Tetrahedron: *Asymmetry* 20 (2009) 652–671

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Tetrahedron: *Asymmetry* Report Number 110

A silver-lined anniversary of Fleet iminosugars: 1984–2009, from DIM to DRAM to LABNAc

Benjamin G. Davis *

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, United Kingdom

ARTICLE INFO

Article history:
Received 10 February 2009
Accepted 16 March 2009
Available online 22 April 2009

Special edition of Tetrahedron: Asymmetry in honour of Professor George Fleet's 65th birthday

ABSTRACT

The synthesis of iminosugars, polyhydroxylated N-heterocylces, has profoundly influenced the understanding of carbohydrate-processing and other enzyme systems. This review examines the prescient work over 25 years of one of the leading protagonists in the synthesis of these powerful compounds, examining strategy, detail and outcome.

Contents

1. Introduction

Since his first endeavours in the field of carbohydrate chemistry George Fleet has been one of the most profoundly influential[1] exponents of the synthesis of polyhydroxylated nitrogen-containing heterocycles. His reviews[2–5] in the area have insightfully analyzed the potential applications and utility of these so-called iminosugars. This review aims to summarize the elegant strategies that he has used over the past 25 years to build a remarkable collection of these sugar mimetics. These syntheses have proven to be both powerful and scalable.[6]

2. The strategy of heterocycle synthesis

It is useful to consider iminosugar heterocycle construction on a basic but nonetheless informative level: the size of the ring to be constructed. Specifically, a five-membered pyrrolidine is formed when two carbon atoms three apart from each other are linked by a nitrogen atom. In the scaffold of six carbon centres that are provided by, say, hexoses, this translates into one of three options: (i) C1–N–C4 (ii) C2–N–C5 and (iii) C3–N–C6. For piperidines the choice is smaller (C1–N–C5 and C2–N–C6), yet, there is no need to stay loyal to hexoses. The flexibility of the Kiliani ascension lets us extend the size of our scaffold and hence the range of options. For example, heptoses not only offer more choices for the synthesis of monocyclic heterocycles (e.g., C3–N–C7 for piperidines) but also allow us to synthesize bicyclic [3.3.0] pyrrolizidines, C1–N–C4–N–C7, and correspondingly octoses allow access to [4.3.0] indolizidines, C1–N–C4–N–C8.

The second layer of strategy is stereochemical. With few exceptions (vide infra), the readily available sources of nucleophilic N that we employ, for example, azide ion or benzylamine, cause configurational inversion upon their introduction. The ideal scenario is therefore one in which the two C atoms to be linked have the opposite configuration to the target. If the choice of available starting materials is limited, and there is a need to introduce with retention

* Tel.: +44 1865 275652; fax: +44 1865 285002.
E-mail address: Ben.Davis@chem.ox.ac.uk

0957-4166/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2009.03.013

of configuration, this may be achieved by simply inverting twice; this double inversion of configuration giving required retention. A number of techniques for achieving this have efficiently expanded configurational control in sugars. Since, unfortunately, several standard methods (such as the Mitsunobu reaction) work only poorly, three tried and tested methods produce good results: (i) anchimeric assistance by a neighbouring hydroxyl group leading to epoxide formation; (ii) oxidation and then reduction of the product ketone with Steric Approach Control;[7–9] and (iii) displacement of triflate by caesium trifluoroacetate.[10] In specific circumstances other strategies, such as epimerization of 2-azidolactones,[11] may also allow overall retention.[12] The examples that are outlined below illustrate these tactics in practice. The details of reagents have been deliberately omitted from schemes to maintain an emphasis on strategic elegance. Where essential or noteworthy these have been discussed in the main text; the reader is referred to the primary sources for experimental details.

3. Pyrrolidines

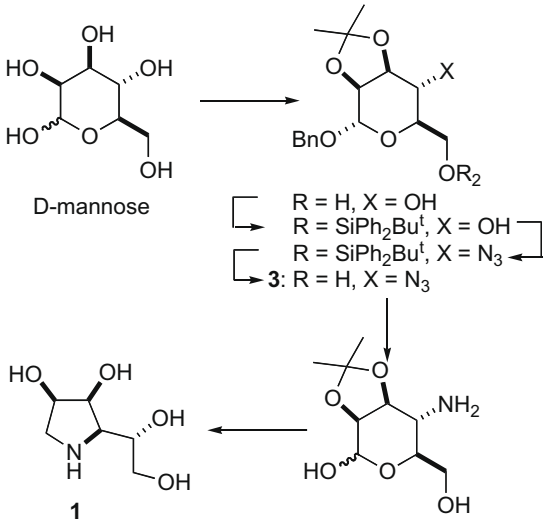
Fleet's interest and subsequently that of others was first sparked in 1984 when he synthesised DIM **1**, the first pyrrolidine analogue of a furanose sugar to inhibit a sugar processing enzyme (Scheme 1).[13] Until that point the mimicry of the pyranose substrates of these enzymes was intuitively thought to rely on the six-membered nature of piperidines such as DNJ **2**. It is now clear, through the synthesis of many such potent inhibitors, that pyrrolidines such as DIM **1** are at least as good, if not better than their piperidine counterparts, probably due to their close conformational resemblance to the postulated half-chair conformation of the transition state of glycosidases (Fig. 1) and acid–base interactions with catalytic residues in active sites.

The synthesis of DIM **1** (Scheme 1) used a C1–N–C4 strategy and was achieved in 32% yield from benzyl mannoside, which was suitably protected to allow selective access to the C-4 hydroxyl. Subsequent introduction of azide with retention of configuration was achieved through a double inversion sequence; PCC oxidation–$NaBH_4$ reduction allowed the first inversion followed by azide displacement of a triflate ester for the second.

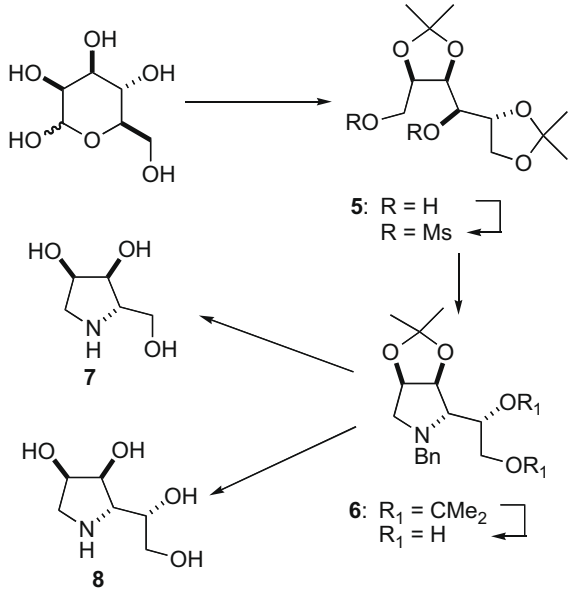
In this way an azide **3** ready for cyclization was constructed with the correct stereochemistry by the introduction of nitrogen with overall retention. Exhaustive reduction of **3**, which required a change of solvent from MeOH to CH_3COOH to avoid N-methylation,[14] formed an amine at C-4, deprotected C-1 and then allowed intramolecular reductive amination to form DIM **1** in 65% yield. One carbon degradation of DIM (**1**) also allowed the synthesis of the D-lyxitol **4**.[15]

Isomers of DIM were also synthesized using the C1–N–C4 tactic. For example, the D-talitol C-4 epimer of DIM, was synthesized in 52% yield from D-mannose (Scheme 2).[16] Diacetone mannose was reduced to the corresponding mannitol **5**, di-mesylated and then cyclized via treatment with benzylamine to the fully protected talitol **6**, which following deprotection, afforded D-talitol **8**. Oxidative cleavage of the side chain and direct $NaBH_4$ reduction also gave the L-ribitol **7**.

In 1985 Fleet et al. synthesized DMDP **9**, which at that time was the only known example of a naturally occurring polyhydroxylated pyrrolidine alkaloid, in order to establish its absolute configura-



Scheme 1.



Scheme 2.

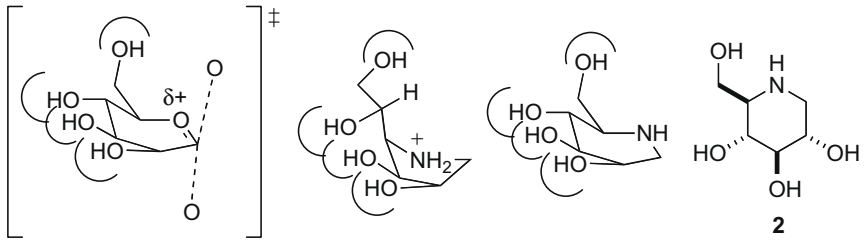


Figure 1.

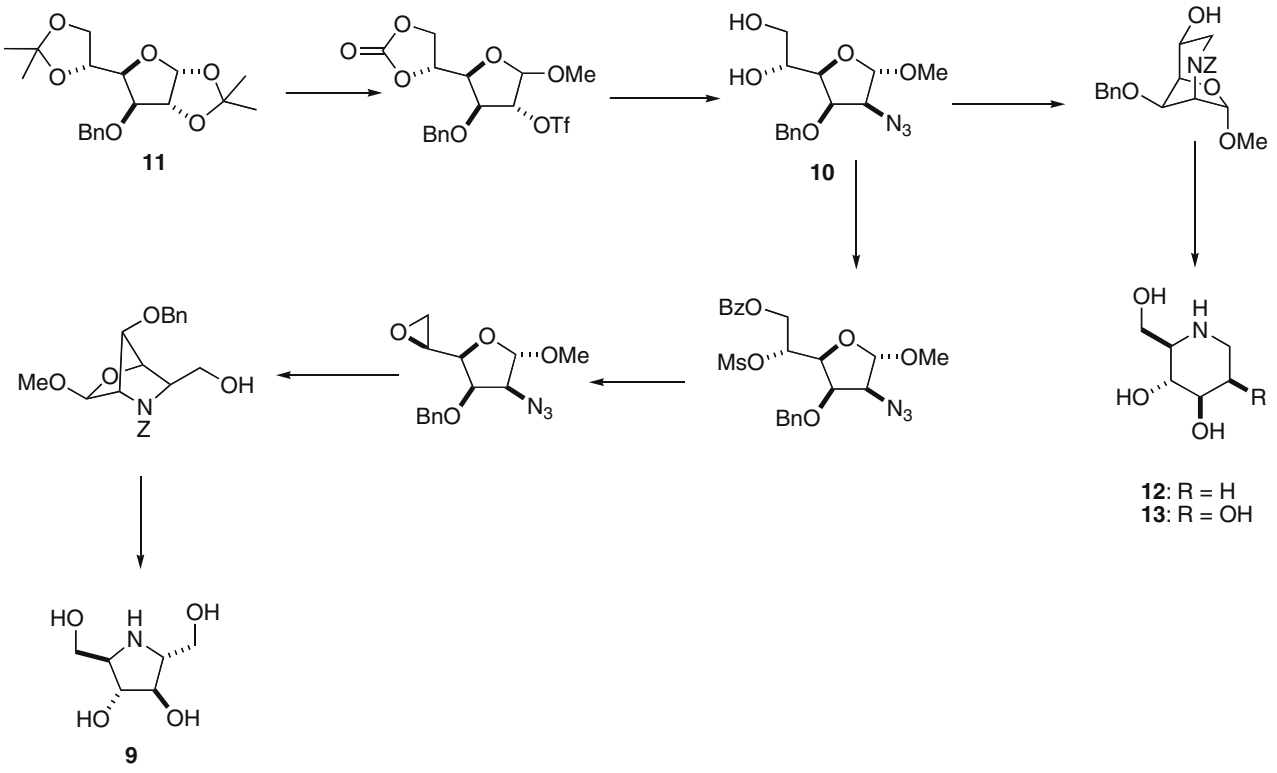
tion.[17] The key divergent intermediate, the 2-azidodiol **10**, which was prepared from the benzyl ether of diacetone glucose (DAG) **11** on a gram scale (Scheme 3), already has N introduced at C-2. Simply by choosing whether to close this onto C-5 or C-6 they were able to synthesize pyrrolidines and piperidines, respectively. In this case elaboration led to DMDP or to the piperidines DMJ **13** and fagomine **12**.

Unfortunately, a major practical limitation to the use of 2-azidofuranoside intermediates such as **10** (Scheme 3) is the efficient introduction of nitrogen at C-2 (see Section 6). However, this problem can be circumvented by using an intramolecular approach as an alternative variation of the C5–N–C2 strategy. A good example is shown in Scheme 4.[18] DAG **14** was converted to xylofuranside **15** into which was introduced azide and nitrile groups via the corresponding mesylate and triflate, respectively. Reduction of the azide **16** caused cyclization onto a triflate group at C-2 and the formation of the [2.2.1] bicyclic furanoside **17**. Similarly, the nitrile **18** was reduced and converted to the [3.2.1] bicycle. This method of introducing of N at either C-5 or C-6 and subsequent closure onto C-2 allows cyclizations with much greater efficiencies, without encountering difficulties such as anomer separation (see Section 6). Elaboration of **17** and **19** through hydrolysis and oxidation gave the proline **20** and the pipecolic acid **21**, respectively, in excellent yields.

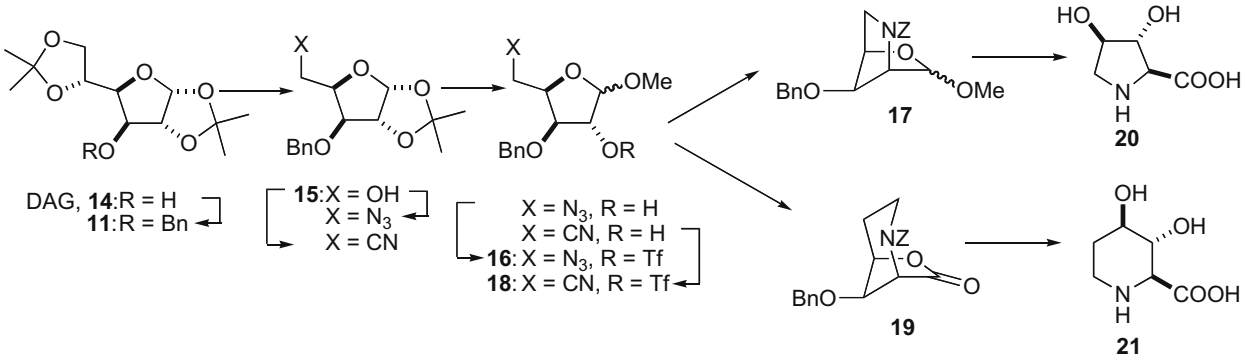
Xylose provides a good example of the often-special diversity that sugar starting materials can offer (Scheme 5). The C_2 axis of symmetry that xylitol possesses means that the simply by linking its C-2 and C-5 atoms D-arabinitol (DAB1, **22**) [23% overall yield] may be formed whereas joining of the C-1 and C-4 atoms allows access, just as simply, to the enantiomeric L-arabinitol (LAB1) **23** [30% overall yield].[15] Screening shows **22** and **23** to be active as inhibitors whereas isomeric D-lyxitol and L-ribitol are not. LAB1 was also readily synthesized from lyxonolactone using the C2–N–C5 method[19] in which retention of configuration at C-2 was achieved using the epoxide method. Recently, using appropriate lyxonolactones as starting materials the 2-deoxy-2-acteamide analogues LABNac and DABNAc have been prepared.[20] LABNAc is the first potent pyrrolidine inhibitor (non-competitive) of hexosaminidases with DABNAc showing almost no activity at all. The inhibitory behaviour of LAB1/DAB1 and LABNAc/DABNAc amongst other enantiomeric iminosugars has prompted interesting speculation on modes of action.[21]

Sugar lactones have proved themselves to be ideal chirons for several syntheses of highly functionalized homochiral compounds, but they are especially suitable for the preparation of polyhydroxylated pyrrolidines. In particular, available γ-lactones, in which C-1 and C-4 are protected as the lactone function, are ideal for use in the C1–N–C4 strategy. In two parallel syntheses (Schemes 6 and 7) fully protected D-galacto- **24** and D-gulono- **25** lactones were reduced to their corresponding alditols.[22] Diesterification of these diols with MsCl allowed closure, using benzylamine, to the corresponding D-glucitol **26** and D-allitol **27** pyrrolidines. Deprotection of **26** and **27** allowed the preparation of D-glucitol **28**, a powerful glucosidase inhibitor, and of D-allitol **29**. Compound **27** was also elaborated to D-ribitol **30** and the corresponding dihydroxyproline. More recently, a near identical approach was used for the synthesis of the D-galactitol **31** from gluconolactone.[23]

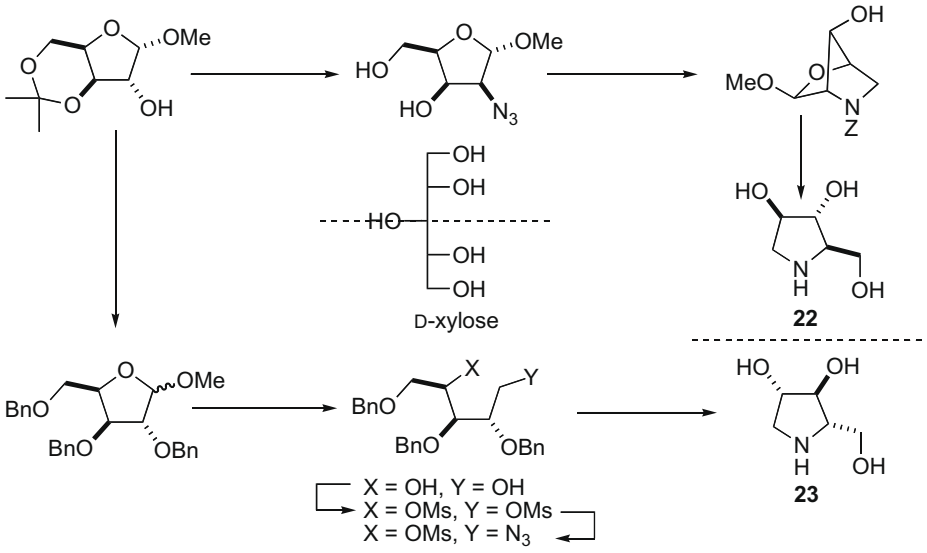
Diastereomeric azido lactones **32** and **33** have been used in parallel C2–N–C5 strategies for the synthesis of DGDP **34** and corresponding polyhydroxylated prolines **35** and **36**, respectively (Scheme 8).[24] Starting from the appropriate monoacetonide 1,4-lactone, selective triflation and then azide displacement under thermodynamic conditions[11] allowed the introduction of azide at C-2 with retention of configuration. Suitable protecting group manipulation then allowed the triflation of C-5. Reduction of the C-2 azido group resulted in the formation of the [2.2.1] bicyclic amine **37**, following intramolecular ring closure, and of the monocyclic lactone **38**, which cannot cyclize due to the *trans* arrangement of its C-2 amine group and the C-4 side chain. Reduction and deprotection to give DGDP **34** confirmed the structures of both



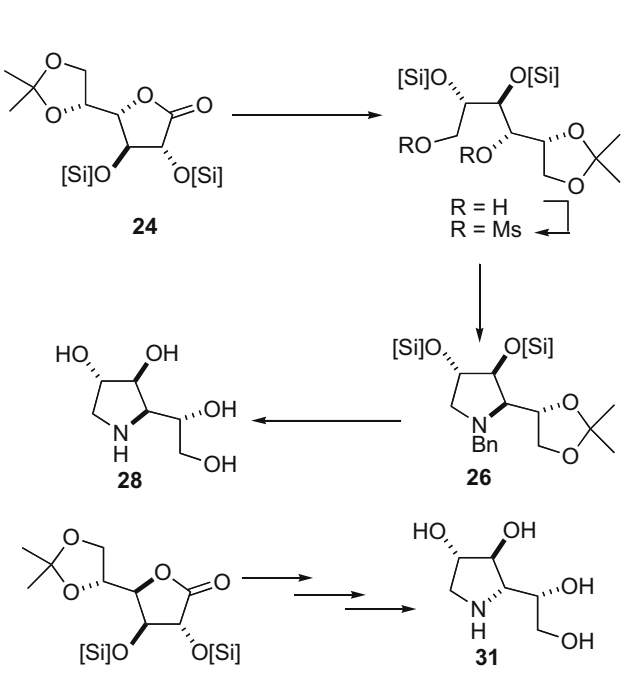
Scheme 3.



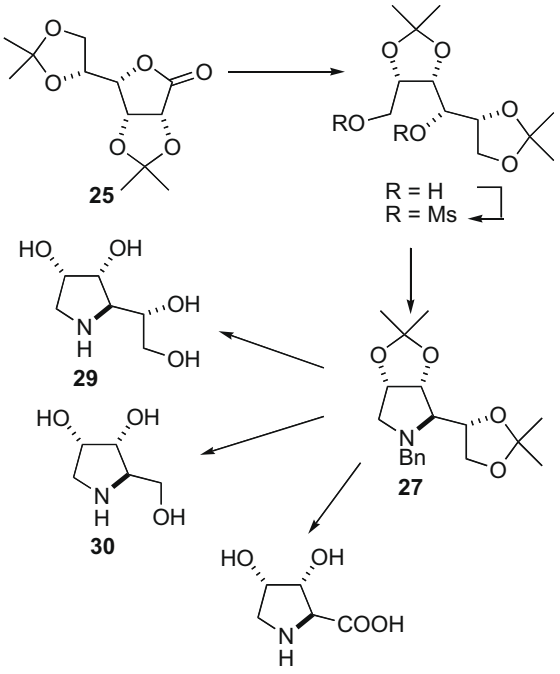
Scheme 4.



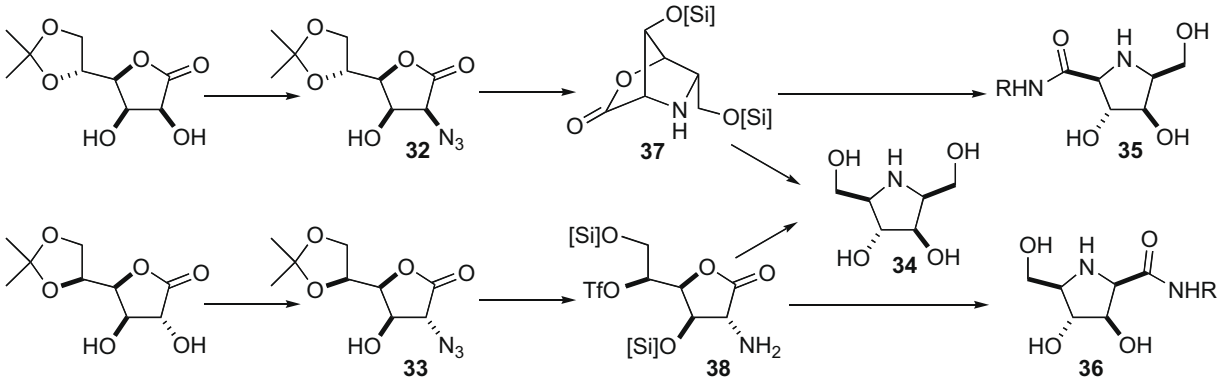
Scheme 5.



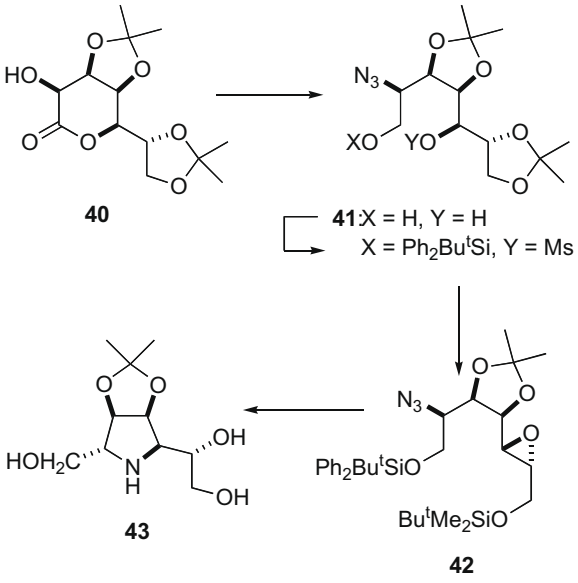
Scheme 6.



Scheme 7.



Scheme 8.



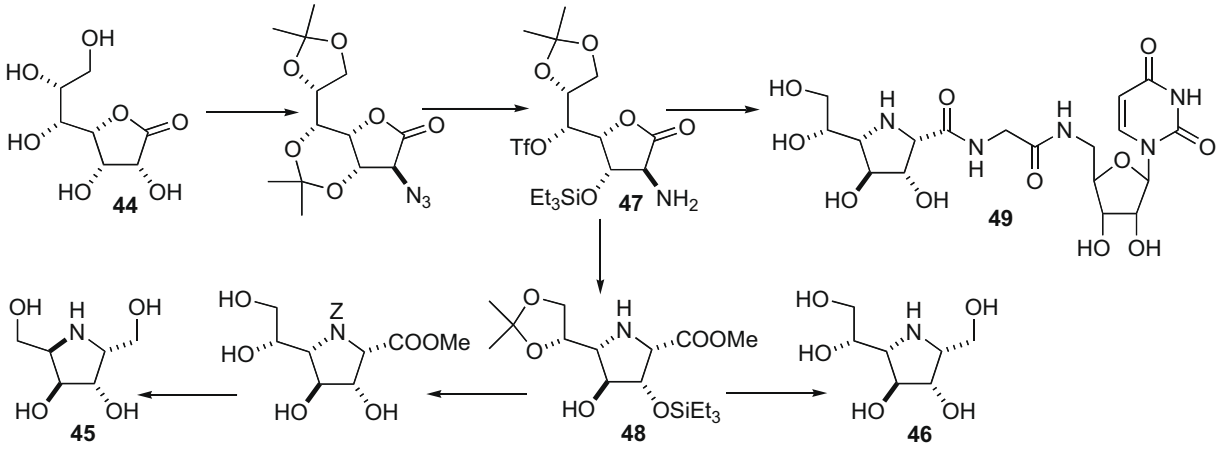
Scheme 9.

37 and **38**; treatment with amines gives the proline amides of type **35** and **36**, respectively.

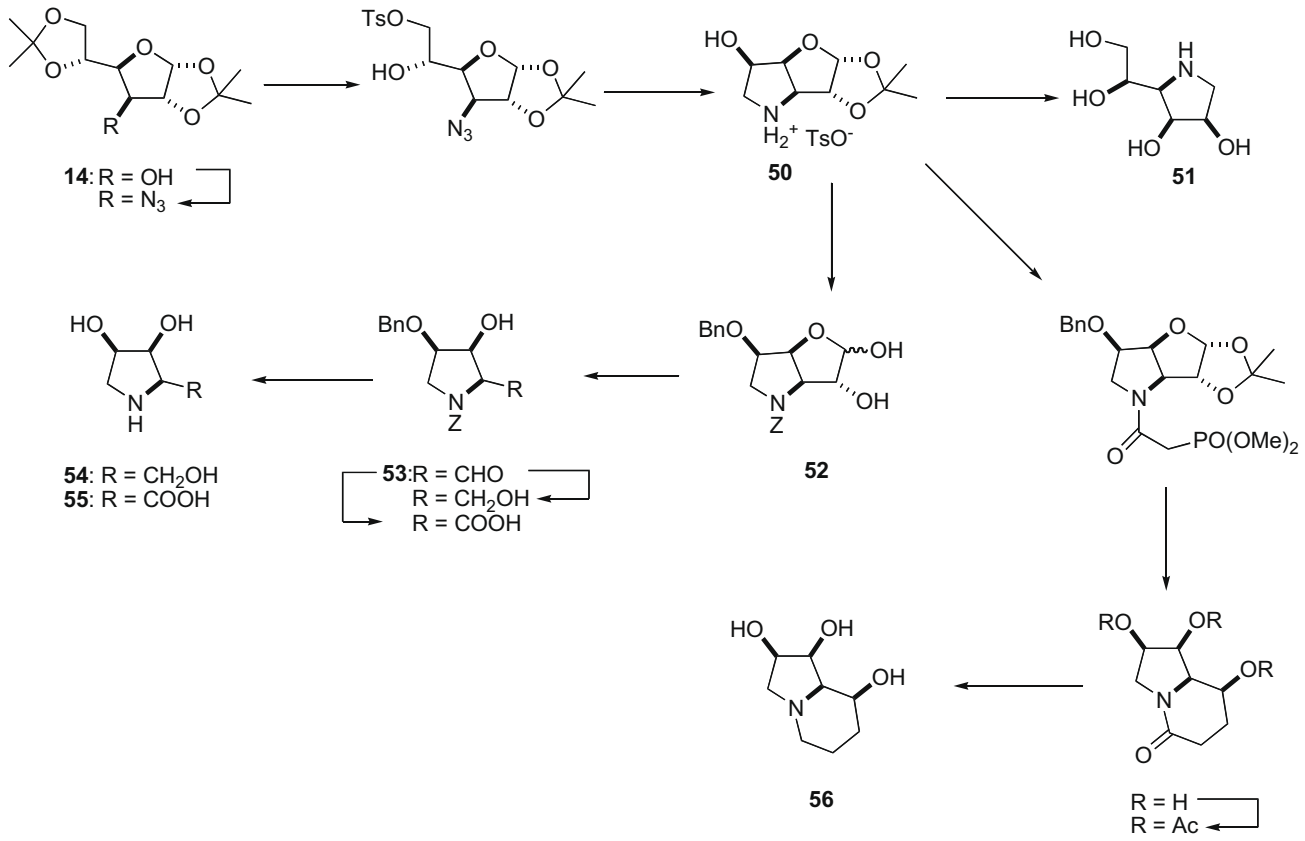
To investigate the effect of pseudoanomeric substituents upon inhibitory activity, Fleet et al. have extended their synthetic efforts to seven carbon pyrrolidines; homoazasugars bearing an extra carbon as a substituent at the pseudoanomeric centre (Scheme 9).[25] The major Kiliani product of diacetone mannose (DAM, **39**), is the δ-lactone **40**. Employment of the C2–N–C5 method required the introduction of N with retention at both C-2 and C-5. At C-2, an advantageous epimerization yielded the more thermodynamically stable azide **4** upon treatment of the triflate of **40** with NaN_3 (which could then be correlated to **41**),[26] while at C-5, the formation of the epoxide **42** caused the first inversion of C-5 and reduction cyclized the C-2 azide to cause the second. After deprotection, α-homoDIM (**43**) showed increased specificity, as a result of its extra pseudoanomeric hydroxymethyl group, but similar potency to DIM **1** for Golgi α-mannosidases.

L-DMDP, the unnatural enantiomer of DMDP **9** was recently synthesized[12] from D-gulonolactone using a C2–N–C5 strategy via the appropriate 2-azidolactone. Correct configuration at C-2 was accessed through appropriate azidolactone equilibration.[11] Remarkably, unnatural L-DMDP is 2–4 orders of magnitude more potent against plant and mammalian α-glucosidases than DMDP. Results such as these and those for DAB1/LAB1 and DABNAc/LABNAc have prompted Asano and Fleet to speculate that iminosugar enantiomers generally have different binding mechanisms (competitive vs non-competitive), modes and even sites for a given enzyme.[21]

A different seven carbon scaffold, α-glucoheptonolactone **44**, was used as the starting material for the preparation of the homoazasugar pyrrolidines **45** and **46** (Scheme 10).[23] The introduction of nitrogen between C-2 and C-5 with inversion at both centres was achieved through the initial displacement of a C-2 triflate with



Scheme 10.



Scheme 11.

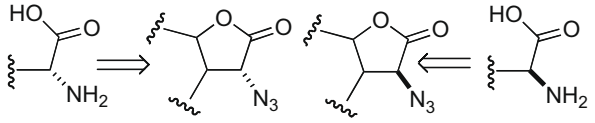
azide. Protecting group adjustment allowed the selective esterification of the C-5 hydroxyl with Tf_2O; subsequent reduction of the C-2 azide group affords the amine **47**. Treatment of the aminotriflate **47** with a range of nucleophiles caused sequential ring opening of the lactone function and displacement of the triflate ester. This ring opening and then closing sequence allowed the formation of the pyrrolidine moiety with introduction of a variety of carboxy substituents at the pseudoanomeric centre. For example, treatment with methanol gave the methyl ester **48** which after reduction and deprotection gave the α-homoiminogalactitol **46**. Furthermore, treatment with amines allowed the synthesis of peptidomimetics such as the galactofuranosyl uridine diphosphate (UDP-Gal*f*) mimic **49**.[23,27] Alternatively, the L-enantiomer **45** of the previously synthesized DGDP,[28] can be made from **48** through oxidative degradation of its diol side chain. Both **46** and **49** are the first examples of specific inhibitors of mycobacterial galactan biosynthesis, probably by inhibition of UDP-Gal*f* mutase with the pseudoanomeric substituent perhaps resembling UDP, and, as such, represent a novel strategy for the treatment of TB. This notion has been much studied by others in the 10 years since Fleet's first prescient investigations.

The bicyclic ammonium salt **50** (Scheme 11) proved useful as a key divergent intermediate for the synthesis of both pyrrolidines and indolizidines.[29] It was readily prepared in 53% yield on a multigram scale from diacetone glucose **14**, using the oxidation/reduction method to initially invert C-3 and then azide displacement of a C-3 triflate to introduce nitrogen with overall retention of configuration. The yield of 92% for this introduction of azide illustrates the utility of triflates as leaving groups in carbohydrate chemistry; the use of mesylate or tosylate gave much lower yields and required harsher conditions.[30,31] The required pyrrolidine ring was constructed by cyclizing the C-3 azide group, through reduction, onto a C-6 tosylate group—an example of the well established C3–N–C6 strategy.[32,33] Subsequent deprotection of **50** and then reduction gave gulitol **51**, epimeric at C-5 to DIM **1**, whilst protecting group adjustment gave lactol **52** which underwent oxidative cleavage of the C-1 to C-2 bond. The resulting aldehyde **53** was treated with $NaBH_4$ to give, after deprotection, lyxitol **54**, a potent inhibitor of coffee bean α-galactosidase. Alternatively, oxidation yielded the dihydroxyproline **55**. As Scheme 9 illustrates, the bicycle **50** was also used as a building block for the synthesis, via an intramolecular Wadsworth–Emmons reaction, of 8-*epi*-swainsonine **56**.

Sugar lactones in which all but the C-2 hydroxyl can be readily protected are ideal for the synthesis, by introducing nitrogen with suitable configuration at C-2, of polyhydroxylated D or L-amino acids (Scheme 12).

For example, glucoronolactone acetonide **57** (Scheme 13) possesses the following features: (i) protection to give only the α-hydroxy group free is readily accomplished, (ii) substitutions at this α-position are facile (to give e.g. azide **58**) and (iii) the required +3 oxidation state is already in place at C-1.

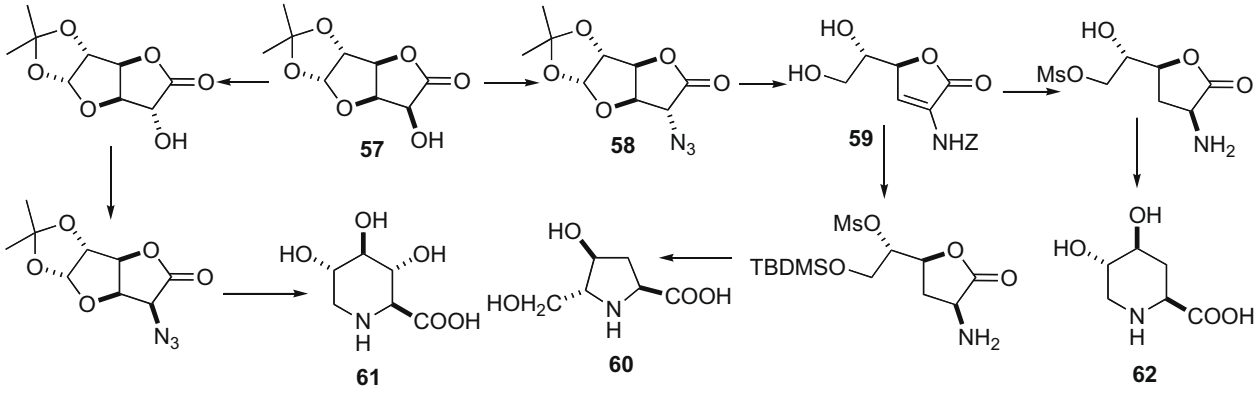
Reduction and then protection of **58** followed by base catalyzed fragmentation gave the versatile unsaturated intermediate **59**.[34] Compound **59** was elaborated to the C-5 mesylate which was converted, using reduction and ring opening of the lactone, to Bulgecinine **60**. Compounds **57** and **59** were also easily transformed into



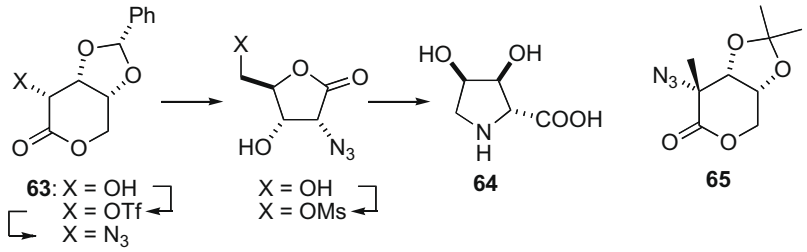
Scheme 12.

the pipecolic acids **61** and **62**, respectively. A further example of the use of 2-azidolactones stems from Zinner's lactone **63** as a starting material for the synthesis of proline **64** (Scheme 14).[35] Following triflation, azide was introduced at C-2 with an unexpected retention of configuration, and deprotection and reduction allowed cyclization (C2–N–C5) of the resulting amine via hydroxide-mediated ring opening of a corresponding C-5 mesylate. A 2-C-methyl-2-azido-lactone **65** has recently been used to prepare examples of C-branched pyrrolidines and prolines.[36] This route also featured a remarkable azide displacement of a tertiary triflate, presumably via an S_N1 mechanism despite neighbouring C-1 C=O.

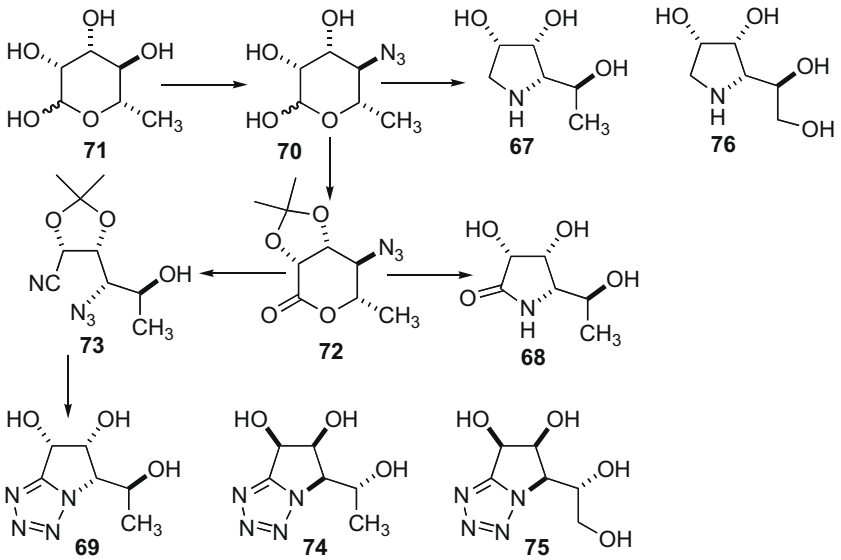
So far this account has concentrated exclusively on nucleophilic ring-closing methods for the synthesis of pyrrolidine-containing sugar mimics, but as Scheme 15 shows the use of azidolactone intermediates in cycloadditions as part of a C1–N–C4 strategy is also possible. Despite success in synthesizing a wide range of glycosidase inhibitors by 1995, Fleet had until that point not found a potent inhibitor of rhamnosidases. The piperidine analogue LRJ **66** (see Section 6 and Scheme 30) had shown no inhibitory properties, and so instead pyrrolidine mimics **67**–**69** were investigated. A flexible route that allowed the synthesis of all three materials from the key divergent intermediate azidolactol **70**, which was prepared on



Scheme 13.



Scheme 14.



Scheme 15.

a gram scale using a double inversion approach to introduce azide at C-4 with overall retention from L-rhamnose **71**.[37,38] Reduction of this unprotected intermediate **70** gave the pyrrolidine DRAM **67** directly, whilst bromine oxidation of C-1 allowed the formation of the γ-lactam **68** via the lactone **72**. Vasella had already successfully designed piperidine tetrazoles as neutral transition state analogues for the inhibition of glucosidases.[39] However until the synthesis of pyrrolidine tetrazole **69**[40] it was unclear whether the same design elements, such as an sp^2 pseudoanomeric centre, would translate successfully to a smaller system. Indeed, there are only two naturally occurring compounds, nagstatin and kifunensine, in which a second nitrogen-containing ring is fused to a polyhydroxylated one in this manner and both are piperidines. Ring opening of **72** with ammonia and dehydration of the resulting open-chain primary amide allowed the formation of azidonitrile **73**. This was the substrate for a highly efficient thermally induced 1,3-dipolar [3+2] cycloaddition of the C-4 azide and the C-1 nitrile groups which, after deprotection, gave **69**. Both **67** and **69** were good inhibitors of an α-L-rhamnosidase, with K_i's of 1 and 56 μM, respectively. Near-parallel routes[37,40] allowed the preparation of the D-mannose **75** and D-rhamnose **74** equivalents of **69** but interestingly neither showed any inhibitory potency towards mannosidases.[41,42] The hydroxylated analogue of DRAM is L-DIM **76** and was also recently synthesized[43] for the first time from α-gluco-heptonolactone **44** using a C1–N–C4 strategy. L-DIM is also a rhamnosidase inhibitor; the same route also yielded a heptitol homologue that was a less active inhibitor.

The future for pyrrolidine inhibitors as tools for elucidating the mechanism of action of glycosidases has recently been highlighted by the isolation of a further series of naturally occurring derivatives of DMDP, which have extended and derivatized C-6 side chains.[44,45] These compounds suggest that hydroxyl groups in the side chain of DMDP may be involved in the mechanism of inhibitory action in contrast to the traditional mode illustrated in Figure 1. Interestingly, an open chain equivalent of DMDP has been synthesized through the reductive animation of dihydroxyacetone and this compound shows no inhibition of either glycosidases or glycosyltransferases.[46]

4. Indolizidines

In 1984, Fleet et al. were able to confirm the absolute stereochemistry of an indolizidine that is still the most potent inhibitor of many mannosidases, namely D-(−)-swainsonine **77**.[47] Retrosynthetic analysis (Fig. 2) had revealed that the synthesis of (−)-swainsonine required a two carbon chain extension from the C-6 of the azido mannopyranoside **78** (Scheme 16).

This was achieved conveniently through a Wittig reaction of the C-6 aldehyde of **78** with formylmethylene triphenylphosphorane. The resulting *E*-azidoenal **79** was then cyclized through two sequential hydrogenations, which as for the synthesis of DIM **1** required a change of solvent from MeOH to CH_3COOH. Consumption of 5 equiv of hydrogen gave, after deprotection, (−)-swainsonine **77** in four steps from intermediate **79**; thus completing the first enantiospecific synthesis of this important alkaloid. An alternative approach involving initial construction of the pyrrolidine moiety of swainsonine, also proved successful.[48] The azido-epoxide **80**, was extended by two carbons through triflate esterification of the primary alcohol and treatment with lithium *tert*-butyl acetate. The resulting chain extended ester **81** was hydrogenated, which

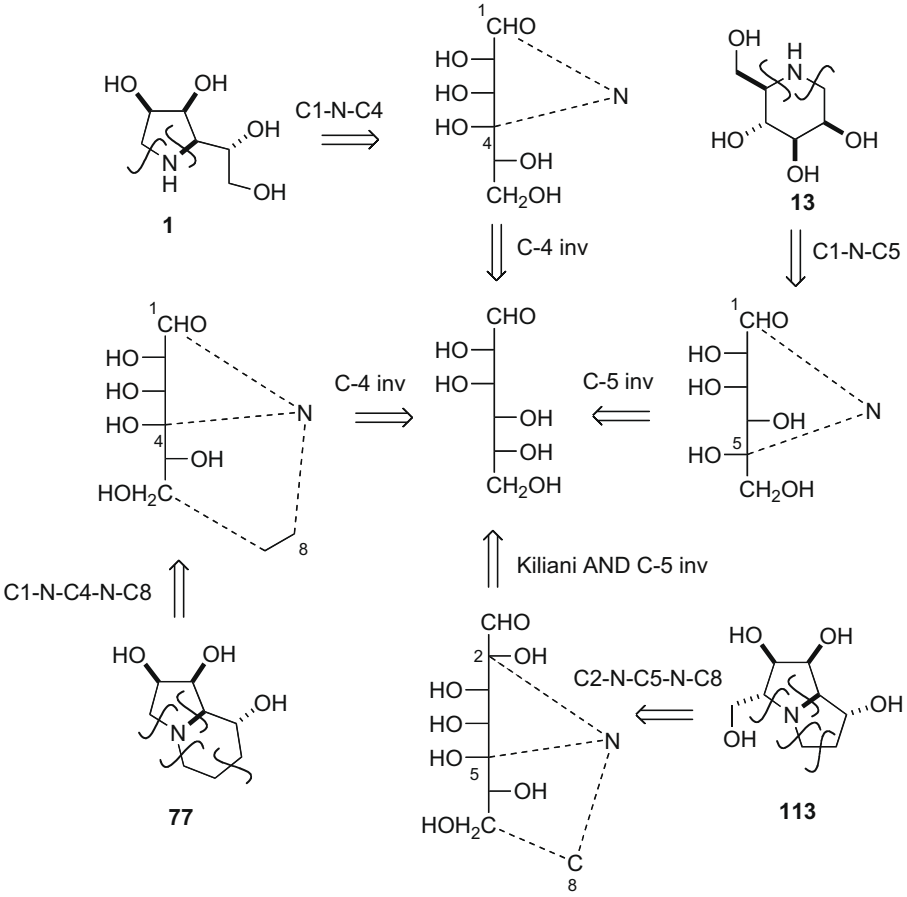
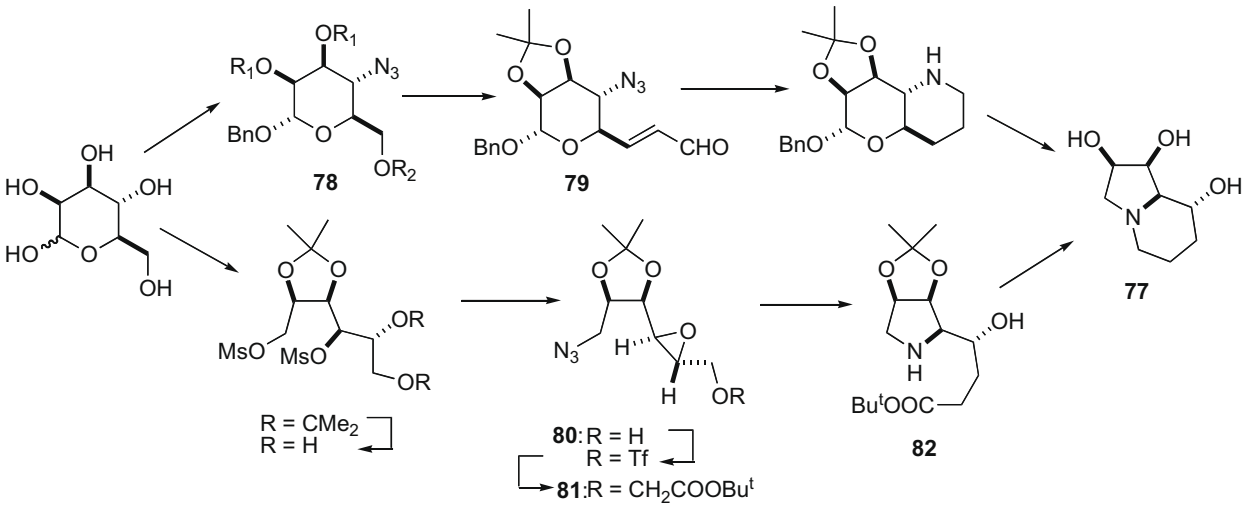


Figure 2.



Scheme 16.

allowed the formation of the pyrrolidine ester **82**. Treatment with NaOMe closed **82** to a δ-lactam, which upon reduction and deprotection gave (−)-swainsonine. The flexibility of this method is such that by extending **80** by only one carbon, ring contracted swainsonines can also be made (see Section 5).

More recently, Fleet et al. have synthesised indolizidines that have proved to be as powerful inhibitors of the α-L-rhamnosidase, naringinase. L-Rhamnose is the enantiomer of 6-deoxy-D-mannose and the structural features that are responsible for the inhibition of D-mannosidases by swainsonine **77** and DIM **1**, are mirrored by those in L-rhamnosidases. The work that led to the elucidation of this mirror-image ('looking glass') relationship was initiated by the synthesis of the highly oxygenated 2-hydroxycastanospermines (pentahydroxyindolzidines) **83**, **84** and **85** (Scheme 17).[49]

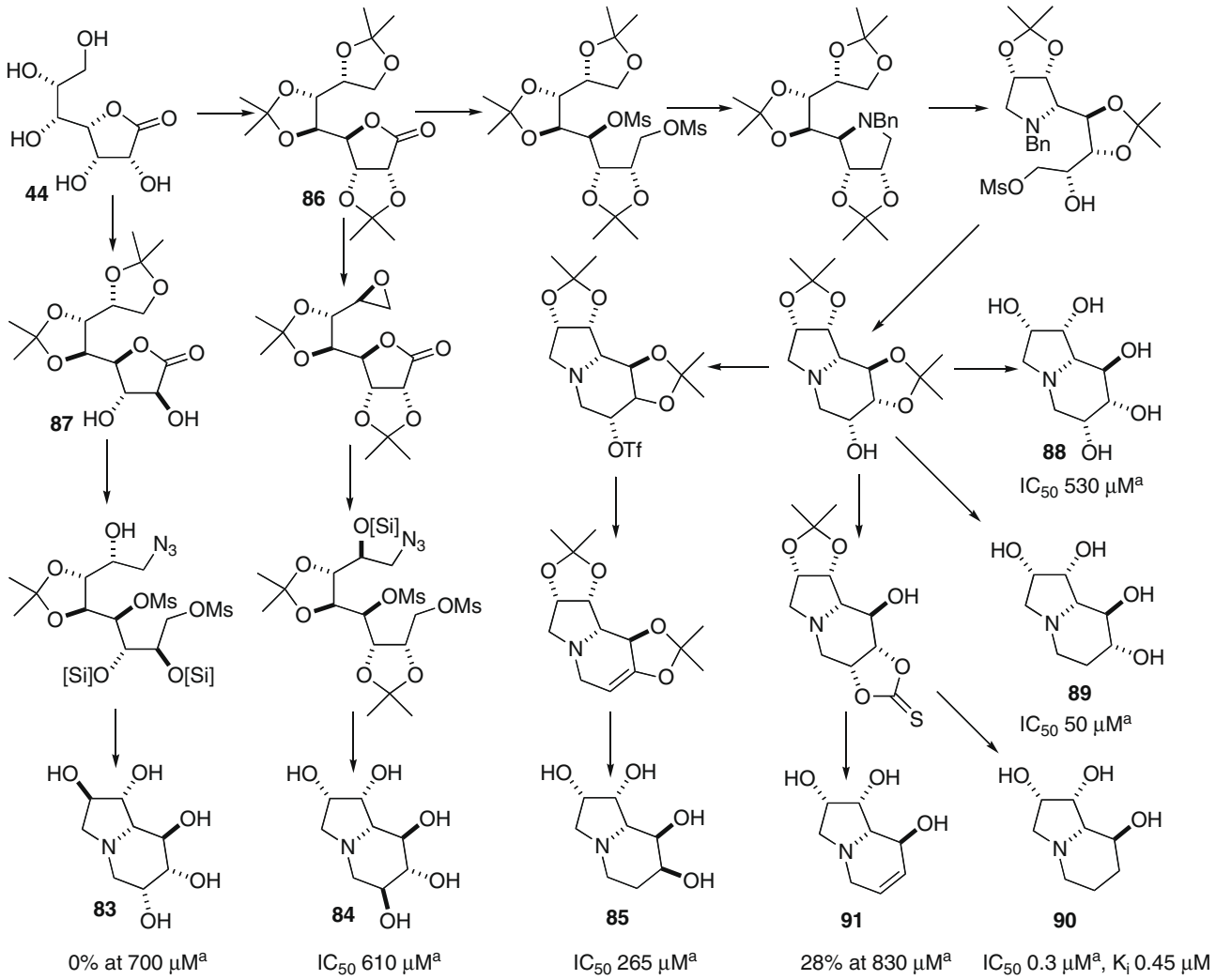
Although the synthesis of these highly oxygenated derivatives would appear to increase the synthetic difficulty, ready access to these compounds was attained through the synthesis of eight-carbon sugar lactones **86** and **87**. These are available in large amounts by Kiliani ascension of α-glucoheptonolactone **44**, itself the major Kiliani product of D-glucose. By connecting the C-1, C-4 and C-8 of **86** with nitrogen Fleet was able to synthesize the 2*S*-2-hydroxycastanospermine **84** and its C-6 epimer **88** in good overall yields (Scheme 17). Similarly, 2,6-diepimer **83** was synthesised from the C-2 epimeric lactone **87**, protecting the now *trans*-diol unit at C-2 and C-3 as silyl ethers. As Scheme 17 illustrates, two different strategies were used: for **88** N was introduced first at C-1, closed onto C-4 and then onto C-8 whereas for **83** and **84** the order was reversed and N was introduced onto C-8 first and closed onto C-4 and then C-1 in one step. Interestingly, these routes all involve high yielding cyclizations to form piperidines with *trans*-acetonides. This success contrasts with similar attempted syntheses of castanospermines, and the key may be that, even if epoxides are formed, the rigidity of the ketal protection precludes unwanted cyclization. The interesting upshot of these syntheses was that, although designed as glucosidase and mannosidase inhibitors, **84** and **88** were, in fact, moderate inhibitors of naringinase whereas **83**, containing a *trans*-diol unit in the pyrrolidine moiety, showed no such inhibition. Thus, the pyrrolidine azafuranose-mimic moiety predominates over the piperidine azapyranose-mimic moiety and **84** and **88** are better described as dihydroxy-L-swainsonines. These surprising inhibitory properties associated with the *cis*-diol pyrrolidine unit of **84** and **88** gave Fleet the first indication of the potential of these compounds as a new class of rhamnosidase inhibitors. This was explored further by synthesizing the corresponding monohydroxy-L-swainsonines: **89**, via a Barton–McCombie deoxygenation, and **85**, via the reduction of an enol ether.[38] L-(+)-Swainsonine **90** and an unsaturated derivative **91** were accessed using a Corey–Winter fragmentation. As the inhibitory data in Scheme 17 show, the inhibitory potency increases markedly as the C-6 and C-7 hydroxyl groups are removed and L-(+)-swainsonine proved to be the most potent competitive inhibitor of rhamnosidase at that time. It is interesting to consider that this type of mirror-image relationship may also extend to other enantiomeric pairs, such as D-galactose versus L-fucose.

Very recently, use of appropriate stabilized Wittig reagents ($Bu_3P{=}C(Me)CO_2Me$ or $Bu_3P{=}C(H)CO_2Me$) to extend a C-6 aldehyde **92** of a protected DRAM derivative followed by reduction or stereoselective dihydroxylation (Scheme 18) gave access to a further range of indolizidine analogues of L-swainsonine **93**–**96** as well as L-(+)-swainsonine **90** itself.[50] From these, C-6-methyl-analogue **93** was >10-fold more potent than L-(+)-swainsonine **90** as an inhibitor of naringinase.

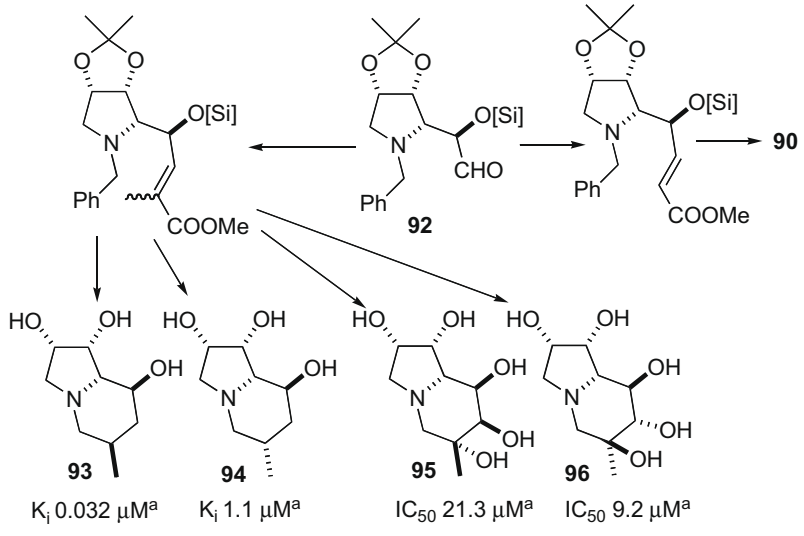
The correct stereochemistry of 6-*epi*-castanospemine **97**, the third indolizidine after swainsonine and castanospermine to be isolated from natural sources, was also confirmed by Fleet.[51] A C1–N–C5 synthetic strategy (Scheme 19) starting from L-gulonolactone **98** allowed the initial construction of the mannopiperidine ring in **99**. Extension from C-6 using vinyl magnesium bromide to introduce a 2 carbon unit allowed, after hydroboration, the formation of the pyrrolidine ring and yielded **97** in addition to the C-3 epimer **100**. An identical sequence from D-gulonolactone also allowed the synthesis of the L-enantiomers **101** and **102**. Rigorous inhibition studies on all four showed that only **97** showed the same potent inhibition of amyloglucosidase as the natural product.

5. Pyrrolizidines

For the synthesis of alexine **103**, the first naturally occurring pyrrolizidine alkaloid with a carbon substituent at C-3, the azido furanoside **10**, used previously in the synthesis of DMDP **9** (Scheme 3), proved an ideal starting material (Scheme 20).[52] Closure of the C-2 azide group onto C-5 formed the [2.2.1] bicycle **104** containing a pyrrolidine moiety with the correct stereochemistry for **103**. Using the same strategy as that used for castanospermines (Scheme 19), the second pyrrolidine ring was constructed through

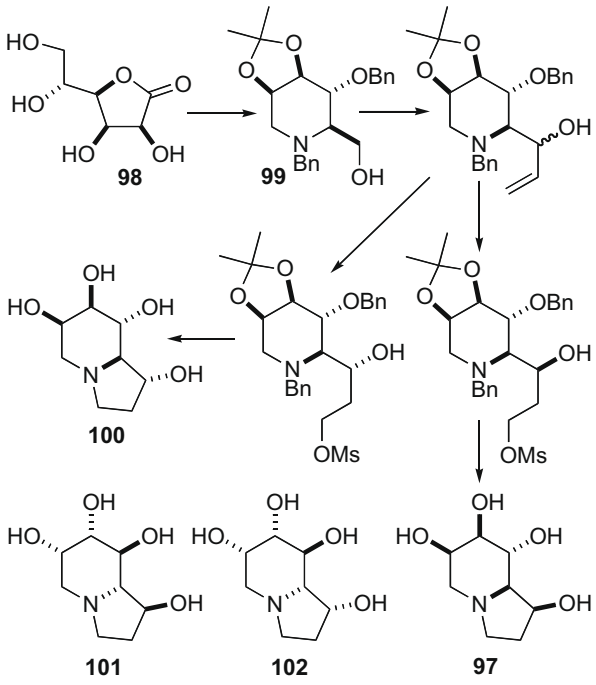


Scheme 17. [a]Inhibition of naringinase (α-L-rhamnosidase from *P. decumbens*) activity.

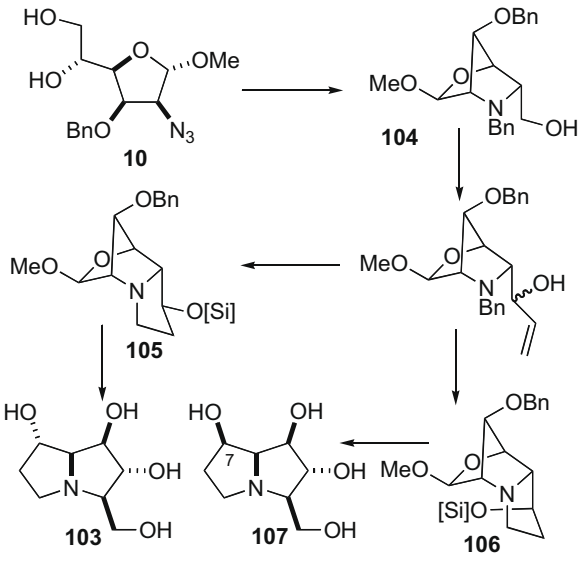


Scheme 18. [a]Inhibition of naringinase (α-L-rhamnosidase from *P. decumbens*) activity.

a two carbon extension from C-6 using vinyl magnesium bromide. The resulting tricycles **105** and **106** were fully deprotected and reduced with $NaBH_4$ to give alexine **103** and 7-*epi*-alexine **107**, respectively.



Scheme 19.



Scheme 20.

Heptonolactones represent ideal starting materials for alexines, trihydroxy(hydroxymethyl)indolizidines, since in contrast to the above syntheses the required additional stereogenic centre is already present. Fleet has explored two approaches to alexines along these lines (Scheme 21).[53] Both involved a one carbon homologation of C-7 and a C2–N–C5–N–C8 cyclization strategy; one starting from the Kiliani product of L-gulose, and the other from the readily available azidoheptonolactone **108**, derived by ascension of D-mannose. Thus, reduction of **109** to the corresponding mannitol, followed by protection and esterification with MsCl formed the mesylate **110**. The primary ketal was selectively hydrolyzed and the diol treated with $Ba(OMe)_2$ to form an epoxide with inversion at C-5. Triflation of OH-6 and treatment with LiCN allowed the formation of extended nitrile **111**. Hydrogenation led to closure of the first pyrrolidine ring, and introduced nitrogen at C-5 with a second inversion, (overall retention from **109**). Treatment of **112** with NH_4Cl in aqueous NH_3 led to cyclization of the second ring and subsequent reduction and deprotection gave 1,7,7a-triepialexine **113** via **115**. Interestingly, although the stereochemistry at C-6 in δ-lactone **108** is already correct for the synthesis of 1,7a-diepialexine **114**, the epimerization of **115**, in fact, represents a more efficient synthesis than an essentially analogous route from **108**. The problem step in the latter sequence was the key pyrrolidine-forming cyclization, which only afforded a yield of 5%. This illustrates the potentially striking differences in the crowding of epimeric transition states.

It should be noted that a thorough study of the proton NMR spectra of alexines has revealed that chemical shifts are unreliable as a means of unequivocally identifying diastereomers.[54] However ^3J coupling constants provide reliable and valuable information on both configuration and conformation.

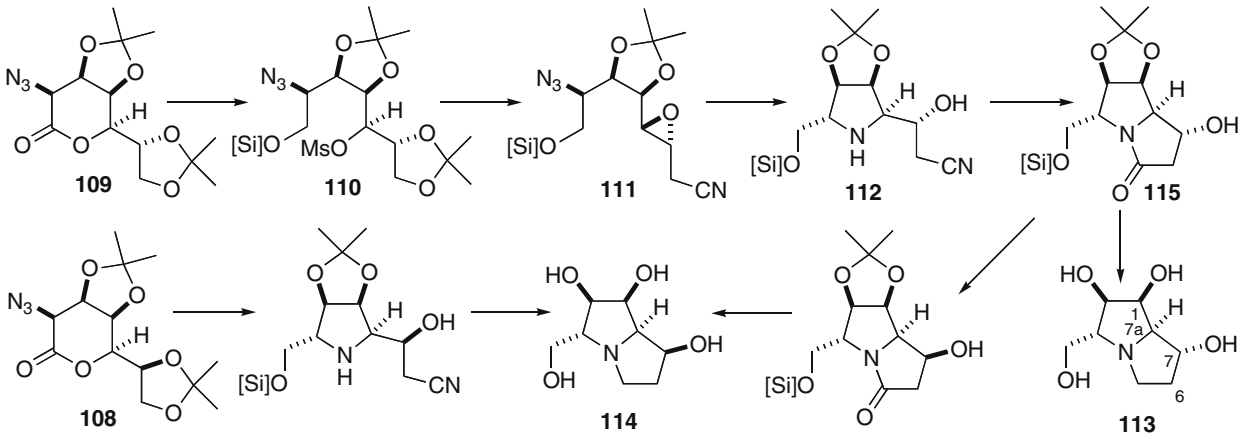
The other and more prevalent class of naturally occurring pyrrolizidines are the necine bases which have a one carbon branch at C-1. This branching would prevent the adoption of the two carbon extension of the terminus of a sugar skeleton used as a strategy for alexines, but this problem can be overcome by introducing carbon–carbon bonds at the centre of the nascent carbon scaffold instead. For the synthesis of platynecine **116** the exocyclic carbon was derived from C-1 of the carbohydrate and a two carbon extension was introduced at C-2 by a Wittig olefination (Scheme 22).[55] Starting from the protected amine **117**, which was readily derived from D-glucose, deoxygenation using $NaBH_4$ mediated reduction of the corresponding triflate and subsequent protecting-group adjustment gave the furanoside **118** in which only the C-2 hydroxyl was left free. PCC oxidation and treatment with carboxymethylenetriphenylphosphorane extended C-2. Highly stereoselective reduction and treatment with NaOMe formed the second pyrrolidine ring and allowed, after hydrolysis and exhaustive $LiAlH_4$ reduction, the synthesis of platynecine **116**.

Heptonolactone **119**, also derived from D-mannose, was the starting material for the synthesis for pseudo C_2 symmetric tetrahydroxypyrrolizidine **120** (Scheme 23).[56] Only a seven-carbon skeleton is required and, following the initial introduction of azide at C-7, a C1–N–C4–N–C7 strategy allowed the synthesis of **120** in only five steps. Despite its similar structure to potent mannosidase inhibitor DIM **1**, **120** is only a weak inhibitor and this is probably, as for *N*-methyl DIM **121**, due to N-alkylation.

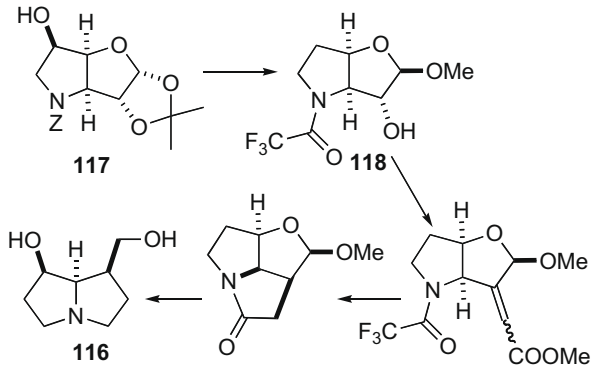
Ring contracted swainsonines (trihydroxypyrrolizidines) can be made by one carbon extension of the azidotriflate epoxide **122** using LiCN (Scheme 24).[48] Closure of the first pyrrolidine ring is achieved by hydrogenation of the azide group which closes onto the epoxide in a 5-*exo*-tet fashion. Hydrolysis of the nitrile allowed the formation of the γ-lactam **123** which was reduced using borane to give, after deprotection ring-contracted swainsonine **124**. Clean inversion of the configuration of the C-7 hydroxyl group of **123**, through PCC oxidation–$NaBH_4$ reduction, allowed, after reduction and deprotection, the formation of epimer **125**.

The casuarines are 6-hydroxy-alexines. Despite the potential stereochemical diversity in this scaffold until recently only casuarine **126** had been identified as a natural product. Isolation and X-ray crystal structure determination confirmed the identity of 3-*epi*-casuarine **127**. In an intriguing synthesis from D-gluconolactone (Scheme 25) the key step required base catalyzed cyclization of fully deprotected octitol mesylate **128**; a small amount of **126** was also formed, presumably via the epoxide.

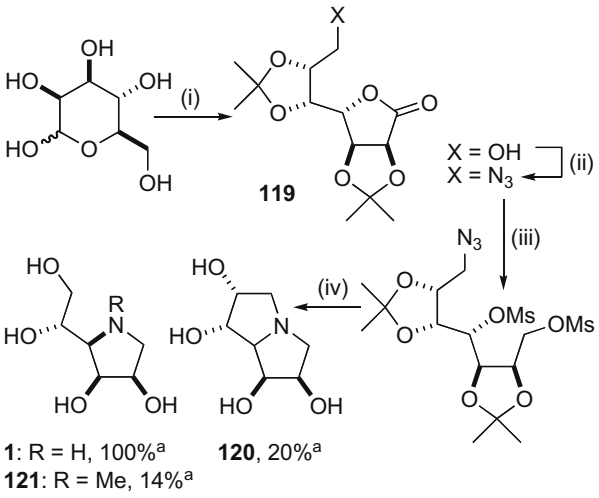
Four other diastereomers **129**–**132** (Scheme 26) have also been synthesized.[57] Using the triflate **133**, derived from octonolatone **86** and also used for the synthesis of 2-hydroxycastanospermines (Scheme 17), Fleet and co-workers employed the same C1–N–C4–N–C7 strategy that had proved successful for **120**. Thus, intro-



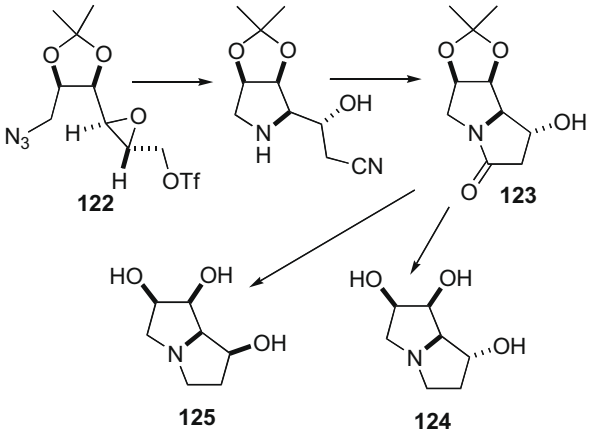
Scheme 21.



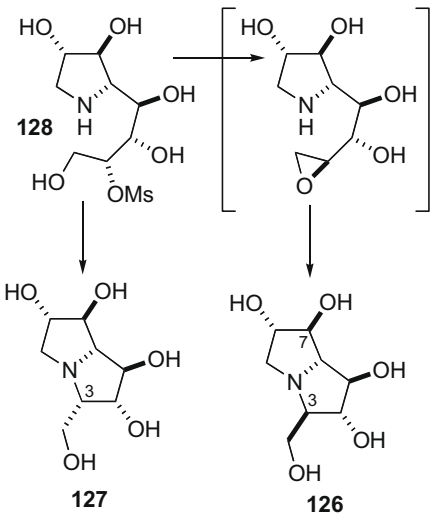
Scheme 22.



Scheme 23. [a]Percentage inhibition of lysosomal Golgi human liver α-D-mannosidase at 1 mM concentration.



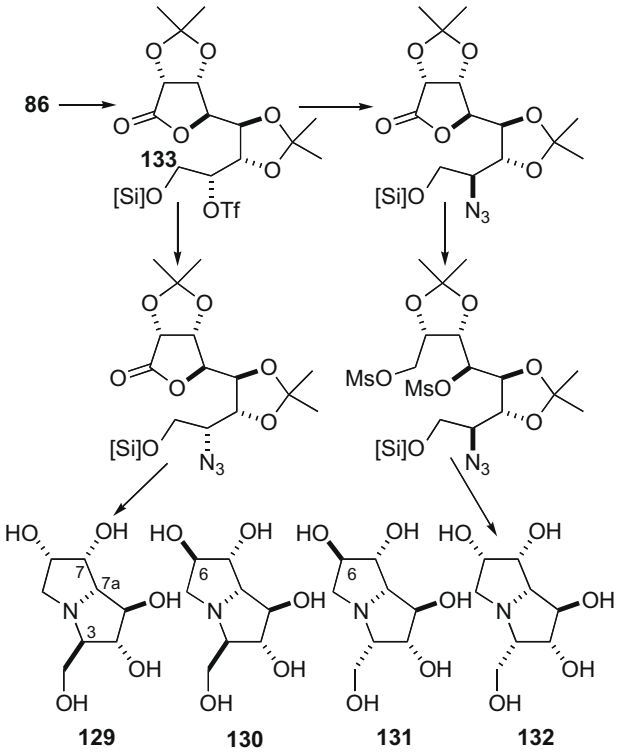
Scheme 24.



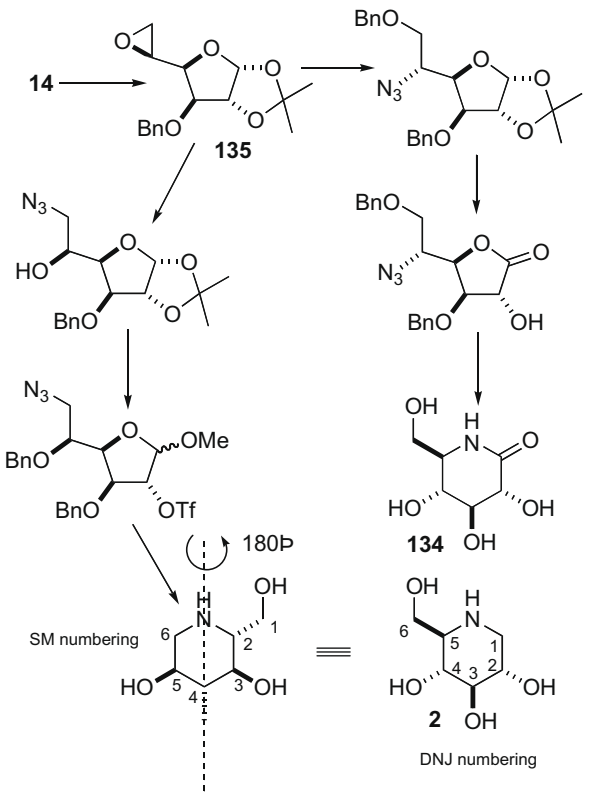
Scheme 25.

duction of azide with inversion at C-7 and cyclization onto C-1 and C-4 gave 7-*epi*casuarine **132** and correspondingly introduction of azide with overall retention gave 3,7-*diepi*casuarine **129**. Interestingly, in both cases $NaBH_4$/Te allowed clean reductive cyclization where hydrogenation gave a mixture of products. The C-6 epimers **130** and **131** were prepared by parallel routes from the C-2 epimeric octonolactone **87** (Scheme 17).

The recent isolation of a new class of highly oxygenated pyrrolizidines (hyacinthacines) from hyacinth bulbs, which are inhibitors of β-glucosidase and β-galactosidase, shows that Nature continues to provide both valuable inhibitors and exciting synthetic targets.[45]



Scheme 26.



Scheme 27.

6. Piperidines

Deoxynojirimycin **2**, an analogue of D-glucose in which the ring oxygen has been replaced by nitrogen, is the archetypal aza sugar. Two parallel syntheses of **2** and the corresponding lactam **134** from D-glucose excellently illustrate the two C2–N–C6 and C1–N–C5 strategies for piperidine synthesis (Scheme 27).[58] Both involved the epoxide intermediate **135**, constructed from D-glucose, in which C-5 has been inverted; opening with BnO^- at C-6 allowed the introduction of N with a second inversion at C-5, and therefore with overall retention. Alternatively, opening with azide and cyclization onto C-2, resulted in inversion of both C-2 and C-5 and yet led, as 180° rotation illustrates, to the formation DNJ; C-6 of **135** having become the C-1 of **2**.

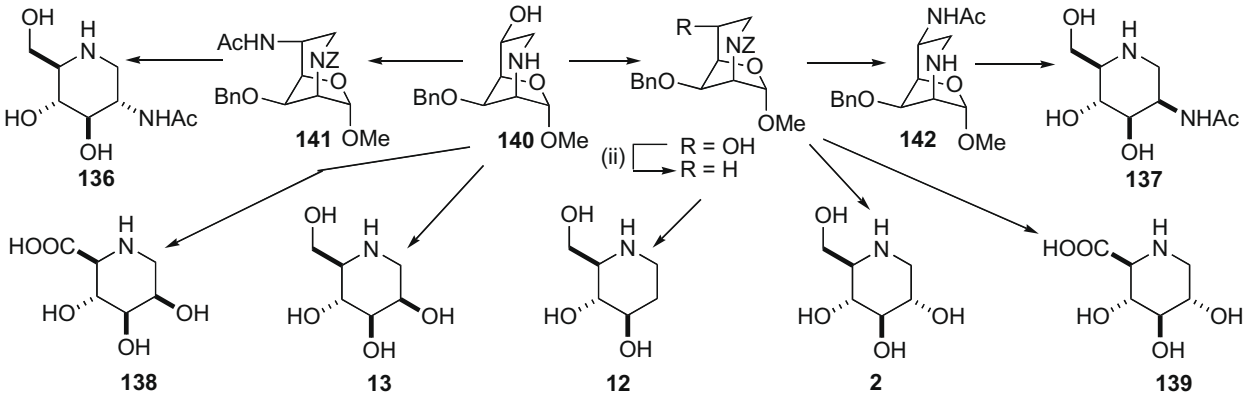
The power of a single homochiral, divergent intermediate was demonstrated in the synthesis of DNJ **2**, 2-*N*-Ac-DNJ **136**, 2-*N*-Ac-DMJ **137**, DMJ **3**, fagomine **12** and pipecolic acids **138**, **139** all from the mannofuranoside **140** (Scheme 28). A C2–N–C6 strategy was used to construct **140**, which through appropriate functionalization, defunctionalization and stereochemical control of C-5 gave the targets. Interestingly, neighbouring group participation by the carbamate groups allowed the formation of both **141** and **142** in a flexible way from **140**.[59]

Synthetic diversity in a converse sense allows the synthesis of a single target using several different convergent routes and gives an invaluable choice between methods which may vary in scale, suitability, overall yield and ease of purification. For example, DMJ **13** was synthesized from D-mannose and D-glucose using the three different routes illustrated in Scheme 29.[60] From mannose a C5–N–C1 strategy, required inversion of C-5 using acetate prior to introduction of azide, deprotection and then reductive amination. Alternatively, from glucose a C2–N–C6 strategy could be used in two directions: either closing the C-6 amine of triflate **143** or the C-2 amine of mesylate **144** gave bicycle **145**, the precursor to DMJ (**13**); the latter in a slightly better 26% overall yield.

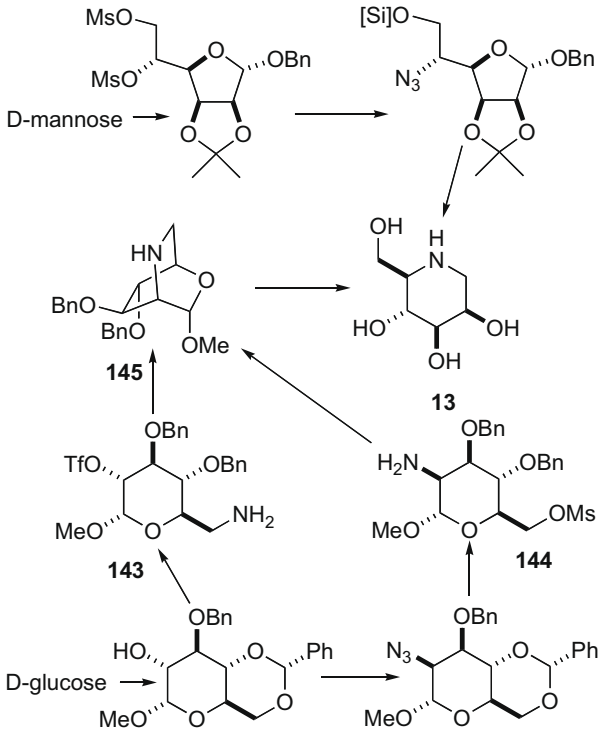
One disadvantage of this approach is that formation of the bicycle **145** from pyranoside **143** or **144** (in a 2→6 or 6→2 manner) is slow, as is the subsequent hydrolysis of the [2.2.2]-acetal. Consequently this method only proved useful for the preparation of small quantities of DMJ **13**.[61] A solution to these problems was to utilize a furanoside of mannose as a more efficient intermediate. In contrast to pyranosides **143** and **144**, not only is the cyclization of a furanoside derived from **10** (Scheme 3) rapid but so is the hydrolysis of the resulting bicycle. Unfortunately, the major practical problem in these syntheses is the introduction of nitrogen by nucleophilic substitution by azide ion of a triflate at C-2. Whilst 2-*O*-triflates of furanosides which are *cis* to the anomeric substituent are efficiently displaced, those that are *trans* give poor yields. The result is that an often wasteful and tricky anomer separation step is necessary. Furthermore, in this instance, the *cis* α anomer that is the substrate for azide displacement is the minor product of the route. Fleet found a simple solution to all of these problems by simply reversing the mode of cyclization (Scheme 30), namely the use of a C6–N→C2 strategy. The intramolecular introduction of nitrogen at C-2 suffered from none of the drawbacks of its intermolecular counterpart and this allowed the ready synthesis via a mixture of bicyclic anomers **146** and **147**, both DMJ and the trihydroxypipecolic acid **148** from D-glucose on a 10 g scale in 35% and 33% overall yields, respectively.[61]

Although in the previous example either choice of closure direction proved highly effective, added synthetic flexibility can be introduced by considering both the direction of closure and the substrate for cyclization. For example, introducing N at C-2 of the furanoside **10** allowed not only the closure onto C-6 to form DMJ **13** and establishment of the absolute configuration of fagomine **12** (C2–N→C6) but also the formation of DMDP by closure onto C-5 (Scheme 3), something that the use of a pyranoside would have precluded.[17]

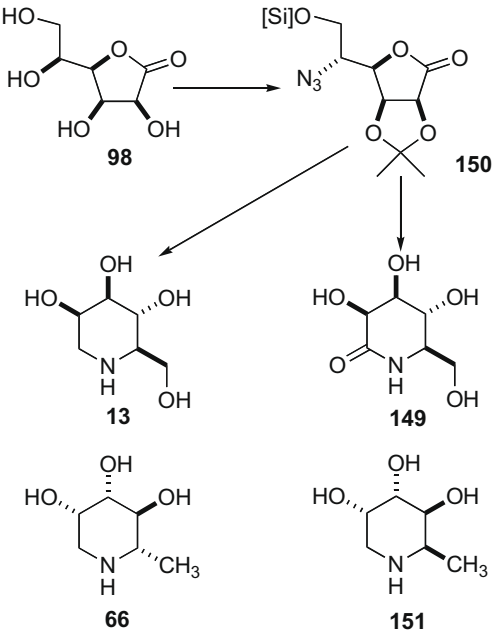
In 1988, Fleet extended the use of carbohydrate starting materials to encompass sugar lactones. In many respects, they are ideal



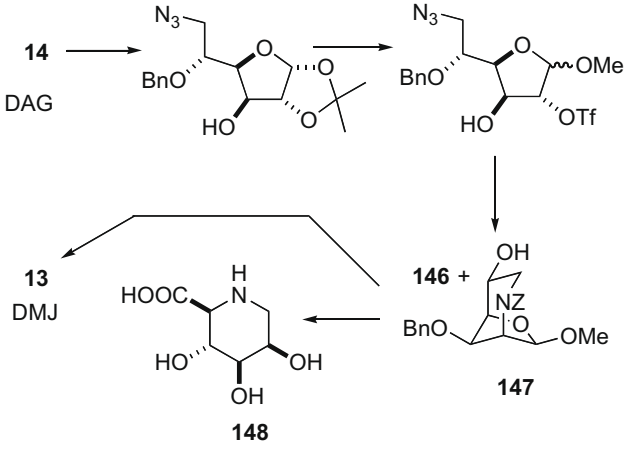
Scheme 28.



Scheme 29.



Scheme 31.

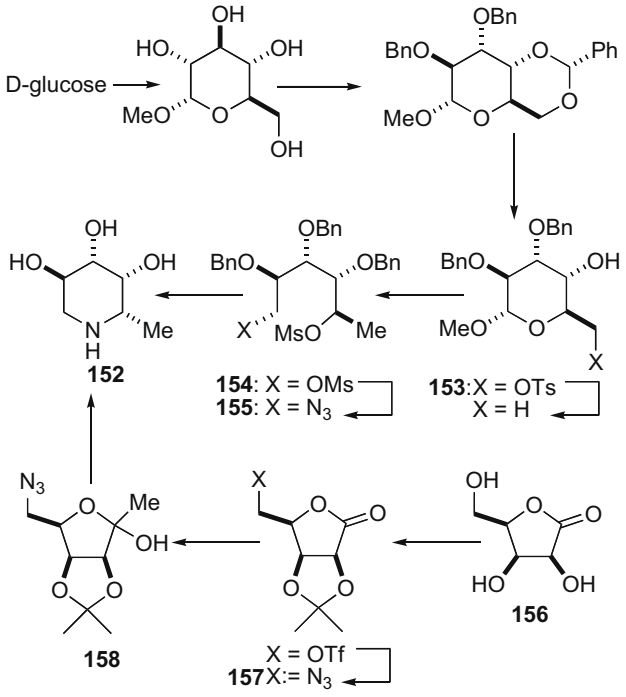


Scheme 30.

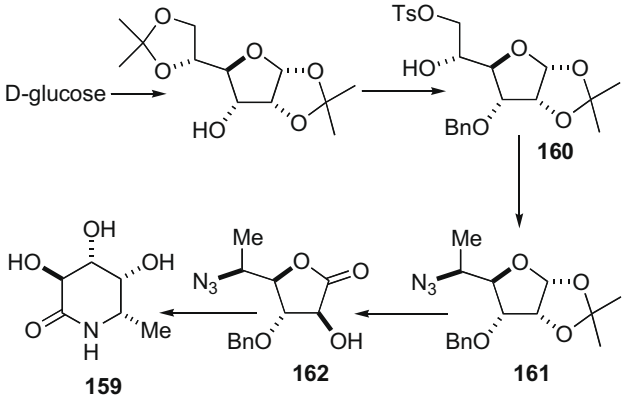
starting materials and some of their advantages have already been outlined above. A further point in their favour was that the introduction of nitrogen at C-2 is facile, especially when compared with the difficulties encountered with glycosides. For example, Fleet made both DMJ, in 25% overall yield, and the corresponding δ-lactam **149** in five and six steps, respectively, from L-gulonolactone **98** (Scheme 31). The C5–N–C1 strategy works particularly well in this case as the introduction of nitrogen inverts C-5 to give **150** which bears D-mannose stereochemistry. Lactones minimize the need for protection as C-1 and C-4 are not only tied up as the lactone but C-1 is already at a synthetically useful oxidation level. The additional ready availability of D-gulonolactone also allowed the first preparations of the L enantiomers of **13** and **149**.[62,63] A later extension of this method added a fused five-membered ring to these mannopiperidine scaffolds and hence allowed the confirmation of the stereochemistry of 6-*epi*-castanospermine **97** (Scheme 19).[51] Furthermore, introduction of an intervening C-6 deoxygenation sequence, through Pd-mediated reduction of primary bromides,[64] allowed the synthesis of the corresponding rhamnose derivatives including LRJ **66** which remarkably showed no significant inhibition of the α-L-rhamnosidase, naringinase. Almost invariably

piperidine analogues cause inhibition of the corresponding glycosidases and some puzzling inhibitory data later contradicted Fleet's findings by attributing potencies of up to K_i 34 μM to **66**.[65] In this work Wong had repeated both the Fleet sequence and those involving an aldolase-catalyzed key step. The chemoenzymatically synthesized samples showed over 10-fold greater inhibitory potency than LRJ itself, which he speculated, on the basis of ambiguities in the chemoenzymatic syntheses, could have been due to the presence of 5-*epi*-LRJ **151**.[66] Using L-rhamnose as the starting material Fleet later synthesized **151** and confirmed its unique potency despite being a stereochemically 'incorrect' analogue; a result that coupled with molecular modelling suggested $^1C_4$ conformation as a paradigmatic model for successful rhamno- and mannosidase inhibitors.[67]

Despite the widespread occurrence of L-fucose in nature it was not until 1985 that the first aza-sugar inhibitor of fucosidases, DFJ **152**, was synthesized (Scheme 32).[68] Starting from D-glucose, using a C1–N–C5 strategy, this required the inversion of C-2, C-3 and C-5.



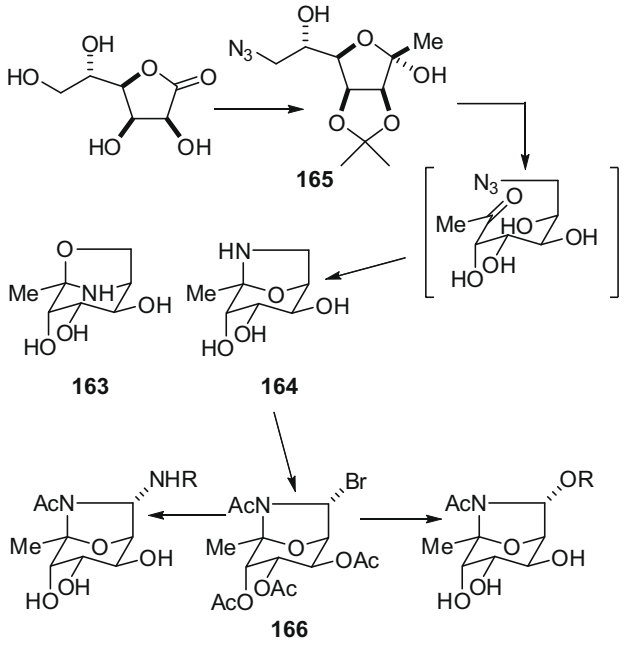
Scheme 32.



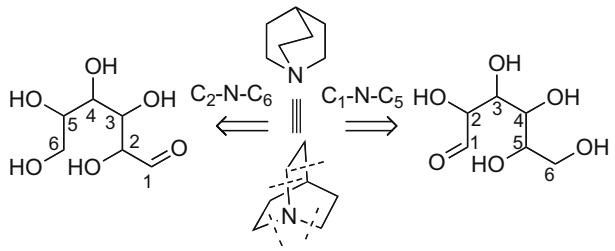
Scheme 33.

Although a superficially daunting prospect the former two were readily achieved through *trans*-diaxial epoxide-opening, and the latter is concomitant with ring cyclization. Thus, after deoxygenation of C-6 by reduction of tosylate **153**, a remarkably regioselective azide substitution reaction on dimesylate **154** allowed final closure of **155** using the Suzuki–Takoaoka reduction.[69] DFJ (**152**) is still the most potent inhibitor of fucosidase to date, with a K_i of 4.8 nM. In 1989 a more efficient synthesis was devised (Scheme 32), suitable for the preparation of large amounts of DFJ, from D-lyxonolactone (**156**), itself prepared from D-galactose. This was surprisingly, the first use of **156** as a chiral pool starting material.[70] This utilized a C6–N–C2 strategy, which introduced the C-5 methyl group of DFJ through the attack of MeLi upon the C-1 lactone moiety of **157**. The reduction of **158** is entirely stereocontrolled by the adjacent acetonide group and allowed the formation of DFJ in an excellent 41% overall yield. An essentially identical route has allowed the synthesis of enantiomer 6-deoxy-DGJ;[71] this has also been performed on a kg scale.[6] The use of a 2-*C*-methyl branched lactone has allowed the synthesis of 4-*C*-methyl-DFJ,[72] which is interestingly >1000-fold weaker as a fucosidase inhibitor. The corresponding δ-lactams of DNJ and DMJ are potent inhibitors of glucosidases and mannosidases, respectively, so it was somewhat of a surprise to find that L-fuconic-δ-lactam **159** was only a weak but specific inhibitor of α-L-fucosidase.[73] Compound **159** was prepared from D-glucose (Scheme 33) and so, as for the synthesis of DFJ shown in Scheme 32, this required inversions at C-2, 3 and 5 as well as deoxygenation at C-6. Firstly C-3 inversion was achieved through reduction of a ketone, subsequently C-6 was deoxygenated using superhydride to reduce the tosylate **160** and then azide was introduced with inversion at the only free hydroxyl at C-5 to give **161**. Following hydrolysis, C-1 was oxidized to give a γ-lactone using buffered aq Br_2 and this allowed the subsequent and final required inversion of C-2 by trifluoroacetate displacement of a C-2 triflate to give **162**. Hydrogenation of **162** and deprotection gave **159** in 24% overall yield from DAG.

MeLi was also used for chain extension in the syntheses of the bicyclic hemiaminals **163** and **164**, which are conformationally restricted mimics of α-L-fucose (Scheme 34).[74] A C2–N–C7 strategy was adopted for **164.** Thus, the C-6 hydroxyl of the acetonide of



Scheme 34.



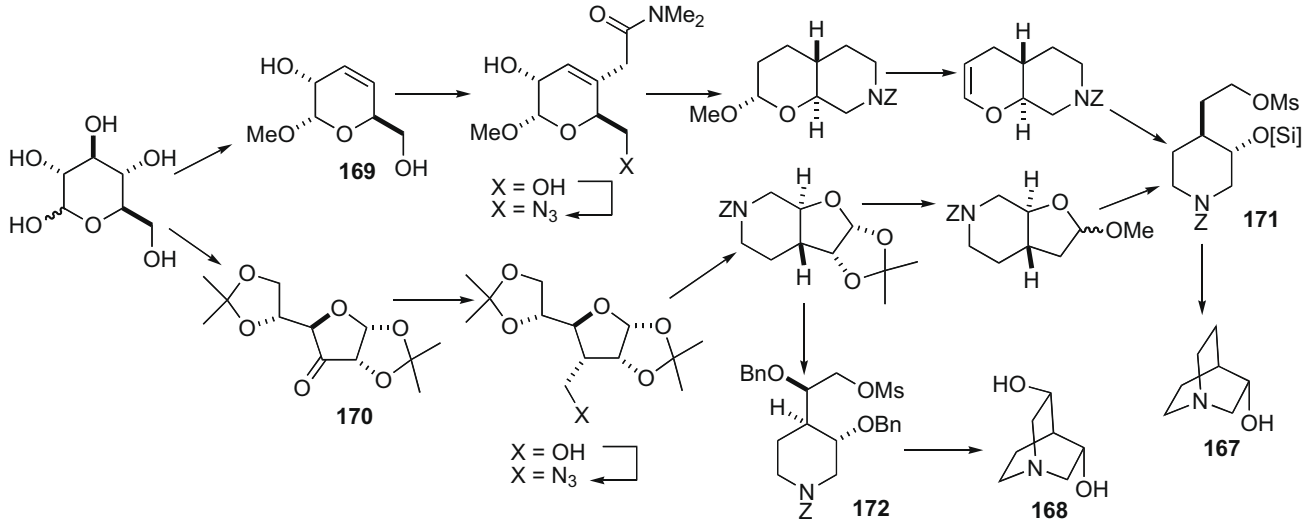
Scheme 35.

L-gulonolactone, was selectively mesylated and displaced with azide before treatment with MeLi to give hemiketal **165**. Subsequent deprotection and then reduction of **165** yielded the hemiaminal **164**, which showed moderate inhibition of both fucosidase and, excitingly, human α(1→3)fucosyltransferase. A parallel route from D-mannonolactone using a C2–N–C5 strategy gave hemiaminal **163**, which showed no inhibitory potency, possibly as a result of its chemical instability.

Valuably, photobromination of the peracetate of **164** gives a single *exo*-bromide **166** which may be elaborated to a wide range of bicyclic fucose analogues through displacements of the bromide with either oxygen or nitrogen nucleophiles, which all proceed with retention of configuration.[75]

There are a large number of alkaloids containing the quinuclidine nucleus, which in these structures is often extensively substituted. Despite the use of carbohydrates for the synthesis of other highly functionalized structures, there are only a handful of examples of their use in the synthesis of homochiral bridgehead heterocycles. In fact, as Scheme 35 shows, carbohydrates are near ideal starting materials. Simply by extending the C2–N–C6 or C1–N–C5 strategies, used so successfully in the synthesis of piperidines, quinuclidine synthesis may be achieved through the introduction of a two-carbon chain that is destined to become the quinuclidine bridge at C-4 or C-3, respectively. This is exemplified by the syntheses of the mono- **167** and di- **168** hydroxy quinuclidines from D-glucose shown in Scheme 36, which rely upon reaction of allylic alcohol **169** with *N*,*N*-dimethylacetamide dimethylacetal according to Corey's procedure, or of C-3 ketone **170** with a stabilized ylid to introduce two carbon bridges at C-4 and C-3, respectively.[76–78] A key element of these syntheses is the need to protect any free hydroxyl groups in mesylates **171** and **172** during the formation of the bridgehead to nitrogen because of competition from furan formation.[79] A similar approach from D-arabinose also allowed the synthesis of the C-2 epimer of **168**.[80]

The isolation[81] of the first naturally occurring homoazasugar, an azasugar which bears a extra methylene unit between the anomeric hydroxyl and carbon, α-homonojirimycin (α-HNJ, **173**, Fig. 3) initiated a new direction in the design of glycosidase inhibitors. As a consequence of its α-oriented anomeric hydroxymethyl substituent, α-HNJ **173** showed an enhanced level of specificity for α-glucosidases.[82] Fleet considered that a similar increase in specificity might be observed for other aza sugars and tested this hypothesis with the synthesis of the L-fucose mimic β-HFJ **174**.[83] He had initially intended to synthesize both epimers of HFJ β- **174** and α using a C5–N–C1 strategy in which the C-7 methyl would be introduced through the reaction of MeLi at C-1 of a suitable lactone. For



Scheme 36.

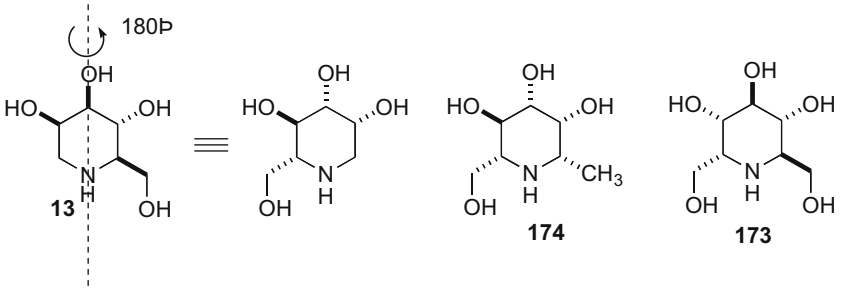
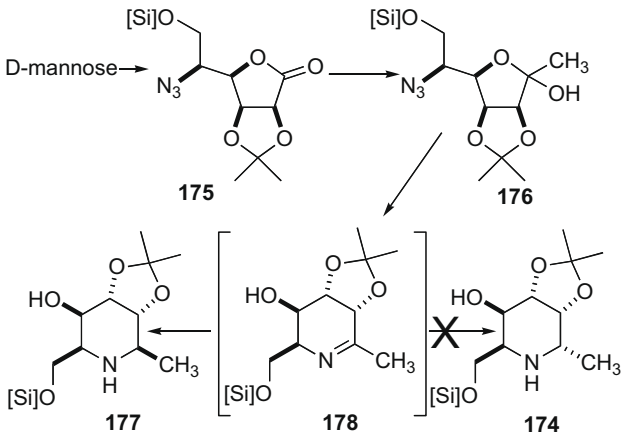
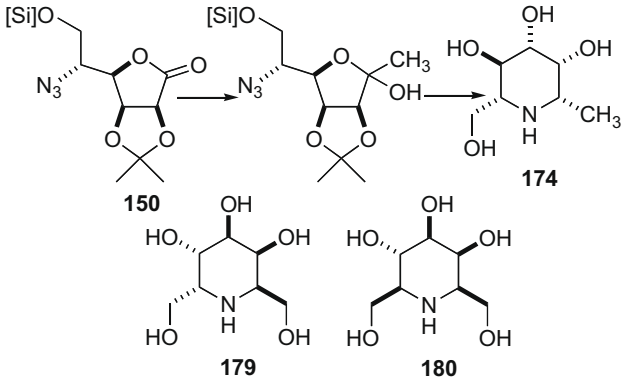


Figure 3.



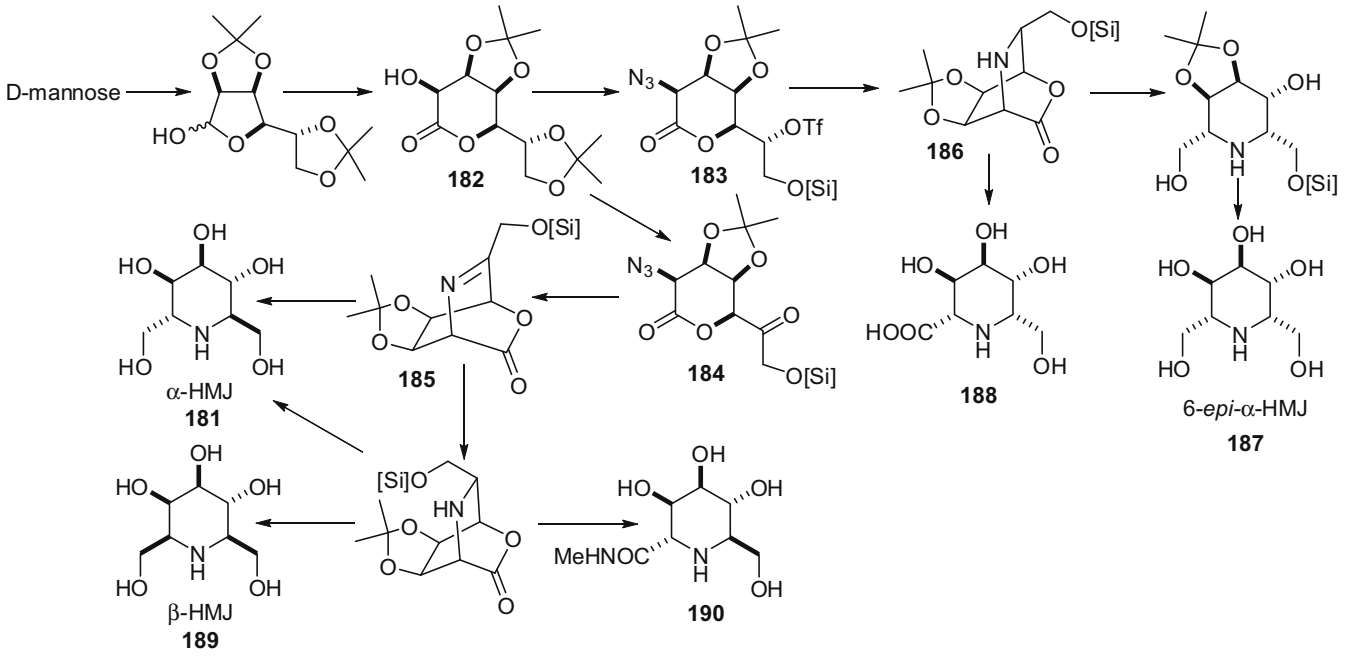
Scheme 37.



Scheme 38.

the synthesis of **174** (Scheme 37), lactone **175**, itself formed by introducing azide at the C-5 position of a mannonolactone, was successfully treated to give adduct **176**. However upon hydrogenation the only product isolated was **177**. The approach of hydrogen to the C=N bond of **178** was apparently determined by the protected hydroxymethyl substituent on the piperidine ring, rather than the isopropylidene group. Despite this setback, the synthesis of **174** (Scheme 38), starting from the azidolactone **150** used also for the synthesis of DMJ **13** shown in Scheme 31, proceeded without any hitches to give the target β-HFJ **174**. Interestingly, specificity for α-fucosidase was elicited by β-HFJ **174**, in spite of the apparently wrong pseudoanomeric stereochemistry. More recently, this approach of introducing the C-7 moiety using organometallic reagents was extended to the synthesis of galactose analogues α- **179** and β-HGJ **180**, as well as three other diastereomers. In these syntheses the transmetalation of MOM-protected stannylmethanol with BuLi[84] produced an effective source of a hydroxymethyl anion equivalent.[85] These compounds displayed a pattern of inhibition of galactosidases consistent with the anticipated configurational mimicry.[86] Furthermore, pseudoanomeric and C-6 substituents seen crucial in determining whether analogues, which can potentially be viewed as either L-rhamnose or D-galactose mimics, inhibit rhamnosidase or galactosidase.

It is an interesting feature of the inhibitory spectrum of DMJ **13** that its potency towards fucosidases is actually higher than that towards mannosidases.[87] This is presumably due to the correspondence of the stereochemistry of the hydroxyl functions at C-2, 3 and 4 of DMJ with those in both D-mannose and L-fucose and the less stringent structural requirements for inhibition of α-fucosidase than of α-mannosidase. Indeed, as Figure 3 illustrates, save for the methyl substituent, DMJ **13** resembles β-HFJ **174**, itself being a potent α-fucosidase inhibitor (vide supra, Scheme 38). Fleet considered that α-HMJ **181** might be a more specific inhibitor of α-mannosidases than is DMJ **13** but a worse inhibitor of fucosidases; not only might the α-hydroxymethyl substituent mimic an α-mannopyranoside link, but the polar hydroxyl group of this substituent would be thrust into the hydrophobic binding pocket in the fucosidase active site which usually accommodates the nonpolar methyl group of fucose. He adopted a C2–N–C6 strategy (Scheme 39), using a Kiliani ascension of diacetone mannose to introduce the extra carbon needed at the start of the synthesis, in contrast



Scheme 39.

to the relatively late introduction used for the synthesis of β-HFJ (Scheme 38).[88,89] Azide displacement of the triflate of **182** resulted in an equilibration of azide products and led to the formation of an azidolactone in which nitrogen had been introduced at C-2 with overall retention of configuration. After suitable protecting group adjustment, a lactone in which only the C-5 hydroxyl group is free was elaborated to the triflate **183** and ketone **184**. Reaction of **184** with $P(OEt)_3$ resulted in an intramolecular aza-Wittig reaction[90,91] to form the bicyclic imine lactone **185**, which when reduced further with $LiBH_4$ and deprotected ultimately gave α-HMJ **181** as a final product. The overall result was closure of the nitrogen at C-2 onto C-6 with overall retention of configuration and the stereochemical outcome of this reduction implied that the imine functionality in **185** is predominantly reduced in the bicyclic form from the least-hindered side before the lactone ring is opened. Hydrogenation of triflate **183** in the presence of NaOAc allowed the closure of the resultant C-2 amine group onto C-6 with inversion of configuration to form the [2.2.2]-bicycle **186**. Reduction of this bicyclic lactone **186** with $LiAlH_4$ and subsequent deprotection gave 6-*epi*-α-HMJ **187**. Alternatively, simple treatment of **186** with aqueous TFA and ion exchange chromatography allowed the synthesis of the highly functionalized pipecolic acid **188**, and further illustrates the value of sugar-derived azidolactones in the synthesis of amino acids. As had been hoped, α-HMJ **181** showed both enhanced levels of α-mannosidase inhibition and, unlike DMJ **13**, a significantly greater specificity for mannosidases over fucosidases. Furthermore chemoselective reduction of the imine **185** with sodium cyanoborohydride allowed the formation of β-HMJ **189** via an epimeric bicyclic lactone and the amide **190** which is an unexpectedly potent inhibitor of human placenta β-*N*-acetylglucosaminidase (K_i = 0.01 μM).[92]

As a result of the success of this approach, essentially parallel routes were used to prepare the L-rhamnose homoazasugars α-HRJ **191** and β-HRJ **192** (Fig. 4) using a Kiliani ascension of L-rhamnose.[93] As in the D-mannose series, α-HRJ **191** showed enhanced potency (K_i 5.3 μM) towards an α-L-rhamnosidase. The mirror-image resemblance of β-HRJ **192** to DGJ (β-HRJ is, in fact, β-1-Me-DGJ) results in a potent inhibition of galactosidase.[94] The great flexibility of this route also allowed preparation of the homologated azasugar of 5-*epi*-LRJ **151** which had shown unusual potency, despite its apparently incorrect stereochemistry; interestingly, this 6-*epi*-α-HRJ **193** has only weak inhibitory properties. Furthermore, methanolysis and subsequent aminolysis of a key bicyclic lactone intermediate yielded C-1 ester and amide derivatives that, in addition to showing moderate naringinase inhibition, were the first examples of inhibitors of dTDP-L-rhamnose biosynthesis.

A thorough comparison of homoazasugars isolated from natural sources has confirmed that α-HNJ displays μM IC_{50} values for the inhibition of a range of α-glucosidases although β-HNJ, α- and β-HMJ were surprisingly poor inhibitors of their corresponding glycosidases.[82] Interestingly, despite the fact that α-HNJ and N-alkylated derivatives are all potent inhibitors of processing α-glucosidase I, they are poor inhibitors of HIV replication; thereby raising doubts about a previously associated anti-HIV mode of action.

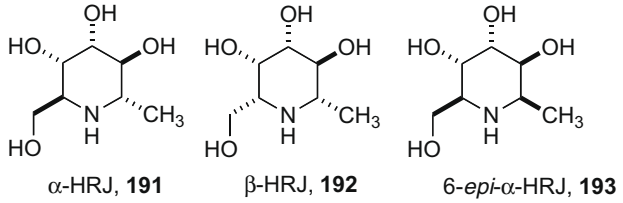
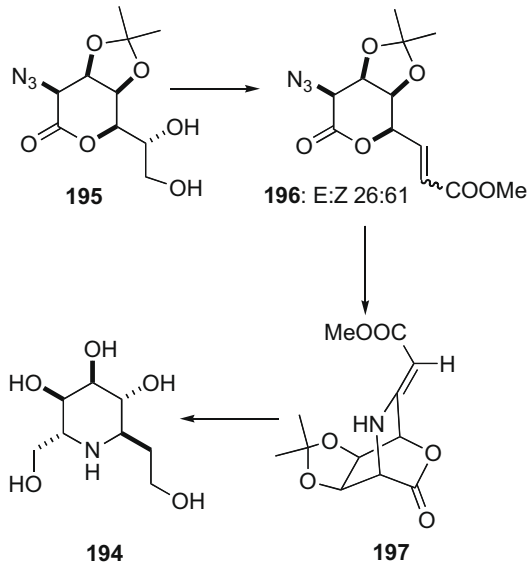


Figure 4.



Scheme 40.

The isolation of a hydroxyethyl containing DMDP analogue[44] prompted the design and synthesis of a corresponding hydroxyethyl containing piperidine **194** as a new class of homoazasugar pyranose mimics (Scheme 40).[95] Periodate cleavage of the diol moiety in the seven-carbon azidolactone **195** gave an aldehyde, which was extended by Wittig olefination. Heating the resultant enoates **196** induced an intramolecular 1,3-dipolar cycloaddition of the azido and C=C groups to give the bicyclic vinylogous urethane **197**. Reduction by $NaBH_3CN$ and then superhydride gave the desired eight-carbon homologue of α-HMJ **194**.

The successful use of cycloadditions in a C4–N–C1 strategy for the synthesis of pyrrolidine-containing sugar mimics prompted an investigation of this methodology in a C5–N–C1 strategy for piperidine analogues. This type of compound had first been made by Vasella in 1991[39] and Fleet et al. were successful in expanding their method to the D- **198**[96,97] and L- **199** rhamnose and D-mannose **200**[98] compounds (Fig. 5) using essentially analogous routes to those used for the synthesis of the pyrrolidine equivalents (Scheme 15).[41,93,42]

Gratifyingly, each of **198**–**200** showed greater inhibitory properties than the corresponding monocyclic polyhydroxylated piperidine. More recently, this C1–N–C5 cycloaddition strategy was taken one step further.[99] Such fused frameworks allowed the preparation of sugar mimics with negatively charged groups close to the pseudoanomeric centre such as in the triazole carboxylates **201** and **202** (Scheme 41). From D-glucose the glucono γ-lactone **203** was prepared into which an azide group was introduced with overall retention at C-5, using an initial caesium trifluoroacetate displacement of a triflate ester. Reduction at 0 °C using DIBAL-H gave the lactol **204** which reacted via its open chain form with stabilized carboxymethylenetriphenylphosphorane ylid to give, after

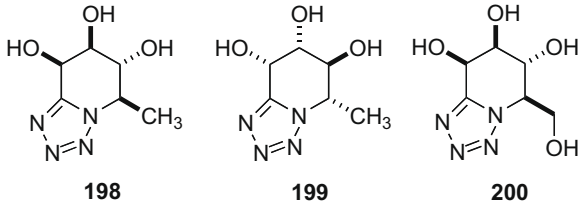
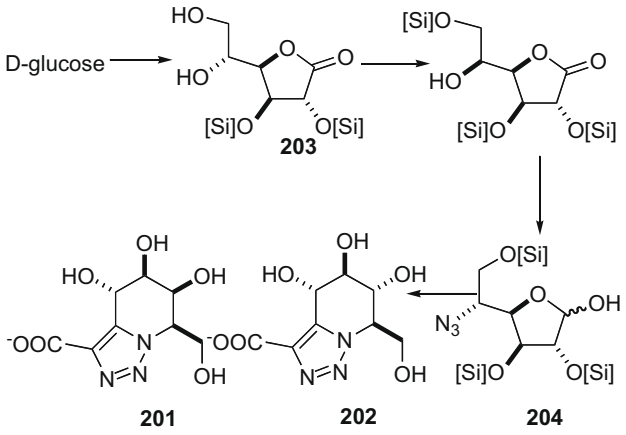


Figure 5.



Scheme 41.

mild oxidation and deprotection, the triazole **202**. The galactose triazole **201** was similarly prepared from D-galactose. Its should be noted that although in these two cases this type of 1,3-dipolar cycloaddition yielded the target triazoles, the factors that determined the products formed depend on a number of variables, including temperature and solvent and, in particular, the stereochemistry of the substrate. In theory, control of these processes would allow the formation of four types of piperidine mimics from one reaction.

7. Conclusions

Through insightful analysis of configurational equivalence, comparative analyses of alternative strategies for heterocycle formation and the development of a panoply of carbohydrate synthesis methodology, George Fleet has been one of the primary drivers in small molecule glycomimetics. These compounds, and in particular the iminosugars, are now paving the way for some of the first examples of clinical and therapeutic strategies that allow selective targeting of carbohydrate-processing enzymes.

Acknowledgements

I would like to thank Professor Fleet for his inspirational mentorship and insight and Dr A. J. Fairbanks for useful discussions during the preparation of this manuscript.

References

1. Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, Ix.
2. Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199.
3. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.
4. Butters, T. D.; van den Broek, L. A. G. M.; Fleet, G. W. J.; Krulle, T. M.; Wormald, M. R.; Dwek, R. A.; Platt, F. M. *Tetrahedron: Asymmetry* **2000**, *11*, 113.
5. Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.
6. Batra, H.; Moriarty, R. M.; Penmasta, R.; Sharma, V.; Stanciuc, G.; Staszewski, J. P.; Tuladhar, S. M.; Walsh, D. A. *Org. Process Res. Dev.* **2006**, *10*, 484.
7. Dauben, W. G.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2573.
8. Klein, J. *Tetrahedron Lett.* **1973**, *44*, 4307.
9. Ashby, A. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890.
10. Bell, A. A.; Pickering, L.; Finn, M.; de la Fuente, C.; Krülle, T. M.; Davis, B. G.; Fleet, G. W. J. *Synlett* **1997**, 1077.
11. Krülle, T. M.; Davis, B.; Ardron, H.; Long, D. D.; Hindle, N. A.; Smith, C.; Brown, D.; Lane, A. L.; Watkin, D. J.; Marquess, D.; Fleet, G. W. J. *J. Chem. Soc., Chem. Commun.* **1996**, 1271.
12. Yu, C. Y.; Asano, N.; Ikeda, K.; Wang, M. X.; Butters, T. D.; Wormald, M. R.; Dwek, R. A.; Winters, A. L.; Nash, R. J.; Fleet, G. W. J. *Chem. Commun.* **2004**, 1936.
13. Fleet, G. W. J.; Smith, P. W.; Evans, S. V.; Fellows, L. E. *Chem. Commun.* **1984**, 1240.
14. Bashyal, B. P.; Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 3083.
15. Fleet, G. W. J.; Nicholas, S. J.; Smith, P. W.; Evans, S. V.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1985**, *26*, 3127.
16. Fleet, G. W. J.; Son, J. C.; Green, D. S. C.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1988**, *44*, 2649.
17. Fleet, G. W. J.; Smith, P. W. *Tetrahedron Lett.* **1985**, *26*, 1469.
18. Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asymmetry* **1990**, *1*, 119.
19. Behling, J. R.; Campbell, A. L.; Babiak, K. A.; Ng, J. S.; Medich, J.; Farid, P.; Fleet, G. W. J. *Tetrahedron* **1993**, *49*, 3359.
20. Rountree, J. S. S.; Butters, T. D.; Wormald, M. R.; Dwek, R. A.; Asano, N.; Ikeda, K.; Evinson, E. L.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron Lett.* **2007**, *48*, 4287.
21. Asano, N.; Ikeda, K.; Yu, L.; Kato, A.; Takebayashi, K.; Adachi, I.; Kato, I.; Ouchi, H.; Takahata, H.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2005**, *16*, 223.
22. Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637.
23. Lee, R. E.; Smith, M. D.; Nash, R. J.; Griffiths, R. C.; McNeil, M.; Grewal, R. K.; Yan, W.; Besra, G. S.; Brennan, P. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1997**, *38*, 6733.
24. Long, D. D.; Frederiksen, S. M.; Marquess, D. G.; Lane, A. L.; Watkin, D. J.; Winkler, D. A.; Fleet, G. W. J. *Tetrahedron Lett.* **1998**, *39*, 6091.
25. Myerscough, P. M.; Fairbanks, A. J.; Jones, A. H.; Bruce, I.; Choi, S. S.; Fleet, G. W. J.; Al-daher, S. S.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1992**, *48*, 10177.
26. Bruce, I.; Fleet, G. W. J.; Girdhar, A.; Haraldsson, M.; Peach, J. M.; Watkin, D. J. *Tetrahedron* **1990**, *46*, 19.
27. Lee, R. E.; Smith, M. D.; Pickering, L.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 8689.
28. Liu, K. K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6280.
29. Austin, G. N.; Baird, P. D.; Fleet, G. W. J.; Peach, J. M.; Smith, P. W.; Watkin, D. J. *Tetrahedron* **1987**, *43*, 3095.
30. Kovar, J.; Jary, J. *Collect. Czech. Chem. Commun.* **1969**, *34*, 2619.
31. Richardson, A. C. *Methods Carbohydr. Chem.* **1972**, *6*, 218.
32. Verheyden, J. P. H.; Richardson, A. C.; Bhatt, R. S.; Grant, B. D.; Fitch, W. L.; Moffatt, J. D. *Pure Appl. Chem.* **1978**, *51*.
33. Nishimura, Y.; Kondo, S.; Umezawa, H. *J. Org. Chem.* **1985**, *50*, 5210.
34. Bashyal, B. P.; Chow, H.-F.; Fleet, G. W. J. *Tetrahedron Lett.* **1986**, *27*, 3205.
35. Dho, J. C.; Fleet, G. W. J.; Peach, J. M.; Prout, K.; Smith, P. W. *Tetrahedron Lett.* **1986**, *27*, 3203.
36. da Cruz, F. P.; Horne, G.; Fleet, G. W. J. *Tetrahedron Lett.* **2008**, *49*, 6812.
37. Davis, B.; Brandstetter, T. W.; Smith, C.; Hackett, L.; Winchester, B. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 7507.
38. Davis, B.; Bell, A. A.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Jones, M. G.; Smith, C.; Fleet, G. W. J. *Tetrahedron Lett.* **1996**, *37*, 8565.
39. Ermert, P.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2043.
40. Davis, B. G.; Nash, R. J.; Watson, A. A.; Smith, C.; Fleet, G. W. J. *Tetrahedron* **1999**, *55*, 4501.
41. Brandstetter, T. W.; Davis, B.; Hyett, D.; Smith, C.; Hackett, L.; Winchester, B. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 7511.
42. Davis, B. G.; Brandstetter, T. W.; Hackett, L.; Winchester, B. G.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Smith, C.; Fleet, G. W. J. *Tetrahedron* **1999**, *55*, 4489.
43. Hakansson, A. E.; van Ameijde, J.; Guglielmini, L.; Horne, G.; Nash, R. J.; Evinson, E. L.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2007**, *18*, 282.
44. Asano, N.; Kato, A.; Miyauchi, M.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *J. Nat. Prod.* **1998**, *61*, 625.
45. Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **1999**, *316*, 95.
46. Scott, D. A.; Krulle, T. M.; Finn, M.; Fleet, G. W. J. *Tetrahedron Lett.* **2000**, *41*, 3959.
47. Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron Lett.* **1984**, *25*, 1853.
48. Carpenter, N. M.; Fleet, G. W. J.; Cenci di Bello, I.; Winchester, B.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1989**, *30*, 7261.
49. Bell, A. A.; Pickering, L.; Watson, A. A.; Nash, R. J.; Griffiths, R. C.; Jones, M. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1996**, *47*, 8561.
50. Hakansson, A. E.; van Ameijde, J.; Horne, G.; Nash, R. J.; Wormald, M. R.; Kato, A.; Besra, G. S.; Gurcha, S.; Fleet, G. W. J. *Tetrahedron Lett.* **2008**, *49*, 179.
51. Fleet, G. W. J.; Ramsden, N. G.; Molyneux, R. J.; Jacob, G. S. *Tetrahedron Lett.* **1988**, *29*, 3603.
52. Fleet, G. W. J.; Haraldsson, M.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1988**, *29*, 5441.
53. Choi, S.; Bruce, I.; Fairbanks, A. J.; Fleet, G. W. J.; Jones, A. H.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1991**, *32*, 5517.
54. Wormald, M. R.; Nash, R. J.; Hrnciar, P.; White, J. D.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2549.
55. Fleet, G. W. J.; Seijas, J. A.; Vázquez-Tato, M. P. *Tetrahedron* **1991**, *47*, 525.
56. Fairbanks, A. J.; Fleet, G. W. J.; Jones, A. H.; Bruce, I.; Al-Daher, S.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1991**, *47*, 131.
57. Bell, A. A.; Pickering, L.; Watson, A. A.; Nash, R. J.; Pan, Y. T.; Elbein, A. D.; Fleet, G. W. J. *Tetrahedron Lett.* **1997**, *38*, 5869.
58. Fleet, G. W. J.; Carpenter, N. M.; Petursson, S.; Ramsden, N. G. *Tetrahedron Lett.* **1990**, *31*, 409.
59. Fleet, G. W. J.; Fellows, L. E.; Smith, P. W. *Tetrahedron* **1987**, *43*, 979.
60. Fleet, G. W. J.; Gough, M. J.; Shing, T. K. M. *Tetrahedron Lett.* **1984**, *25*, 4029.
61. Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 327.
62. Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron Lett.* **1988**, *29*, 2871.
63. Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 319.
64. Fairbanks, A. J.; Carpenter, N. C.; Fleet, G. W. J.; Ramsden, N. G.; Cenci di Bello, I.; Winchester, B. G.; Al-Daher, S. S.; Nagahashi, G. *Tetrahedron* **1992**, *48*, 3365.

65. Zhou, P.; Salleh, H. M.; Chan, P. C. M.; Lajoie, G.; Honek, J. F. *Carbohydr. Res.* **1993**, *239*, 155.
66. Provencher, L.; Steensma, D. H.; Wong, C.-H. *Bioorg. Med. Chem.* **1994**, *2*, 1179.
67. Davis, B. G.; Hull, A.; Smith, C.; Nash, R. J.; Watson, A. A.; Winkler, D. A.; Griffiths, R. C.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2947.
68. Fleet, G. W. J.; Shaw, A. N.; Evans, S. V.; Fellows, L. E. *Chem. Commun.* **1985**, 841.
69. Suzuki, H.; Takaoka, K. *Chem. Lett.* **1984**, 1733.
70. Fleet, G. W. J.; Peturrson, S.; Campbell, A. L.; Mueller, R. A.; Behling, J. R.; Babiak, K. A.; Ng, J. S.; Scaros, M. G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 665.
71. Bleriot, Y.; Gretzke, D.; Krulle, T. M.; Butters, T. D.; Dwek, R. A.; Nash, R. J.; Asano, N.; Fleet, G. W. J. *Carbohydr. Res.* **2005**, *340*, 2713.
72. Hotchkiss, D. J.; Kato, A.; Odell, B.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2007**, *18*, 500.
73. Fleet, G. W. J.; Ramsden, N. G.; Dwek, R. A.; Rademacher, T. W.; Fellows, L. E.; Nash, R. J.; Green, D. S. C.; Winchester, B. *Chem. Commun.* **1988**, 483.
74. Beacham, A. R.; Smelt, K. H.; Biggadike, K.; Britten, C. J.; Hackett, L.; Winchester, B. G.; Nash, R. J.; Griffiths, R. C.; Fleet, G. W. J. *Tetrahedron Lett.* **1998**, *39*, 151.
75. Smelt, K. H.; Harrison, A. J.; Biggadike, K.; Muller, M.; Prout, K.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 3259.
76. Fleet, G. W. J.; James, K.; Lunn, R. J. *Tetrahedron Lett.* **1986**, *27*, 3053.
77. Fleet, G. W. J.; James, K.; Lunn, R. J.; Matthews, C. J. *Tetrahedron Lett.* **1986**, *27*, 3057.
78. Fleet, G. W. J.; Matthews, C. J.; Seijas, J. A.; Tato, M. P. V.; Brown, D. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1067.
79. Vázquez-Tato, M. P.; Seijas, J. A.; Fleet, G. W. J.; Matthews, C. J.; Hemmings, P. R.; Brown, D. *Tetrahedron* **1995**, *51*, 959.
80. Fleet, G. W. J.; Matthews, C. J.; Seijas, J. A.; Tato, M. P. V.; Brown, D. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1065.
81. Kite, G. C.; Fellows, L. E.; Fleet, G. W. J.; Liu, P. S.; Scofield, A. M.; Smith, N. G. *Tetrahedron Lett.* **1988**, *29*, 6483.
82. Asano, N.; Nishida, M.; Kato, A.; Kizu, H.; Matsui, K.; Shimada, Y.; Itoh, T.; Baba, M.; Watson, A. A.; Nash, R. J.; Lilley, P. M. D.; Watkin, D. J.; Fleet, G. W. J. *J. Med. Chem.* **1998**, *41*, 2565.
83. Fleet, G. W. J.; Namgoong, S. K.; Barker, C.; Baines, S.; Jacob, G. S.; Winchester, B. *Tetrahedron Lett.* **1989**, *30*, 4439.
84. Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. K.; Johnson, C. R.; Medlich, J. R. *Org. Synth.* **1992**, *71*, 133.
85. Shilvock, J. P.; Fleet, G. W. J. *Synlett* **1998**, 554.
86. Shilvock, J. P.; Nash, R. J.; Watson, A. A.; Winters, A. L.; Butters, T. D.; Dwek, R. A.; Winkler, D. A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2747.
87. Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 1953.
88. Bruce, I.; Fleet, G. W. J.; Cenci di Bello, I.; Winchester, B. *Tetrahedron Lett.* **1989**, *30*, 7257.
89. Bruce, I.; Fleet, G. W. J.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1992**, *48*, 10191.
90. Eguchi, S.; Takeuchi, H. *Chem. Commun.* **1989**, 602.
91. Takeuchi, H.; Yanigada, S.; Ozaki, T.; Hagiwara, S.; Eguchi, S. *J. Org. Chem.* **1989**, *54*, 431.
92. Shilvock, J. P.; Nash, R. J.; Lloyd, J. D.; Winters, A. L.; Asano, N.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3505.
93. Shilvock, J. P.; Wheatley, J. R.; Davis, B.; Nash, R. J.; Griffiths, R. C.; Jones, M. G.; Müller, M.; Crook, S.; Watkin, D. J.; Smith, C.; Besra, G. S.; Brennan, P. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1996**, *37*, 8569.
94. Shilvock, J. P.; Wheatley, J. R.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Butters, T. D.; Muller, M.; Watkin, D. J.; Winkler, D. A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2735.
95. Shilvock, J. P.; Hsia, K. Y.; Nash, R. J.; Lloyd, J. D.; Winters, A. L.; Asano, N.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 4157.
96. In the following reference review this compound is incorrectly drawn with L-fucose stereochemistry; the description of its inhibitory potency towards fucosidases may have caused this confusion.
97. deRaadt, A.; Ekhart, C. W.; Ebner, M.; Stutz, A. E. *Top. Curr. Chem.* **1997**, *187*, 157.
98. Ermert, P.; Vasella, A.; Weber, M.; Rupitz, K.; Withers, S. G. *Carbohydr. Res.* **1993**, *250*, 113.
99. Krülle, T.; delaFuente, C.; Pickering, L.; Aplin, R. T.; Tsitsanou, K. E.; Zographos, S. E.; Oikonomakos, N. G.; Nash, R. J.; Griffiths, R. C.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1997**, *8*, 3807.