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Recent Developments in the Synthesis of Pyrrolidine-Containing Iminosugars

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As noted inhibitors of glycosidases, iminosugars have enormous therapeutic potential in the treatment of a number of diseases such as cancer, diabetes, and lysosomal storage disorders. Accordingly, much effort has been expended over the past decades in developing novel and efficient methodologies for the synthesis of iminosugars. This microreview highlights recent (post 2005) developments in the synthesis of pyrrolidine-containing iminosugars and includes discussions of methodologies such as ring-closing metathesis, aldol and pericyclic reactions, and protecting-group free strategies.

1. Introduction

Over the past 40 years, interest in iminosugars has increased as their potential in the treatment of disease is realised. Iminosugars (or azasugars) are structural analogues of traditional carbohydrates where the ring oxygen is replaced by a nitrogen atom. Arguably, the most valuable property of iminosugars is their ability to inhibit glycosidase enzymes. At physiological pH the nitrogen atom of the iminosugar is protonated and it is this charged species that resembles the cationic transition-state formed during glycosidase catalysis. Glycosidases, in turn, play an important role in a number of diseases. Cancerous tumours express unusual carbohydrate structures resulting from abnormalities in the N- and O-glycan biosynthesis, and the inhibition of key enzymes involved in glycosidase reactions, such as Golgi α-mannosidase II (dGMII), has shown potential in cancer treatment.[1] In Gaucher's disease, which results from deficient glucocerebrosidase activity leading to the accumu-

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Anna L. Win-Mason (front centre) completed her bachelor's degree in Chemistry at VUW in 2000, and her BSc (hons) degree (Chemistry) in 2001. In 2008, Anna returned to Victoria University to commence a PhD within the Immunoglycomics group. Anna's research interests are in the development of novel methodology for the synthesis of iminosugar therapeutics.

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lation of glucosylceramide, the use of iminosugar pharmacological chaperones, to assist variant glucocerebrosidase folding, has been shown to aid in the treatment of the disease.[2] Type II diabetes can also be controlled via the administration of glycosidase inhibitors that prevent the breakdown of carbohydrate polysaccharides and thus regulate blood sugar levels.[3] For additional information on iminosugars, including previous syntheses and biological activity, a number of elegant reviews have been published in this area.[4]

1.1. Natural Occurrence of Pyrrolidine-Containing Iminosugars

There are four structural classes of iminosugars containing a five-membered ring – pyrrolidines, pyrrolizidines, indolizidines, and nortropanes. Representative structures of each are given (Figure 1). 2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine (**1**, DMDP) was the first pyrrolidine iminosugar isolated.[5] It was extracted from the leaves of *Derris elliptica* in 1976, however its biological activity was not discovered until several years later.[6] DMDP is best known for its ability to inhibit glucosidase I (a glycoprotein processing enzyme), but is also a moderate antiviral agent and is toxic to insects.[7] Additionally, DMDP can inhibit multidrug resistant efflux pumps, an attractive target for the treatment of cancer.[8] In 1991, 2,5-dideoxy-2,5-imino-D-glucitol [DGDP (**2**)] was synthesised and was shown to have potent α- and β-glucosidase inhibition.[9] Since then, DGDP has been isolated from the Thai traditional medicine "Non tai yak" (*Stemona tuberosa*). Interestingly, in the later studies, DGDP was found to be a weak inhibitor of α- and β-glucosidases (IC_{50} 300 to 1000 μM).[10]

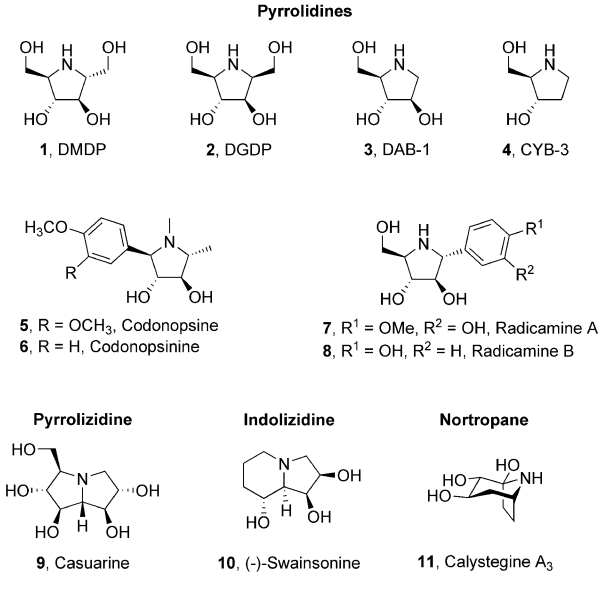


Figure 1. Representative structures of naturally occurring iminosugars.

The first azapentose, 1,4-dideoxy-1,4-imino-D-arabinitol [DAB-1 (**3**)], also know as DAB and ^{d}-AB1, was originally isolated from the fruit of *Angylocalyx boutiqueanus*.[11] DAB-1 is a potent inhibitor of glycogen phosphorylase (the enzyme responsible for the breakdown of glycogen into glucose monomers), and is currently being investigated for the treatment of type II diabetes.[12] The first isolated 1,2-dideoxy iminosugar, 2-hydroxymethyl-3-hydroxypyrrolidine [CYB-3 (**4**)], was extracted from *Castanospermum australe* in 1985.[13] Its biological activity is the least studied of the three primary structures. Other notable pyrrolidines include codonopsine (**5**) and codonopsinine (**6**), first isolated in 1969 from *Codonopsis clematidea*,[14] and the radicamines A (**7**) and B (**8**), recently isolated from *Lobelia chinensis* LOUR.[15] Of the bicyclic pyrrolidine-containing iminosugars, representative examples include the pyrrolizidine casuarine (**9**),[16] and the indolizidine swainsonine (**10**), the first bicyclic alkaloid to be discovered. Due to its ability to competitively inhibit α-mannosidase II, swainsonine is currently being investigated for the treatment of cancer.[17] The nortropanes are the most recently discovered class of pyrrolidine-containing iminosugars and includes members such as calystegine A_3 (**11**), first isolated from the roots of *calystegia sepium* in 1988.[18]

More recently, a number of new pyrrolidine-containing iminosugars have also been isolated. In 2005, Asano et al. extracted Thai medicinal plants and, in combination with several previously identified iminosugars, isolated 3-*O*-β-D-glucopyranosyl-DMDP (**12**) (Figure 2).[11] In 2008, Kato et al. extracted ten iminosugars from the leaves of the African medicinal tree *Baphia nitida* and discovered the novel 1-*O*-β-D-fructofuranoside of DMDP (**13**).[19] Compared to DMDP, the β-D-fructosyl derivative **13** had markedly lower inhibitory activity toward β-galactosidases but enhanced inhibitory potential toward porcine kidney trehalase (IC_{50} = 26 μM) by about 10-fold. The novel pyrrolizidine, 3-*epi*-casuarine (**14**), was also recently isolated from *Myrtus communis* by Fleet and co-workers.[20] 3-*epi*-Casuarine was found to have a different biological profile to that of casuarine – as illustrated by its ability to inhibit almond β-glucosidase to a greater extent than the α-glucosidases tested.

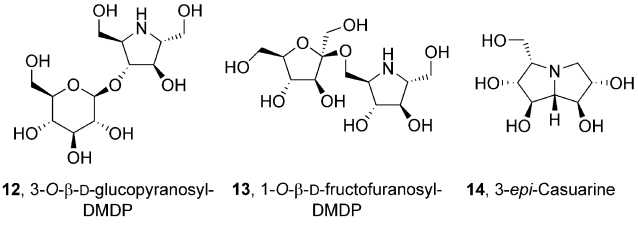


Figure 2. Pyrrolidine-containing iminosugars isolated post 2005.

Of particular note during the last few years has been the role of chemical synthesis to resolve the absolute stereochemistry of several iminosugars. Since their isolation in 1969,[14] the stereochemistry of codonopsine and codonopsinine has been in question. To resolve these issues, the methyl iodide of codonopsine was prepared and the X-ray

crystal structure solved.[21] This work confirmed the previous chemical formulas for codonopsine (**5**) and codonopsinine (**6**), however the stereochemistry was corrected to that of the structures shown (Figure 1). The absolute stereochemistry of the pyrrolidines, radicamine A (**7**) and B (**8**), was also recently determined via a series of elegant syntheses[22–24] and the absolute stereo-chemistries of the isolated natural products reassigned to those shown (Figure 1). In 2008, Pyne and co-workers unequivocally proved that uniflorine B, once thought to be an indolizidine, was in fact the known pyrrolizidine alkaloid casuarine (**9**), and proposed that uniflorine A was in fact 6-*epi*-casuarine.[25]

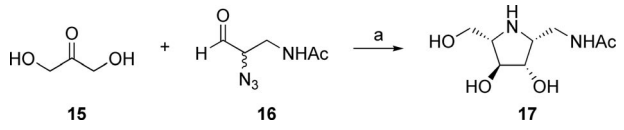
1.2. Syntheses of Pyrrolidine-Containing Iminosugars

Given the enormous therapeutic potential of iminosugars, the development of improved synthetic methodologies for their synthesis has become the objective of many synthetic chemists. This review highlights recent developments (post 2005) in the synthesis of pyrrolidine-containing iminosugars. Synthetic methodologies are classified according to key steps.

2. Addition/Condensation Reactions

2.1. Aldol Reactions

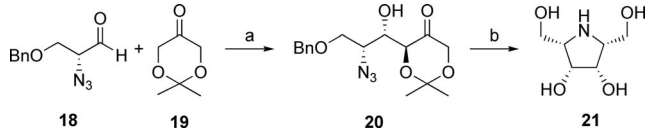
In recent years, the use of enzymatically catalysed aldol reactions has enabled a variety of pyrrolidine iminosugars to be prepared in remarkably few steps. In studies by Wong and co-workers,[26] it was found that L-rhamnulose-1-phosphate aldolase (RhaD) accepts dihydroxyacetone (DHA) as a donor in a borate buffer (presumably by reversible formation of the DHA borate ester in situ), thus enabling the remarkable one-pot synthesis of iminosugars. For example, DHA (**15**) was treated with the azido aldehyde acceptor **16** in the presence of RhaD and an inorganic borate buffer to produce the corresponding azido ketone aldol product which underwent subsequent diastereoselective reductive cyclisation to give the L-iminoglucitol **17** exclusively (Scheme 1). Here, RhaD reacted selectively with the D-azido aldehyde. Wong and co-workers also explored the use of the unnatural DHA related donors hydroxyacetone (HA) and 1-hydroxy-2-butanone (HB) in the borate buffer aldolase reaction with fructose-6-phosphate aldolase (FSA).[26b] To their surprise, DHA, HA, and HB all had catalytic efficiencies within the same order of magnitude. This non-specificity with respect to the donor is unprecedented for an aldolase and suggests that FSA could have a wide scope as a biocatalyst.



Scheme 1. Reagents and conditions: a) *i*. RhaD, sodium borate; *ii*. Pd/C, H_2, MeOH (9%, 2 steps).

In contemporary work, Clapés and co-workers[27] used L-fuculose-1-phosphate aldolase (FucA) to catalyse the aldol addition between dihydroxyacetone phosphate (DHAP) and various *N*-Cbz-protected amino aldehydes.[27a] The reaction was attempted in emulsions [e.g. $H_2O/C_{14}H_{29}(OCH_2CH_2)_4OH$/tetradecane] and DMF/water (1:4) systems, with the use of the emulsion system leading to a two- to threefold improvement in the molar percent conversion of DHAP to the aldol adduct. The *N*-protected amino alcohols thus obtained were converted to iminosugars by deprotection and reductive amination/cyclisation with H_2 on Pd/C. In addition, enzymatic methodology was developed by Clapés and co-workers *en route* to a series of novel pyrrolizidines from the hyacinthacine A family using an L-rhamnulose-1-phosphate aldolase (RhuA) catalysed condensation of DHAP with both (*S*)- and (*R*)-*N*-Cbz-prolinal.[27b] More recently, the same group used a D-fructose-6-phosphate aldolase (FSA) for the synthesis of DAB-1 (**3**) and 5-deoxy-DAB-1.[27c]

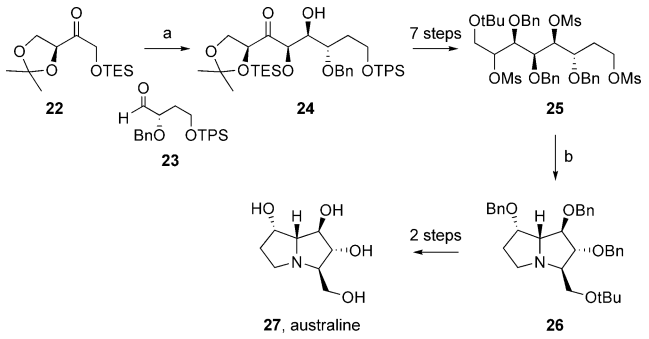
In addition to the aldolases, proline has been widely used as a catalyst for the enantioselective synthesis of polyhydroxylated iminosugars. An interesting application of this catalyst was recently reported by Doyagüez et al. whereby (*S*)-proline was immobilised on mesoporous silicate in order to investigate the use of non-polar solvents in proline-catalysed aldol additions.[28] Use of this solid supported proline catalyst in the aldol reaction between azido aldehyde **18** and 2,2-dimethyl-1,3-dioxan-5-one (**19**) resulted in *anti*-selective aldol product **20** in both formamide and wet toluene (Scheme 2). Subsequent one-pot reduction/cyclisation of azide **20** led to the formation of pyrrolidine **21**. In the same year, Sudalai and co-workers reported a highly efficient L-proline-catalysed tandem α-amination-Horner–Wadsworth–Emmons olefination on a variety of aldehydes to yield γ-amino-α,β-unsaturated esters that were subsequently cyclised to their corresponding 2-pyrrolidinones.[29]



Scheme 2. Reagents and conditions: a) (*S*)-Proline on mesoporous support, 24–72 h, 57%, 3:1 (4*R*,3*S*)/(4*S*,3*S*); b) H_2, Pd/C.

In 2007, Ribes et al. implemented a highly convergent, 11-step, procedure for the synthesis of the pyrrolizidine australine. The eight-carbon framework was formed by the stereoselective aldol reaction between two four-carbon fragments (Scheme 3).[30] Here, aldol condensation of the *Z* boron enolate of L-erythruloside **22** with L-malic acid derived aldehyde **23** provided the polyoxygenated ketone **24** with excellent stereoselectivity. Reduction of the ketone and protecting group manipulations, then gave trimesylate **25**, the key precursor for the formation of the pyrrolizidine skeleton. Reaction of trimesylate **25** with benzylamine and NaI in DMSO led to S_N2 substitution of the primary mesylate by benzylamine followed by two subsequent intramolecular

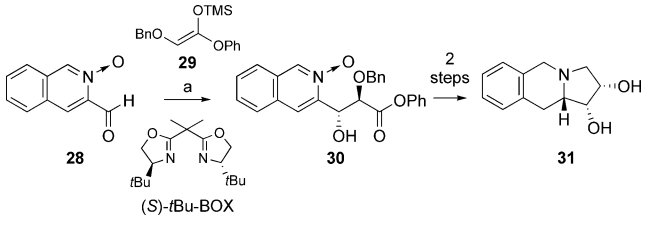
S_N2 substitutions of the remaining two mesylates. The resulting pyrrolizidine **26** was then fully deprotected to give the natural compound australine (**27**) in a total of 11 steps and 10% overall yield.



Scheme 3. Reagents and conditions: a) *i*. Chx_2BCl, Et_3N, Et_2O; *ii*. **23**, 72% (2 steps); b) $BnNH_2$, NaI, DMSO, 60%.

Further elegant work involving the use of aldol chemistry in the formation of pyrrolizidines was reported in 2006 when Hoye et al. used a silylative Dieckmann-like cyclisation to create the pyrrolizidine core of the telomerase inhibitor UCS1025A.[31] Chandrasekhar et al.[32] used a Julia olefination reaction between a four-carbon L-xylose-derived aldehyde containing a formyl group and a benzothiazolylsulfone to introduce the *para*-methyoxy phenyl group present in (–)-codonopsinine. Remarkably, the formyl group was unaffected.

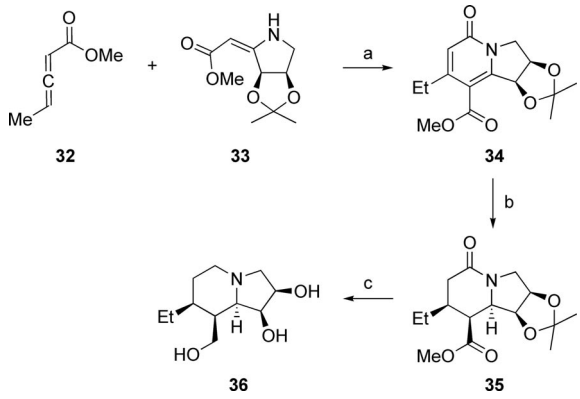
An application of a Mukaiyama aldol reaction in the synthesis of iminosugars has also been recently reported. Landa et al. investigated the stereoselectivity of the Mukaiyama aldol reaction between a variety of pyridine-2-carbaldehydes and silyl enol ethers en route to the preparation of indolizidine derivatives (Scheme 4).[33] Here, it was found that oxidation of the pyridine nitrogen to the corresponding oxypyridine allowed for bidentate co-ordination to a chiral catalyst [copper triflate with (*S*)-*t*Bu-BOX as chiral ligand], resulting in good *anti* diastereoselectivity and excellent enantioselectivity. The best result was achieved using isoquinoline-2-carbaldehyde *N*-oxide (**28**) with phenyl (benzyloxy)acetate-derived trimethylsilyl enolate **29** to give the *anti* aldol product **30** in high yield and with outstanding enantioselectivity. The *anti* aldol product **30** was easily separated and was subsequently converted into indolizidine derivative **31** in 2 steps.



Scheme 4. Reagents and conditions: a) 10 mol-% $[Cu(OTf)_2(S)$-*t*Bu-BOX], CH_2Cl_2, –40 °C, 91% (12:1 *anti*/*syn*, *anti* 99% *ee*).

2.2. Michael Addition

In the development of a versatile strategy for the synthesis of various polyhydroxylated indolizidines, Cheng and co-workers employed a diastereoselective Michael addition as a key step (Scheme 5).[34] Initial attempts to form the indolizidine core involved Michael addition and subsequent intramolecular cyclisation between the D-erythronic acid γ-lactone derived enaminoester **33**, and various *trans*-substituted α,β-unsaturated methyl esters, however this resulted in diastereomeric mixtures with poor selectivity.[34a] To circumvent this, methyl allenoate (**32**) was treated with enaminoester **33** to produce pyridinone **34** in good yield and diastereoselectivity. Pyridinone **34** was stereoselectively hydrogenated to give the indolizidinone **35** that was then reduced, providing indolizidine **36**. The versatility of this strategy was illustrated by the use of different electrophiles, including dimethyl acetylenedicarboxylate and malonyl dichloride to give indolizidines with different substitution patterns.

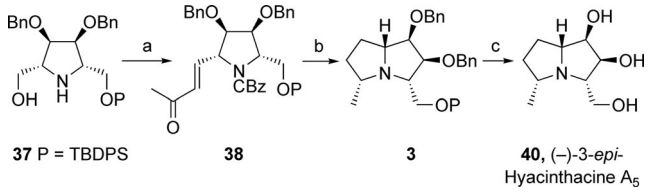


Scheme 5. Reagents and conditions: a) NaH, THF, –5 to 0 °C, 1 h, 87%; b) H_2, Pd/C, 10–15 atm, 88%; c) *i*. BH_3, THF; *ii*. 6 M HCl, 82% (2 steps).

2.3. Wittig

Wittig and Horner–Wadsworth–Emmons (HWE) reactions have been used by several groups to synthesise a number of iminosugars. In particular, this methodology is a versatile means by which to synthesise a variety of pyrrolizidine and indolizidine iminosugars where, in general, the olefination reaction is used to extend a suitably protected pyrrolidine with an alkyl chain that is subsequently used for the generation of a second ring. Notably, Izquierdo and coworkers have used this methodology to create a number of pyrrolizidines from the hyacinthacine A and casuarine families whereby D-fructose was used as the starting material.[35] For example, in the synthesis of (–)-3-*epi*-hyacinthacine A_5 (**40**), pyrrolidine **37** was Cbz-protected, oxidised, and subjected to a Wittig olefination with 1-(triphenylphosphoranylidene)-2-propanone to give the α,β-unsaturated ketone **38** (Scheme 6).[35c] Ketone **38** was then hydrogenated, which resulted in the one-pot reduction of the double bond, *N*-deprotection and in situ cyclisation to give the protected pyrrolizidine **39**. Global deprotection then

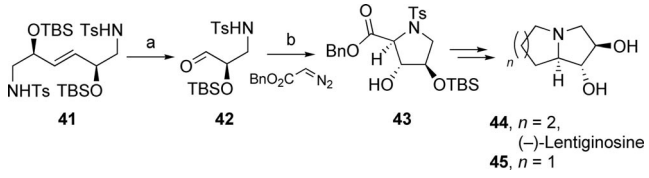
gave (–)-3-*epi*-hyacinthacine A_5 (**40**). Cao et al.[36] and Chaudhari et al.[37]also used similar methodology in the synthesis of the hyacinthacine A and lentiginosine alkaloids, respectively. Here both groups used D-glucose as the starting material.



Scheme 6. Reagents and conditions: a) *i*. CbzCl, K_2CO_3, acetone; *ii*. TPAP, NMO, CH_2Cl_2; *iii*. $Ph_3P{=}CHCOCH_3$, toluene, 40% (3 steps); b) H_2, Pd/C, MeOH, 52%; c) *i*. H_2, Pd/C, HCl, MeOH, then Amberlite IRA-400 (OH^- form); *ii*. TBAF·$3H_2O$, THF, 93% (2 steps).

2.4. Miscellaneous Condensations

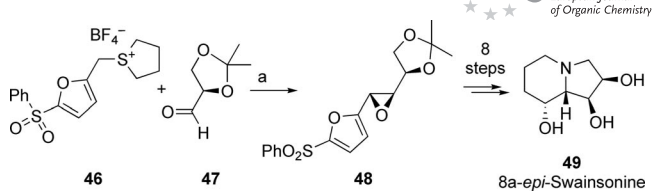
Several other types of condensation reactions have been employed in the construction of iminosugars. For example, Angle et al.[38] reported the use of a diazoacetate for the synthesis of a proline intermediate that proved useful in the synthesis of bicyclic iminosugars (Scheme 7). By making use of the C_2 symmetry of D-mannitol-derived diamide **41**, two molecules of the protected α-hydroxy aldehyde **42** were formed following the ozonolysis of alkene **41**. Enantiopure aldehyde **42** was then reacted with benzyl diazoacetate to produce proline **43** with a *trans*-*trans* relative configuration. This key intermediate was then transformed into (–)-lentiginosine (**44**) and its pyrrolizidine analogue (**45**).



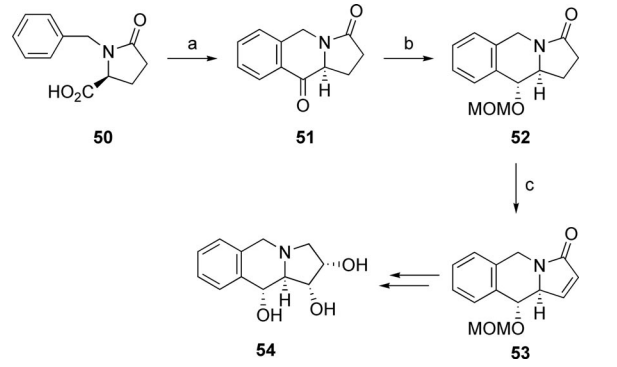
Scheme 7. Reagents and conditions: a) O_3, CH_2Cl_2, –78 °C then thiourea, 0 °C, 3 h, 81%; b) BnO_2CCHN_2, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C, 9 h, 65%.

In another interesting condensation reaction en route to the synthesis of 8a-*epi*-swainsonine, Bi and Aggarwal reacted the furyl-stabilised sulfur ylide of **46** with glyceraldehyde **47** to give a mixture of epoxides (Scheme 8).[39] The major product **48** (formed in a 86:11:6 ratio with two minor isomers) was then transformed into 8a-*epi*-swainsonine (**49**) with minimal use of protecting groups and an aza-Achmatowicz reaction to convert the furan into the required piperidine ring.

In 2005, Kadlečíková et al. produced a series of benzindolizidines with the phenyl ring fused at C-6 and C-7 of the indolizidine through the use of a Friedel–Crafts cyclisation (Scheme 9).[40] Here, reaction of L-glutamic acid derived pyrrolidine **50** with thionyl chloride and in situ Friedel–Crafts cyclisation using $AlCl_3$ provided benzindolizidinone **51** stereoselectively and in 78% yield. Stereoselective reduction of the ketone in **51**, followed by MOM-protection of the resulting hydroxy group gave amide **52**, which was subjected to a selenoxide-elimination to provide α,β-unsaturated amide **53**. Amide **53** could in turn be transformed into a wide range of indolizidines (e.g. **54**) through hydroxylation reactions.



Scheme 8. Reagents and conditions: a) **46**, KHMDS, –78 °C, then **47**, 72%.



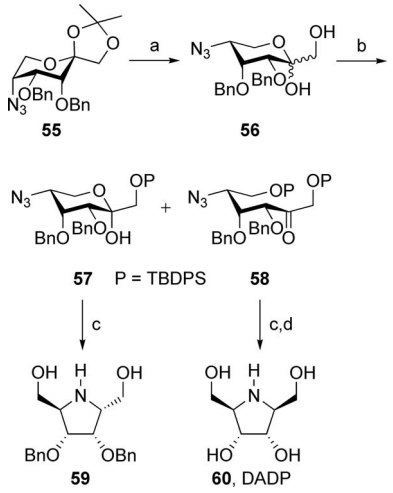
Scheme 9. Reagents and conditions: a) $SOCl_2$, CH_2Cl_2, 40 °C, 5 h, then $AlCl_3$, 0 °C, 1 h, then room temp., 2 h, 78%; b) *i*. $NaBH_4$, MeOH, 0–5 °C, 2 h, 81%; *ii*. MOMCl, THF, room temp., 1 h, 75%; c) *i*. LiHMDS, THF, –78 °C, 30 min, PhSeBr, –80 °C, 45 min, 66%; *ii*. H_2O_2, EtOAc, 0 °C, 30 min, then $NaHCO_3$, 85%.

3. Amination Methodologies

3.1. Reductive Amination

Reductive amination continues to be a popular method for the synthesis of a variety of polyhydroxylated pyrrolidines. Izquierdo et al. synthesised 2,5-dideoxy-2,5-imino-D-allitol [DADP (**60**)] and the protected 2,5-dideoxy-2,5-imino-D-altritol (DALDP) derivative **59**, using a one-pot reductive amination/cyclisation of 5-azido-5-deoxy-D-psicose derivatives (Scheme 10).[41a] In this work, removal of the isopropylidene group of D-fructose-derived D-psicoside **55** under acidic conditions provided diol **56** and subsequent protection of the primary hydroxy with *tert*-butyldiphenylsilyl (TBDPS) chloride then gave **57** (70% yield) as well as a discernible amount (26%) of the unexpected bis-TBDPS derivative **58**. Hydrogenation of **57** with concomitant intramolecular reductive amination of the intermediate amine afforded the corresponding pyrrolidine **59** in good yield and stereoselectivity. Applying the same protocol to bis-silane **58** gave, after removal of the benzyl protecting groups, pyrrolidine **60** with the inverse stereochemistry at the newly formed stereogenic centre. This stereoselectivity could be

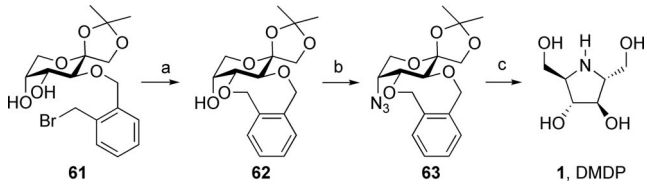
explained by the presence or absence of the bulky TBDPS group on O-6 shielding one face of the imine intermediate during the hydrogenation reaction. Izquierdo et al. also used similar methodology to synthesise 2,5-dideoxy-2,5-imino-D-galactitol (DGADP), however here the configuration at C-4 played an important role in determining the stereoselectivity during the reduction of the intermediate cyclic imine.[41b]



Scheme 10. Reagents and conditions: a) 60% TFA (aq.), room temp., 2 h, 85%; b) TBDPSCl, imidazole, DMF, room temp., 20 h, **57**:70%, **58**:26%; c) *i*. Raney-Ni, H_2, 60 psi MeOH/THF, 5–20 h; *ii*. nBu_4NF, H_2O/THF, 1–2 h, **59**:47% (2 steps); d) 10% Pd/C, H_2, MeOH, HCl, 1 d, **60**:28% (3 steps).

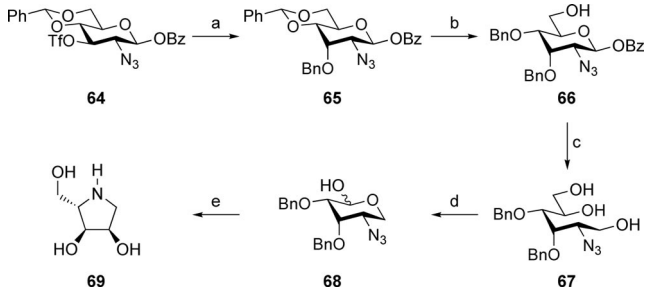
Improved syntheses of the natural polyhydroxylated pyrrolidines 2,5-dideoxy-2,5-imino-D-mannitol [DMDP (**1**)] and 2,5-dideoxy-2,5-imino-D-glucitol [DGDP (**2**)] were recently developed by Fernández and co-workers.[42] An effective intramolecular benzyl protection/delivery system was employed (Scheme 11) using the D-fructose-derived 3-*O*-(2-bromomethyl)benzyl ether **61** to form the alcohol **62** that possessed a fused eight-membered ring *o*-xylylene tether between the C-3 and C-4 hydroxy groups. The 5-hydroxy was then available for the ensuing azide substitution reaction with either retention or inversion of stereochemistry. Conversion of alcohol **62** into the iodide and subsequent treatment with sodium azide gave azide **63** with net retention of stereochemistry. Acidic conditions removed the acid labile protecting groups in **63** and catalytic hydrogenation effected a one-pot reductive amination-cyclisation to yield DMDP (**1**) in 93% yield. Conversely, elaboration of the 5-isomer of **63** (formed via azide substitution of the triflate of **62**) led to the isolation of DGDP (**2**, Figure 1). Other polyhydroxylated pyrrolidines have also recently been formed using reductive amination methodology.

In 2006, Hung and co-workers used reductive amination as the key step in the formation of the rare L-sugar 1,4-dideoxy-1,4-imino-L-ribitol.[43] In their synthesis, triflate **64**, accessible from glucosamine in four steps, was substituted with sodium nitrite, to affect the desired inversion at C-3,



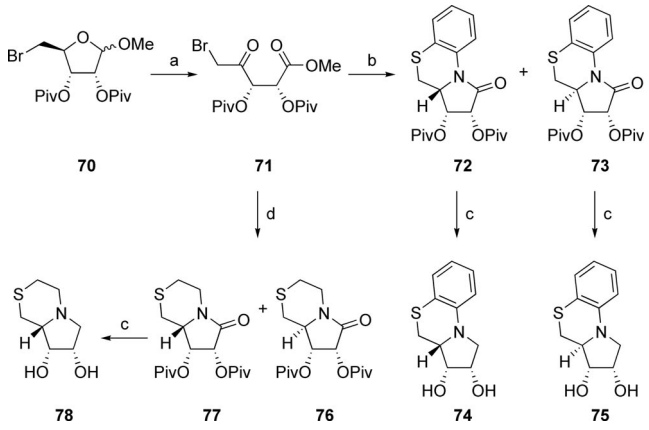
Scheme 11. Reagents and conditions: a) NaH, DMF, room temp., 15 min, 93%; b) *i*. I_2, PPh_3, imidazole, toluene, 80 °C, 16 h, 98%; *ii*. NaN_3, DMF, 80 °C, 12 h, 91%; c) *i*. TFA/H_2O (9:1), room temp., 30 min, 98%; *ii*. H_2, Pd/C, HCl, MeOH/H_2O (2:1), 4 bar, 24 h, 95%.

then benzylated to yield **65**. Next, reductive cleavage of the benzaldehyde acetal using borane yielded alcohol **66**, which was anomerically deprotected and reduced using sodium borohydride, to give triol **67**. Subsequent periodate cleavage of the 1,2-diol in **67** gave the protected azido-L-ribose **68**. Finally, the one-pot debenzylation\reductive amination/cyclisation led to the formation of iminoribose **69** in excellent yield (Scheme 12). In later work, Aravind et al. employed reductive amination of a cyclic hemiaminal using $BF_3{\cdot}Et_2O/Et_3SiH$ as the reducing agent en route to the synthesis of the glycosidase inhibitor 1,4-dideoxy-1,4-imino-L-xylitol.[44]



Scheme 12. Reagents and conditions: a) *i*. $NaNO_2$, 15-crown-5, HMPA, 74%; *ii*. Ag_2O, BnBr, 81%; b) $VO(OTf)_2$, $BH_3{\cdot}THF$, 0 °C, 20 h, 90%; c) $NaBH_4$, MeOH, 75%; d) $NaIO_4$, MeOH, 94%; e) H_2, Pd/C, 91%.

Reductive amination has also been used as a key step during the formation of thiazines designed to present favourable transition-state mimics for the inhibition of ribosidases (Scheme 13).[45] Here Hollingsworth and Gao subjected methyl bromo-riboside **70**, itself prepared in three steps from D-ribose, to a solution of chromium oxide in acetic anhydride and acetic acid to give ulosonic acid **71** in excellent yield. The one-pot treatment of **71** with aminothiophenol followed by sodium cyanoborohydride then sodium carbonate produced the L-*lyxo* **72** and D-*ribo* **73** isomers in 57% and 10% yields, respectively. Subsequent reduction of the lactams **72** and **73** with diborane and deprotection furnished tricyclic thiazines **74** and **75** in excellent yields. The bicyclic L-*lyxo* derivative **78** was produced in an analogous manner via use of aminoethanethiol instead of 2-aminothiophenol to give the intermediate lactams **76** and **77**.

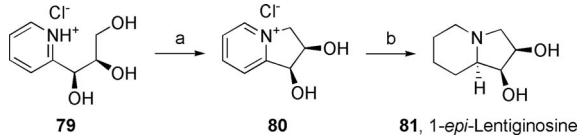


Scheme 13. Reagents and conditions: a) CrO_3, Ac_2O, AcOH, room temp., 2 h, 97%; b) *i.* 2-aminothiophenol, MeOH, room temp., 1 h; *ii.* $NaCNBH_3$, MeOH, room temp., 18 h; *iii.* Na_2CO_3, CH_2Cl_2, room temp., 18 h, 67% (3 steps); c) *i.* BH_3·THF; *ii.* NaOMe, MeOH, **74**:91%, **75**:87%, **78**:85% (2 steps); d) *i.* $HS(CH_2)_2NH_2$, MeOH; *ii.* $NaCNBH_3$, TFA, 57% (2 steps).

In addition to polyhydroxylated pyrrolidines and thiazines, reductive amination has played a key role in the synthesis of azanucleotide analogues. Recently, Rosenburg and co-workers developed strategies for the synthesis of *trans*-3,4-dihydroxypyrrolidines and the related 3-hydroxy-4-pyrrolidinyl derivatives of nucleobases.[46] The key steps of this work involved refluxing the monobenzylammonium salt of tartaric acid under Dean–Stark conditions to furnish benzyl-imides that, after treatment with diborane, gave *N*-benzylpyrrolidinediols.

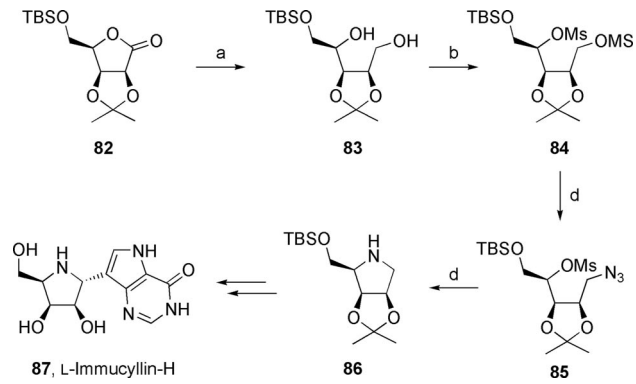
3.2. Substitution Reactions

Nucleophilic substitution reactions involving the displacement of good leaving groups by primary and secondary amines continues to be a method of choice for the formation of iminosugars. For example, Kumar and Ramesh applied a Mitsunobu cyclisation reaction for the formation of imino-hexitols from tri-*O*-benzyl-D-glucal,[47] while Azzouz et al. used a unique Mitsunobu strategy in the synthesis of 1-*epi*-lentiginosine and structural isomers thereof (Scheme 14).[48] The key step in the work by Azzouz et al. was the quaternization of the fully unprotected pyridinium-polyol **79** using original Mitsunobu methodology. The reduction of the bicyclic pyridinium salt **80** then led to the formation of 1-*epi*-lentiginosine **81** in high stereoselectivity and yield.



Scheme 14. Reagents and conditions: a) PPh_3, DIAD, 92%; b) *i.* H_2, PtO_2·H_2O, 93%, 95% *de*; *ii.* KOH, 95%.

Of the nucleophilic substitution reactions used in iminosugar synthesis, the introduction and subsequent displacement of a mesyl group by an amine remains a popular methodology. During the synthesis of the pyrrolidine antibiotic (+)-anisomycin, Rao and co-workers used an intramolecular displacement of a mesylate with a Cbz protected amine.[49] Eustache and co-workers also relied on the introduction of a mesylate and subsequent intramolecular displacement by a protected amine during the synthesis of an arabinofuranosyltransferase inhibitor,[50] while, en route to the synthesis of aminopyrrolidinediols, Robina and co-workers[51] introduced a mesylate group then an azide whose subsequent reduction led to intramolecular cyclisation. Similar azide/reduction methodology was used by Clinch et al. when preparing the enantiomer of the azanucleoside immucillin H.[52] Here, protected lyxonolactone **82** was reduced to diol **83**, di-mesylated to provide **84**, then mono-substituted (→**85**). Subsequent hydrogenation of azide **85** and cyclisation gave iminolyxose **86**. Elaboration of **86**, including NCS mediated oxidation and alkylation of the intermediate cyclic imine, then gave access to L-immucyllin-H (**87**) (Scheme 15).

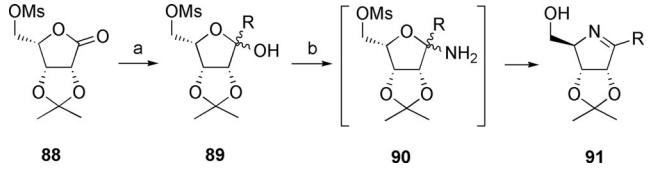


Scheme 15. Reagents and conditions: a) $LiBH_4$, THF, –30 to 20 °C, 24 h, 75%; b) $(MeSO_2)_2O$, pyr, 0 to 20 °C, 18 h, 88%; c) NaN_3, DMF, 100 °C, 2 h, 42%; d) H_2, Pd black, NaOAc, 1,4-dioxane, 20 °C, 72 h, 94%.

Mesylate displacement was also used by Behr and co-workers during the syntheses of polyhydroxylated pyrrolidine derivatives, which were developed as potential chitin synthase inhibitors.[53] Behr recently synthesised a pyrrolidine with strong inhibition against α-L-fucosidase (IC_{50} = 0.65 μm) via the introduction of a nitrile moiety that, following alkylation with a Grignard reagent, yielded an imine that subsequently displaced an internal mesylate.[54]

In an interesting application of mesylate displacement, Moriarty et al. recently reported a facile synthesis of five-membered ring iminosugars from pentonolactones[55] (Scheme 16). Here, alkylation of lactone **88** with Grignard reagents (e.g. MeMgBr, *n*BuMgBr, *n*-$C_9H_{19}MgBr$) produced keto sugars **89**, which were subsequently reacted with ammonia to yield the *endo*-imine **91** following rearrangement of the initially formed *exo*-amine **90**. Imine products

91 could also be readily hydrogenated to provide the saturated pyrrolidine products – some of which showed potent antiviral activity.

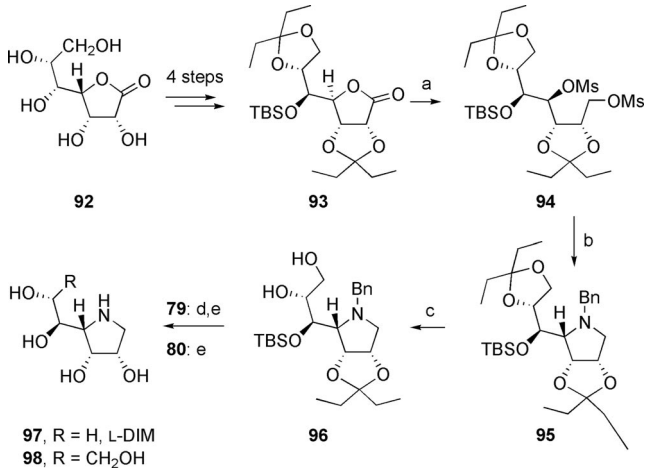


Scheme 16. Reagents and conditions: a) RMgBr, –77 to 0 °C, 95–97%; b) NH_3, EtOH, H_2O, room temp., 30–36%. (R = Me, *n*Bu or *n*-C_9H_{19}).

A double displacement substitution strategy, whereby an activated hydroxy group is displaced using a primary amine that subsequently partakes in a second, intramolecular, substitution reaction, is another versatile means by which to synthesise iminosugars. Indeed, the naturally occurring 3,4-dihydroxyprolines, valuable intermediates in peptide synthesis, were recently synthesised by Taylor et al. using double displacement chemistry,[56] and Behr and Guillerm employed similar methodology in a short practical synthesis of the glycosidase inhibitors 2,5-dideoxy-2,5-imino-D-mannitol (DMDP) and HomoDMDP.[57] Pinto and co-workers also used bis-mesylation/double displacement methodology to synthesise analogues of the naturally occurring glycosidase inhibitor salacinol containing different ring heteroatom substituents and acyclic chain extensions.[58] Vankar et al. synthesised (+)-lentiginosine and (+)-swainsonine from D-glucose using double nucleophilic displacement of mesylates.[59]

In 2007, Fleet and co-workers described the first synthesis of 1,4-dideoxy-1,4-imino-L-mannitol [L-DIM (**97**)] and 1,4-imino-D-*glycero*-L-*talo*-heptitol **98** using a bis-mesylation double nucleophilic displacement strategy (Scheme 17).[60] Here, lactone **93**, itself synthesised in four steps from heptonic acid γ-lactone **92**, was reduced with $LiBH_4$ to produce a diol that was subsequently bis-mesylated to yield dimesylate **94** in 96% yield. Treatment of **94** with neat benzylamine at elevated temperatures then gave pyrrolidine **95**. Selective deprotection of the 6,7-diethylketal in acidic media then led to diol **96** which, following periodate treatment, reduction and deprotection, was transformed into L-DIM **97**. Alternatively, diol **96** was deprotected to produce imino-heptitol **98**. In earlier work, Fleet and co-workers used a step-wise nucleophilic substitution cyclisation sequence whilst synthesising 3-*epi*-casuarine and casuarine from D-gulonolactone.[20]

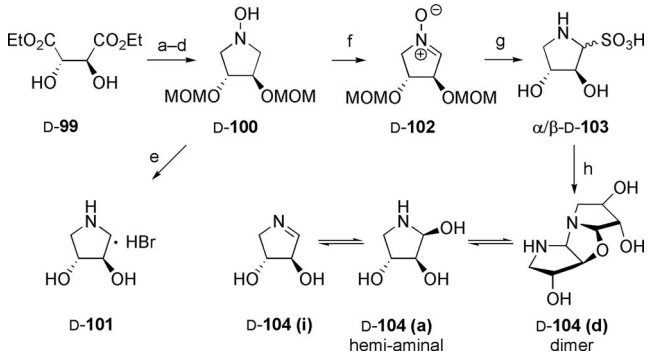
A bis-mesylation/double displacement strategy was also key in the synthesis of a variety of pyrrolidines used to further understand the relationship between glycosidase activity and functional group conformation (Scheme 18).[61] Here, the synthesis of the D-series commenced with the transformation of (*S*,*S*)-D-tartrate (D-**99**) into the (*R*,*R*)-*N*-hydroxypyrrolidine D-**100** via MOM-protection, ester hydrolysis, bis-mesylation of the resulting diol, and the subsequent addition of hydroxylamine leading to in situ double substitution/cyclisation. Hydrogenation and deprotection of



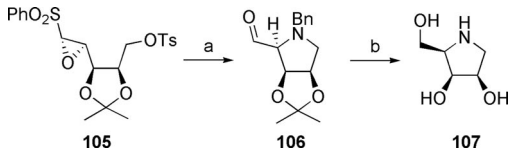
Scheme 17. Reagents and conditions: a) *i*. $LiBH_4$, THF, 85%; *ii*. MsCl, DMAP, pyr., 96%; b) $BnNH_2$, 120 °C, 89%; c) 80% AcOH (aq.), 80 °C, 57%; d) $NaIO_4$, MeOH/H_2O, then $NaBH_4$, 81%; e) *i*. 90% TFA (aq.), reflux; *ii*. H_2, $Pd(OH)_2$/C, dioxane/H_2O, **97**:97%, **98**:68%.

hydroxypyrrolidine D-**100** led to the isolation of diol D-**101**. Alternatively, pyrrolidine **100** was oxidised with HgO to give nitrone D-**102**, which was subsequently treated with aqueous sulfur dioxide to yield the crystalline sulfite adducts D-**103** (obtained as a 3:1 mixture of both the α- and β-anomers). Recrystallisation in water/ethanol did not change the anomer proportions suggesting that, in solution, the isomers are in equilibrium with imino-sugars D-**104**. Reaction of the anomeric mixture of α/β-D-**103** with barium hydroxide then afforded imino-sugar D-**104** as a mixture of dimer (**d**), imine (**i**), alcohol (**a**), and an unknown compound in a ratio of 50:30:8:12, respectively. The synthesis of the L-series was also conducted according to the same reaction sequence and the inhibitory data of all D- and L-pyrrolidines (e.g. **101**, **103** and **104** for the D-series) were then established against a variety of glycosidases and their activities contrasted to the relative inhibitory properties of other 5- and six-membered iminosugars. Of note was that the simple imino-threose D-**104** (2 μM K_i, α-glucosidase) appeared to be more active than nojirimycin (6.3 μM K_i, α-glucosidase). Using this and other examples, the relative influence of each hydroxy group, methyl group, or anomeric centre to the different glycosidase binding profiles was analysed. that the simple imino-threose D-**104** (2 μM K_i, α-glucosidase) appeared to be more active than nojirimycin (6.3 μM K_i, α-glucosidase). Using this and other examples, the relative influence of each hydroxy group, methyl group, or anomeric centre to the different glycosidase binding profiles was analysed.

Díez et al. used an epoxy-sulfone in the synthesis of pyrrolidine **107**. By treatment of the bis-electrophile **105** with benzylamine, and hydrolysis of the initially formed imine on silica, gave aldehyde **106** in good yield (79%). Subsequent reduction and deprotection gave the triol **107** (Scheme 19).[62] During the synthesis of (–)-codonopsinine, Rao and co-workers also used the opening of an epoxide with a Boc-protected amine as a key step.[49]



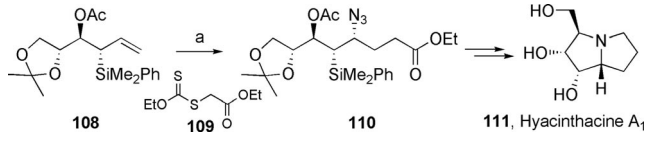
Scheme 18. Reagents and conditions: a) $(MeO)_2CH_2$, P_2O_5, CH_2Cl_2, room temp., 2–4 h; b) $LiAlH_4$, Et_2O, 0 °C to room temp., 1–2 h, 78% (2 steps); c) MsCl, NEt_3, CH_2Cl_2, 0 °C, 30 min; d) $NH_2OH{\cdot}HCl$, NEt_3, reflux, 1.5 h, 82% (2 steps); e) H_2, Ra-Ni, H_2O, then HBr, 60%; f) HgO, CH_2Cl_2, room temp., 30 min, 95%; g) SO_2/H_2O, 45%; h) $Ba(OH)_2$, D_2O, 2 h.



Scheme 19. Reagents and conditions: a) *i.* $BnNH_2$, MeOH, reflux; *ii.* Silica gel, 79% (2 steps); b) *i.* $NaBH_4$, MeOH, 90%; *ii.* H_2, Pd/C, MeOH; *iii.* HCl 6 M, 68% (2 steps).

3.3 Radical Reactions

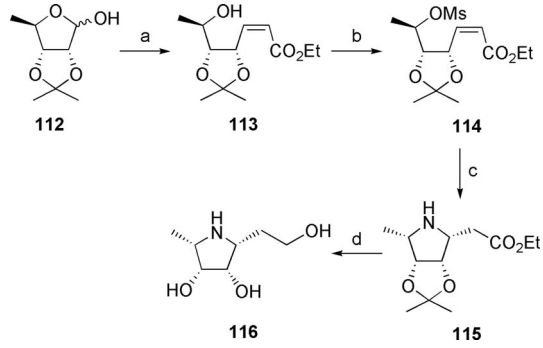
Though less common than other amination strategies, radical reactions have nonetheless been elegantly used during the synthesis of several bicyclic iminosugars, as recently reported by Chabaud et al.[63] and Chen and Tsai.[64] In Chabaud's synthesis of hyacinthacine A_1 (**111**) and its 3-epimer, the stereocontrolled carboazidation of chiral allylsilane **108** with xanthate **109** provided the required carbon-framework **110** (Scheme 20). C–Si bond oxidation and reduction of the azide, with ring-closure, completed the total synthesis and established the absolute configuration of hyacinthacine A_1 (**111**).[62] In the work by Chen and Tsai,[63] a radical cyclisation of acylsilanes was used during the synthesis of lentiginosine and related indolizidine alkaloids.



Scheme 20. Reagents and conditions: a) $(Bu_3Sn)_2$, $PyrSO_2N_3$, 60 °C, 84% (*dr* = 85:15, *syn*/*anti*).

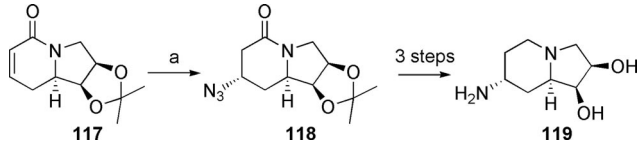
3.4 Conjugate Addition Reactions

Conjugate additions are a convenient means to introduce nitrogen, either for subsequent incorporation in the pyrrolidine ring or as a substituent on the alkaloid framework. Recently, Moreno-Clavijo et al. used a 1,4-addition reaction as the key step in the synthesis of a series of aza-*C*-glycosides (Scheme 21).[65] Here 5-deoxy-D-ribose derivative **112** was subjected to a Wittig olefination to yield the readily separable *Z* and *E* isomers of α,β-unsaturated ester **113** in a 5.2:1 ratio. Reaction of the major isomer *Z*-**113** with mesyl chloride and subsequent treatment of the mesylate **114** with ammonia in MeOH then afforded the pyrrolidine **115** via a tandem conjugate addition/S_N2 cyclisation. Manipulations of ester **115** provided hydroxyethyl-pyrrolidine **116** and also benzimidazolyl, biphenyl, and naphthalene-1-aminoethyl-pyrrolidine analogues.



Scheme 21. Reagents and conditions: a) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 90%; b) MsCl, pyr.; c) NH_3, EtOH, 76% (2 steps); d) *i.* Boc_2O, pyr.; *ii.* $LiBH_4$, THF; *iii.* HCl 1 M, THF, 80% (3 steps).

A conjugate addition reaction was also used by Tinarelli and Paolucci to functionalise an indolizidine scaffold (Scheme 22).[66] The reaction of nitrogen-, sulfur-, carbon-, and oxygen-centred nucleophiles on the α,β-unsaturated δ-lactam **117** were investigated and proved completely stereoselective, resulting in nucleophilic attack on the convex face of the indolizidinone. The potential of such methodology was demonstrated by the transformation of indolizidinone **118** into (7*R*)-7-amino-8-deoxy-swainsonine (**119**).

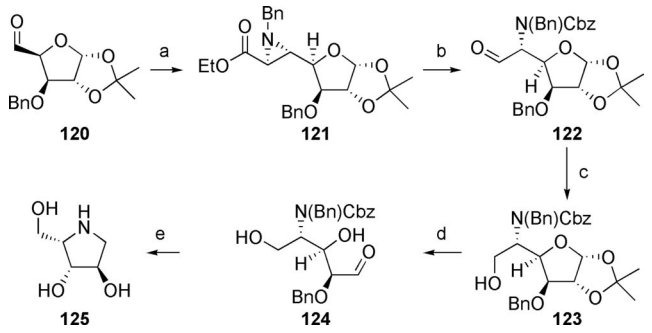


Scheme 22. Reagents and conditions: a) Me_3SiN_3, AcOH, DBU, toluene, 73%.

3.5. Miscellaneous Amination Methodologies

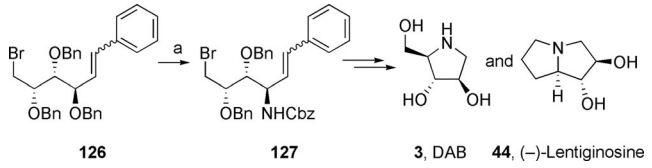
Aziridine formation has been a useful tool for installing the amine functionality en route to the synthesis of pyrrolidine and indolizidine alkaloids, as illustrated by Dhavale and co-workers (Scheme 23).[67] Here, conversion of D-glucose-derived aldehyde **120** into the key aziridine-2-carboxylate **121** and subsequent aziridine ring-opening, carboxylate reduction, and periodate cleavage gave the α-amino aldehyde **122**. This versatile intermediate could then be used for the synthesis of pyrrolidine **125** via reduction of the aldehyde (**122**→**123**), deprotection and oxidative cleavage (**123**→**124**), and reductive amination/cyclisation

(**124**→**125**).[67a] Aldehyde **122** also proved useful in the synthesis of piperidines, pentahydroxyindolizidines, and quinolizidines.[67b,67c]



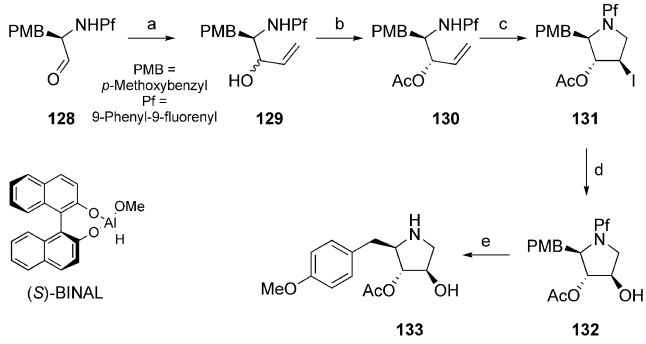
Scheme 23. Reagents and conditions: a) *i*. PPh_3=CBrCOOEt, CH_2Cl_2, 25 °C, 12 h, 77%; *ii*. $BnNH_2$, benzene, 10 to 20 °C, 6 h, 70%; b) *i*. TFA (1 equiv.), acetone/water (2:1), 25 °C, 24 h, 82%; *ii*. $LiAlH_4$, THF, 0 to 25 °C, 2 h; *iii*. CbzCl, $NaHCO_3$, MeOH/water, 0 to 25 °C, 6 h, 82%; *iv*. $NaIO_4$, acetone/water (3:1), 0 to 15 °C, 1.5 h; c) $NaBH_4$, EtOH, 15 °C, 15 min, 93% (2 steps); d) *i*. TFA/water (9.5:0.5), 0 °C, 4 h; *ii*. $NaIO_4$, acetone/water (8:2), 0 °C, 2 h; e) $HCOONH_4$, 10% Pd/C, reflux, 3 h, 46%.

A versatile method for the synthesis of hydroxylated alkaloids by use of chlorosulfonyl isocyanate (CSI) was recently developed by Jung and co-workers.[68] Here the regio- and diastereoselective amination of polybenzyl ethers (derived from D-lyxose) using chlorosulfonyl isocyanate (**126**→**127**, Scheme 24), led to the total syntheses of 1,4-dideoxy-1,4-imino-D-arabinitol [DAB-1 (**3**)] and (–)-lentiginosine (**44**).[67a] Using similar methodology, 2,5-dideoxy-2,5-imino-D-glucitol (DGDP) was also synthesised from D-mannose in excellent overall yield.[67b]



Scheme 24. Reagents and conditions: a) *i*. $ClSO_2$–NCO, Na_2CO_3, toluene, 0 °C, 24 h; *ii*. Na_2SO_3, 84% (2 steps).

Iodo-cyclisations have also been elegantly applied in iminosugar syntheses. Indeed, Park and co-workers used such a strategy in 2005 when they reported the synthesis of anisomycin isomers from D-tyrosine aldehyde (Scheme 25).[69] Here, Grignard addition to protected D-tyrosine aldehyde **128** yielded allylic alcohols **129** as a 1:1 mixture of diastereoisomers. Following oxidation, stereoselective reduction, and acetylation, the desired acetate **130** was then obtained in enantiomerically pure form, with the iodocyclisation of the homo-allylic amine yielding iodide **131**, also as a single diastereoisomer. Finally, hydrolysis using silver triflate (**131**→**132**) and hydrogenation provided the anisomycin isomer **133** in excellent yield. In 2006, Knight and co-workers used iodo and seleno cyclisations in the synthesis of pyrrolidines with various substitution patterns,[70] while in 2009, Brigaud and co-workers used iodo-cyclisation of amino-acid-derived CF_3-allylmorpholinones as the key step during the synthesis of enantiopure α-CF_3-prolines and α-CF_3-dihydroxyprolines.[71]



Scheme 25. Reagents and conditions: a) H_2C=CHMgBr, THF, –40 °C, 93%; b) *i*. Swern oxidation, 98%; *ii*. (*S*)-BINAL, THF, –78 °C, 89% (*dr* > 95:1); *iii*. Ac_2O, Et_3N, 98%; c) I_2, $NaHCO_3$, 90%; d) $AgOC(O)CF_3$, 84%; e) H_2, Pd/C, 91%.

4. Organometallic Catalysis

4.1. Ring-Closing Metathesis

With the advent of more potent, functional group tolerant, and commercially available catalysts (Figure 3), Ring-Closing Metathesis (RCM) has become a popular means by which to synthesise cyclic molecules.

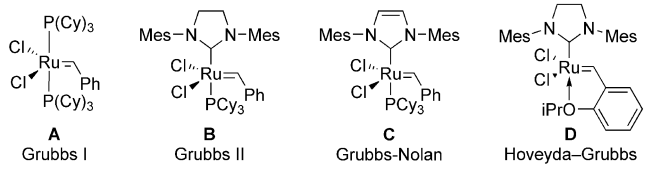
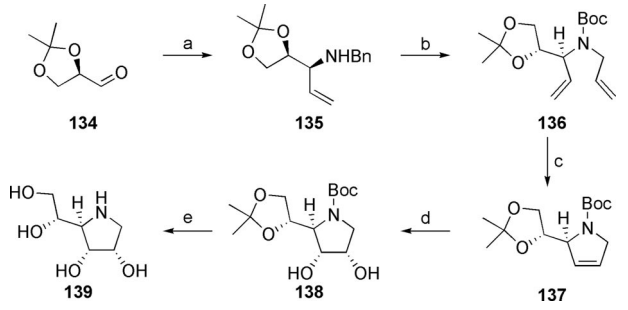


Figure 3. Metathesis Catalysts.

In the construction of iminosugars, the combination of RCM and *cis*-hydroxylation has become an especially valuable methodology. A large number of 1,4-dideoxy-1,4-imino-hexitols have been prepared using this dual strategy with a typical procedure for the preparation of an iminohexitol involving the RCM of a suitably functionalized nitrogen containing diene to yield a dehydropyrrolidine that is subsequently dihydroxylated, often using OsO_4.

To synthesise the prerequisite diene, a variety of reaction conditions have been used. For the recent syntheses of 1,4-dideoxy-1,4-imino-L-allitol and 1,4-dideoxy-1,4-imino-D-ribitol,[72] the diene was prepared via the regioselective C-3 ring opening of enantiomerically pure 2,3-epoxypent-4-en-1-ol by allylamine, while the first asymmetric synthesis of 1,4-dideoxy-1,4-imino-D-talitol was achieved via the addition of vinylmagnesium bromide to a protected (*S*)-glyceraldimine derivative prior to RCM and dihydroxylation.[73] Rao and co-workers[74] also used a Grignard addition to prepare the diene of desired stereochemistry for the synthesis of 1,4-dideoxy-1,4-imino-D-allitol (**139**) (Scheme 26).

Here, (*R*)-2,3-*O*-isopropylidine glyceraldehyde (**134**) was condensed with benzylamine and subjected to a Grignard reaction with vinylmagnesium bromide to provide alkene **135**. The nitrogen in **135** was then Boc-protected, debenzylated, and allylated to give diene **136**. RCM of the nitrogen-tethered diene provided pyrrole **137**, which was subsequently dihydroxylated (→**138**) and finally deprotected to give imino-D-allitol **139**. The syntheses of 1,4-dideoxy-1,4-imino derivatives of L-allitol and D-talitol were also accomplished using similar methodology.



Scheme 26. Reagents and conditions: a) *i*. $BnNH_2$, $MgSO_4$, Et_2O, 0 °C to room temp., 2 h; *ii*. CH_2=$CHMgBr$, Et_2O, 0 °C to room temp., 15 h, 76% (2 steps); b) *i*. NEt_3, Boc_2O, CH_2Cl_2, 0 °C to room temp., 24 h, 72%; *ii*. Li, liq. NH_3, THF, –50 °C, 1 h, 81%; *iii*. NaH, All–Br, DMF, 0 °C to room temp., 12 h, 75%; c) 10 mol-% Grubbs I cat. (**A**), CH_2Cl_2, room temp., 12 h, 75%; d) OsO_4, NMO, acetone/H_2O (3:1), 12 h, 80%; e) MeOH/HCl, room temp., 10 h, 82%.

In the synthesis of 1,4-dideoxy-1,4-imino-D-ribitol as described by Cooper et al., a chiral oxime, *O*-(1-phenylbutyl)-benzyloxy-acetaldoxime, was used to control the diastereoselectivity of alkylation prior to RCM and dihydroxylation.[75] The combination of RCM and dihydroxylation was also used in the synthesis of (–)-2,3-*trans*-3,4-*cis*-dihydroxyproline – here an α-amino aldehyde, prepared by the addition of a 1,3-dithiane to a chiral *N*-sulfinyl imine, was used as the key chiral starting material.[76] More recently, a formal synthesis of (+)-anisomycin was achieved by Normura and Richards,[77] whereby an Overman rearrangement (to form a chiral allylic imidate), allylation, and RCM were key steps. A Baylis–Hillman reaction was used by Doddi and Vankar in the synthesis of an olefinic amine, which, after RCM and dihydroxylation, gave access to branched pyrrolidine iminosugars.[78]

Of particular note in the past five years has been the use of RCM as an essential tool in determining the correct structure of uniflorine A. Following seminal work by Pyne and co-workers who eluded to differences in the spectroscopic data for the isolated and synthesised uniflorine A,[79] a number of groups have sought to resolve this disparity. Dhavale and co-workers employed RCM of a D-glucose-derived diene-substrate containing a nitrogen functionality, followed by asymmetric dihydroxylation to afford a variety of "uniflorine A′ analogues, however all had different spectroscopic data to that of the isolated material.[80] In 2008, Pyne and co-workers used RCM and a stereoselective osmium-catalysed dihydroxylation reaction to achieve the synthesis of the 2-epimer **140** and the 1,2-di-epimer **141** of the putative structure of uniflorine A (**142**) (Figure 4).[25] From a comparison of the NMR spectroscopic data of uniflorine A with that of casuarine and known synthetic pyrrolizidine isomers, the structure of uniflorine A was thus suggested to be 6-*epi*-casuarine (**143**). In addition, Pyne and co-workers showed that uniflorine B is in fact the known alkaloid casuarine (**9**, Figure 1).

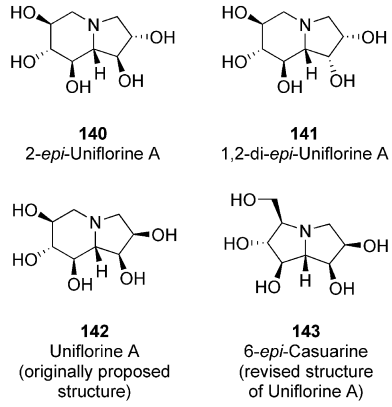
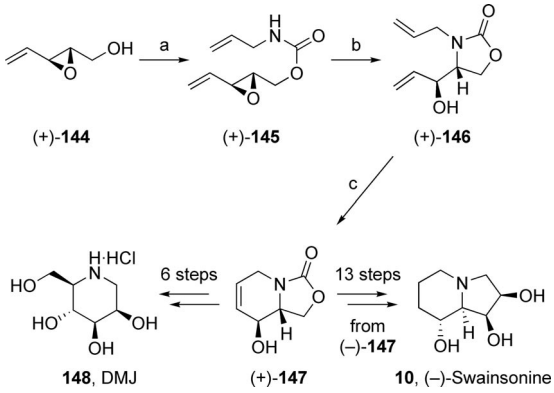


Figure 4. Proposed and revised structures of Uniflorine A.

The RCM methodology used by the Pyne group in the uniflorine work was later exemplified to allow for the syntheses of (–)-swainsonine[81] and castanospermine.[82] In the latter synthesis an RCM on a diene-containing carbamate was a key step. In earlier work, Riera and co-workers also illustrated that deoxymannojirimycin [DMJ (**148**)] and (–)-swainsonine (**10**) could be synthesised from enantiomers of the same carbamate precursor **147** (Scheme 27).[83] This synthesis commenced with the addition of known epoxy alcohol (+)-**144**, readily obtained as either enantiomer, to allyl isocyanate to provide allyl carbamate **145** in 94% yield. Subsequent intramolecular epoxide opening of **145** using sodium bis(trimethylsilyl)amide as the base gave the desired oxazolidinone **146**, which was then treated with 5 mol-% Grubbs I catalyst (**A**, Figure 3) to form the desired carbamate precursor (+)-**147** in excellent yield. From this precursor, DMJ (**148**) could be prepared in six steps. (–)-Swainsonine (**10**) could be prepared from (–)-**147** in thirteen steps using a strategy that included a HWE olefination and a dihydroxylation.

In addition to the synthesis of the uniflorines, castanospermine, and swainsonine, RCM has been an important tool in the synthesis of other bicyclic iminosugars including (+)-lentiginosine,[84] (–)-lentiginosine, and eight-membered nitrogen-containing rings (azocanes). In 2005, the synthesis of (–)-lentiginosine and an original pyrrolizidinic analogue was accomplished by Ayad et al. and included RCM as a key step,[85] while in 2006, a formal total syntheses of australine was achieved via the formation of an eight-membered ring, itself synthesised via RCM.[86] Sletten and Liotta also used RCM to form an eight-membered ring that was subsequently converted to a tetrahydroxylated pyrrolizidine.[87] More recently, Kaliappan et al. employed an ef-

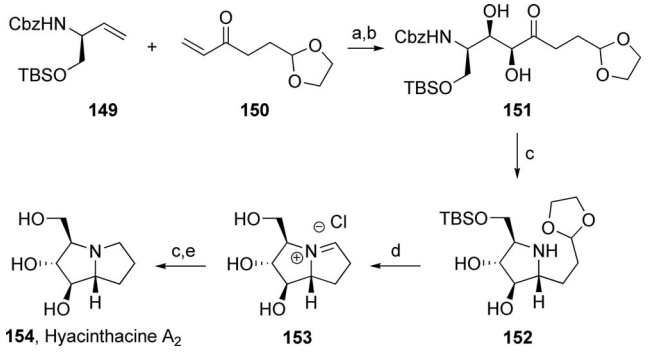


Scheme 27. Reagents and conditions: a) Allyl isocyanate, Et_3N, Et_2O, reflux, 94%; b) sodium bis(trimethylsilyl)amide, THF, 93%; c) 5 mol-% Grubbs I cat. (**A**), CH_2Cl_2, room temp., 98%.

ficient metathesis strategy and nitrone chemistry to construct 8-azabicyclo[3.2.1]octanes as precursors for the synthesis of several calystegine analogues.[88]

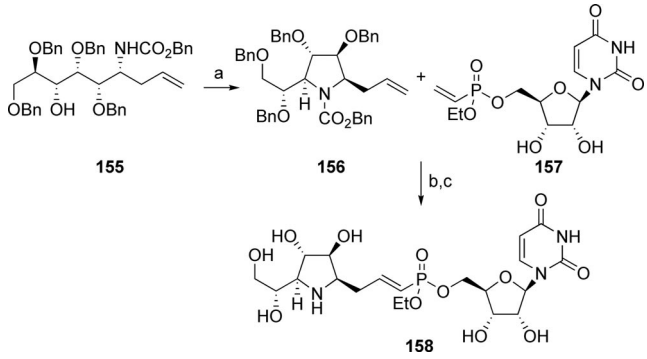
4.2. Cross Metathesis

Key in the Dewi-Wulfing and Blechert synthesis of hyacinthacine A_2 (**154**) was a Cross-Methathesis (CM) reaction.[89] Here, CM between allylamine **149** [prepared via the enzymatic resolution of (±)-*N*-Cbz-vinylglycine] and enone **150** using the Hoveyda–Grubbs ruthenium catalyst (**D**, Figure 3) gave the (*E*)-alkene which was subsequently dihydroxylated with AD-mix-β to yield diol **151** (88% *de*) (Scheme 28). Attempts to cyclise diol **151** were first made using a one-pot four-step procedure, however this resulted in low yields and the formation of side products. A sequential double reductive cyclisation protocol was then employed involving hydrogenation (→**152**), followed by treatment with HCl to cleave the dioxolane and the TBS protecting groups, which gave iminium salt **153**. Imine **153** was further hydrogenated, and then neutralised via the addition of amberlite (OH^- form), to give hyacinthacine A_2 (**154**) in an overall yield of 39% for the four steps.



Scheme 28. Reagents and conditions: a) Hoveyda–Grubbs cat. (**D**), CH_2Cl_2, 40 °C, 3 d, 73%; b) AD-Mix-β, $NaHCO_3$, $MeSO_2NH_2$, $K_2OsO_4{\cdot}2H_2O$, *t*BuOH/H_2O, room temp., 10 min, 67%; c) H_2, Pd/C, MeOH, 4 bar, room temp., 3 d; d) MeOH, HCl, room temp., 14 h; e) Amberlite IRA 401 (wet, OH^- form), then NH_3, 39% (4 steps).

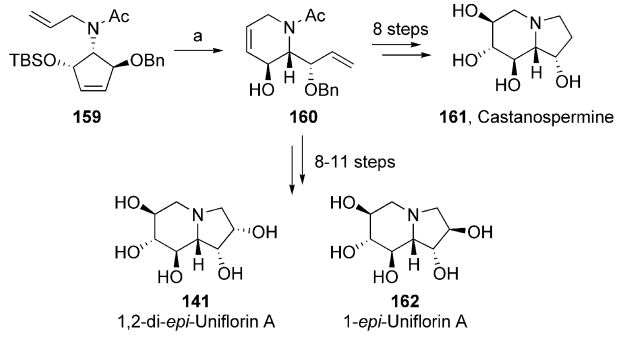
CM has also been used by Martin and co-workers to prepare a UDP-Galf mimick.[90] To this end, linear amine **155**, accessible from a protected glycosylamine via reaction with allyltrimethylsilane and TMSOTf, was mesylated and treated with potassium *tert*-butoxide to give D-*galacto* pyrrolidine **156** (Scheme 24). Pyrrolidine **156** was then subjected to a CM reaction with ethyl uridin-5′-yl vinylphosphonate **157** (itself prepared in two-steps via chlorination of diethyl vinylphosphonate and subsequent coupling with 2′,3′-*O*-isopropylidine-uridine) using 10 mol-% of Grubbs–Nolan catalyst (**C**, Figure 3). BCl_3-Mediated global deprotection then gave the iminosugar nucleotide conjugate **158** (Scheme 29).



Scheme 29. Reagents and conditions: a) *i*. MsCl, Et_3N, CH_2Cl_2; *ii*. *t*BuOK, THF, 74% (2 steps); b) Grubbs–Nolan cat. (**C**), CH_2Cl_2, 40 °C, 44 h, 51%; c) BCl_3, CH_2Cl_2, 0 °C, 52%.

4.3. Ring-Rearrangement Metathesis

Ring-rearrangement metathesis (RRM) was elegantly used by Mariano et al. to prepare (+)-castanospermine and, at the time, what were thought to be isomers of the putative structure given to uniflorine A (Figure 4).[91] The routes to these targets relied on the extension of an earlier developed photocyclisation reaction used to concisely prepare a key *N*-allylacetamidocyclopentenediol from pyridinium perchlorate. The key diene **159** was thus subjected to a RRM to yield the allyltetrahydropyridine **160**, which was subsequently transformed into (+)-castanospermine (**161**) and the polyhydroxylated indolizidines **141** and **162** via regio-

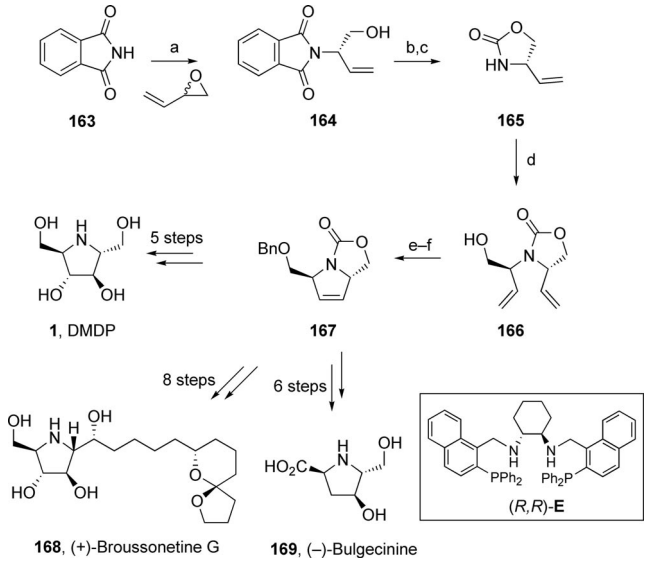


Scheme 30. Reagents and conditions: a) Grubbs II cat. (**B**), ethylene, CH_2Cl_2, 93%.

and stereo-controlled hydroxylation processes (Scheme 30). Using this approach, it was demonstrated that the natural product uniflorine A, does not possess the pentahydroxylated indolizidine structures represented by **141** and **162**. This work was one study of many that aided in the elucidation of the structure of uniflorine A.

4.4. Allylic Alkylation

Palladium-catalyzed asymmetric allylic alkylation reactions have been extensively investigated by Trost et al. for the synthesis of a variety of iminosugars. Here a racemic compound is transformed into a single enantiomer by way of a process known as dynamic kinetic asymmetric transformation (DYKAT). DYKAT reactions differ from traditional asymmetric reactions in that both enantiomers of the racemic starting material are converted into a single chiral product. In 2006, Trost et al. highlighted the scope of DYKAT for the synthesis of iminosugars via the expedient synthesis of *trans*- and *cis*-2,5-dihydropyrroles – with the *trans*-2,5-dihydropyrrole **167** being a key synthetic precursor for the synthesis of (+)-DMDP (**1**), (+)-broussonetine G (**168**), and (–)-bulgecinine (**169**) (Scheme 31).[92] Trost's methodology involved the combination of two asymmetric allylic alkylations and commenced with the palladium catalysed DYKAT reaction of phthalimide (**163**) and butadiene monoxide, mediated by the addition of chiral ligand **E**. Under these conditions, enantiopure alcohol **164** was prepared in excellent yield and enantioselectivity. Aminolysis and subsequent cyclisation with triphosgene then afforded oxazolidinone **165**, which was subjected to a second palladium catalysed DYKAT reaction to yield diene **166**. Diene **166** was then protected with a benzyl group – a necessary step

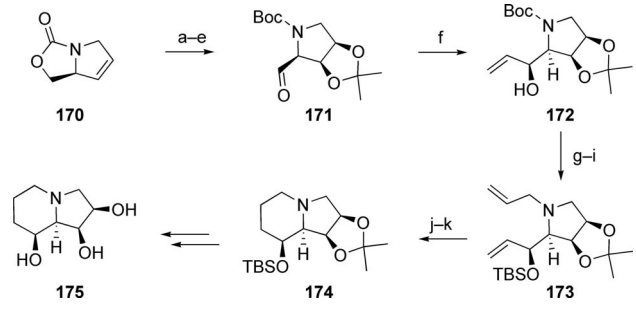


Scheme 31. a) 0.4 mol-% $[(\eta^3\text{-}C_3H_5)PdCl]_2$, 1.2% (*R*,*R*)-**E**, 1% Na_2CO_3, CH_2Cl_2, room temp., 12 h, 99% (94% *ee*); b) ethylenediamine, EtOH; c) triphosgene, $NaHCO_3$, 71% (2 steps); d) 1% $[Pd_2dba_3]$, 3% (*R*,*R*)-**E**, 1% DBU, CH_2Cl_2, room temp., 8 h, 91% (*dr* = 93:7); e) NaH, BnBr, TBAI; f) 3 × 0.4 mol-% Grubbs II cat. (**B**), CH_2Cl_2, 76% (2 steps).

to achieve the required RCM and thus, formation of the key dihydropyrrole **167**. In subsequent work by Trost et al., two palladium-catalysed asymmetric allylic alkylation reactions were used during the 13-step synthesis of (+)-australine.[93] The first involved use of a mixture of *dl*- and *meso*-divinylethylene carbonate as the electrophile, while the second proceeded in an analogous manner to the aforementioned work and used butadiene monoxide as the electrophile.

4.5. Dihydroxylation

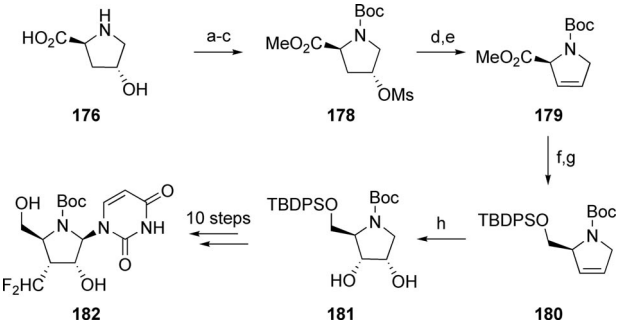
Dihydroxylation reactions using osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide (NMO) have found wide application in the synthesis of a variety of iminosugars. In recent work by Parsons and co-workers, a diastereoselective dihydroxylation of a cyclic carbamate was key during the formal synthesis of (–)-8-*epi*-swainsonine (Scheme 32).[94] Earlier calculations from the Parson laboratory indicated that the HOMO of **170** has an unsymmetrical π-bond with higher electron-density on the *endo*-face of the bicyclic system and accordingly, dihydroxylation of **170** using OsO_4/NMO led to formation of the *endo* diol. This diol was subsequently protected as the acetonide, the carbamate was hydrolysed, the resulting amine Boc-protected and primary hydroxy-oxidised using TPAP to give aldehyde **171** in excellent overall yield. Addition of vinylmagnesium bromide to aldehyde **171** then gave allylic alcohol **172** as the sole product – presumably via chelation of magnesium to both the aldehyde and Boc carbonyl groups. Silylation, removal of the Boc group, and *N*-allylation using allyl bromide then gave the diene **173**. RCM of diene **173**, using 20 mol-% of the Grubbs second-generation catalyst **B** (Figure 3), followed by hydrogenation, led to the formation of the indolizidine core **174**, Indolizidine **174** could then be converted to (–)-8-*epi*-swainsonine (**175**) following previously published procedures.



Scheme 32. Reagents and conditions: a) OsO_4, NMO, acetone/H_2O, 85%; b) $(CH_3O)_2C(CH_3)_2$, PPTS, acetone, reflux, 95%; c) LiOH, EtOH, reflux; d) $(Boc)_2O$, Et_3N, MeCN, 85% (2 steps); e) TPAP, 4 Å MS, NMO, CH_2Cl_2, 98%; f) CH_2=$CHMgBr$, THF, 85%; g) TBSOTf, NEt_3, CH_2Cl_2, 98%; h) $ZnBr_2$, CH_2Cl_2, 81%; i) CH_2=$CHCH_2Br$, K_2CO_3, THF, reflux, 91%; j) 20 mol-% Grubbs II cat. (**B**), CH_2Cl_2, reflux, 70%; k) H_2, Pd/C, EtOAc, 54%.

An OsO_4-catalysed dihydroxylation was also a key step in the synthesis of azanucleosides from *trans*-4-hydroxy-L-proline as reported by Qiu and Qing in 2005

(Scheme 33).[95] Here mesylate **177**, formed in three steps from proline **176**, was treated with diphenyl diselenide under reflux conditions to yield a phenyl selenide that was subsequently eliminated to give alkene **178**. The methyl ester of **178** was then reduced and the primary hydroxy protected with the *tert*-butyldiphenyl silyl group to give **179**. The large TBDPS-group provided the necessary steric bulk to effect excellent stereoselectivity in the subsequent dihydroxylation reaction, with diol **180** being the only isomer formed (92% yield). Further elaboration of diol **180** then led to a series of azanucleosides, such as fluorinated derivative **181**. In an analogous manner, Chiba et al. synthesised a series of dihydroxyprolines via elimination of a hydroxyproline mesylate followed by subsequent dihydroxylation,[96] while a protecting-group directed stereoselective dihydroxylation was used by Kim and co-workers en route to the synthesis of D-iminolyxitol, a potent α-galactosidase inhibitor.[97] In Kim's work, the key step involved the OsO_4-catalysed *syn*-selective dihydroxylation reaction of the acyclic γ-amino-α,β-unsaturated (*Z*)-ester of D-serine. The stereoselectivity of the dihydroxylation was controlled by an *N*-diphenylmethylene group resulting in selectivities of over 10:1 (*syn*/*anti*). Stereoselective dihydroxylation using the OsO_4/NMO system was also used by Ham and co-workers in the synthesis of (–)-swainsonine.[98]

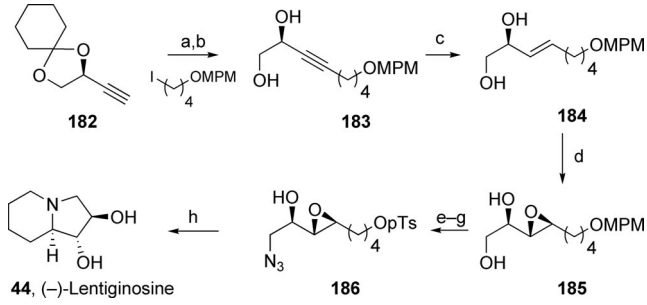


Scheme 33. Reagents and conditions: a) $SOCl_2$, MeOH, 0 °C to room temp.; b) Boc_2O, CH_2Cl_2, room temp.; c) MsCl, Et_3N, DMAP, CH_2Cl_2, room temp., 78% (3 steps); d) PhSeSePh, MeOH, reflux; e) H_2O_2, pyr., room temp., 63% (2 steps); f) $LiAlH_4$, Et_2O, room temp., 89%; g) TBDPSCl, imidazole, DMAP, CH_2Cl_2, room temp., 82%; h) OsO_4, NMO, Me_2CO, H_2O, room temp., 92%.

In addition to the OsO_4/NMO dihydroxylation system, the Sharpless asymmetric dihydroxylation has also been used in the synthesis of a number of iminosugars. In 2005, Reiser and co-workers employed such methodology during an efficient synthesis of the indolizidines (–)-swainsonine and (–)-2,8a-di-*epi*-swainsonine from readily available 2-pyridinecarbaldehyde and 3-hydroxypyridine.[99] In the following year, Grison and co-workers used a strategy based on the Sharpless asymmetric dihydroxylation of vinylogous aminoesters with subsequent intramolecular cyclisation to produce a variety of 3,4-dihydroxypyrrolidin-2-one and 1,2-dihydroxypyrrolizidin-3-ones, respectively.[100]

4.6 Asymmetric Epoxidation

In the synthesis of the indolizidine (–)-lentiginosine (**44**) by Chandraeshar et al., a Sharpless asymmetric epoxidation, using (+)-diisopropyl L-tartrate, was a key step (Scheme 32).[101] Here, dioxa-spiro derivative **182**, obtained from cyclohexylidene protected glyceraldehyde, was alkylated and deprotected to give the alkynediol **183**. Reduction to the alkene **184** and "mismatched" Sharpless asymmetric epoxidation then yielded epoxydiol **185** with *syn* selectivity (≈ 20:1, *syn*/*anti*). Protecting group manipulations allowed for the introduction of an azide and tosylate at the primary positions to give **186** (Scheme 34), the azide of which was then reduced leading to a double intramolecular epoxide opening/tosyl displacement, thus providing a succinct synthesis of (–)-lentiginosine (**44**).



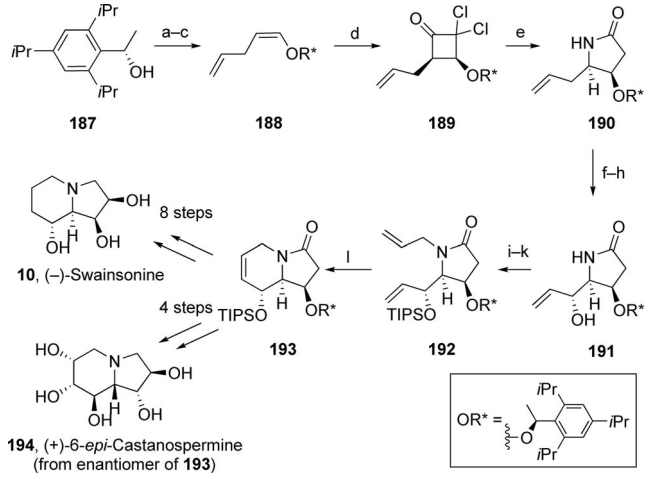
Scheme 34. Reagents and conditions: a) *n*BuLi, THF, –78 °C, 52%; b) CH_3CN/1 M HCl (1:1), room temp., 98% c) $LiAlH_4$, Et_2O, 0 °C to room temp., 70%; d) (+)-DIPT, $Ti(OiPr)_4$, TBHP, CH_2Cl_2, –20 °C, 72 h, 65%; e) *i*. TsCl, pyr., Bu_2SnO, room temp., 84%, *ii*. NaN_3, DMF, 80 °C, 90%; f) DDQ, THF/H_2O (1:1), 62%; g) *p*TsCl, pyr., 0 °C, 57%; h) 10 mol-% Lindlar's catalyst, MeOH, room temp., 3 h, then MeOH, KOH, 39%.

5. Pericyclic Reactions

5.1. [2+2] Annulations

In 2006, Poisson and co-workers employed a [2+2] cycloaddition of dichloroketene (DCK) to a chiral enol ether to provide an efficient enantioselective approach for the synthesis of (–)-swainsonine and (+)-6-*epi*-castanospermine.[102] Here, chiral enol ether **188**, prepared in three steps from (*S*)-1-(2,4,6-triisopropylphenyl)ethanol (**187**), was treated with dichloroketene in a [2+2] cycloaddition to yield dichlorocyclobutanone **189**. Cyclobutanone **189** was then subjected to a Beckmann ring expansion using Tamura's reagent and the intermediate pyrrolidine dechlorinated to afford pyrrolidinone **190** (34% from **187**). Allylic oxidation of **190** under Sharpless conditions afforded the corresponding allylic alcohol as a 1:1 diastereomeric mixture, which necessitated a two-step oxidation/reduction protocol to produce the desired diastereomer **191** (*dr* = 92:8). Disilylation, selective removal of the *N*-silyl group, and *N*-allylation then provided diene **192**. The ensuing RCM, using Grubbs II catalyst (**B**, Figure 3), proved effective and indolizidinone **193** was isolated in excellent yield. Indolizidinone **193** was subsequently transformed into (–)-swainsonine (**10**) in eight steps, with key steps including hydrogenation of the double bond, cleavage of the auxiliary, and elimination of the secondary hydroxy group to afford an alkene that was sub-

sequently dihydroxylated. Alternatively, from the enantiomer of indolizidinone **193**, (+)-6-*epi*-castanospermine (**194**) was prepared in four steps (Scheme 35).

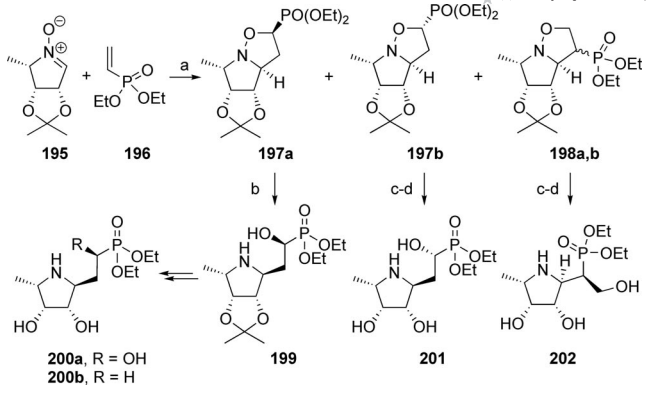


Scheme 35. Reagents and conditions: a) KH, THF, $Cl_2C{=}CHCl$; b) *n*BuLi; c) DiBAl-H; d) Cl_2CCO; e) H_2N–OMs, Zn/Cu, H^+, 34% (5 steps); f) SeO_2, 56%; g) Dess–Martin periodinane; h) $LiAlH_4$, (82%, 2 steps); i) TIPS–OTf, iPr_2NEt; j) AcOH, 81% (2 steps); k) Allyl bromide, 95%; l) Grubb's II cat (**B**), CH_2Cl_2, reflux, 84%.

5.2. [2+3] Annulations

The [2+3] dipolar cycloaddition reaction of nitrones with a variety of dienophiles has been creatively used to prepare a variety of five-membered ring iminosugars.[103] In work by Defoin and co-workers,[104] a [2+3] dipolar cycloaddition of nitrone **195** with vinylphosphonate **196** was used as a key step in the synthesis of α-L-fucosidase inhibitors (Scheme 36). This cycloaddition reaction was weakly regio- and stereoselective and two pairs of *endo* and *exo* regio adducts **197a**,**b** and **198a**,**b** were formed in 52:30:6:13 proportions, respectively. The major adduct **197a** (together with **198a**) and a mixture of *exo* adducts **197b**/**198b** were separated by chromatography and the N–O bond of the bicyclic adducts hydrogenolysed over Pd/C at 40 °C. The major adduct **197a** gave the imino-alditol **199**, which was converted to phosphonate **200a** after removal of the isopropylidine group, while the mixture of **197b**/**198b** was subjected to hydrogenolysis and 6 M HCl to yield **201** and **202**, which were then separated by chromatographic separation. To obtain pyrrolidine phosphonate **200b**, containing an ethyl chain, the alcohol function of **199** was eliminated via a Barton–McCombie radical elimination of the corresponding xanthate.

Shortly following the work by Defoin and co-workers, Martin and co-workers published an elegant strategy for the synthesis of diphosphono-β-Galf mimics via use of a highly regio- and stereoselective cycloaddition of an uridin-5′-yl allylphosphonate with a 1,4-dideoxy-1,4-iminogalactitol-derived cyclic nitrone.[105] Brandi and co-workers also exploited a 1,3-dipolar cycloaddition to synthesise a novel class of homonucleoside mimetics where the furanose ring

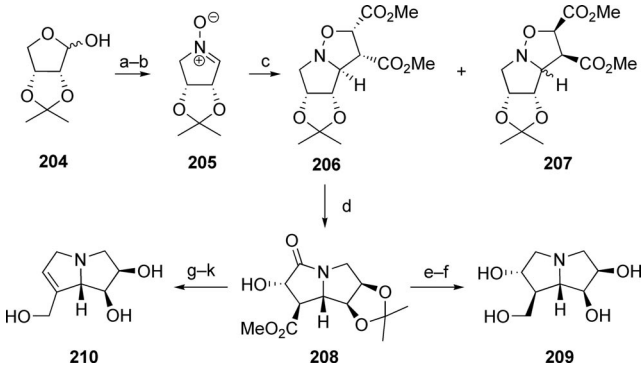


Scheme 36. Reagents and conditions: a) C_2Cl_4, 50 °C, 16 h, 99%; b) H_2, Pd/C, EtOH, 40 °C, 61%; c) H_2, Pd/C, EtOH, 40 °C, 68%; d) 6 M HCl, EtOH, quant.

was replaced by a pyrrolo[1,2-*b*]isoxazolidine system.[106] Here, cyclic hydroxylated nitrones were treated with allyl nucleobases. In 2008, Argyropoulos et al. used a 1,3-dipolar cycloaddition to synthesise enantiomerically pure trihydroxylated pyrrolizidines.[107] In this synthesis an L-erythrose glycosylhydroxylamine acted as a masked acyclic nitrone and reacted diastereoselectively from its *Re*-face with methyl acrylate to give the corresponding isoxazolidine which, after reductive N–O cleavage, was cyclised to a trihydroxypyrrolizidine via a Mitsunobu condensation. Earlier work by Argyropoulos et al. reported on the 1,3-dipolar cycloaddition reactions of azomethine ylides, generated from MOM- or TBS-protected 3,4-dihydroxypyrrolidine derivatives and ethyl glyoxylate.[108]

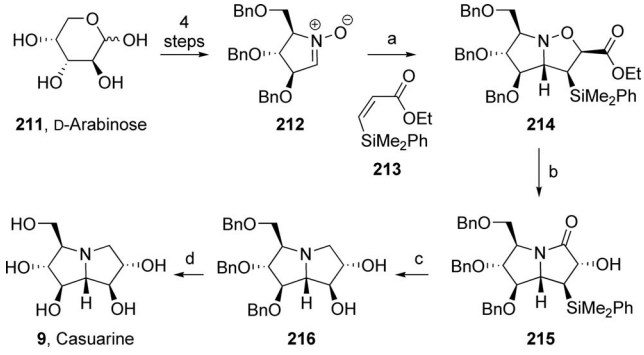
A straightforward and inexpensive one-pot procedure for the preparation of enantiopure five-membered ring cyclic nitrones from their corresponding lactols was recently reported by Goti and co-workers.[109] The cyclic nitrones themselves are versatile precursors for the synthesis of a number of interesting aza sugars. A representative synthesis of nitrone **205** and its role in a [3+2] cycloaddition reaction is provided (Scheme 37). Here 2,3-*O*-isopropylidene-D-erythrose (**204**) is reacted with hydroxylamine in dry pyridine and subsequently treated with methanesulfonyl chloride to give nitrone **205** in 54% yield. Nitrone **205** was then reacted with dimethyl maleate to give a 9.6:6:1 mixture of cycloadducts *anti-exo*-**206**, *anti-endo*-**207** and *syn-exo*-**207**, respectively. Hydrogenolysis of **206** then gave pyrrolizidinone **208**, which was subsequently converted into the polyhydroxylated pyrrolizidine alkaloid **209** (via reduction of the lactam and ester with $LiAlH_4$) and pyrrolizidine alkaloid **210** (via selective reduction of the lactam with $BH_3{\cdot}SMe_2$, mesylation of the alcohol and treatment with DBU to give the α,β-unsaturated ester, and reduction of the ester with DiBAl-H). While **209** exhibited no significant glycosidase inhibitory activity, **210** was shown to be a good, selective inhibitor of α-mannosidases.

Goti extended this work in 2009[110,111] and developed an efficient synthesis of casuarine and its 6-*O*-α-glucoside derivative. Starting from D-arabinose (**211**), nitrone **212** was prepared in 4 steps, and a subsequent [3+2] cycloaddition



Scheme 37. Reagents and conditions: a) $NH_2OH·HCl$, pyr., 3 Å MS, 20 °C, 15 h; b) MsCl, pyr., 20 °C, 24 h, 54% (2 steps); c) dimethyl maleate, CH_2Cl_2, 20 °C, 15 h, 92%; d) $Pd(OH)_2/C$, H_2, 98%; e) $LiAlH_4$, THF, 65 °C, 1.5 h; f) HCl, MeOH, 20 °C, 1 h, 79%; g) $BH_3·SMe_2$, THF, 65 °C, 1 h, 81%; h) CH_3SO_2Cl, CH_2Cl_2, room temp., 15 h; i) DBU, 20 °C, 0.5 h, 81% (2 steps); j) DiBAl-H, CH_2Cl_2, 0 °C, 0.5 h; k) HCl, MeOH, 20 °C, 1 h, 82%.

reaction of **212** with acrylate **213** then provided the bicyclic adduct **214** with excellent stereoselectivity. Reduction of the alkoxyamine in **214** led to spontaneous cyclisation into amide **215**. Finally, oxidative cleavage of the silane and reduction of the carbonyl gave diol **216**, which, following deprotection, yielded casuarine (**9**). The binding of casuarine and casuarine 6-*O*-α-D-glucoside to glucoamylase NtMGAM and trehalase Tre37A, respectively, was then investigated and revealed interesting similarities in the catalytic sites of these two enzymes (Scheme 38).

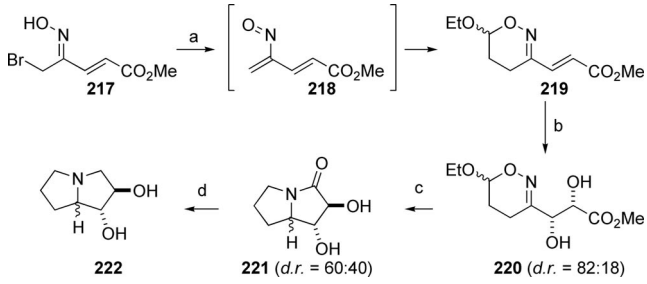


Scheme 38. Reagents and conditions: a) CH_2Cl_2, room temp., 36 h, 79%; b) Zn, AcOH/H_2O, 60–65 °C, 5 h, 93%; c) *i*. $Hg(CF_3CO_2)_2$, TFA, AcOH, AcOOH, $CHCl_3$, 76%; *ii*. $LiAlH_4$, THF, reflux, 78%; d) H_2, Pd/C, MeOH, HCl, 100%.

Chemielewski and co-workers also used a 1,3-dipolar cycloaddition as a key step in the synthesis of a number of iminosugars including casuarine and aminoindolizidine derivatives,[112] while a microwave assisted 1,3-dipolar cycloaddition of an iminosugar nitrone and methacrylate was used by Li et al. for the preparation of a variety of polyhydroxylated indolizidine derivatives containing an amino group.[113]

5.3. [2+4] Annulations

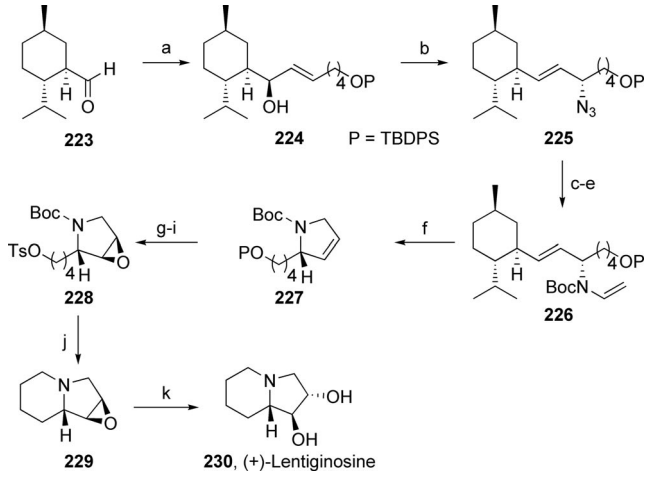
In 2008, Zimmer et al. illustrated the versatility of a [2+4] Diels–Alder cycloaddition reaction in the synthesis of pyrrolizidines, (Scheme 39).[114] In this work, nitrosoalkene **218**, generated in situ from oxime **217**, underwent a hetero Diels–Alder reaction with an enol ether, such as ethyl vinyl ether shown here, to afford the 1,2-oxazine **219** bearing an exocyclic C=C bond. The olefin of oxazine **219** was then dihydroxylated to give diols **220** in a 82:18 diastereomeric ratio, though the relative configuration of the diastereomers was not determined. Subsequent hydrogenolysis of diols **220** furnished pyrrolizidinones **221** in good yield and with moderate diastereoselectivity. Finally, reduction of the amide with $BH_3·SMe_2$ then yielded pyrrolizidines **222**.



Scheme 39. Reagents and conditions: a) Na_2CO_3, *t*BuOMe, H_2C=CHOEt, room temp., 5 d, 93%; b) $KMnO_4$, $MgSO_4$, EtOH, –45 °C, 45 min, 75%; c) H_2, Pd/C, MeOH, 21 h, 79%; d) $BH_3·SMe_2$, THF, 48 h, 93%.

5.4. [3,3]-Sigmatropic Rearrangement

In a novel synthesis of (+)-lentiginosine (**230**), Spino and co-workers illustrated how a sterically-biased tandem Mitsunobu/[3,3]-sigmatropic rearrangement of allylic azides on a chiral auxiliary could be used to prepare a key azide intermediate (Scheme 40).[115] Here the auxiliary, *p*-menthane-3-carbaldehyde (**223**), readily prepared from menthone in either enantiomeric form, was used to induce stereochemistry and to also bias the equilibrium mixture of the required allylic azide. Thus, aldehyde **223** was treated with a vinyllithium reagent to give alcohol **224** which was then subjected to Mitsunobu reaction conditions to yield azide **225** in 98% yield and in an excellent diastereomeric ratio (> 95:5). To explain these results, an S_N2 displacement of the intermediate phosphonyloxy leaving group by the azide followed by a [3,3]-sigmatropic rearrangement to the thermodynamically more stable regioisomer was proposed. Azide **225** was then converted to diene **226** in three steps and the diene subjected to RCM using 1% of the Grubbs–Nolan catalyst (**C**, Figure 3) to yield pyrrolidine **227** quantitatively. Stereoselective epoxidation of the alkene, removal of the TBDPS-group and installation of the tosylate then gave **228**, which underwent in situ cyclisation following removal of the Boc-group to give the pyrrolizidine core **229**. Finally, selective opening of the epoxide gave (+)-lentiginosine (**230**) in good yield. In earlier work, Ichikawa et al. used a [3,3]-sigmatropic rearrangement of an allylic cyanate en route to the synthesis of (+)-lentiginosine.[116]

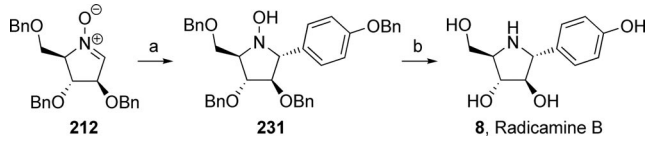


Scheme 40. Reagents and conditions: a) IHC=CH(CH$_2$)$_4$OTBDPS, *t*BuLi, AlMe$_3$, 56% (*dr* = 35:1); b) PPh$_3$, DEAD, HN$_3$, 98% (*dr* > 95:5); c) LiAlH$_4$, Et$_2$O, 0 °C to room temp., 13 h, 86–96%; d) K$_2$CO$_3$, MeCN, allyl bromide, 59%; e) (Boc)$_2$O, NEt$_3$, room temp., 23 h, 92%; f) 5 mol-% Grubbs–Nolan cat. **C**, CH$_2$Cl$_2$, 18 h, quant.; g) Oxone, NaHCO$_3$, CF$_3$COCH$_3$, MeCN, 0 °C to room temp., 18.5 h, 89%; h) TBAF, THF, room temp., 4.5 h, 87%; i) TsCl, pyr., CH$_2$Cl$_2$, room temp., 26 h, 85% j) TFA, CH$_2$Cl$_2$, room temp., 1 h, then NEt$_3$, 63%; k) H$_2$SO$_4$, dioxane, 71%.

6 Addition Reactions

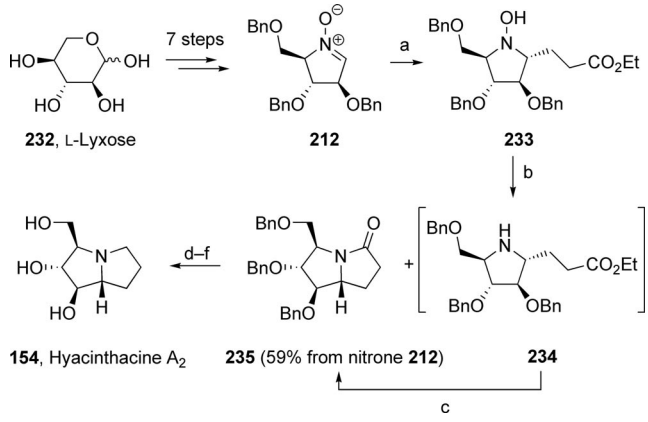
6.1. Addition to Nitrones

Literature precedent for the *anti*-addition of an organometallic reagent to a nitrone carbon atom (with respect to the α-substituent) has been well documented and recently exploited in the synthesis of a variety of pyrrolidines.[23,24,82,115,116] The direct diastereoselective addition of dialkyl phosphonates, to yield pyrrolidinylphosphonates, has also been illustrated.[102] Of the pyrrolidines synthesised from cyclic nitrone precursors, perhaps the most common target has been the radicamines A and B. Indeed, via a highly diastereoselective addition of 2-benzyloxy-3-methoxy-phenylmagnesium bromide or phenylmagnesium bromide to a xylose-derived nitrone, Yu and Huang[22] were able to illustrate that the absolute configuration of radicamines A and B was initially incorrectly assigned, with the revised structures being those discussed in section 1.1 (**7** and **8**, Figure 1). The synthesis of radicamine B by Gurjar et al., also by the addition of a Grignard reagent to a cyclic nitrone, drew a similar conclusion.[23] A variety of radicamine derivatives were also recently prepared by Goti and co-workers by the combination of nucleophilic addition to a nitrone and a subsequent oxidation/reduction protocol (Scheme 41).[24] In this work, stereoselective addition of phenylmagnesium bromide to the benzyl-protected nitrone **212** yielded hydroxylamine **231**, which was subsequently reduced and deprotected to obtain radicamine B (**8**). This work followed earlier studies by Goti and co-workers, whereby the C-2 epimers of 2-aminomethyl- and 2-hydroxymethyl-3,4-dihydroxypyrrolidines were synthesised by the stereocontrolled addition of TMSCN or LiCH$_2$OMOM to a nitrone and subjection of the resulting hydroxylamine to an oxidation-reduction inversion sequence.[117]



Scheme 41. Reagents and conditions: a) 4-BnOC$_6$H$_4$MgBr, THF, 0 °C, 89%, *d.s.* > 95%; b) *i*. H$_2$ (5 atm), Pd(OH)$_2$/C, HCl/MeOH, room temp., 100%; *ii*. Dowex 5WX8–200, NH$_4$OH (1 M), 90%.

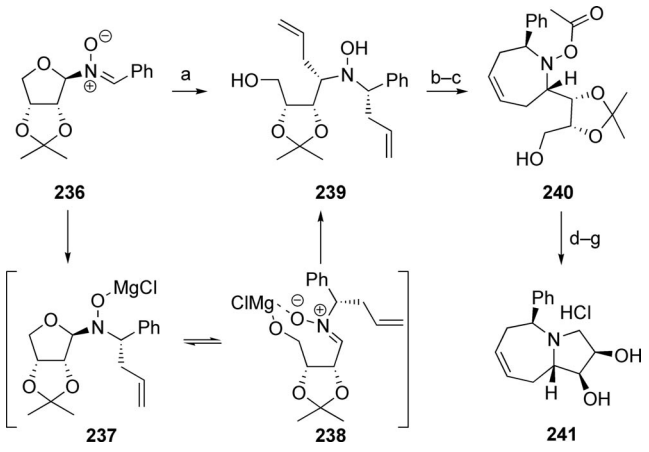
Nucleophilic additions to nitrones have also been used in the recent syntheses of a number of pyrrolizidines including (+)-lentiginosine and analogues thereof,[82] and (+)-hyacinthacine A$_2$.[118] Key steps in Goti and co-workers lentiginosine synthesis included the diastereoselective addition of vinylmagnesium bromide to a nitrone and RCM, while Valle and co-workers used a SmI$_2$-mediated addition to a nitrone and a subsequent SmI$_2$-mediated reduction (Scheme 42). In Valle's synthesis, nitrone **212** [prepared from L-xylose (**232**) in seven steps] was treated with SmI$_2$ and ethyl acrylate to afford the expected *N*-hydroxyamine **233** in 64% yield and with good stereoselectivity (*dr* = 90:10). Given the propensity of *N*-hydroxyamines to be reduced to amines in the presence of SmI$_2$, attempts were then made to prepare pyrrolizidinone **235** in a single step from nitrone **212**. Thus, following the complete conversion of nitrone **212** to **233**, as indicated by t.l.c., excess SmI$_2$ was added to the reaction vessel. This protocol led to a mixture of amine **234** and lactam **235**, however treatment of the crude reaction mixture with K$_2$CO$_3$ in EtOH/H$_2$O induced total conversion of the amine to the lactam **235** (59% overall yield from **212**). Reduction of the amide, hydrogenation and purification via a basic Dowex column then followed to give (+)-hyacinthacine A$_2$ (**154**).



Scheme 42. Reagents and conditions: a) ethyl acrylate, SmI$_2$, H$_2$O, THF, –78 °C, 3 h; b) SmI$_2$, THF, –78 °C to room temp., 24 h; c) K$_2$CO$_3$, EtOH/H$_2$O, 59% (3 steps); d) LiAlH$_4$, THF, 66 °C, 1 h; e) Pd/C, H$_2$, MeOH, THF, 6 M HCl, room temp., 4 d; f) Dowex 1x8; 62% (3 steps).

A novel double addition of Grignard reagents to *N*-glycosyl nitrones has also been used by Goti and co-workers in the synthesis of a biologically active a pyr-

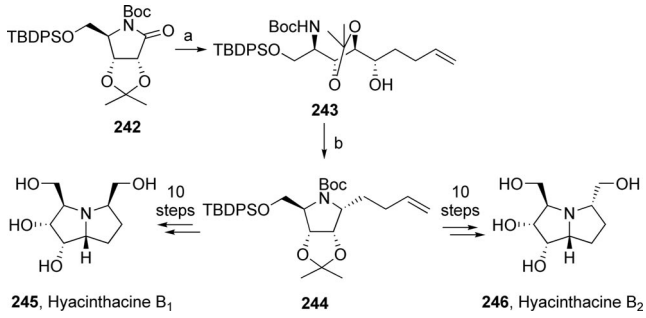
roloazepine (Scheme 43).[119] Here, the addition of a threefold excess of allylmagnesium chloride to *C*-phenyl-*N*-erythrosylnitrone **236** lead to the formation of the bis-adduct **239**, presumably via intermediates **237** and **238**. Though four diastereomers were possible, only two were observed with a *dr* of 4:1 in favour of **239**. Surprisingly, addition of the first equivalent of allylmagnesium chloride thus occurred at the *Si* face of *N*-glycosylnitrone **236** – a result opposite to that observed when other Grignard reagents were used in the same system. Following acetylation of the hydroxylamine of diene **239** and RCM using Grubbs II catalyst (**B**, Figure 3), azepine **240** was formed in almost quantitative yield. The acetate in **240** was then cleaved in situ to give the corresponding hydroxylamine that was subsequently reduced with Zn dust, cyclised, and deprotected to give pyrroloazepine **241** in 65% yield over the four steps.



Scheme 43. Reactions and conditions: a) Allylmagnesium chloride, THF, 0 °C, 1 h, 98%; b) Ac_2O, THF, 65 °C, 1 h; c) Grubbs II cat. (**B**), CH_2Cl_2, 40 °C, 5.5 h, 98%; d) $KHCO_3$, MeOH, room temp., 12 h; e) Zn, AcOH, room temp., 2 h; f) Tf_2O, pyr., room temp., 2 h; g) HCl, MeOH; room temp., 2 h, 65% (4 steps).

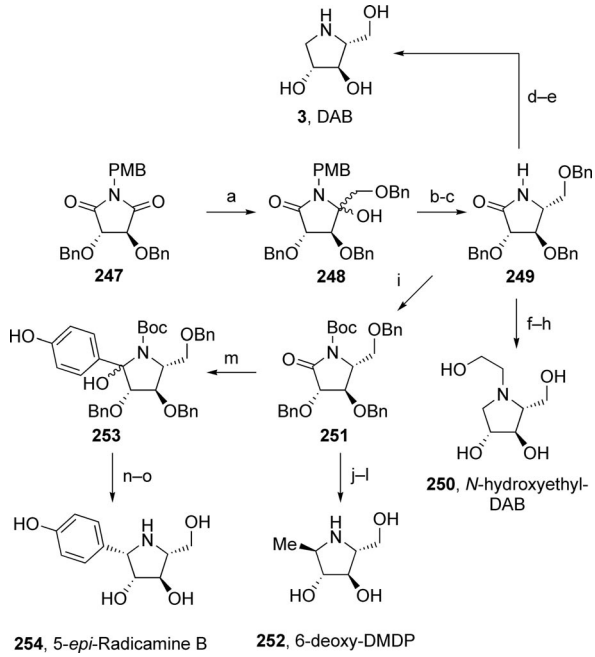
6.2. Addition to Imides

Nucleophilic addition to a lactam has also proven to be a versatile tool in the synthesis of a variety pyrrolidines, as illustrated by recent work by Hanessian et al.,[120] Yoda and co-workers[121] and Huang and co-workers.[122] In Hanessian's work, two unnatural polyhydroxylated indolizidines were synthesised via methodology that included the $BF_3{\cdot}OEt_2$ mediated addition of 2-(trimethylsilyloxy)furan to iminium salts,[118] while Yoda and co-workers used a Grignard addition to a lactam en route to the first total syntheses of the pyrrolizidine tetrols hyacinthacine B_1 (**245**) and hyacinthacine B_2 (**246**) (Scheme 44).[119] Here lactam **242** [itself prepared form commercially available (*S*)-(–)-2-pyrrolidine-5-carboxylic acid] was treated with butenylmagnesium bromide to give a ketone that was diastereoselectively reduced using excess $NaBH_4$ in the presence of $CeCl_3$ in dilute EtOH solution (0.005 M) to yield alcohol **243**. Mesylation, treatment with *t*BuOK and in situ cyclisation then gave a separable mixture of diastereoisomers, with the major product being the desired isomer **244**. Both hyacinthacine B_1 (**245**) and hyacinthacine B_2 (**246**) were then synthesised in 10 steps from pyrrolidine **244** with overall yields of 21% and 24%, respectively.



Scheme 44. Reagents and conditions: a) *i*. $CH_2{=}CH(CH_2)_2MgBr$, THF, room temp., 5 min; *ii*. $NaBH_4$, $CeCl_3$, EtOH, 0 °C, 4 h, quant. (2 steps); b) *i*. MsCl, Et_3N, CH_2Cl_2; *ii*. *t*BuOK, THF, 91% (2 steps).

In 2007, Huang and co-workers used nucleophilic addition to an imide as a key methodology in the synthesis of a variety of polyhydroxylated pyrrolidines.[120] Central to

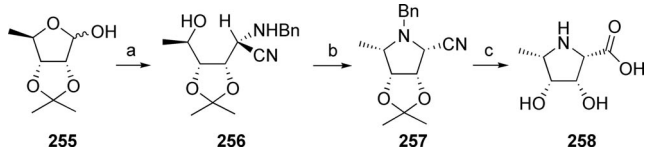


Scheme 45. Reagents and conditions: a) $BnOCH_2Cl$, Mg, $HgCl_2$ (cat.), THF, –78 °C, 9 h; or $BnOCH_2Cl$, SmI_2, $FeCl_3$ (cat.), 0 °C to room temp., 1 h; b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to room temp., 8 h, 61% (2 steps); c) CAN, CH_3CN/H_2O, 0 °C 4 h, room temp. 1.5 h, 85%; d) $LiAlH_4$, THF, 60 °C, 12 h, 92%; e) 10% Pd/C, HCOOH, MeOH, room temp., 24 h, then HCl, 100%; f) $LiAlH_4$, THF, 60 °C, 12 h, 92%; g) 2-bromoethanol, K_2CO_3, MeOH, room temp., 2 d, 80%; h) 10% Pd/C, H_2, HCOOH, MeOH, room temp., 24 h, then HCl, 100%; i) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, room temp., 4 h, 95%; j) MeMgI, CH_2Cl_2, –20 °C, 2 h, 82%; k) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to room temp., 14 h, 80%; l) 10% Pd/C, HCOOH, MeOH, room temp., 24 h, HCl, 98%; m) *p*$BnOC_6H_4MgBr$, CH_2Cl_2, –20 °C, 2 h; n) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to room temp., 14 h, 58% (2 steps); o) 10% $PdCl_2$, H_2, EtOH, room temp., 12 h, 92%.

this work was the preparation of the all *trans*-3,4-dibenzyloxy-5-benzyloxymethyl-2-pyrrolidinone (**249**), a versatile building block that was subsequently transformed into DAB-1 (**3**), *N*-hydroxyethyl-DAB-1 (**250**), 6-deoxy-DMDP (**252**) and 5-*epi*-radicamine B (**254**) (Scheme 45). Lactam **249** was itself prepared in 3-steps from tartarimide **247** through either a $HgCl_2$-mediated Grignard reaction under Barbier-type conditions or a SmI_2 mediated benzyloxymethylation, to give the *N*,*O*-ketal **248** that was then subjected to reductive dehydroxylation and removal of the PMB-group (**248**→**249**). Conversion of **249** into DAB-1 (**3**) was achieved in two steps, through a $LiAlH_4$-mediated reduction of the amide and debenzylation, while conversion into *N*-hydroxyethyl-DAB-1 (**250**) required an additional alkylation of the nitrogen following reduction of the lactam. Conversion of lactam **249** into the Boc-derivative **251**, a second stepwise reductive alkylation [via treatment with methylmagnesium iodide and a $BF_3{\cdot}OEt_2$-mediated triethylsilane reduction (*dr* = 9.4:1)], and global deprotection then gave 6-deoxy-DMDP (**252**). Alternatively, addition of a 4-benzyloxy-phenylmagnesium bromide to the Boc-protected lactam **251** gave **253** as a diastereomeric mixture alongside the open form ketone. The isomeric mixture **253** was diastereoselectively reduced with $Et_3SiH/BF_3{\cdot}OEt_2$ to give, after global deprotection, 5-*epi*-radicamine B (**254**). The enantiomer of lactam **249** was also used for the synthesis of LAB, the enantiomer of DAB-1.

6.3. Addition to Imines

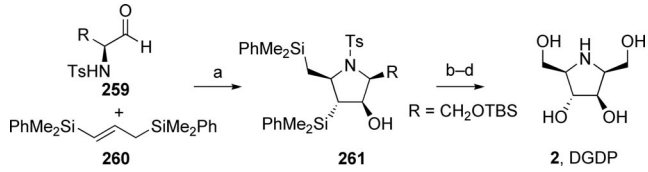
Nguyen Van Nhien and Postel and co-workers used a Strecker reaction to obtain cyano-pyrrolidines that could be conveniently converted into 2-(aminocyclopropyl)pyrrolidines and polyhydroxy prolines (Scheme 46).[123] To this end, protected 5-deoxyribose **255** was treated with benzylamine and a Lewis acid to form the benzylimine, which was reacted in situ with TMSCN to provide α-aminonitrile **256** in good (80%) yield alongside a small percentage of the *S*-diastereoisomer. Cyclisation of **256** was affected using mesyl chloride and yielded cyanopyrrolidine **257**, which could be readily hydrolysed and deprotected to give hydroxyproline **258** in excellent yield. In contemporary work, aminonitrile **257** and derivatives were also cyclopropanated to produce a series 2-(aminocyclopropyl)pyrrolidines.[123b] Yoda and co-workers also employed a strategy involving addition to glycosylamines. Using a vinyl-Grignard reagent on an L-xylosamine derivative gave access to (–)-7-*epi*-alexine and (+)-alexine.[124]



Scheme 46. Reagents and conditions: a) *i*. $Ti(OiPr)_4$, MeOH, HCO_2NH_3Bn, room temp., 14 h, then TMSCN, room temp., 5 h, 80%; b) MsCl, 80 °C, 1–2 h, 85%; c) *i*. conc. HCl, 80 °C; *ii*. H_2, Pd/C, room temp., 2 d, 78% (2 steps).

6.4. Addition to Aldehydes with In-situ Cyclisation

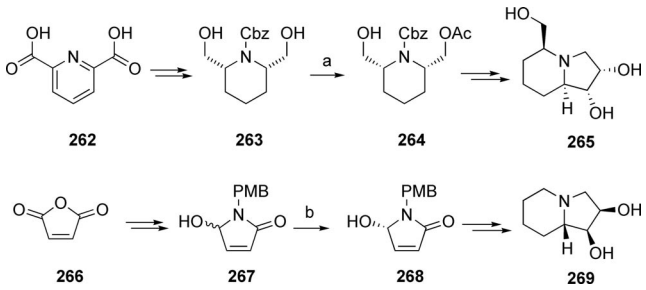
In a novel and efficient approach for the stereoselective construction of densely functionalised pyrrolidines, Somfai and co-workers employed a Lewis acid promoted [3+2]-annulation of *N*-tosyl-α-amino aldehydes **259** and 1,3-bis-(silyl)propenes.[125] In this strategy, silane **260** functioned as a 1,2-dipole equivalent, and stereoselectively reacted with amino aldehyde **259** to yield a β-silyl cation that underwent a subsequent annulation reaction to form pyrrolidine **261** (Scheme 47). A number of *N*-*p*Ts-α-amino aldehydes were amenable to these reaction conditions and gave a variety of substrates suitable for further synthetic transformations. For example, the addition of silane **260** to **259** (where R = CH_2OTBS) yielded pyrrolidine **261** (R = CH_2OTBS) which was subsequently transformed into DGDP (**2**) following desilylation, a stereo-specific Tamao–Fleming oxidation, and detosylation.



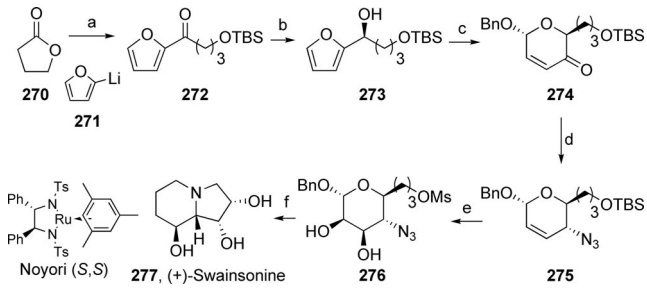
Scheme 47. Reagents and conditions: a) $MeAlCl_2$, CH_2Cl_2, –78 °C, 33–77% (*dr* >98:2); b) AcOH/THF/H_2O, room temp., c) KBr, AcOOH, room temp., 50% (2 steps); d) Li/NH_3(*l*), 65%.

7.1. Enzymatic Desymmetrisation

Several groups have employed chemical or enzymatic resolution as a key aspect in the synthesis of iminosugars with examples of recent chemical or enzymatic resolutions being depicted (Scheme 48). Silvani et al. used the commercially available pyridine-2,6-dicarboxylic acid (**262**) for the synthesis of Cbz-protected piperidine **263**.[126] Resolution of this pro-chiral diol was achieved using *Candida Cylindracea* lipase (CCL) and vinyl acetate in ionic liquid to yield acetate **264**, which was subsequently transformed into hydroxymethylindolizidine **265** in nine steps (including RCM and dihydroxylation). Takabe and co-workers also employed enzymatic resolution for the synthesis of indolizidine alkaloids.[127] Here maleic anhydride (**266**) was transformed into PMB-protected pyrrols **267** through reaction with PMB-NH_2 and Luche reduction. Lipase PS-D catalyzed kinetic resolution of **267** then gave alcohol **268** with excellent enantioselectivity. The total yield of the reaction could be improved through the base-induced hydrolysis/epimerisation of the enantiomeric acetate so as to regenerate alcohols **267**. Conversion of alcohol **268** to the indolizidine **269** was achieved in a further ten steps.



Scheme 48. Reagents and conditions: a) CCL, H_2C=CHOAc, ionic liquid, 40 °C, 24 h, 90% (98% *ee*); b) lipase PS-D, H_2C=CHOAc, dioxane, room temp., 24 h, 49% (>99% *ee*).



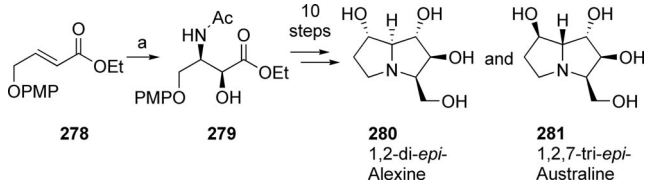
Scheme 49. Reagents and conditions: a) THF, –78 °C, 74%; b) *i*. TBSCl, imidazole, DMF, 98%; *ii*. Noyori (*S*,*S*), HCO_2H, Et_3N, 89%; c) *i*. NBS, H_2O, 0 °C, 84%; *ii*. $(Boc)_2O$, DMAP, –78 °C, 85% (*dr* = 8:1); *iii*. BnOH, Pd^0, Ph_3P, 88%; d) *i*. $NaBH_4$, CH_2Cl_2, MeOH, –78 °C, 94%; *ii*. $CH_3OC(O)Cl$, DMAP, pyr., 72%; *iii*. $[Pd(allyl)Cl]_2$, dppb, $TMSN_3$, 77%; e) *i*. TBAF, THF, 99%; *ii*. MsCl, Et_3N, 99%; *iii*. OsO_4, NMO, 93%; f) H_2 (100 psi), $Pd(OH)_2$/C, 3 d, 88%.

In addition, Donohoe et al. developed enantioselective and high yielding routes to both enantiomers of monoacetylated *cis*-2,5-bis(hydroxymethyl)-*N*-Boc-pyrroline from achiral precursors via desymmetrisation using lipoprotein lipase from a *Pseudomonas* species,[128] while Reiser and coworkers developed methodology for the synthesis of functionalised pyrrolidin-2-ones from pyrrole involving simulated moving bead (SMB) chromatography of a racemic intermediate with extraordinary productivity.[129] In more recent work, Chênevert et al. explored the enzymatic desymmetrisation of *meso*-pyrrolidine and *meso*-pyrroline derivatives as a method to generate enantiomerically enriched compounds.[130] Acylation/hydrolysis reactions of several substrates with various enzymes were investigated and efficient protocols were established for the synthesis of protected pyrrolidines with high enantiomeric selectivities.

8. De novo

De novo synthetic methodology has proven to be a fast and versatile way of constructing indolizidine and pyrrolizidine alkaloids. In 2006, Guo and O'Doherty presented the de novo syntheses of both enantiomers of swainsonine in thirteen steps from γ-butyrolactone (**270**) and lithiated furan **271** (Scheme 49).[131] The asymmetry of swainsonine was introduced by Noyori reduction of addition product **272** to give alcohol **273** in excellent yield and *ee* (>96%). Achmatowicz rearrangement and protecting group manipulations produced pyran **274** and subsequent azide introduction (→**275**) and osmylation gave diol **276**. The indolizidine ring system was formed via a one-pot deprotection/azide reduction/intramolecular reductive amination reaction to yield (.)-swainsonine (**277**).

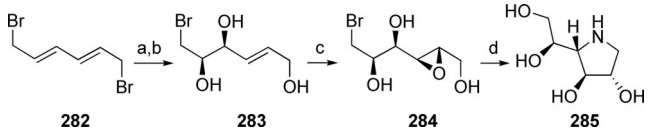
In 2005, Han and co-workers used a regioselective asymmetric aminohydroxylation (RAA) reaction during the synthesis of two pyrrolizidine alkaloids[132] (Scheme 50). RAA reaction of α,β-unsaturated ester **278** with $(DHQD)_2PHAL$ as the ligand and *N*-bromoacetamide as the nitrogen source and oxidant afforded the *syn*-amino alcohol **279** with an excellent regio- (>20:1) and enantioselectivity (>99% after one recrystallisation). Further elaboration of the hydroxylamine, involving allylation/cross metathesis for chain extension and tosylate substitution for cyclisation, provided the pyrrolizidines 1,2-di-*epi*-alexine (**280**) and 1,2,7-tri-*epi*-australine (**281**).



Scheme 50. Reagents and conditions: a) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2$-PHAL, LiOH, *N*-bromoacetamide, *t*BuOH/H_2O (2:1), 4 °C, 8 h, 70%.

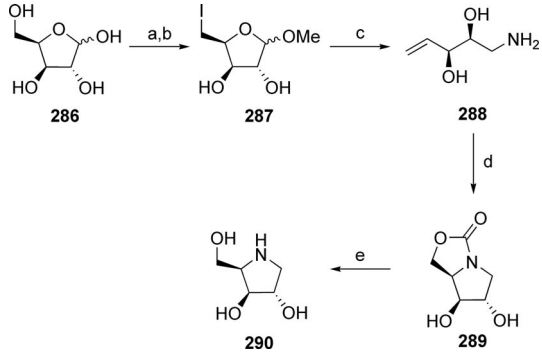
9. Protecting Group-Free Synthesis

The recent growth in environmental concern and awareness has seen a development of more efficient and less hazardous chemical processes. This also holds true for the synthesis of iminosugars with several groups having developed methodologies that allow for the synthesis of iminosugars without the need for protecting groups. Recently, Lindström et al. completed an extremely efficient protecting-group-free asymmetric synthesis of a pyrrolidine in water (Scheme 51).[133] The synthesis commenced with a modified Sharpless asymmetric dihydroxylation of 1,6-dibromodiene **282**, itself prepared in one step from cheap, commercially available 1,5-hexadiene-3,4-diol. The diol product was then selectively hydrolysed at the allylic position to afford triol **283** in 98% yield after solid-phase extraction. A number of epoxidation protocols were then explored and it was found that the use of a dinuclear peroxotungstate catalyst, $K_2[W_2O_3(O_2)_4(H_2O)_2]$, gave the best results with the required epoxide **284** being formed in excellent (99%) yield and diastereoselectivity (92% *d.s.*). Nucleophilic displacement of the bromide in **284** by ammonia led to spontaneous intramolecular ring-opening of the epoxide to afford iminosugar **285** in 88% yield. The overall yield for this total synthesis was an impressive 60%.



Scheme 51. Reagents and conditions: a) AD-mix α, $NaHCO_3$, $MeSO_2NH_2$, H_2O/*t*BuOH (1:1), 0 °C, 16 h, 70% (97% *ee*); b) H_2O, 50 °C, 3 h, 98%; c) H_2O_2, cat·$K_2[W_2O_3(O_2)_4(H_2O)_2]$, H_2O, room temp., 8 h, 99%, (92% *d.s.*); d) 10% NH_3/H_2O, 4 h, 88%.

In our own protecting group free synthesis of pyrrolidines, two novel reaction methodologies, the formation of primary amines via a modified Vasella/reductive amination reaction and the stereoselective formation of cyclic carbamates from alkenylamines, were developed.[134] Synthesis of the D-*xylo*-pyrrolidine **290** commenced with the conversion of D-xylose (**286**) into the corresponding methyl iodoglycoside **287** (Scheme 52). The modified Vasella/reductive amination protocol, which involves the addition of satd. NH_4OAc and NH_3 to a solution of methyl glycoside **287** in ethanol, then gave linear alkenylamine **288** as the only product. Alkenylamine **288** was then subjected to aqueous $NaHCO_3$ and iodine to give carbamate **289** via an unprecedented, highly diastereoselective, iodine-mediated carbamate annulation reaction. Hydrolysis of carbamate **289** then gave D-*xylo* pyrrolidine **290** in excellent yield. In summary, 1,4-dideoxy-1,4-imino-D-xylitol (**290**) was prepared in five steps and in a 57% overall yield. 1,4-Dideoxy-1,4-imino-L-lyxitol[132] and 1,2,4-trideoxy-1,4-imino-L-xylitol[135] were also prepared via similar methodology and in good overall yields.



Scheme 52. Reagents and conditions: a) 1% AcCl in MeOH, room temp., 24 h; b) PPh_3, I_2, imidazole, THF, reflux, 2 h, 61% (2 steps); c) Zn, NH_4OAc, NH_3, $NaCNBH_3$, EtOH, reflux, 18 h, 91%; d) I_2, $NaHCO_3$, H_2O, room temp., 18 h, 99%; e) NaOH, EtOH, reflux, 2 h, 99%.

Conclusions

Iminosugars are an important class of compounds and many new methodologies have been implemented for the synthesis of both known and novel iminosugars. Since 2005, methodologies for pyrrolidine iminosugar synthesis have ranged from the extension of well-precedented procedures such as reductive amination, substitution, and metathesis, to the development of strategies that include de novo methodologies, bioorgano-catalysis, and protecting-group free syntheses. Given the growing biological importance of iminosugars, it is important that synthetic effort toward the more efficient syntheses of this class of compounds continues.

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