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Homochiral carbon branched piperidines from carbon branched sugar lactones: 4-*C*-methyl-deoxyfuconojirimycin (DFJ) and its enantiomer—removal of glycosidase inhibition

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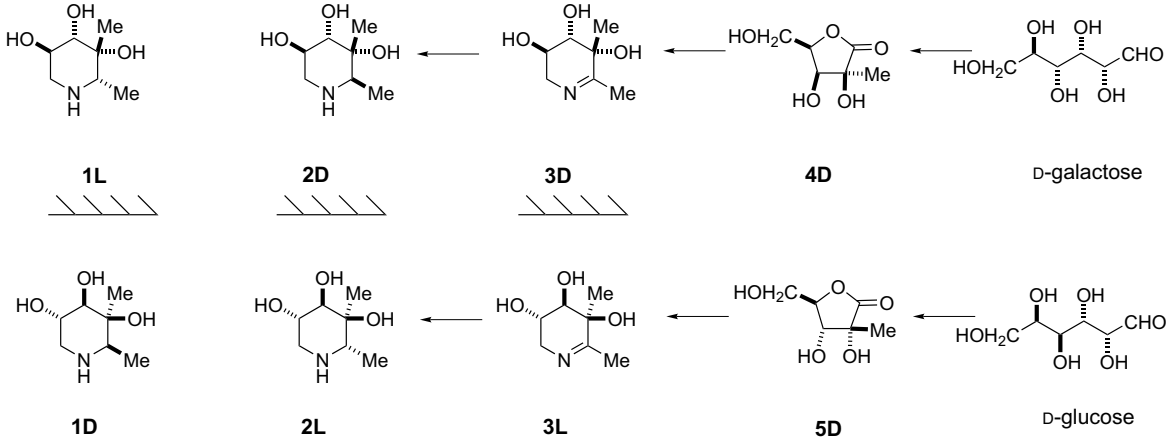
Abstract—The value of readily available 2-*C*-methyl aldonic acids in short syntheses of carbon branched piperidines containing quaternary centers is demonstrated. The effect of the introduction of a 4-*C*-methyl group into piperidine imino sugar inhibitors of L-fucosidases and D-galactosidases is reported.

1. Introduction

Although carbohydrate scaffolds are amongst the most diverse set of chirons available,[1] the isomerisation of aldoses to the 2-*C*-methyl aldonic acids [saccharinic acids] provides a rare set of carbon branched sugars. Herein we report the easy synthesis of piperidines bearing a carbon branch at a quaternary centre from branched sugar lactones available by environmentally friendly one pot procedures from aldohexoses. 4-*C*-Methyl-deoxyfuconojirimycin (DFJ) **1L**[2]and its C-5 epimer **2D** are formed by reduction of imine **3D** obtained from 2-*C*-methyl-D-lyxonolactone **4D**; **4D** is prepared and isolated in 11% yield from D-galactose (Scheme 1).[3] Enantiomers **1D** and **2L** can be similarly



Scheme 1.

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prepared from imine **3L**, synthesised from 2-*C*-methyl-D-ribonolactone **5D**; the tandem Amadori and calcium hydroxide rearrangements on D-glucose make **5D** available on a large scale.[4] The effect of the substitution of a hydrogen at C-4 by a methyl group on the ability of piperidine sugar mimics to inhibit glycosidases is reported.

Naturally occurring and synthetic polyhydroxylated piperidines, analogues of carbohydrates in which the oxygen of the pyranose ring is replaced by nitrogen, constitute a family of efficient glycosidase inhibitors.[5] The piperidine DFJ **6L**, a synthetic analogue of L-fucose,[6] is a potent inhibitor of many α-fucosidases,[7] with a K_i typically in the nanomolar range.[8] A *N*-alkyl derivative of DFJ **6L** has antiviral properties[9] and has been used for the purification of an α-fucosidase.[10] *N*-Alkylation of imino sugar mimics can affect their biological properties significantly.[11] The natural product deoxymannojirimycin (DMJ) **7** is generally regarded as a mannose mimic, even though it is a more powerful inhibitor of α-L-fucosidases than of α-D-mannosidases;[12] DMJ **7** is related to DFJ **6L** by the removal of the equatorial methyl group at C-5 and the introduction of an equatorial hydroxymethyl group at C-1.

Homologues of the azasugars by the introduction of a hydroxymethyl group occur in many plants;[13] their biological properties[14] have caused much synthetic interest.[15] The addition of an axial hydroxymethyl group to C-1 of DFJ **6L** gives α-homo-DFJ **8**, which is a natural product[16] and a potent α-fucosidase inhibitor (Fig. 1). The introduction of an equatorial hydroxymethyl to C-1 of DFJ **6L**- or of an equatorial methyl group to C-1 of DMJ **7**- gives β-homo-DFJ **9** (or α-methyl-DMJ **9**), which is also a specific and potent α-fucosidase inhibitor.[17] These compounds have also allowed the design of inhibitors of fucosyl transferases.[18] Thus substitution by carbon at C-1 or C-5 of the imino sugar does not substantially affect the ability of such piperidines to inhibit α-fucosidases; as long as the absolute stereochemistry of the secondary hydroxyl groups is the same as that in L-fucose the structure provides significant inhibition. No study on the effects of substitution at any of the hydroxyl groups on fucosidase inhibition or on other fucose related processes has been reported; the synthesis of 4-*C*-methyl-DFJ **1L** with an equatorial methyl group at C-4 and of other related structures is described.

The piperidine analogue of D-galactose is deoxygalactonojirimyin (DGJ) **10**, which is a nanomolar α-D-galactosidase inhibitor (Fig. 2).[19] Homo-DGJ **11** is a potent but more specific D-galactosidase inhibitor.[20] 6-Deoxy-DGJ **6D** [the enantiomer of DFJ **6L**] still inhibits α-galactosidases but with a K_i that is micromolar rather than nanomolar.[21] Some *N*-alkylated derivatives of **6D** have antiviral activity. The *N*-nonyl derivative of **6D** dramatically reduced the amount of hepatitis B virus produced by tissue cultures under conditions where cell viability is not affected;[22] the corresponding *N*-oxanonyl derivative blocked the protein p7 ion channels of hepatitis C virus.[23]

Herein we report the synthesis of the 4-*C*-methyl analogue **1D** of 6-deoxy-DGJ **6D** and related analogues; the addition of an equatorial methyl group at C-4 of 6-deoxy-DGJ **6D** removes all glycosidase inhibition. However, some of the chemotherapeutic properties of imino sugars do not rely on glycosidase inhibition for their mode of action.[24] Thus Zavesca,[25] the *N*-butyl analogue of deoxynojirimycin DNJ **12**, is used for the treatment of Gaucher's disease although it is a mimic of ceramide rather than glucose.[26] The mechanism of long term male contraception by

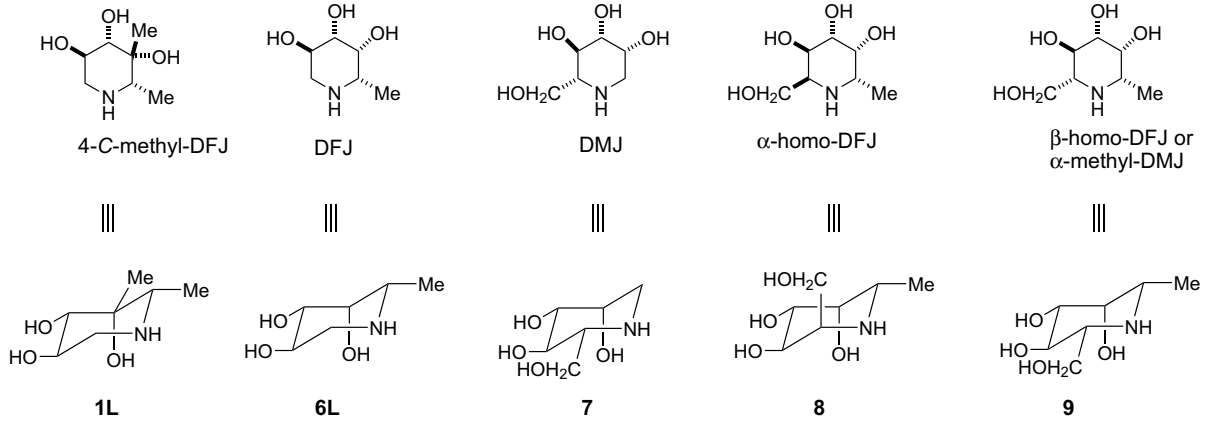


Figure 1. Piperidine analogues as α-L-fucosidase inhibitors.

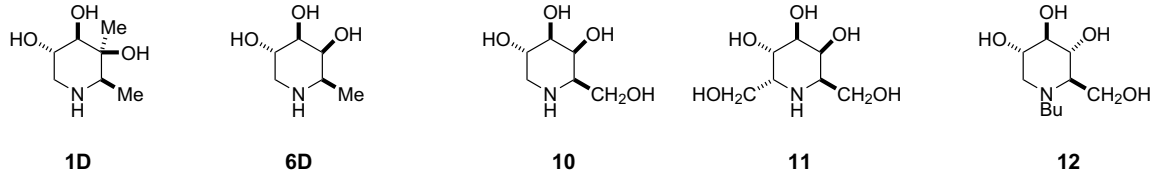


Figure 2. Piperidine analogues as D-galactose mimics.

N-butyl DNJ **12** is not correlated with glucosidase inhibition.[27] The efficacy of imino sugars as chaperones for protein folding may not depend on their glycosidase inhibition.[28]

2. Results and discussion

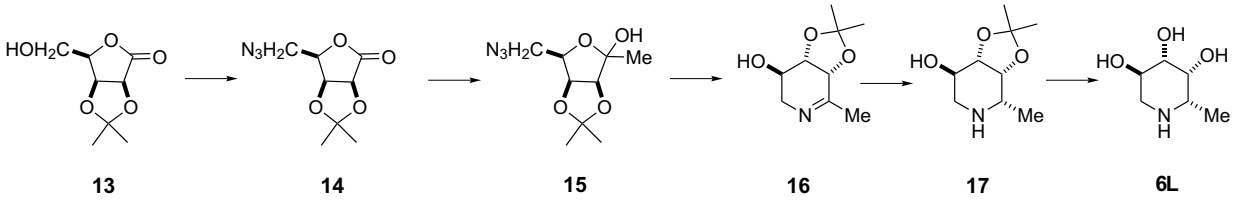
2.1. Synthesis of 4-*C*-methyl piperidines from the 2-*C*-methyl branched lactones 4D and 5D

The strategy used for the C-4 branched piperidines is the same as that used in the short and efficient synthesis of DFJ **6L** from D-lyxonolactone, as shown in Scheme 2;[29] the only protecting group in the syntheses in Scheme 2 of **6L** and in Schemes 3 and 4 of all the 4-*C*-methyl branched piperidines is a single isopropylidene group.

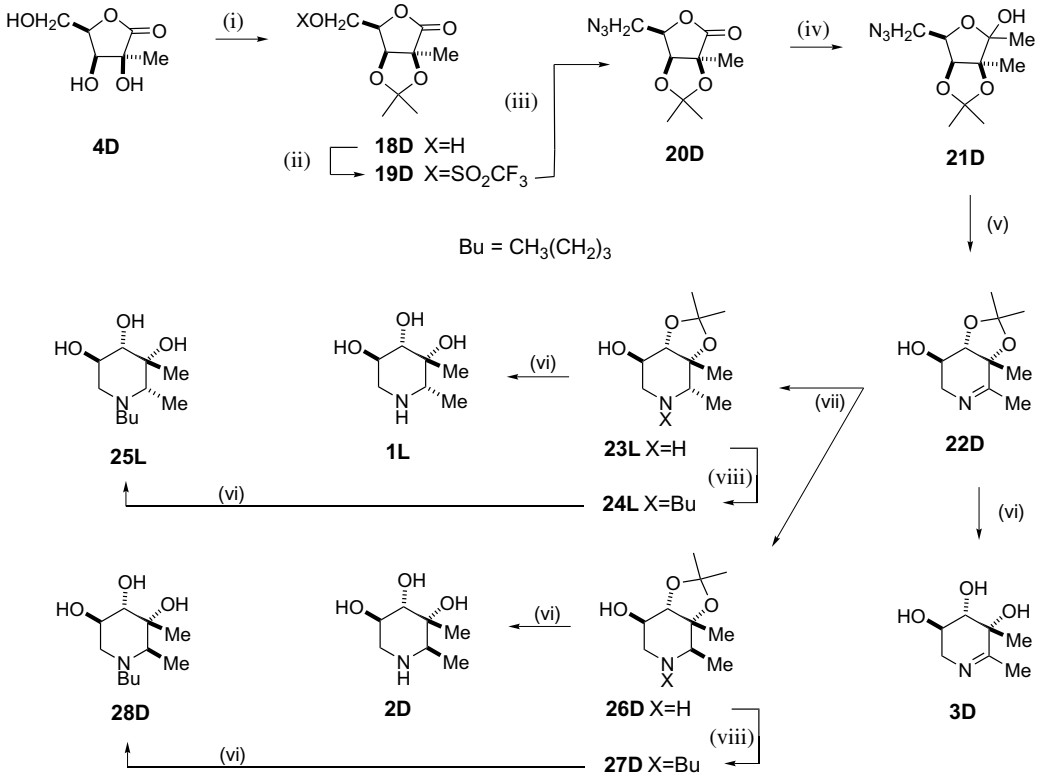
The protected lactone **13** was converted by esterification with trifluoromethanesulfonic (triflic) anhydride followed by treatment with azide to give lactone **14** (89% yield), which with methyl lithium gave lactols **15** (97% yield). Hydrogenation of **15** caused reduction of the azide to imine **16** [as an isolated intermediate], which on further reduction afforded the ketal **17** (83% yield). Quantitative removal of the isopropylidene protecting group in **17** by aqueous trifluoroacetic acid gave DFJ **6L** in an overall yield of 72% from **13**. A similar sequence on the enantiomer of **13** gave 6-deoxy-DGJ **6D**;[21] this route has been performed on a multi-kilogram scale.[30]

For the synthesis of the L-fucopyranose mimics 4-*C*-methyl-DFJ **1L** and D-*altro*-epimer **2D** and related piperidines, 2-*C*-methyl-D-lyxonolactone **4D**[31] was used as the starting material (Scheme 3).

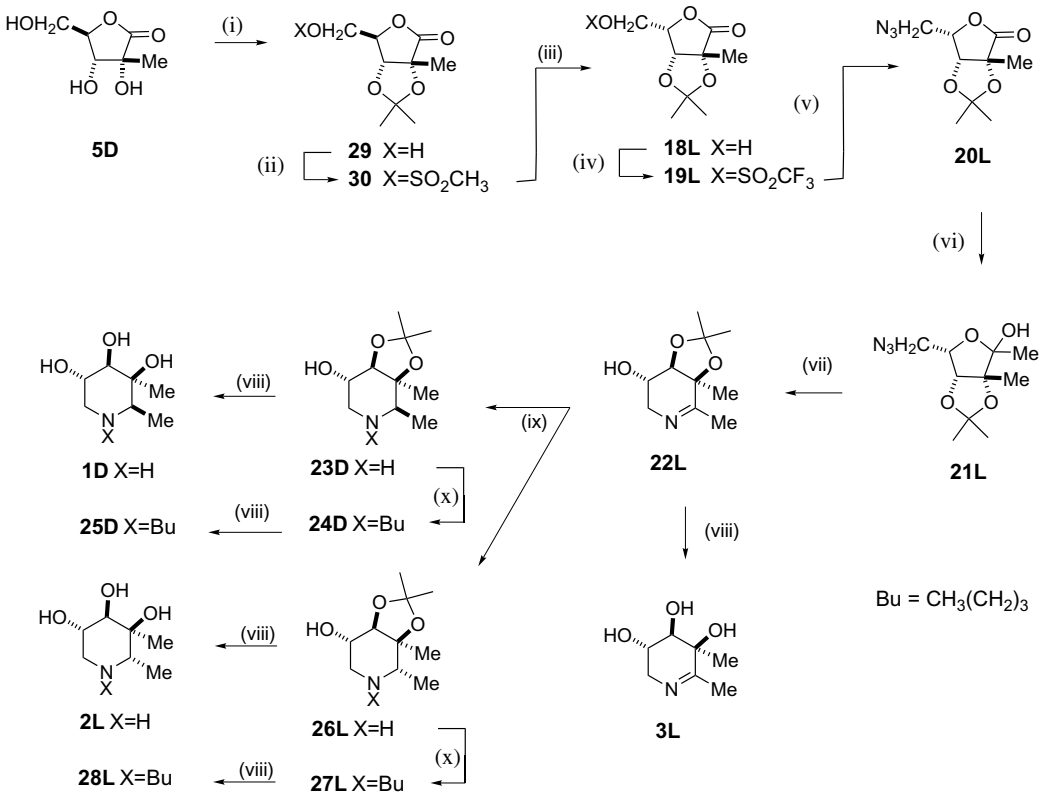
Thus the branched lyxonolactone **4D** was treated with acetone in the presence of copper sulfate and sulfuric acid to afford acetonide **18D** in 99% yield. It is noteworthy that this protection is far more efficient than protection of



Scheme 2. Synthesis of the α-fucosidase inhibitor DFJ **6L**.



Scheme 3. Reagents and conditions: (i) Me_2CO, $CuSO_4$, concd H_2SO_4; (ii) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; (iii) NaN_3, DMF; (iv) MeLi, THF; (v) H_2, 10% Pd–C, MeOH; (vi) CF_3COOH, H_2O; (vii) H_2, PtO_2, dioxane–H_2O; (viii) H_2, $MeCH_2CH_2CHO$, $Pd(OH)_2$, dioxane–H_2O, THF.



Scheme 4. Reagents and conditions: (i) Me_2CO, $CuSO_4$, concd H_2SO_4; (ii) $MeSO_2Cl$, pyridine, DMAP; (iii) KOH, dioxane–H_2O; then dil aqueous HCl; (iv) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; (v) NaN_3, DMF; (vi) MeLi, THF; (vii) H_2, 10% Pd–C, MeOH; (viii) CF_3COOH, H_2O; (ix) H_2, PtO_2, dioxane–H_2O; (x) H_2, $MeCH_2CH_2CHO$, $Pd(OH)_2$, dioxane–H_2O, THF.

unbranched D-lyxonolactone; in that case a significant amount of the 3,5-ketal—as well as the 2,3-ketal **13**—was formed. Esterification of the C-5 alcohol with triflic anhydride in dichloromethane gave crystalline triflate **19D** in quantitative yield and subsequent reaction with sodium azide in DMF afforded azide **20D** in 91% yield. Treatment of azidolactone **20D** with methyl lithium in THF gave lactols **21D** in 97% yield. Hydrogenation of **21D** in the presence of 10% palladium on carbon in methanol gave the corresponding amine, which cyclised to crystalline imine **22D** in quantitative yield; the overall yield of **22D** from 2-*C*-methyl lactone **4D** was 87% with every intermediate crystallising readily.

Under the hydrogenation conditions with palladium as the catalyst, imine **22D** did not undergo further reduction; this is in contrast to the synthesis of DFJ **6L** in Scheme 2, where imine **16** underwent complete and stereoselective hydrogenation to **17**. Imine **22D**, also much more stable under acidic conditions than **16**, with aqueous trifluoroacetic acid gave imine **3D**, in quantitative yield; **3D** is a piperidine analogue of the pyrrolidine imine nectrisine, a potent inhibitor of α-glucosidases[32] with anti-viral properties.[33] The methyl group at the quaternary centre in **3D** added considerable stability to the imine function, presumably since an imine–enamine equilibration is impossible.

Hydrogenation of imine **22D** was successfully achieved using platinum oxide in aqueous dioxane to give a mixture of ketals **23L** and **26D** in yields of 41% and 56%, respectively. There is little diastereoselectivity in the reduction of the imine, indicating that the isopropylidene has much the same steric hindrance as is caused by the methyl group in **22D**; this is in contrast to the hydrogenation of **16** where the reduction is completely stereoselective. Epimeric amines **23L** and **26D** can be separated cleanly by chromatography. Hydrolysis of **23L** by aqueous trifluoroacetic acid removed the isopropylidene protecting group to afford 4-*C*-methyl-DFJ **1L** in 97%; similar treatment of **26D** afforded C-5 epimer **2D** (100%).

NOESY experiments were used to establish the configuration at C-5 of the epimeric imino sugars **1L** and **2D** (Fig. 3). In 4-*C*-methyl-DFJ **1L**, NOE enhancements were observed between H-3 and H-5, H-1′ and Me-4′; enhancements were also observed between H-5 and H-1′ and Me-4′. These observations were consistent with H-1′, H-3 and H-5 all occupying axial positions (Fig. 3a). The diaxial couplings between H-2 and H-3 of 9.5 Hz and between H-2 and H-1′ of 11.2 Hz were consistent with the chair conformation of a sugar (Table 1); as expected the axial-equatorial coupling between H-2 and H-1 was only 5.4 Hz. Conversely, in imino sugar **2D**, NOE enhancements were observed between H-3 and Me-6, H-1′ and Me-4′, whilst enhancements were only observed between H-5 and Me-6 and Me-4′. These observations were consistent with H-1′, H-3 and Me-6 all occupying axial positions and H-5 being equatorial (Fig. 3b). The diaxial couplings between H-2 and H-3

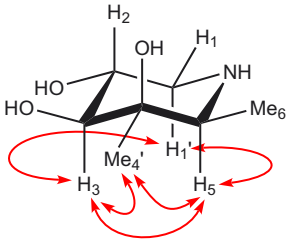


Figure 3a. 4-*C*-Methyl-DFJ **1L**.

Table 1. Proton *J*-couplings for imino sugars **1L** and **2D**

	J-Values (Hz)	Multiplicity
Proton couplings for **1L**		
H-1–H-2	5.4	dd
H-1′–H-2	11.2	dd
H-1′–H-1	12.9	dd
H-3–H-2	9.5	d
H-5–Me-6	6.6	q
Proton couplings for **2D**		
H-1–H-2	5.2	dd
H-1′–H-2	9.4	dd
H-1′–H-1	13.8	dd
H-3–H-2	8.2	d
H-5–Me-6	7.3	q

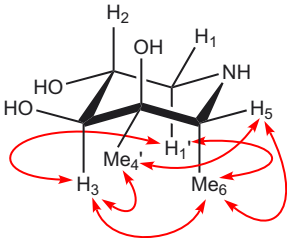


Figure 3b. Imino sugar **2D**.

of 8.2 Hz and between H-2 and H-1′ of 9.4 Hz were again consistent with the chair conformation of a sugar, as was the axial–equatorial coupling between H-2 and H-1 of 5.2 Hz.

The *N*-butyl derivatives of **1L** and **2D** were also prepared. Hydrogenation of *C*-methyl DFJ ketal **23L** and butyraldehyde in the presence of palladium hydroxide in aqueous dioxane resulted in reductive amination to form tertiary amine **24L** (61%); removal of the ketal protecting group by aqueous trifluoroacetic acid afforded *N*-butyl-4-*C*-methyl DFJ **25L** (100%). Similar reductive amination of the epimeric amine **26D** gave **27D** (71%), which on deprotection formed C-5 epimeric altritol **28D** (90%).

For the synthesis of enantiomeric 4-*C*-methyl D-galactose mimics **1D** and related piperidines, the enantiomeric 2-*C*-methyl-L-lyxonolactone **18L** was prepared from 2-*C*-methyl-D-ribonolactone **5D**, readily available from D-glucose [Scheme 4]. Inversion of configuration at C-4 by base treatment of a carbohydrate lactone with a C-5 leaving group is a well established procedure.[34] Treatment of lactone **5D** with acetone in the presence of acid gave acetonide **29** in 100% yield. Mesylation of the free hydroxyl group in **29** with methanesulfonyl chloride in pyridine in the presence of *N*,*N*-dimethylaminopyridine (DMAP) gave the corresponding mesylate **30** (100% yield). Treatment of **30** with potassium hydroxide in aqueous dioxane, followed by acid work-up, caused sequential ring opening of the lactone, formation of an epoxide intermediate and ring closure with inversion of configuration at C-4 of the sugar to give L-lyxonolactone **18L** in 91% overall yield. The overall yield of **18L** from D-ribonolactone **29** was 91%.

With L-acetonide **18L** an identical sequence of reactions [Scheme 4] to those reported above for D-acetonide **18D** [Scheme 3] gave the target galactose mimics. Thus triflation of **18L** gave **19L** (96%), which with azide gave **20L** (92%). Addition of methyl lithium to azidolactone **20L** afforded lactols **21L** (100%), which on palladium catalysed hydrogenation gave imine **22L** (98%). The overall yield of the protected key imine intermediate **22L** from 2-*C*-methyl-D-ribonolactone **5D** was 78%.

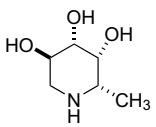
Hydrolysis of **22L** gave piperidine nectrisine analogue **3L** (91%), whereas hydrogenation of **22L** in the presence of platinum oxide (Adams' catalyst) formed the easily separated saturated amines **23D** (51%) and **26L** (46%). Hydrolysis of **23D** gave 6-deoxy-4-*C*-methyl-DGJ **1D** (100%) and of **26L** gave the epimeric L-iminoaltritol **2L** (100%). The *N*-butyl derivatives were also prepared. Reductive amination of **23D** afforded protected amine **24D** (72%), which was hydrolysed to the *N*-butyl deoxy-DGJ derivative **25D** (80%). Similarly **26L** gave **27L** (88%) and subsequent hydrolysis formed *N*-butyl L-iminoaltritol **28L** (85%).

The above high yielding sequences show the value of carbon branched carbohydrate lactones in the synthesis of piperidines with quaternary centres and many functional groups.

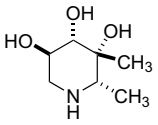
2.2. Enzyme inhibition assays

The concentrations of the 4-*C*-methyl branched iminosugars that caused 50% inhibition of α-L-fucosidase (from human placenta, assayed at pH 5.5), α-D-mannosidase (from almond, assayed at pH 4.5), α-D-galactosidase (from coffee beans, assayed at pH 6.5), and α-L-rhamnosidase (from *Penicillium decumbens*) were assayed. The glycosidase activities were determined using an appropriate *p*-nitrophenyl glycoside as substrate at the optimum pH of each enzyme.

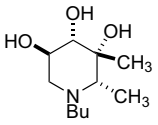
DFJ **6L** is a very potent and specific inhibitor of fucosidases. The results of the assays on the 4-*C*-methyl fucose mimics are shown in Figure 4. None of the compounds showed any inhibition of α-D-mannosidase, α-D-galactosidase, or α-L-rhamnosidase (from *P. decumbens*). The 4-*C*-methyl analogue **1L** gave modest inhibition of fucosidase with an IC_{50} of 50 μM, at least 1000 times weaker than **6L**. The *N*-butyl analogue **25L** still gave significant though weak fucosidase inhibition; the nectrisine analogue **3D** gave very weak inhibition. The epimeric compounds at C-5 **2D** and the butyl amine **28D** gave no inhibition.



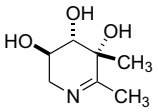
6L



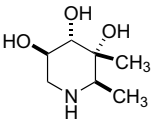
1L



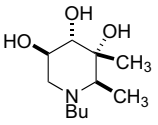
25L



3D



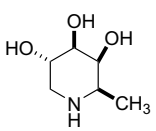
2D



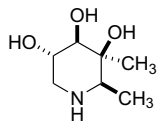
28D

IC_{50} (μM)	50	137	839	NI	NI

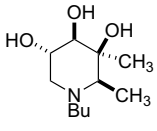
Figure 4. IC_{50} (μM) causing 50% inhibition of α-L-fucosidase [NI = less than 50% inhibition at 1000 μM].



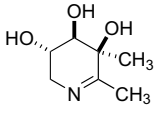
6D



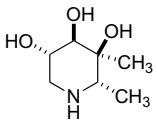
1D



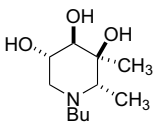
25D



3L



2L



28L

IC_{50} (μM)	350	NI	375	NI	NI

Figure 5. IC_{50} (μM) causing 50% inhibition of α-L-fucosidase [NI = less than 50% inhibition at 1000 μM].

The results of the assays on the 4-*C*-methyl 6-deoxy-D-galactose mimics are given in Figure 5. None of the compounds showed any inhibition of α-D-mannosidase, α-L-fucosidase or α-L-rhamnosidase (from *P. decumbens*). The 4-*C*-methyl analogue **1D** and imine **3L** both gave very weak inhibition of galactosidase with IC_{50} of 350 μM and of 375 μM, respectively. The *N*-butyl analogue **25D** caused no inhibition. The epimeric compounds at C-5 **2L** and the butyl amine **28L** also gave no inhibition.

Thus the introduction of a branching methyl group at C-4 of the piperidine sugar mimics significantly reduced glycosidase inhibition.

3. Conclusion

Very efficient syntheses via crystalline intermediates have shown the value of newly available branched sugar lactones in the synthesis of highly functionalised piperidines with a carbon branch at a quaternary centre. The introduction of a 4-*C*-methyl group to very potent glycosidase inhibitors caused a considerable loss of potency although no other inhibition of other glycosidases was observed; the residual inhibition still showed specific recognition of the carbohydrate moiety. Other receptors that interact with sugars may have a lipophilic cleft in the binding site; other biological assays on the fucose and galactose analogues are in progress.

4. Experimental

Proton nuclear magnetic resonance spectra (δ_H) were recorded on a Bruker AV400 (400 MHz) or a Bruker AV500 (500 MHz) spectrometer and were calibrated according to the chemical shift of residual protons in the deuterated solvent. ^{13}C NMR spectra (δ_C) were recorded on a Bruker AV400 (100.6 MHz) and calibrated according to the chemical shift of the deuterated solvent. Chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. The following abbreviations are used to denote multiplicities: s, singlet; d, doublet; dd, double-doublet; ddd, double-double-doublet; t, triplet; q, quartet; dt, double-triplet; m, multiplet; br, broad; a, apparent. Nuclear Overhauser Effect Spectroscopy (NOESY) experiments were performed at 500 MHz and 298 K with a mixing time of 800 ms. Infrared spectra were recorded on a Bruker Tensor 27 FT IR spectrophotometer using thin films on NaCl or Ge plates and peaks are given in cm^{-1}. Low-resolution mass spectra (LRMS) were recorded on a Fisons Platform (ESI) spectrometer or a Micromass VG Autospec 500 OAT ($CI(NH_3)$) spectrometer. High-resolution mass spectra (HRMS) were recorded on a Micromass LCT (ESI) spectrometer, a Micromass VG Autospec 500 OAT ($CI(NH_3)$) spectrometer or a Micromass GCT (FI) spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm; concentrations (c) are quoted in g/100 mL. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory (Oxford). Melting points (mp) were measured on a Kofler hot-block apparatus and are uncorrected. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with $60F_{254}$ silica from Merck, and plates were developed by dipping in 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid with subsequent heating. Flash column chromatography was carried out using Sorbsil C60 40/60 silica. The solvents (HPLC grade) and the commercially available reagents were used as supplied.

4.1. 2,3-*O*-Isopropylidene-2-*C*-methyl-D-lyxono-1,4-lactone 18D

2-*C*-Methyl-D-lyxono-1,4-lactone **4D** (556 mg, 3.43 mmol) was dissolved in acetone (56 mL) and stirred under argon with anhydrous copper(II) sulfate (3.0 g) and catalytic

concentrated sulfuric acid (12 drops, ~0.1 mL). After 16 h, TLC analysis (ethyl acetate) revealed the presence of no starting material (R_f 0.19) and one major product (R_f 0.66). The reaction mixture was neutralised with excess anhydrous sodium carbonate, filtered through Celite® with acetone as eluent and the filtrate concentrated in vacuo to afford acetonide **18D** (690 mg, 99%) as a colourless oil, which crystallised on standing; mp 64–66 °C; $[\alpha]_D^{23} = +77.2$ (*c* 1.8, acetone); ν_{max} (film): 1784 (γ-lactone C=O) 3447 (O–H) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.40, 1.43 (2 × 3H, 2 × s, C(CH_3)$_2$), 1.57 (3H, s, 2′-CH_3), 2.43 (1H, br s, 5-O*H*), 3.94 (1H, dd, $J_{5,5'}$ 12.2 Hz, $J_{4,5'}$ 5.0 Hz, H-5′), 4.02 (1H, dd, $J_{5,5'}$ 12.2 Hz, $J_{4,5}$ 6.7 Hz, H-5), 4.47 (1H, d, $J_{3,4}$ 3.4 Hz, H-3), 4.52 (1H, ddd, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 6.7 Hz, $J_{4,5'}$ 5.0 Hz, H-4); δ_C ($CDCl_3$, 100.6 MHz): 18.2 (2′-CH_3), 26.7, 26.8 (C(CH_3)$_2$), 60.8 (C-5), 78.1 (C-4), 80.8 (C-3), 83.1 (C-2), 113.5 (C(CH_3)$_2$), 176.3 (C-1); LRMS *m*/*z* (ESI +ve): 220.12 (M+NH_4^+, 100%); HRMS *m*/*z* (ESI +ve): found 220.1186 (M+NH_4^+); $C_9H_{18}NO_5$ requires 220.1185.

4.2. 2,3-*O*-Isopropylidene-2-*C*-methyl-5-*O*-trifluoromethanesulfonyl-D-lyxono-1,4-lactone 19D

A solution of ketal **18D** (513 mg, 2.54 mmol) in dichloromethane (12 mL) was stirred under argon with pyridine (0.62 mL, 7.61 mmol) at −30 °C. Trifluoromethanesulfonic anhydride (0.68 mL, 4.06 mmol) was added drop-wise to the reaction mixture and the mixture stirred for 3 hours when TLC analysis (ethyl acetate/cyclohexane, 1:1) revealed the presence of no starting material (R_f 0.25) and one major product (R_f 0.65). The reaction mixture was diluted with dichloromethane (40 mL) and washed with dilute hydrochloric acid (1.0 M, 20 mL). The aqueous layer was then washed with dichloromethane (2 × 30 mL), the organic extracts were combined, dried over magnesium sulfate and filtered. The filtrate was then concentrated in vacuo to afford triflate **19D** (878.3 mg, quantitative) as a white crystalline solid; mp 66–68 °C; $[\alpha]_D^{21} = +60.9$ (*c* 0.6, acetone); ν_{max} (film): 1783 (γ-lactone C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.42, 1.45 (2 × 3H, 2 × s, C(CH_3)$_2$), 1.61 (3H, s, 2′-CH_3), 4.50 (1H, d, $J_{3,4}$ 3.1 Hz, H-3), 4.69–4.83 (3H, m, H-4, H-5 & H-5′); δ_C ($CDCl_3$, 100.6 MHz): 18.1 (2′-CH_3), 26.6, 26.8 (C(CH_3)$_2$), 72.9 (C-5), 74.5 (C-4), 79.8 (C-3), 82.9 (C-2), 114.3 (C(CH_3)$_2$), 174.8 (C-1); HRMS *m*/*z* (FI +ve): found 334.0480 (M^+); $C_{10}H_{13}F_3O_7S$ requires 334.0334.

4.3. 2,3-*O*-Isopropylidene-2-*C*-methyl-5-*O*-trifluoromethanesulfonyl-L-lyxono-1,4-lactone 19L

2,3-*O*-Isopropylidene-2-*C*-methyl-L-lyxono-1,4-lactone (969 mg, 4.80 mmol) **18L** treated in a similar manner gave enantiomer **19L** (1.54 g, 96%) as a white crystalline solid; mp 79–81 °C, $[\alpha]_D^{21} = -55.9$ (*c* 2.0, acetone); the other physical data for **19L** were consistent with those of **19D**.

4.4. 5-Azido-5-deoxy-2,3-*O*-isopropylidene-2-*C*-methyl-D-lyxono-1,4-lactone 20D

A solution of triflate **19D** (885 mg, 2.65 mmol) in *N*,*N*-dimethylformamide (30 mL) was stirred at room temperature under argon in the presence of sodium azide (258 mg, 3.97 mmol). After 16 h, TLC analysis (ethyl acetate/cyclohexane, 1:1) revealed the presence of one major product (R_f 0.65). The reaction mixture was concentrated in vacuo, the residue dissolved in dichloromethane (75 mL) and the resulting solution washed with water (75 mL) and brine (75 mL). The combined aqueous phases were then washed with dichloromethane (2 × 75 mL). The organic phases were then combined, dried over magnesium sulfate, filtered and concentrated in vacuo to afford a yellow oil (607 mg). Purification by flash column chromatography (ethyl acetate/cyclohexane, 1:3) afforded azide **20D** (549 mg, 91%) as a white crystalline solid; mp 59–60 °C; $[\alpha]_D^{20} = +73.9$ (*c* 0.9, acetone); ν_{max} (film): 2106 (N_3), 1788 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.42, 1.45 (2 × 3H, 2 × s, C(CH_3)$_2$), 1.58 (3H, s, 2′-CH_3), 3.64 (1H, dd, $J_{4,5}$ 6.2 Hz, $J_{5,5'}$ 12.9 Hz, H-5), 3.72 (1H, dd, $J_{4,5'}$ 7.0 Hz, $J_{5,5'}$ 12.9 Hz, H-5′), 4.42 (1H, d, $J_{3,4}$ 3.3 Hz, H-3), 4.47 (1H, ddd, $J_{4,5}$ 6.2 Hz, $J_{4,5'}$ 7.0 Hz, $J_{3,4}$ 3.3 Hz, H-4); δ_C ($CDCl_3$, 100.6 MHz): 18.1 (2′-CH_3), 26.7, 26.9 (2 × C(CH_3)$_2$), 49.5 (C-5), 76.1 (C-4), 80.3 (C-3), 83.0 (C-2), 113.6 (C(CH_3)$_2$), 175.5 (C-1); LRMS *m*/*z* (ESI +ve): 286.25 (M+ CH_3CN+NH_4^+, 100%); HRMS *m*/*z* (ESI +ve): found 291.1067 (M+CH_3CN+Na^+); $C_{11}H_{16}N_4O_4Na$ requires 291.1069. Found: C, 47.58; H, 5.86; N, 18.31; $C_9H_{13}N_3O_4$ requires C, 47.57; H, 5.77; N, 18.49.

4.5. 5-Azido-5-deoxy-2,3-*O*-isopropylidene-2-*C*-methyl-L-lyxono-1,4-lactone 20L

2,3-*O*-Isopropylidene-2-*C*-methyl-5-*O*-trifluoromethanesulfonyl-L-lyxono-1,4-lactone **19L** (654 mg, 1.96 mmol) treated in a similar manner gave enantiomer **20L** (407 mg, 92%) as a white crystalline solid; mp 59–61 °C, $[\alpha]_D^{21} = -72.0$ (*c* 0.4, acetone); the other physical data for **20L** were consistent with those of **20D**.

4.6. 6-Azido-1,6-dideoxy-3,4-*O*-isopropylidene-3-*C*-methyl-D-tagatofuranose 21D

Methyl lithium (1.6 M in Et_2O, 0.6 mL) was added drop-wise to a stirred solution of azidolactone **20D** (197 mg, 0.87 mmol) in tetrahydrofuran (2 mL) at −78 °C under an argon atmosphere. After 4 h TLC analysis (ethyl acetate/cyclohexane, 1:1) revealed the presence of one major product (R_f 0.70) and no starting material (R_f 0.65). The reaction mixture was carefully quenched by addition of aqueous saturated ammonium chloride solution (1 mL) and the mixture extracted with ethyl acetate (3 × 8 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and concentrated in vacuo to afford a crude white crystalline solid (215 mg). Purification by flash column chromatography (ethyl acetate/cyclohexane, 1:4) afforded lactols **21D** (203 mg, 97%) as a white crystalline solid; mp 80–81 °C; $[\alpha]_D^{24} = +7.1$ (*c* 0.5, acetone); ν_{max} (film): 3443 (O–H), 2099 (N_3) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.37 (3H, s, 1_B-CH_3), 1.42, 1.45 (2 × 3H, 2 × s, C(CH_3)$_2$-A), 1.46 (3H, s, $3'_B$-CH_3), 1.47 (3H, s, C(CH_3)$_2$-B), 1.49, 1.49 (2 × 3H, 2 × s, 1_A-CH_3 & $3'_A$-CH_3), 1.54 (3H, s, C(CH_3)$_2$-B), 2.15 (1H, br s, 2_A-O*H*), 3.54 (2H, d, $J_{5A,6A}$ 6.5 Hz, 6_A-CH_2N_3), 3.55 (2H, d, $J_{5B,6B}$ 6.6 Hz, 6_B-CH_2N_3), 3.70 (1H, dt, $J_{5B,6B}$ 6.6 Hz, $J_{4B,5B}$ 3.5 Hz, H-5_B),

4.20 (1H, dt, $J_{5A,6A}$ 6.5 Hz, $J_{4A,5A}$ 3.4 Hz, H-5_A), 4.33 (1H, br s, 2_B-O*H*), 4.38 (1H, d, $J_{4B,5B}$ 3.5 Hz, H-4_B), 4.39 (1H, d, $J_{4A,5A}$ 3.4 Hz, H-4_A), A:B ≈ 3:1; δ_C ($CDCl_3$, 100.6 MHz): 20.3, 20.8 (1_B-*C*H_3 & $3'_B$-*C*H_3), 20.5, 22.4 (1_A-*C*H_3 & $3'_A$-*C*H_3), 27.1 (C(*C*H_3)$_2$–B), 27.3, 27.8 (2× C(*C*H_3)$_2$–A & C(*C*H_3)$_2$–B), 49.6 (C-6_B), 49.8 (C-6_A), 73.9 (C-5_B), 76.4 (C-5_A), 85.7 (C-4_B), 86.6 (C-4_A), 89.1 (C-3_B), 92.3 (C-3_A), 104.6 (C-2_B), 106.5 (C-2_A), 113.2 (*C*(CH$_3$)$_2$–A), 113.5 (*C*(CH$_3$)$_2$–B), A:B ≈ 3:1; LRMS *m*/*z* (ESI −ve): 242.29 (M−H$^+$, 100%); HRMS *m*/*z* (ESI +ve): found 266.1106 (M+H$^+$); $C_{10}H_{17}N_3NaO_4$ requires 266.1111. Found: C, 49.62; H, 7.08; N, 17.04; $C_{10}H_{17}N_3O_4$ requires C, 49.37; H, 7.04; N, 17.27.

4.7. 6-Azido-1,6-dideoxy-3,4-*O*-isopropylidene-3-*C*-methyl-L-tagatofuranose 21L

5-Azido-5-deoxy-2,3-*O*-isopropylidene-2-*C*-methyl-D-lyxono-1,4-lactone **20L** (366 mg, 1.61 mmol) treated in a similar manner gave enantiomer **21L** (402 mg, quant.) as a white crystalline solid; mp 80–83 °C; $[\alpha]_D^{24} = -5.1$ (*c* 0.5, acetone); the other physical data for **21L** were consistent with those of **21D**.

4.8. 2,6-Imino-3,4-*O*-isopropylidene-3-*C*-methyl-1,2,6-trideoxy-D-tagatopyranose [(3*R*,4*S*,5*R*)-5,6-dimethyl-4,5-*O*-isopropylidene-2,3,4,5-tetrahydropyridine-3,4,5-triol] 22D

A solution of azidolactols **21D** (544 mg, 2.24 mmol) in methanol (150 mL) was stirred at room temperature under an argon atmosphere. Palladium (10%) on carbon (109 mg) was added to the stirred solution and the flask flushed twice with argon before flushing three times with hydrogen gas. The reaction mixture was then left to stir vigorously under an atmosphere of hydrogen for 3 hours, when TLC analysis (ethyl acetate) revealed the presence of one major product (R_f 0.08) and no starting material (R_f 0.89). The reaction mixture was filtered through Celite® with methanol and the filtrate concentrated in vacuo to afford imine **22D** (445 mg, quant.) as a colourless oil which crystallised on standing; mp 95–97 °C; $[\alpha]_D^{20} = +49.0$ (*c* 1.6, CH_3OH); ν_{max} (film): 3175 (O–H), 1666 (C=N) cm^{-1}; δ_H (CD_3OD, 400 MHz): 1.28, 1.40 (2 × 3H, 2 × s, C(C*H*$_3$)$_2$), 1.45 (3H, s, 3′-C*H*$_3$), 2.06 (3H, m, 1-C*H*$_3$), 3.60 (2H, m, 2 × H-6), 3.97 (2H, m, H-4 & H-5); δ_C (CD_3OD, 100.6 MHz): 19.7 (C-1), 22.3 (3′-*C*H$_3$), 26.5, 26.6 (2 × C(*C*H$_3$)$_2$), 51.1 (C-6), 65.3 (C-5), 77.2 (C-3), 80.0 (C-4), 109.3 (*C*(CH$_3$)$_2$), 172.4 (C-2); HRMS *m*/*z* (FI +ve): found 199.1207 (M$^+$); $C_{10}H_{17}NO_3$ requires 199.1208. Found: C, 60.08; H, 8.57; N, 6.81; $C_{10}H_{17}NO_3$ requires C, 60.28; H, 8.60; N, 7.03.

4.9. 2,6-Imino-3,4-*O*-isopropylidene-3-*C*-methyl-1,2,6-trideoxy-L-tagatopyranose [(3*S*,4*R*,5*S*)-5,6-dimethyl-4,5-*O*-isopropylidene-2,3,4,5-tetrahydropyridine-3,4,5-triol 22L

6-Azido-1,6-dideoxy-3,4-*O*-isopropylidene-3-*C*-methyl-L-tagatofuranose **21L** (360 mg, 1.48 mmol) treated in a similar manner gave enantiomer **22L** (290 mg, 98%) as a colourless oil which crystallised on standing; mp 96–98 °C; $[\alpha]_D^{21} = -46.0$ (*c* 1.5, CH_3OH); the other physical data for **22L** were consistent with those of **22D**.

4.10. 2,6-Imino-3-*C*-methyl-1,2,6-trideoxy-D-tagatopyranose [(3*R*,4*S*,5*R*)-5,6-dimethyl-2,3,4,5-tetrahydropyridine-3,4,5-triol] 3D

A solution of the protected imine **22D** (65 mg, 0.33 mmol) in water (1 mL) and trifluoroacetic acid (1 mL) was stirred for 24 h. After this time more trifluoroacetic acid (1 mL) was added and the reaction mixture stirred for a further 24 h. The reaction mixture was then concentrated in vacuo and co-evaporated three times with toluene. The residue was dissolved in water (10 mL) and eluted with water through a plug of Dowex® 50WX8-100 (H$^+$) ion exchange resin. Subsequent elution of the resin plug with aqueous ammonium hydroxide solution (2 M) afforded an ammoniacal eluate which was concentrated in vacuo to afford the unprotected imine **3D** (53 mg, quant.) as a yellow oil; $[\alpha]_D^{21} = -34.7$ (*c* 0.3, CH_3OH); ν_{max} (film): 3385 (O–H), 1663 (C=N) cm^{-1}; δ_H (CD_3OD, 400 MHz): 1.30 (3H, s, 3′-C*H*$_3$), 1.93 (3H, m, 1-C*H*$_3$), 3.10 (1H, m, H-6), 3.34 (1H, d, $J_{4,5}$ 9.7 Hz, H-4), 3.62–3.76 (2H, m, H-5 & H-6′); δ_C (CD_3OD, 100.6 MHz): 20.4 (3′-*C*H$_3$), 22.5 (C-1), 53.7 (C-6), 65.9 (C-5), 72.9 (C-3), 75.5 (C-4), 173.3 (C-2); HRMS *m*/*z* (FI +ve): found 160.0969 (M+H$^+$); $C_7H_{14}NO_3$ requires 160.0974.

4.11. 2,6-Imino-3-*C*-methyl-1,2,6-trideoxy-L-tagatopyranose [(3*S*,4*R*,5*S*)-5,6-dimethyl-2,3,4,5-tetrahydropyridine-3,4,5-triol] 3L

2,6-Imino-3,4-*O*-isopropylidene-3-*C*-methyl-1,2,6-trideoxy-L-tagatopyranose **22L** (73 mg, 0.37 mmol) treated in a similar manner gave enantiomer **3L** (53 mg, 91%) as a yellow oil; $[\alpha]_D^{21} = +30.6$ (*c* 1.4, CH_3OH); the other physical data for **3L** were consistent with those of **3D**.

4.12. 1,5-Imino-3,4-*O*-isopropylidene-4-*C*-methyl-1,5,6-trideoxy-D-altritol 26D and 1,5-dideoxy-1,5-imino-3,4-*O*-isopropylidene-4-*C*-methyl-L-fucitol 23L

A solution of the protected imine **22D** (105 mg, 0.53 mmol) in aqueous dioxane (1:1, 11.2 mL) was stirred at room temperature under an atmosphere of argon. Platinum oxide (20 mg) was added to the stirred solution and the flask flushed twice with argon before flushing three times with hydrogen gas. The reaction mixture was then left to stir vigorously under an atmosphere of hydrogen for 16 h, after which TLC analysis (10% methanol in ethyl acetate) revealed the presence of two major products (R_f 0.05 and R_f 0.09) and no starting material (R_f 0.37). The reaction mixture was filtered through Celite® with water and the filtrate concentrated in vacuo. Purification of the residue by flash column chromatography (chloroform/ethanol/concd ammonium hydroxide solution, 25:3:0.3) afforded imino-D-altritol **26D** (59 mg, 56%, R_f 0.09) as a colourless oil which crystallised on standing, mp 116–118 °C; $[\alpha]_D^{22} = +17.5$ (*c* 1.2, acetone); ν_{max} (film): 3385 (O–H) cm^{-1}; δ_H (CD_3OD, 400 MHz): 1.06 (3H, d, $J_{5,6}$ 6.8 Hz, 6-C*H*$_3$), 1.26 (3H, s, 4′-C*H*$_3$), 1.36, 1.44 (2 × 3H, 2 × s, 2 × C(C*H*$_3$)$_2$), 2.82 (1H, q, $J_{5,6}$ 6.8 Hz, H-5), 2.86 (1H, m, H-1), 2.94 (1H, dd, $J_{1,1'}$ 13.9 Hz, $J_{2,1'}$ 2.2 Hz, H-1′), 3.85 (1H, d, $J_{2,3}$ 1.7 Hz, H-3), 3.94 (1H, a–q, *J* 2.3 Hz, H-2); δ_C (CD_3OD, 100.6 MHz): 14.0 (C-6), 17.2 (4′-*C*H$_3$), 26.3,

27.7 (2 × C(CH_3)$_2$), 48.1 (C-1), 56.0 (C-5), 66.0 (C-2), 79.3 (C-4), 81.7 (C-3), 108.0 (C(CH$_3$)$_2$); LRMS m/z (ESI +ve): 202.06 (M+H$^+$, 100%); HRMS m/z (ESI +ve): found 202.1439 (M+H$^+$); $C_{10}H_{20}NO_3$ requires 202.1438. Found: C, 59.49; H, 9.34; N, 6.83; $C_{10}H_{19}NO_3$ requires C, 59.68; H, 9.52; N, 6.96; and the imino-L-fucitol **23L** (44 mg, 41%, R_f 0.05) as a colourless oil which crystallised on standing, mp 86–90 °C; $[\alpha]_D^{22} = +8.2$ (c 2.2, acetone); ν_{max} (film): 3357 (O–H) cm^{-1}; δ_H (CD$_3$OD, 400 MHz): 1.11 (3H, d, $J_{5,6}$ 6.7 Hz, 6-CH_3), 1.36 (3H, s, 4′-CH_3), 1.42, 1.47 (2 × 3H, 2 × s, 2 × C(CH_3)$_2$), 2.64 (1H, m, H-1), 2.85 (1H, q, $J_{5,6}$ 6.7 Hz, H-5), 3.16 (1H, dd, $J_{1,1'}$ 13.7 Hz, $J_{2,1'}$ 5.3 Hz, H-1′), 3.90–3.95 (2H, m, H-3 & H-2); δ_C (CD$_3$OD, 100.6 MHz): 14.3 (C-6), 25.4 (4′-CH$_3$), 26.6, 27.6 (2 × C(CH$_3$)$_2$), 47.9 (C-1), 54.9 (C-5), 66.9 (C-2), 80.9 (C-4), 83.5 (C-3), 108.9 (C(CH$_3$)$_2$); LRMS m/z (ESI +ve): 202.08 (M+H$^+$, 100%); HRMS m/z (ESI +ve): found 202.1438 (M+H$^+$); $C_{10}H_{20}NO_3$ requires 202.1438. Found: C, 59.60; H, 9.43; N, 6.89; $C_{10}H_{19}NO_3$ requires C, 59.68; H, 9.52; N, 6.96.

4.13. 1,5-Imino-3,4-*O*-isopropylidene-4-*C*-methyl-1,5,6-trideoxy-L-altritol 26L and 1,5-dideoxy-1,5-imino-3,4-*O*-isopropylidene-4-*C*-methyl-D-fucitol 23D

2,6-Imino-3,4-*O*-isopropylidene-3-*C*-methyl-1,2,6-trideoxy-L-tagatopyranose **22L** (263 mg, 1.32 mmol) treated in a similar manner gave enantiomer **26L** (121 mg, 46%, R_f 0.09) as a colourless oil which crystallised on standing, mp 117–119 °C; $[\alpha]_D^{21} = -23.1$ (c 1.6, acetone); the other physical data for **26L** were consistent with those of **26D**; and enantiomer **23D** (134 mg, 51%, R_f 0.05) as a colourless oil which crystallised on standing, mp 86–90 °C; $[\alpha]_D^{21} = -13.0$ (c 0.2, acetone); the other physical data for **23D** were consistent with those of **23L**.

4.14. 4-*C*-Methyl DFJ [1,5-dideoxy-1,5-imino-4-*C*-methyl-L-fucitol] 1L

A solution of acetonide **23L** (56 mg, 0.28 mmol) in water (1.5 mL) and trifluoroacetic acid (1 mL) was stirred for 48 h. The reaction mixture was then concentrated in vacuo and co-evaporated three times with toluene. The residue was dissolved in water (10 mL) and eluted with water through a plug of Dowex® 50WX8-100 (H$^+$) ion exchange resin. Subsequent elution of the resin plug with aqueous ammonium hydroxide solution (2 M) afforded an ammoniacal eluate which was concentrated in vacuo to afford 4-*C*-methyl DFJ **1L** (43 mg, 97%) as a pale yellow oil; $[\alpha]_D^{21} = -25.1$ (c 0.7, CH$_3$OH); ν_{max} (film): 3384 (br, O–H, N–H) cm^{-1}; δ_H (D$_2$O, 500 MHz): 0.97 (3H, d, $J_{5,6}$ 6.6 Hz, 6-CH_3), 1.12 (3H, s, 4′-CH_3), 2.30 (1H, dd, $J_{1,1'}$ 12.9 Hz, $J_{2,1'}$ 11.2 Hz, H-1′), 2.50 (1H, q, $J_{5,6}$ 6.6 Hz, H-5), 2.98 (1H, dd, $J_{1,1'}$ 12.9 Hz, $J_{2,1}$ 5.4 Hz, H-1), 3.08 (1H, d, $J_{2,3}$ 9.5 Hz, H-3), 3.53 (1H, a-ddd, J 10.8 Hz, J 9.7 Hz, J 5.4 Hz, H-2); δ_C (D$_2$O, 100.6 MHz): 13.6 (C-6), 21.3 (4′-CH$_3$), 48.9 (C-1), 57.3 (C-5), 69.1 (C-2), 74.6 (C-4), 78.6 (C-3); LRMS m/z (ESI −ve): 192.29 (M+CH$_3$OH−H$^+$, 100%); HRMS m/z (ESI −ve): found 160.0974 (M−H$^+$); $C_7H_{14}NO_3$ requires 160.0968.

4.15. 1,5-Dideoxy-1,5-imino-4-*C*-methyl-D-fucitol 1D

1,5-Dideoxy-1,5-imino-3,4-*O*-isopropylidene-4-*C*-methyl-D-fucitol **23D** (84 mg, 0.42 mmol) treated in a similar manner gave enantiomer **1D** (67 mg, quant.) as a colourless oil; $[\alpha]_D^{21} = +33.7$ (c 0.4, CH$_3$OH); the other physical data for **1D** were consistent with those of **1L**.

4.16. 1,5-Imino-4-*C*-methyl-1,5,6-trideoxy-D-altritol 2D

A solution of ketal **26D** (23 mg, 0.11 mmol) in water (0.6 mL) and trifluoroacetic acid (0.6 mL) was stirred at room temperature for 72 h. The reaction mixture was then concentrated in vacuo and co-evaporated three times with toluene. The residue was dissolved in water (10 mL) and eluted with water through a plug of Dowex® 50WX8-100 (H$^+$) ion exchange resin. Subsequent elution of the resin plug with aqueous ammonium hydroxide solution (2 M) afforded an ammoniacal eluate which was concentrated in vacuo to afford unprotected 1,5-imino-D-altritol **2D** (18 mg, quant.) as a pale yellow oil; $[\alpha]_D^{21} = -3.9$ (c 0.5, CH$_3$OH); ν_{max} (film): 3385 (br, O–H, N–H) cm^{-1}; δ_H (D$_2$O, 500 MHz): 1.02 (3H, d, $J_{5,6}$ 7.3 Hz, 6-CH_3), 1.13 (3H, s, 4′-CH_3), 2.52 (1H, dd, $J_{1,1'}$ 13.8 Hz, $J_{2,1'}$ 9.4 Hz, H-1′), 2.77 (1H, q, $J_{5,6}$ 7.3 Hz, H-5), 2.79 (1H, dd, $J_{1,1'}$ 13.8 Hz, $J_{1,2}$ 5.2 Hz, H-1), 3.41 (1H, d, $J_{2,3}$ 8.2 Hz, H-3), 3.62–3.68 (1H, m, H-2); δ_C (D$_2$O, 100.6 MHz): 13.3 (C-6), 21.7 (4′-CH$_3$), 43.9 (C-1), 56.5 (C-5), 69.8 (C-2), 74.7 (C-4), 74.9 (C-3); HRMS m/z (ESI +ve): found 162.1125 (M+H$^+$); $C_7H_{16}NO_3$ requires 162.1125.

4.17. 1,5-Imino-4-*C*-methyl-1,5,6-trideoxy-L-altritol 2L

1,5-Imino-3,4-*O*-isopropylidene-4-*C*-methyl-1,5,6-trideoxy-L-altritol **26L** (38 mg, 0.19 mmol) treated in a similar manner gave enantiomer **2L** (30 mg, quant.) as a colourless oil; $[\alpha]_D^{21} = +5.1$ (c 0.4, CH$_3$OH); the other physical data for **2L** were consistent with those of **2D**.

4.18. *N*-Butyl-1,5-dideoxy-1,5-imino-3,4-*O*-isopropylidene-4-*C*-methyl-L-fucitol 24L

A solution of acetonide **23L** (36 mg, 0.18 mmol) in a water/dioxane mixture (2 mL, 1:1) was stirred at room temperature with butyraldehyde (0.16 mL, 1.8 mmol). Palladium hydroxide (3 mg) was added to the stirred solution and the flask flushed twice with argon before flushing three times with hydrogen gas. The reaction mixture was then left to stir vigorously under an atmosphere of hydrogen for 16 h. The reaction mixture was then flushed with argon. Tetrahydrofuran (1 mL) was added followed by a second addition of butyraldehyde (0.08 mL) and palladium hydroxide (10 mg). The flask was flushed twice with argon before flushing three times with hydrogen gas and was then left to stir vigorously under an atmosphere of hydrogen for a further 16 h. TLC analysis (ethyl acetate) revealed the presence of one major product (R_f 0.49) and no starting material (R_f 0.03). The reaction mixture was filtered through Celite® with a water/tetrahydrofuran mixture (1:1) and the filtrate concentrated in vacuo. Purification of the residue by flash column chromatography (ethyl acetate/cyclohexane, 1:1) afforded the protected *N*-butyl-4-*C*-

methyl-DFJ **24L** (26 mg, 61%) as a pale yellow oil; $[\alpha]_D^{23} = -2.4$ (*c* 1.4, CH_3OH); ν_{max} (film): 3385 (br, O–H) cm^{-1}; δ_H (CD_3OD, 400 MHz): 0.93–0.96 (5H, m, $CH_2CH_2CH_2CH_3$), 1.17–1.22 (3H, m, 6-CH_3), 1.33–1.37 (2H, m, $CH_2CH_2CH_2CH_3$), 1.40 (3H, s, 4′-CH_3), 1.43, 1.47 (2 × 3H, 2 × s, $C(CH_3)_2$), 2.32 (1H, dd, $J_{1,1'}$ 12.2 Hz, $J_{1,2}$ 8.1 Hz, H-1), 2.58–2.76 (3H, m, H-5 & $CH_2CH_2CH_2CH_3$), 3.00 (1H, dd, $J_{1,1'}$ 12.2 Hz, $J_{2,1'}$ 4.5 Hz, H-1′), 3.73 (1H, d, $J_{2,3}$ 6.0 Hz, H-3), 3.93 (1H, ddd, $J_{1,2}$ 8.1 Hz, $J_{2,1'}$ 4.5 Hz, $J_{2,3}$ 6.0 Hz, H-2); δ_C (CD_3OD, 100.6 MHz): 11.8 (C-6), 13.3 ($CH_2CH_2CH_2$-CH_3), 20.6 ($CH_2CH_2CH_2CH_3$), 26.7 (4′-CH_3), 26.8 ($CH_2CH_2CH_2CH_3$), 27.9, 28.1 (2 × $C(CH_3)_2$), 53.2 ($CH_2CH_2CH_2CH_3$), 53.4 (C-1), 62.1 (C-5), 68.0 (C-2), 82.0 (C-4), 85.1 (C-3), 109.4 ($C(CH_3)_2$); LRMS *m*/*z* (ESI +ve): 258.23 ($M+H^+$, 100%); HRMS *m*/*z* (ESI +ve): found 258.2064 ($M+H^+$); $C_{14}H_{28}NO_3$ requires 258.2064.

4.19. *N*-Butyl-1,5-dideoxy-1,5-imino-3,4-*O*-isopropylidene-4-*C*-methyl-D-fucitol 24D

1,5-Dideoxy-1,5-imino-3,4-*O*-isopropylidene-4-*C*-methyl-1,5,6-trideoxy-D-fucitol **23D** (37 mg, 0.19 mmol) treated in a similar manner gave enantiomer **24D** (34 mg, 72%) as a pale yellow oil; $[\alpha]_D^{22} = +8.1$ (*c* 0.4, CH_3OH); the other physical data for **24D** were consistent with those of **24L**.

4.20. *N*-Butyl-1,5-dideoxy-1,5-imino-4-*C*-methyl-L-fucitol 25L

A solution of *N*-butylamine **24L** (18 mg, 0.07 mmol) in water (0.5 mL) and trifluoroacetic acid (0.5 mL) was stirred for 24 h. The reaction mixture was then concentrated in vacuo and co-evaporated three times with toluene. The residue was dissolved in water (10 mL) and eluted with water through a plug of Dowex® 50WX8-100 (H^+) ion exchange resin. Subsequent elution of the resin plug with aqueous ammonium hydroxide solution (2 M) afforded an ammoniacal eluate which was concentrated in vacuo to afford the unprotected amine **25L** (15 mg, quant.) as a pale yellow oil; $[\alpha]_D^{22} = -4.2$ (*c* 0.2, CH_3OH); ν_{max} (film): 3423 (br, O–H, N–H) cm^{-1}; δ_H (D_2O, 400 MHz): 0.79 (3H, t, J_{vic} 7.3 Hz, $CH_2CH_2CH_2CH_3$), 1.05 (3H, d, $J_{5,6}$ 6.5 Hz, 6-CH_3), 1.12 (3H, s, 4′-CH_3), 1.13–1.21 (2H, m, $CH_2CH_2CH_2CH_3$), 1.30–1.40 (2H, m, $CH_2CH_2CH_2CH_3$), 2.26 (1H, a–t, *J* 11.2 Hz, H-1), 2.40 (1H, q, $J_{5,6}$ 6.5 Hz, H-5), 2.59 (2H, dd, J_{vic} 9.9 Hz, J_{vic} 6.5 Hz, $CH_2CH_2CH_2CH_3$), 2.96 (1H, dd, $J_{1,1'}$ 11.4 Hz, $J_{2,1'}$ 5.0 Hz, H-1′), 3.02 (1H, d, $J_{2,3}$ 9.6 Hz, H-3), 3.67 (1H, a–dt, *J* 10.3 Hz, *J* 4.9 Hz, H-2); δ_C (D_2O, 100.6 MHz): 11.6 (C-6), 13.5 (CH_2CH_2- CH_2CH_3), 20.4 ($CH_2CH_2CH_2CH_3$), 22.2 (4′-CH_3), 24.8 ($CH_2CH_2CH_2CH_3$), 52.4 ($CH_2CH_2CH_2CH_3$), 55.6 (C-1), 62.0 (C-5), 67.7 (C-2), 74.5 (C-4), 78.5 (C-3); HRMS *m*/*z* (ESI +ve): found 240.1570 ($M+Na^+$); $C_{11}H_{23}NO_3Na$ requires 240.1570.

4.21. *N*-Butyl-1,5-dideoxy-1,5-imino-4-*C*-methyl-D-fucitol 25D

N-Butyl-1,5-dideoxy-1,5-imino-3,4-*O*-isopropylidene-4-*C*-methyl-D-fucitol **24D** (21 mg, 0.08 mmol) treated in a similar manner gave enantiomer **25D** (14 mg, 80%) as a pale yellow oil; $[\alpha]_D^{21} = +1.0$ (*c* 0.7, CH_3OH); the other physical data for **25D** were consistent with those of **25L**.

4.22. *N*-Butyl-1,5-imino-3,4-*O*-isopropylidene-4-*C*-methyl-1,5,6-trideoxy-D-altritol 27D

A solution of the protected amine **26D** (43 mg, 0.21 mmol) in a water/dioxane mixture (2.6 mL, 1:1) was stirred at room temperature with butyraldehyde (0.20 mL, 2.10 mmol). Palladium hydroxide (4 mg) was added to the stirred solution and the flask flushed twice with argon before flushing three times with hydrogen gas. The reaction mixture was then left to stir vigorously under an atmosphere of hydrogen for 16 h. The reaction mixture was then flushed with argon. Tetrahydrofuran (1 mL) was added followed by a second addition of butyraldehyde (0.1 mL) and palladium hydroxide (10 mg). The flask was flushed twice with argon before flushing three times with hydrogen gas and then left to stir vigorously under an atmosphere of hydrogen for a further 16 h. TLC analysis (ethyl acetate) revealed the presence of one major product (R_f 0.59) and no starting material (R_f 0.04). The reaction mixture was filtered through Celite® with a water/tetrahydrofuran mixture (1:1) and the filtrate concentrated in vacuo. Purification of the residue by flash column chromatography (ethyl acetate/cyclohexane, 1:1) afforded the protected altritol **27D** (39 mg, 71%) as a pale yellow oil; $[\alpha]_D^{22} = -9.9$ (*c* 0.8, CH_3OH); ν_{max} (film): 3453 (br, O–H) cm^{-1}; δ_H (CD_3OD, 400 MHz): 0.92–0.99 (5H, m, CH_2CH_2-CH_2CH_3), 1.15–1.20 (3H, m, 6-CH_3), 1.33 (3H, s, 4′-CH_3), 1.36, 1.44 (2 × 3H, 2 × s, $C(CH_3)_2$), 1.50–1.57 (2H, m, $CH_2CH_2CH_2CH_3$), 2.67 (1H, ddd, J_{gem} 13.2 Hz, J_{vic} 9.4 Hz, J_{vic} 6.5 Hz, $CH_2CH_2CH_2CH_3$), 2.77 (1H, q, $J_{5,6}$ 6.7 Hz, H-5), 2.81–2.91 (2H, m, $CH_2CH_2CH_2CH_3$ & H-1), 3.08 (1H, dd, $J_{1,1'}$ 12.4 Hz, $J_{2,1'}$ 2.1 Hz, H-1′), 3.88 (1H, d, $J_{2,3}$ 2.2 Hz, H-3), 4.05–4.10 (1H, m, H-2); δ_C (CD_3OD, 100.6 MHz): 11.0 (C-6), 13.2 (CH_2CH_2-CH_2CH_3), 18.3 (4′-CH_3), 20.5 ($CH_2CH_2CH_2CH_3$), 25.7 ($CH_2CH_2CH_2CH_3$), 26.2, 27.5 (2 × $C(CH_3)_2$), 52.7 ($CH_2CH_2CH_2CH_3$), 54.4 (C-1), 61.7 (C-5), 64.7 (C-2), 80.4 (C-4), 81.0 (C-3), 108.5 ($C(CH_3)_2$); HRMS *m*/*z* (ESI +ve): found 258.2066 ($M+H^+$); $C_{14}H_{28}NO_3$ requires 258.2064.

4.23. *N*-Butyl-1,5-imino-3,4-*O*-isopropylidene-4-*C*-methyl-1,5,6-trideoxy-L-altritol 27L

1,5-Imino-3,4-*O*-isopropylidene-4-*C*-methyl-1,5,6-trideoxy-L-altritol **26L** (33 mg, 0.17 mmol) treated in a similar manner gave the enantiomer **27L** (37 mg, 88%) as a pale yellow oil; $[\alpha]_D^{22} = +13.0$ (*c* 0.3, CH_3OH); the other physical data for **27L** were consistent with those of **27D**.

4.24. *N*-Butyl-1,5-imino-4-*C*-methyl-1,5,6-trideoxy-D-altritol 28D

A solution of acetonide **27D** (19 mg, 0.07 mmol) in water (0.3 mL) and trifluoroacetic acid (0.3 mL) was stirred for 72 h. The reaction mixture was then concentrated in vacuo and co-evaporated three times with toluene. The residue was dissolved in water (10 mL) and eluted with water through a plug of Dowex® 50WX8-100 (H^+) ion exchange

resin. Subsequent elution of the resin plug with aqueous ammonium hydroxide solution (2 M) afforded an ammoniacal eluate which was concentrated in vacuo to afford *N*-butyl-imino-4-*C*-methyl-D-altritol **28D** (14 mg, 90%) as a pale yellow oil; $[\alpha]_D^{21} = -13.4$ (*c* 0.7, CH_3OH); ν_{max} (film): 3384 (br, O–H) cm^{-1}; δ_H (CD_3OD, 400 MHz): 1.00 (3H, t, J_{vic} 7.4 Hz, $CH_2CH_2CH_2CH_3$), 1.30 (3H, d, $J_{5,6}$ 7.1 Hz, 6-CH_3), 1.35 (3H, s, 4′-CH_3), 1.36–1.47 (2H, m, $CH_2CH_2CH_2CH_3$), 1.53–1.63 (1H, m, $CH_2CH_2CH_2CH_3$), 1.64–1.77 (1H, m, $CH_2CH_2CH_2CH_3$), 2.94–3.09 (2H, m, H-1 & $CH_2CH_2CH_2CH_3$), 3.11–3.18 (1H, m, $CH_2CH_2CH_2CH_3$), 3.18–3.26 (1H, m, H-1′), 3.42–3.50 (2H, m, H-3 & H-5), 4.00 (1H, ddd, J_{vic} 10.9 Hz, J_{vic} 8.9 Hz, J_{vic} 5.7 Hz, H-2); δ_C (CD_3OD, 100.6 MHz): 7.0 (C-6), 12.9 ($CH_2CH_2CH_2CH_3$), 19.8 ($CH_2CH_2CH_2CH_3$), 21.9 (4′-CH_3), 26.3 ($CH_2CH_2CH_2CH_3$), 51.4 ($CH_2CH_2CH_2CH_3$), 53.3 (C-1), 63.3 (C-5), 66.8 (C-2), 72.9 (C-4), 73.5 (C-3); LRMS *m*/*z* (ESI +ve): 218.12 ($M+H^+$, 100%); HRMS *m*/*z* (ESI +ve): found 218.1751 ($M+H^+$); $C_{11}H_{24}NO_3$ requires 218.1751.

4.25. *N*-Butyl-1,5-imino-4-*C*-methyl-1,5,6-trideoxy-L-altritol 28L

N-Butyl-1,5-imino-3,4-*O*-isopropylidene-4-*C*-methyl-1,5,6-trideoxy-L-altritol **27L** (22 mg, 0.09 mmol) treated in a similar manner gave enantiomer **28L** (16 mg, 85%) as a pale yellow oil; $[\alpha]_D^{21} = +22.1$ (*c* 0.8, CH_3OH); the other physical data for **28L** were consistent with those of **28D**.

4.26. 2,3-*O*-Isopropylidene-2-*C*-methyl-D-ribono-1,4-lactone 29

2-*C*-Methyl-D-ribono-1,4-lactone **5D** (129 mg, 0.80 mmol) was dissolved in acetone (13 mL) and stirred under argon with anhydrous copper(II) sulfate (0.75 g) and catalytic concentrated sulfuric acid (three drops (~0.03 mL)). After 16 h TLC analysis (ethyl acetate) revealed the presence of no starting material (R_f 0.27) and one major product (R_f 0.67). The reaction mixture was neutralised with excess anhydrous sodium carbonate and filtered through Celite® with acetone as eluent. The filtrate was concentrated in vacuo to afford acetonide **29** (163 mg, quantitative) as a colourless oil which crystallised on standing; mp 52–54 °C; $[\alpha]_D^{19} = -35.6$ (*c* 1.4, acetone); ν_{max} (film): 1781 (γ-lactone C=O) 3490 (O–H) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.39, 1.41 (2 × 3H, 2 × s, $C(CH_3)_2$), 1.64 (3H, s, 2′-CH_3), 2.86 (1H, br s, 5-O*H*), 3.81 (1H, dd, $J_{5,5'}$ 12.5 Hz, $J_{4,5'}$ 2.5 Hz, H-5′), 3.97 (1H, dd, $J_{5,5'}$ 12.5 Hz, $J_{4,5}$ 2.9 Hz, H-5), 4.54 (2H, m, H-3 & H-4); δ_C ($CDCl_3$, 100.6 MHz): 19.8 (2′-CH_3), 26.6, 26.8 ($C(CH_3)_2$), 62.0 (C-5), 82.6 (C-3), 82.9 (C-2), 83.7 (C-4), 112.9 ($C(CH_3)_2$), 177.1 (C-1); LRMS *m*/*z* (ESI −ve): 201.18 ($M-H^+$, 100%); HRMS *m*/*z* (ESI +ve): found 225.0731 ($M+Na^+$); $C_9H_{14}O_5Na$ requires 225.0733. Found: C, 53.48; H, 6.98; $C_9H_{14}O_5$ requires C, 53.46; H, 6.98.

4.27. 2,3-*O*-Isopropylidene-5-*O*-methanesulfonyl-2-*C*-methyl-D-ribono-1,4-lactone 30

Methanesulfonyl chloride (0.06 mL, 0.77 mmol) was added to acetonide **29** (129 mg, 0.64 mmol) in pyridine (0.9 mL) with *N*,*N*-dimethylaminopyridine (8 mg, 0.06 mmol) under argon at 0 °C. The reaction mixture was stirred for 2 h when TLC analysis (ethyl acetate) revealed the presence of no starting material (R_f 0.67) and one major product (R_f 0.75). The reaction mixture was concentrated in vacuo and co-evaporated with toluene (3 × 1 mL). The residue was then dissolved in dichloromethane (25 mL) and washed with water (10 mL) and brine (10 mL). The aqueous layers were then combined and washed with dichloromethane (25 mL). The combined organic extracts were dried over magnesium sulfate and filtered. The filtrate was then concentrated in vacuo to afford mesylate **30** (187 mg, quantitative) as a colourless oil; $[\alpha]_D^{24} = -24.7$ (*c* 1.0, $CHCl_3$); ν_{max} (film): 1789 (γ-lactone C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.42, 1.44 (2 × 3H, 2 × s, $C(CH_3)_2$), 1.65 (3H, s, 2′-CH_3), 3.06 (3H, s, SO_2CH_3), 4.44 (2H, d, $J_{4,5}$ 3.1 Hz, 2 × H-5), 4.52 (1H, d, $J_{3,4}$ 0.5 Hz, H-3), 4.71 (1H, dt, $J_{3,4}$ 0.5 Hz, $J_{4,5}$ 3.1 Hz, H-4); δ_C ($CDCl_3$, 100.6 MHz): 20.0 (2′-CH_3), 26.7, 26.8 ($C(CH_3)_2$), 37.6 (SO_2CH_3), 68.0 (C-5), 79.7 (C-4), 81.8 (C-3), 82.3 (C-2), 113.6 ($C(CH_3)_2$), 175.4 (C-1); LRMS *m*/*z* (ESI −ve): 279.28 ($M-H^+$, 100%); HRMS *m*/*z* (ESI +ve): found 303.0508 ($M+Na^+$); $C_{10}H_{16}O_7SNa$ requires 303.0509. Found: C, 42.76; H, 5.86; $C_{10}H_{16}O_7S$ requires C, 42.85; H, 5.75.

4.28. 2,3-*O*-Isopropylidene-2-*C*-methyl-L-lyxono-1,4-lactone 18L

Solid potassium hydroxide (409 mg, 7.29 mmol) in water (11.7 mL) was added to a solution of mesylate **30** (680.6 mg, 2.43 mmol) in dioxane (15 mL) and stirred vigorously. After 3 h the reaction mixture was acidified to pH 1 with dilute hydrochloric acid (2.0 M). The reaction mixture was then washed with dichloromethane (3 × 40 mL) until no lactone product (R_f 0.66 in ethyl acetate) remained in the aqueous phase. The organic extracts were then combined, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the residue purified by flash column chromatography (ethyl acetate/cyclohexane, (2:1)) to afford *C*-methyl-L-lyxono-1,4-lactone **18L** (447 mg, 91%) as a colourless oil which crystallised on standing; mp 64–66 °C; $[\alpha]_D^{22} = -74.1$ (*c* 0.6, acetone) {Lit.[35] $[\alpha]_D^{18} = -75$ (*c* 2.6, $CHCl_3$)}; ν_{max} (film): 1784 (γ-lactone C=O) 3447 (O–H) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.39, 1.42 (2 × 3H, 2 × s, $C(CH_3)_2$), 1.56 (3H, s, 2′-CH_3), 2.63 (1H, br s, 5-O*H*), 3.93 (1H, dd, $J_{5,5'}$ 12.2 Hz, $J_{4,5'}$ 5.1 Hz, H-5′), 4.01 (1H, dd, $J_{5,5'}$ 12.2 Hz, $J_{4,5}$ 6.7 Hz, H-5), 4.46 (1H, d, $J_{3,4}$ 3.4 Hz, H-3), 4.51 (1H, ddd, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 6.7 Hz, $J_{4,5'}$ 5.1 Hz, H-4); δ_C ($CDCl_3$, 100.6 MHz): 18.2 (2′-CH_3), 26.7, 26.8 ($C(CH_3)_2$), 60.7 (C-5), 78.1 (C-4), 80.8 (C-3), 83.1 (C-2), 113.5 ($C(CH_3)_2$), 176.2 (C-1); HRMS *m*/*z* (ESI +ve): found 225.0732 ($M+Na^+$); $C_9H_{14}O_5Na$ requires 225.0733.

5. Enzyme assays

The enzymes α-L-fucosidase (from human placenta, assayed at pH 5.5), α-D-mannosidase (from almond, assayed at pH 4.5), α-D-galactosidase (from coffee beans, assayed at pH 6.5) and α-L-rhamnosidase (from *P. decumbens*) were

purchased from Sigma Chemical Co. The glycosidase activities were determined using an appropriate *p*-nitrophenyl glycoside as substrate at the optimum pH of each enzyme. The reaction was stopped by adding 2 mL of 400 mM Na_2CO_3. The released *p*-nitrophenol was measured spectrometrically at 400 nm.

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