** Peptidomimetics based on DNJ 52 and glucopyranose 53. Hybrid angiogenesis inhibitor based on DNJ 54.
synthesis is very attractive given its concise nature, involving only four steps and with minimal use of protecting groups. If the sequence was carried out in absence of the Cbz group then the aminoketone generated was unstable, likely due to competing Amadori rearrangement.

The reductive amination of 1,5-dicarbonyl sugars was reported to be major source of DNJ 3 in Streptomyces. Baxter and Reitz reported a biomimetic double reductive amination from dicarbonyl precursors 59 and benzylamine, which afforded 60 (dr 96:4 mixture of D-glucitol: L-iditol isomers). Removal of the benzyl group from 60 by hydrogenolysis, followed by ion exchange and recrystallization, yielded DNJ 3. The dicarbonyl precursor 59 was synthesized from the readily available acetonide derived from d-glucose 57 with the required regioselective oxidation achieved using dibutyltin oxide and bromine (Scheme 9).

In 2008, Overkleeft and co-workers developed a large scale preparation of adamantanyl derivative 61 via 62–66, which has been implemented in a GMP facility on kilogram scale. The route involved reduction of 2,3,4,6-tetra-O-benzyl-d-glucopyranose 64 to the glucitol 65 and oxidation to a 1,5-dicarbonyl precursor, followed by double reductive amination, using ammonium carbonate and sodium cyanoborohydride. After generation of 66, reductive amination with aldehyde 63 using catalytic hydrogenation gave 61 after crystallization (Scheme 10).

Philomena Enright, Julie O’Brien, Manuela Tosin in our laboratory prepared 1,5-dicarbonyl sugars to DNJ and DMJ from vinyl ethers. In this case the required C-5 oxidation is achieved by in situ epoxidation and hydrolysis, giving 5-ketosugars. A formal synthesis of DMJ 4 thus involved conversion of 68 to 69 (Scheme 11). Dihydroxylation of such vinyl ethers also gives 1,5-dicarbonyl derivatives, as reported by Chapleur and co-workers, while epoxidation-methanolysis by Barili et al. also effected the required C-5 oxidation in their syntheses based on galactose.

The structure of 1,5-dicarbonyl derivatives can be complex as shown in Scheme 12. The alkene 70 can be converted to the epoxide 71. Subsequently, nucleophilic attack at the anomeric position can lead to ring opening to form the 72a and 72b which can be in equilibrium in several structures from 73 to 77.

The synthesis of DMJ 4 has been reported by Stütz and co-workers from D-fructose 78 and influenced Florence Chery’s choice of route to, this time a DMJ based peptidomimetic 81 from 78 via 79 and 80, using reductive amination, followed by N-benzylation (Scheme 13).

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Due to an interest in synthesis of carbohydrate based ligands for lectins, our laboratory were increasingly aware that glycosyl azides were useful synthetic intermediates and could be readily prepared in the laboratory. Hence, Julie O’Brien, Ciaran McDonnell and Manuela Tosin, took inspiration from successful reductive amination strategies, and investigated use of 6-deoxyhex-5-enopyranosyl azides for synthesis of DNJ, DMJ, galacto-DNJ and 6-deoxygalacto-DNJ (Scheme 16).

Linda Cronin, took the strategy one step further, and used the one pot reductive cascade reaction of 88 to give lactam 93, via transamidification from piperidine 92. The reduction of 93 gave castanospermine 14 (Scheme 15). Intermediate 88 was prepared by an aldol reaction from an aldehyde that had been generated from 83 (Scheme 14).

The use of azide derivatives as precursors to intermediates for reductive amination reactions were not limited to our own group. Fleet and co-workers converted L-lyxono-1,4-lactone 94 to azide 95 and its catalytic hydrogenation gave imine 96, which upon further reduction gave 97. Then removal of the acetonide gave d-deoxyfuconojirimycin (DFJ) 82 (Scheme 16). A related reaction sequence starting from the corresponding d-lyxonolactone gave enantiomer and mimetic of L-fucopyranose (l-DFJ). Synthesis of 1,6-dideoxynojirimycin from l-sorbose involved similar cyclisation.

Other sources of nitrogen have been investigated in reductive amination type reactions. In 2016, Kumar et al. reported a route to DNJ 3 from 64, via dehydrative-oxidation of oxime 98 to ketonitrile 99 which gave 66/66a (ratio 1 : 1.5) after reaction with Raney-Ni and hydrogen, via reductive amination. Catalytic hydrogenolysis gave DNJ 3 (Scheme 17).

Bayer AG’s chemoenzymatic approach has been a precursor to other approaches. Clapés and co-workers used a d-fructose-6-phosphate aldolase (FSA) catalysed aldol,
followed by reductive amination to generate the piperidine.\(^{[64]}\) Specifically, (S)-100 was converted to (S)-101. Catalytic hydrogenation of (S)-101 gave DNJ 3 (Scheme 18). DMJ 4 was prepared from (R)-100 in a similar manner.\(^{[64]}\) Clapés and co-workers also reported the chemoenzymatic synthesis of D-fagomine 8.\(^{[65]}\)

Wang et al. produced polyhydroxylated compound 4-(S)-103 using bioengineered *Escherichia coli*. The aldehyde (S)-102 underwent the aldol reaction with glycolytic intermediate dihydroxyacetone phosphate in FruA-Y *E. coli* cells followed by in situ dephosphorylation, affording 4-(S)-103, which was then transformed to DNJ 3 (Scheme 19).\(^{[64]}\) These latter approaches illustrate the use of conjugating groups on nitrogen, which again seem required to prevent decomposition of cyclic hemi-aminals.

### 2.3. Intramolecular Nucleophilic Substitution Reactions

Another widely used cyclisation strategy has been use of intramolecular substitution reactions. These are organized here based on nucleophile type and not in chronological order.

#### 2.3.1. Ammonia or Amines as Nucleophiles

In 2007, Hollingsworth *et al.* synthesized DNJ 3 and DMJ 4 through the dialkylation of ammonia.\(^{[67]}\) The dibromo derivative 105, synthesized from 104 was converted to DNJ 3 via 105–106. Preliminary investigations found that the cyclisation to 106 was slow and can be explained by strain in the forming trans fused ring in 106. Successful cyclisation to the piperidine was achieved by firstly reacting ammonia in methanol with 105 followed by heating the intermediate obtained at reflux with sodium acetate in acetonitrile, giving 106. Subsequent protecting group removal gave DNJ 3 (Scheme 20).

Dialkylation of benzylamine was reported for the synthesis of DNJ 3 by Wang *et al.* from dimesylate 107, prepared from d-glucose 1. Reaction of 107 gave the piperidine 108.\(^{[68]}\) Catalytic hydrogenolysis of 108 gave DNJ. Piperidine 112 was generated from 111, using the Mitsunobu reaction by Kazmaier *et al.*\(^{[69]}\) The sequence to give 111 involved diastereoselective aldol reaction which was prepared from aldehyde 110, derived from l-tartaric acid,\(^{[70]}\) and glycine 109. Reduction and protecting group removal gave *altro*-DNJ 113 (Scheme 21).

Ojea and co-workers used diastereoselective aldol condensation of 114 and l-threose derived 115 to give 116, which was later converted to 117. Enantiomer 114 was prepared from valine and glycine. Substitution in 117 afforded 118, which after reduction and protecting group removal gave *galacto*-DNJ 117 (Scheme 22).\(^{[71]}\)
Ham and co-workers used D-serine derivative 119, to prepare 1,3-oxazine 120. Ultimately amine generation from 121 followed by displacement of mesylate gives 122 with later TBS removal giving DNJ 3 (Scheme 23). The strategy was later adapted to synthesise galacto-DNJ 17 and gulo-DNJ.\[73\]

l-Galacto-DNJ 126, the enantiomer of migalastat 17 (galacto-DNJ), is a potent galactosidase inhibitor. Koskinen et al. reported the synthesis of l-galacto-DNJ in eight steps with overall 35% yield (Scheme 24). Intermediate 125 was obtained from Garner’s aldehyde 123 and alkyne 124 in five steps. The N-protecting group removal from 125 under acidic condition followed by heating under basic conditions led to piperidine ring formation via substitution. Finally, removal of the benzyl groups gave l-galacto-DNJ 126.\[77\]

Guaragna and co-workers\[78\] prepared 127 from Garner aldehyde 123 and effected its cyclisation to piperidine 128 using TsCl-Ag$_2$O. Later 128 was converted via 129–131 to N-butyll-l-DNJ (l-NBDNJ) 132, the enantiomer of migalastat (Scheme 25). Guaragna and co-workers\[76\] have shown that l-NBDNJ acts as a non-lysosomal glucosidase 2 inhibitor. Notably, l-NBDNJ did not act as an inhibitor for most glycosidases, in contrast with NBDNJ. l-NBDNJ showed anti-inflammatory effects in mice models infected by P. aeruginosa.\[79\]

Vankar and co-workers synthesised isofagomine 22 via N-glycosyl amide 134, which was prepared by aza-Claisen rearrangement\[80\] via 133 derived from d-xylose. Reduction of 134, with subsequent ring opening and then mesylation gave 135, which was converted to 136. A stereoselective hydroboration reduction followed by oxidative work up and protecting group removal afforded isofagomine 22 along with 138 (Scheme 26).\[81\] Glycan can be used as an intermediate for the synthesis piperidine based iminosugars as reported in literature.\[82\]

Chen et al. reported the synthesis of L-ido-DNJ 142 from 139, via iridium catalysed reductive amination to give 140 (Scheme 27).\[83\] Subsequent iridium catalyzed substitution gave 141 which was converted to l-ido-DNJ 142 (Scheme 27).
The synthesis of bis-epoxide 144 from xylitol 143 was carried out in two steps, using a method first reported by Dreyer et al. from ribitol in four steps.\[84]\] Smith and Thomas used double substitution of 144 with an aliphatic amine giving 146 and 147 (3:1). Cyclisation, as indicated via 145, by 5-exo-tet or 6-endo-tet pathways are possible with the latter preferred (Scheme 28).\[85]\] Later Houston and co-workers synthesised clickable DNJ 149 via bis-epoxide 148.\[86]\]

The epoxide 151 was prepared from D-ribose 150 by Lopez-Herrera and transformed to 152 and 153, with epoxide ring opening occurring via an amine generated from 151 by Staudinger reduction of azide. Piperidine formation was preferred to azepane formation (4:1) and an anomeric C-substituted product was obtained (Scheme 29).

Lindstrom et al. reported the asymmetric synthesis of DNJ 3 from diene 154 via Sharpless asymmetric dihydroxylation leading ultimately to 155. Reduction of 155 promoted formation of 156, which was subsequently transformed into DNJ 3 (Scheme 30).

### 2.3.2. Cyclic Nitrone Formation by Substitution

Cyclic nitrones are useful intermediates in preparation of pyrrolidines, piperidines and azepanes.\[89]\] Py and co-workers reported the synthesis of DMJ 4 from 2-fructopyranose derivative 157.\[90]\] The oxime derivative 158 was obtained from the reaction of 157 and O-tert-butyldiphenylsilylhydroxylamine in the presence of acid catalyst followed by mesylation.
of the latent alcohol. Removal of the silyl ether from 158 led to cyclisation by intramolecular nucleophilic displacement from the oxime derivative to give cyclic nitrone 159. Only the E-isomer cyclised while the Z isomer gave the free oxime. Hydrogenolysis of 159 over palladium catalyst, followed by ion exchange gave DMJ 4 as a single isomer in 83% yield (Scheme 31). Cyclic nitrones react with nucleophiles and diastereoselective nucleophilic addition to nitrone 162 was achieved with Grignard reagent, vinyl magnesium bromide. The resulting 163 was transformed to DMJ 4 in a multistep sequence (Scheme 32). This synthesis by Cheng and co-workers was commenced from 2,3,4-tri-O-benzyl-D-arabinopyranose 160.[91]

### 2.3.3. Imine or Imidazole Nitrogen as a Nucleophile

Baskaran and co-workers used in situ generated imine nucleophiles for piperidine synthesis (Scheme 33). Thus d-ribose derived tosylate 164 gives ultimately an iminium ion 165. The presence of the indole facilitates formation of the bicyclic product 166 (Scheme 34).[92] Similarly Baskaran and coworkers have prepared iminosugar C-nitromethyl glycosides from 167 by the action of an aliphatic amine and nitromethane.[93]

The use of imidazole nitrogen as a nucleophile was employed in the synthesis of nagstatin 16.[94] The precursor 168, an L-ribofuranose derivative, was converted to sulfonate 169 in two steps (addition of lithiated imidazole derivative to the latent aldehyde of 170 and sulfonation). Detritylation in the presence of acetic anhydride and SN2 intramolecular cyclisation gave 170 with the fused ring system found in nagstatin and which was subsequently converted to nagstatin 16 itself.

### 2.4. Ring Closing Metathesis

Ring closing metathesis (RCM) emerged as a practical strategy for organic chemists in the 1990s and early 2000s with the development and commercialization of well-defined metathesis catalysts initially from the Grubbs and Schrock laboratories.[95] Application of RCM has since included iminosugars.[96]
In 2004, Takahata and coworkers reported the synthesis of DNJ \textit{3} via RCM of \textit{171}, which was prepared from Garner’s aldehyde \textit{123}, and led to piperidine \textit{172}. Subsequent oxidation and deprotection led to the formation of DNJ \textit{3} and analogues (Scheme 35).\[97\]

In 2009, Poisson \textit{et al.} reported asymmetric synthesis of DNJ \textit{3} from epoxide \textit{175} prepared via Sharpless epoxidation. The epoxide was converted to \textit{176} and then RCM using a Hoyveda-Grubbs catalyst, followed by regioselective and stereoselective hydroboration gave \textit{177}. Hydrolysis of \textit{177} gave DNJ \textit{3} (Scheme 36).\[98\]

Overkleeft and co-workers reported the asymmetric synthesis of piperidine \textit{180} via RCM from \textit{179}, which had been prepared from cyanohydrin derivative \textit{178},\[99\] in turn obtained by asymmetric hydrocyanation of aldehyde using a cyanohydrin lyase. Dihydroxylation of the alkene of \textit{180} gave a mixture of \textit{allo-DNJ-} and \textit{galacto-DNJ} derivatives after protecting group removal (Scheme 37).

In 2011, Ha \textit{et al.} reported the asymmetric synthesis of \textit{l}-DNJ \textit{184} from chiral aziridine-2-carboxylate \textit{185}, which gave \textit{187} after RCM (Scheme 38). Stereoselective epoxidation was followed by regioselective hydrolysis to give \textit{188}; subsequent protecting group removal gave \textit{l-DNJ} \textit{184}.\[100\]

Takahata and coworkers used \textit{189} to prepare \textit{190} which after RCM gave \textit{191} for the synthesis of \textit{galacto-DNJ} \textit{17} and its congeners. Again, a diastereoselective epoxidation was used and gave \textit{192}; its subsequent hydrolysis followed by protecting group removal gave \textit{galacto-DNJ} \textit{17}.\[101\] This route was also adapted to give \textit{l-deoxyiminoglicosas} (Scheme 39).\[74\]

Ring closing enyne metathesis has also been employed as shown in Scheme 40 for the synthesis of \textit{194} from \textit{193}. Additional transformations gave (+)-isofagomine \textit{22}.\[102\]

### 2.5. Ring Contraction of Azepine

Polyhydroxylated piperidines have been obtained by azepine ring contraction, although there are limited number of examples. Thomson \textit{et al.} synthesised racemic (+/−)-DNJ \textit{3}.

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Scheme 35. Takahata’s synthesis of DNJ \textit{3} and analogues.

Scheme 36. Poisson and co-workers’ asymmetric synthesis of DNJ \textit{3}.

Scheme 37. Synthesis of \textit{d-allo-DNJ} \textit{183} and \textit{d-galacto-DNJ} \textit{17} by Overkleeft \textit{et al.}.

Scheme 38. Ha \textit{et al.}’s synthesis of \textit{l-DNJ} \textit{184} via RCM.

Scheme 39. Synthesis of \textit{galacto-DNJ} by Takahata and co-workers.
from \((Z,Z)\)-hexa-2,4-dienedioic acid, which was used to give 195\(^{[103]}\). Oxidation of 195 and partial hydrolysis gave 196 (dr 99:1), which was converted to 197 via azepine ring contraction, brought about by mesylation in the presence of triethylamine. The mechanism may involve an aziridinium ion intermediate which reacts with chloride ion leading to 197. Epoxide 197 was transformed into \textit{altro}-DNJ 113 while 198 gave DNJ 3 via 199 and 200 (Scheme 41).

2.6. Ring Expansion of Pyrrolidine

Kim \textit{et al}. reported a pyrrolidine ring expansion where reaction of 202 via aziridinium ion 203 gives piperidine 204 after heating (Scheme 42).\(^{[104]}\) Pyrrolidine 200 was prepared from D-ribose 152 via 201.

2.7. Huisgen Azide Alkene Cycloaddition

Organic azides act as 1,3-dipoles\(^{[105]}\) and when reacted with an alkene give a triazole that may decompose via an aziridine, which can undergo further reaction with nucleophiles. If these reactions occur in one pot they are a cascade reaction.\(^{[106]}\) This sequence was initially identified to occur in sorbose derivative 205 (Scheme 43) in our laboratory by Colin O’Brien\(^{[49e]}\) and has stimulated our efforts to apply the reaction more widely since that time. Colin O’Brien attempted to exchange the primary alcohol for an azide in 205 using sulfuryl chloride, to give a cyclic sulfinate and then react this with sodium azide. The expected azide product 206 was not isolated, but instead 209 was isolated in 40% yield. The formation of this product was explained as a result of intramolecular Huisgen 1,3-dipolar cycloaddition, followed by decomposition to an aziridine that went under further reaction with azide nucleophile to give 209.

We recognised the potential for application of this cascade reaction more widely.\(^{[49d]}\) Thus Ying Zhou prepared precursor 211 from D-glucono-\(\delta\)-lactone 210 (Scheme 44), using chemistry developed by Fleet and co-workers.\(^{[107]}\) The cycloaddition from 211 to give triazole 212 was diastereoselective due to the minimisation of allylic strain in the transition state (215 favoured compared to 216) leading to a 1,2-trans arrangement between C-4 and C-5. Decomposition in the presence of nucleophile completed the synthesis of DNJ and derivatives 214.

Work by Sharpless and co-workers\(^{[108]}\) on selective click chemistry based on allylic azide rearrangement\(^{[109]}\) (AAR, Scheme 45), stimulating us to investigate incorporation of this reaction into piperidine synthesis.
Lorna Moynihan’s PhD thesis was concerned with the investigation of AAR\(^\text{[109]}\) (Scheme 46). In tandem with azide-alkene cycloaddition,\(^{[49f]}\) AAR is dynamic and facilitates interconversion of stereoisomeric (R & S) allylic azides, 222 and 223, that can undergo cycloaddition. The heteroannulation led to piperidines with substituents at the anomeric carbon, where 1,2-trans configured products are obtained stereoselectively; this outcome is consistent with higher reactivity for 223 over 222. The preferred formation of the Α-Man mimetic is proposed to be due to minimising steric hindrance in the cycloaddition transition state (Scheme 46). Thus, reaction of 223, prepared from methyl α-d-mannopyranoside ultimately gave 220 in a diastereoselective manner. After protecting group removal, the DMJ derivative 220 was obtained and its NMR data agreed well with that of a natural product. We corrected its structural assignment to 220 from the original assignment of 221\(^\text{[110]}\).

Rekha Chadda, during her PhD thesis work, generated piperidine 227 from 7-azido-hepta-1,5-diene-3,4-diol 224, which was obtained from methyl α-d-mannopyranoside. Allylic azide rearrangement followed by cycloaddition gave 226\(_{a}\), a pyrroolidine fused with a triazoline, the latter decomposing readily to 226\(_{b}\). Ring expansion occurred in the presence of AcOH and subsequent deacetylation under acidic conditions gave the all syn triol containing 227, which is a mimetic of β-d-ribofuranose. The ring expansion and selectivity can also be explained by formation of cation 226\(_{c}\) which may react to give the syn product because reaction from this conformer gives a chair-like transition state, (Scheme 47).\(^{[49g]}\) Reactions of protected 224 and related compounds were also observed to give pyrroolidines.

Methods for synthesis of piperidines with quaternary centres adjacent to ring nitrogen are not very common. The synthesis of aziridinyl iminosugars by Py and coworker\(^{[111]}\) involved nitrone-alkyne cycloaddition.

\(\text{Scheme 44. Synthesis of DNJ 3 via intramolecular Huisgen reaction.}\)

\(\text{Scheme 45. Allylic azide rearrangement (AAR).}\)

\(\text{Scheme 46. Lorna Moynihan’s and Rekha Chadda’s synthesis of substituted DMJ via allylic azide arrangement from 223. Greater steric interactions in cycloaddition transition state from 222 reduces its reactivity and formation of 1,2-trans product 220 from 223 is favoured.}\)

\(\text{Scheme 47. Rekha Chadda’s combination of Huisgen cycloaddition cascade with pyrroolidine ring expansion to give piperidine.}\)
workers reported α-geminal dihydroxymethyl substituted piperidines.\[112\] Fustero, Aceña and co-workers used a carbon trifluoride rearrangement to an iminium ion in a quaternary center forming step and applied the methodology in iminosugar synthesis.\[29a\] Rekha Chadda, during her PhD work, also applied the allylic azide rearrangement reaction of 229, derived from D-mannose to give 231 (diastereoselectivity 9:1 in favour of stereoisomer 232a shown, Scheme 48). The stereoselectivity is accounted by 1,3-diaxial interactions, which disfavour the product with the larger group (i.e. methyl group in 232b) being axial.

2.8. Multicomponent Ugi Reaction

The Ugi reaction is a powerful multicomponent reaction that has many applications in synthesis,\[113\] including within our own laboratory for glyocluster synthesis.\[114\] Saxena et al. reported a three component four centre Ugi reaction from 233 for the preparation of l-allo-DNJ 236.\[115\] In this case, azide reduction is followed by cyclic imine formation, then nucleophilic attack by isocyanide and then carboxylate followed by amide formation giving 234. Subsequent amide hydrolysis and protecting group manipulation gave L-allo-DNJ 236 (Scheme 49).

2.9. Cyclisation by Intramolecular Alkene Addition

Versatile methods have been developed for iminosugar synthesis based on addition to alkenes.\[31a\] Liu et al. reported the mercury ion promoted cyclisation of aminoalkene derivative to the corresponding α-homonojirimycin derivative.\[116\] Ganem and co-workers obtained polyhydroxylated piperidines 241–244 by the attack of nitrogen to a mercury(II) salt activation of alkenes 237–240 respectively.\[117\] However, activation of 237–240 by NIS gave better yields as reported by Martin et al. (Scheme 50).\[118\] Addition to alkenes, activated by mercuration, was later used to give α- and β-homogalactonojirimycin by Martin and coworkers.\[119\]

2.10. Photoinduced Electron Transfer (PET)

Pandey and co-workers reported photoinduced electron transfer for the construction of piperidine based iminosugars.\[120\] The mechanism involves a three-centered radical cation reactive species, which undergoes intramolecular addition to an alkene/alkyne and removal of the TMS cation. In an example the building block 245 was synthesized from D-(−)-
tartaric acid in eight steps.\textsuperscript{121} PET mediated cyclisation led to the formation of 246 which was subsequently converted to isofagomine 22 (Scheme 51).

The PET cyclisation was extended to synthesise bicyclic iminosugar analogues. The key intermediate 247 was synthesised from d-ribose 152; 247 was converted to 248 as a single isomer. The piperidine 248 was converted to 249 by diastereoselective dihydroxylation of the \(\text{exo}\)-methylene group (Scheme 52).\textsuperscript{122}

\subsection{2.11. Transamidification}

De Angelis \textit{et al.} reported asymmetric synthesis of DNJ 3 from the \(\alpha,\beta\)-unsaturated epoxy ester 250,\textsuperscript{123} where preparation of 250 involved asymmetric Sharpless epoxidation and Sharpless dihydroxylation to install the key stereocentres. Reaction of the epoxide 250 with NaN\(_3\) occurred regioselectively to give 251 after addition of TBSOTf. Reduction of the azide to the amine and intramolecular acylation (transamidification) gave lactam 252. Amide reduction and deprotection afforded DNJ 3 (Scheme 53).

\subsection{2.12. Other Method of Piperidine Ring Synthesis}

Piperidines and its derivatives have been synthesized by various methods not discussed in detail here, such as metal catalyzed intramolecular hydroamination of olefins, or inter/intramolecular tin mediated coupling.\textsuperscript{124} Moreover, the Aza-Prins cyclisation or Aza Diels-Alder reaction have been used for the synthesis of piperidine ring previously\textsuperscript{125} and may have potential in iminosugar synthesis.

\section{3. Summary}

Polyhydroxylated piperidines have unique characteristics,\textsuperscript{26a} and have proven successful as drugs.\textsuperscript{126} There has been sustained interest in these and other iminosugars as a class of glycomimetics,\textsuperscript{49b,127} with many strategies being developed, since Paulsen’s first synthesis over 50 years ago. Methods that have proven popular have been inspired by Paulsen’s early reductive amination strategies and include our own group’s reductive cascades from glycosyl azide derivatives. Other cyclisation methods have more recently been employed such as ring closing metathesis. Substitutions, transamidification, addition to alkenes, Ugi multicomponent, azaepine ring contraction, pyrrolidine ring expansion, photoinduced electron transfer mediated cyclisation have all found application. Intermediates required to produce enantiomerically pure iminosugars have been generated from the chiral pool. Sharpless epoxidation\textsuperscript{128} and dihydroxylation,\textsuperscript{129} which emerged in the 1980s have since been used in multiple routes to give both enantiomers. Biotechnological processes involving oxidases, aldolases or cyanohydrin lyase have also contributed. Amongst these various methods the application of cascade reactions based on the Huisgen azide-alkene cycloaddition has been developed in our laboratory. There are still limitations with the latter approach, which would benefit from improving
triazole decomposition to required aziridine intermediate. Efforts to achieve this goal are currently underway as is the further expansion of the cyclisation method to new targets.

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