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Hanessian-Hullar reaction in the synthesis of highly substituted *trans*-3,4-dihydroxypyrrolidines: rhamnulose iminosugar mimics inhibit α-glucosidase

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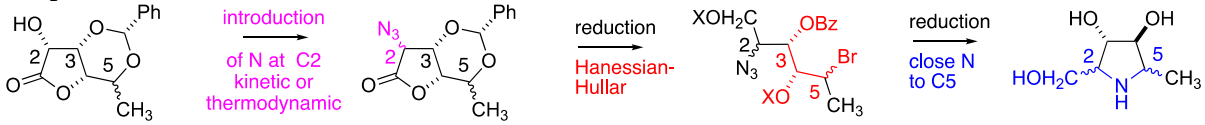
Graphical abstract



Abstract: The key step in the syntheses of highly substituted *trans*-3,4-dihydroxypyrrolidines is introduction of bromide by stereospecific and regiospecific Hanessian-Hullar reactions; benzylidene lactones of L-rhamnonolactone and 6-deoxy-L-gulonolactone allow introduction of N at C2 with inversion or retention of configuration. Initially a protecting group, the benzylidene acetal then provides a bromide at C5 to allow formation of the pyrrolidine ring. With silyl protecting groups, bromide was introduced at C5 with inversion of configuration whereas benzoyl protection gave a mixture of retention and inversion, indicative of neighbouring group participation in a Hanessian-Hullar reaction. Four stereoisomeric pyrrolidines - iminosugar mimics of α- and β-L-rhamnulose and α- and β-6-deoxy-D-sorbose were prepared. Only the α-L-rhamnulose mimic showed moderate inhibition of rhamnosidase but some were good inhibitors of α-glucosidases; none inhibited rhamnose isomerase and they had a small effect as synthetic inducers of the rhamnose catabolic operon in *E. coli*.

1. Introduction

Hundreds of iminosugars,[1] in which the ring oxygen of a monosaccharide has been replaced by nitrogen, have been isolated as natural products. Although one of the largest families of glycosidase inhibitors, iminosugars have many other bioactivities as sugar mimics. The glycosidase inhibition profiles of the 16 piperidine analogues of the 16 aldohexoses are quite well correlated with the structures of the parent sugars; however, the 10 pyrrolidine analogues of the 8 ketohexoses provide many surprises.[2] This paper describes the synthesis and preliminary evaluation of the α- **1** and β- **2** iminosugar analogues of rhamnulose and of their epimers at C5, α- **3** and β- **4**, iminosugars analogues of 6-deoxy-D-sorbose, four of the sixteen

pyrrolidine analogues of 6-deoxy ketohexoses [Figure 1]. An example of neighbouring group participation was found in the Hanessian-Hullar reaction, a key reaction in their syntheses.

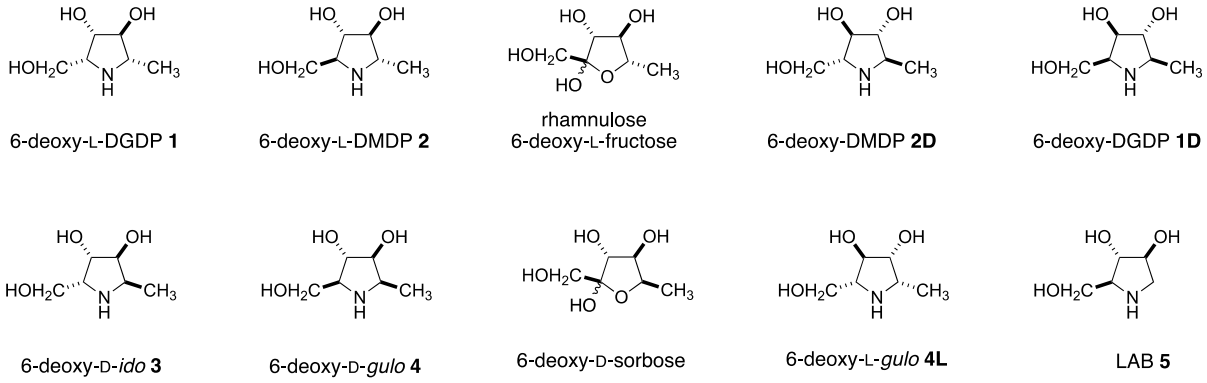


Figure 1: Iminosugar structures

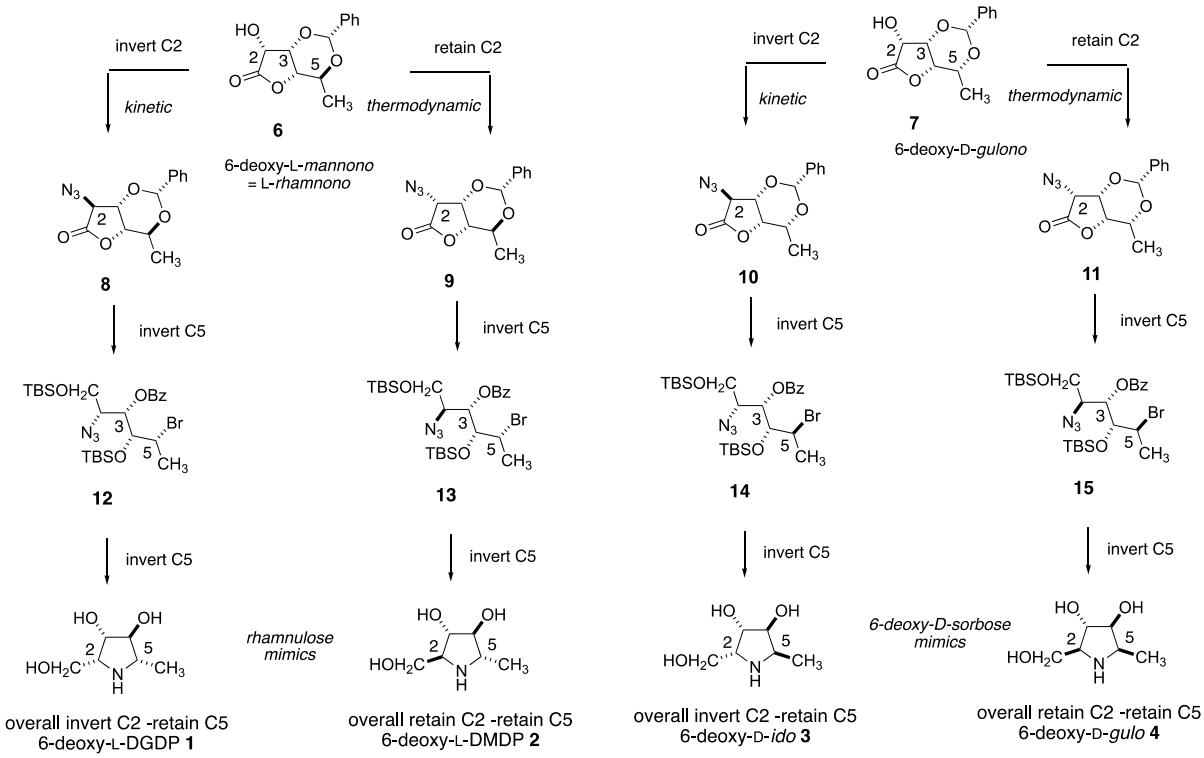
6-Deoxy-DGDP (6-deoxy-2,5-dideoxy-2,5-imino-D-glucitol) **1D**[3] and 6-deoxy-DMDP (6-deoxy-2,5-dideoxy-2,5-imino-D-mannitol) **2D**,[4] the enantiomers of **1** and **2** respectively, have been isolated from *Angylocalyx pynaertii*.[5] A further stereoisomer, a strong inhibitor of α-fucosidase, was also isolated and ascribed the structure **4**; the synthetic **4** prepared in this paper did not inhibit α-L-fucosidase. The natural product is therefore likely to be the enantiomer **4L**, a fuculose analogue prepared previously by Wong.[6] The rhamnulose analogues **2** and **4** may also be considered to be the α- and β-1-*C*-methyl analogues of LAB (1,4-dideoxy-1,4-imino-L-arabinitol) **5**, a potent and specific α-glucosidase inhibitor.[7] The glycosidase inhibition profiles of the new iminosugars are compared with structurally related iminosugars; their effects on rhamnose isomerase and the rhamnose operon were also investigated.

2 Results and Discussion

2.1 Synthesis

2.1.1 Strategy

The key step in the syntheses of the highly substituted *trans*-3,4-dihydroxypyrrolidines **1**-**4** was the introduction of bromide by a stereospecific and regiospecific Hanessian-Hullar reaction [Scheme 1].[8] The benzylidene lactones **6** and **7**, epimeric at C5, have only C2 OH unprotected and allow efficient access to the azidolactones **8**-**11**. In general, displacement of a triflate at C2 of a lactone by sodium azide in DMF can introduce nitrogen with either inversion or retention of configuration. Displacement of the 2-*O*-triflate in a γ-lactone in which all the ring substituents are *cis* gives a kinetic azide with a 2,3-*trans* relationship with the neighbouring oxygen; base catalysed isomerisation by azide gives the thermodynamically more stable azide in which all the substituents on the lactone ring are *cis*.[9] The epimeric azides are always very different in polarity and easily separated by flash chromatography.[10]



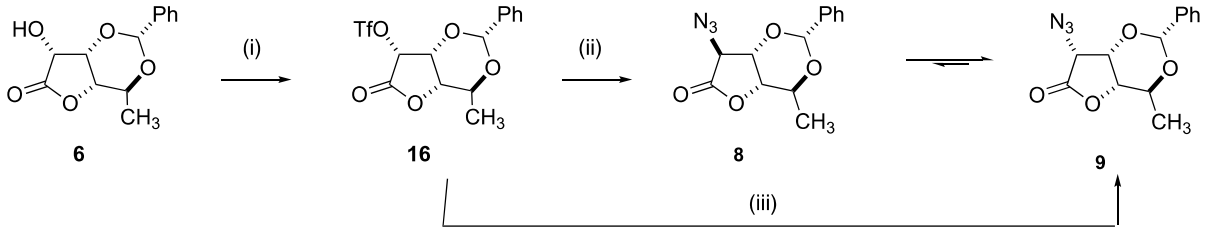
Scheme 1: *Synthetic strategy for trans-3,4-dihydroxypyrrolidines **1-4***

Reduction of the lactones to the corresponding diol, followed by silyl ether protection and oxidation with *N*-bromosuccinimide give the bromo-benzoates **12-15** with inversion of configuration at C5; the benzylidene acetal, initially a protecting group, subsequently allows a Hanessian-Hullar reaction to introduce the bromide leaving group at C5. When benzoate was substituted for silyl ether protection, both retained and inverted bromides were formed, indicating neighbouring group participation; the regiospecificity and stereoselectivity is discussed fully below.

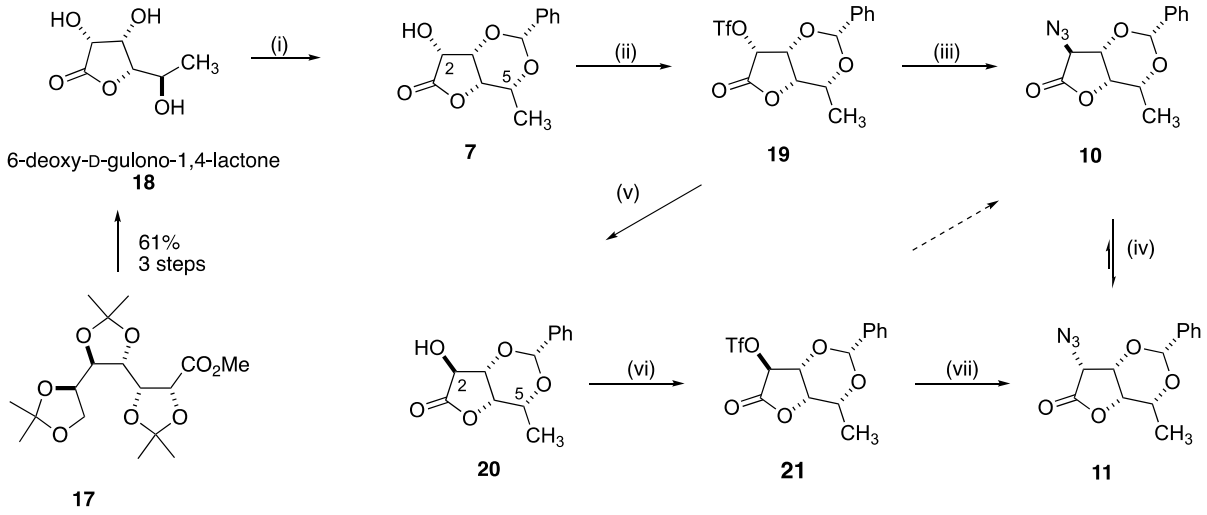
Reduction of the azides **12-15** to the corresponding amines allows cyclization to the pyrrolidines with a second inversion at C5. Deprotection of the pyrrolidines give the diastereomers **1-4** in an efficient and general approach, in which the configuration at C2 of the original sugar may be inverted or retained, but that at C5 is always retained.

2.1.2 Synthesis of azidolactones 8, 9, 10 and 11

For the rhamnonolactones **8** and **9**, the benzylidene derivative **6** can readily be obtained from rhamnose in a one pot sequence on a 50 g scale[11] [Scheme 2]. As previously described,[12] the stable triflate **16**, formed in 95% yield from **6**, with sodium azide in DMF at -40 °C formed the kinetic *glucono*-azide **8** (75%) but at room temperature gave the thermodynamic *mannono*-azide **9** (85%); the initially formed **8** was equilibrated to the more stable all *cis*-azide **9**.



Scheme 2: (i) $(CF_3SO_2)_2O$, pyridine, THF, -20 °C, 95 %; (ii) NaN_3, DMF, -40 °C, 75%; (iv) NaN_3, DMF, rt, 84%, 42 h [as reported in reference 10].



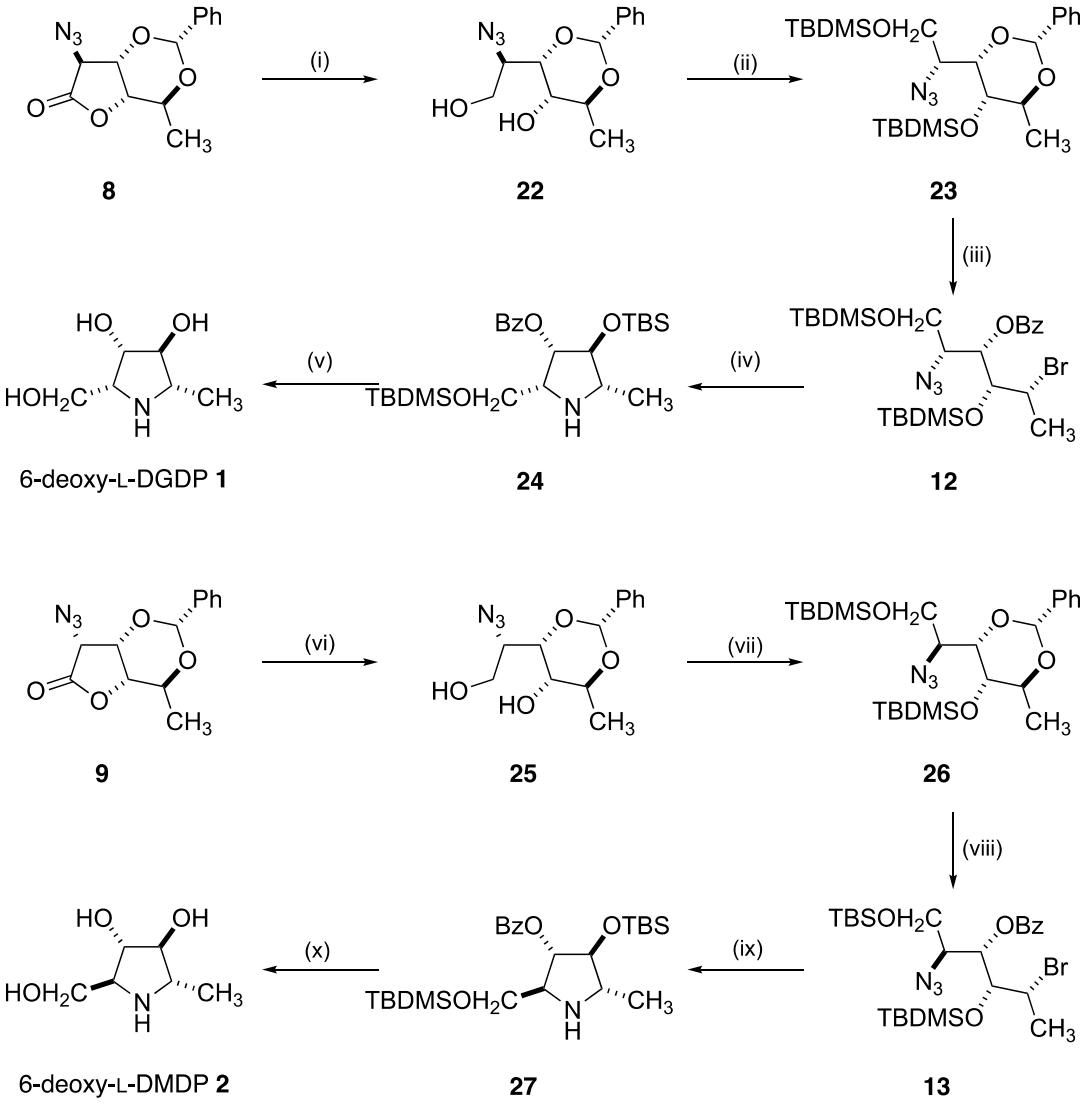
Scheme 3: (i) PhCHO, conc HCl, 92%; (ii) $(CF_3SO_2)_2O$, Pyridine, THF, -20 °C, 98%; (iii) NaN_3, DMF, -10 °C, 20h, 77%; (iv) NaN_3, DMF, rt, 78%, 42 h; (v) CF_3CO_2Cs, DMF, 60 °C, 100% 52 h ; (vi) $(CF_3SO_2)_2O$, Pyridine, THF, -20 °C; (vii) NaN_3, DMF, rt, 30 h, 45% (2 steps)

For the synthesis of the *idono*- and *gulono*-azides **10** and **11**, the starting material 6-deoxy-D-gulonolactone **18** was prepared from the triacetonide **17** in 61% yield with no chromatography required; the route [13] is far more convenient than procedures from L-rhamnose[12] or D-gulonolactone (Scheme 3).[14] Reaction of **18** with benzaldehyde in the presence of concentrated hydrochloric acid gave the crystalline lactone **7** (92%) in which the methyl group is equatorial. The stereochemistry of **7** was confirmed by the Nuclear Overhauser Effect (nOe) NMR analysis; significant 1,3-H nOe effects between the protons on the benzylidene ring showed the phenyl group to be equatorial in **7** in contrast to the axial phenyl substituent in the *rhamnono*-epimer **6**.[15]

Esterification of the alcohol in **7** with triflic anhydride in THF in the presence of pyridine gave the stable triflate **19** (98%) which, on treatment with sodium azide in DMF at -10 °C for 20 h, gave the *ido*-azide **10** with inversion at C2 (77%); when the reaction was performed at room temperature for 42 h, the more stable *gulo*-azide **11** was isolated in 78% yield. The epimeric azides **10** and **11** were easily separated by chromatography. Both nucleophilic displacement by azide and the equilibration to the all *cis*-azide were much slower for the *gulono*-triflate **7** than for the analogous reactions of the *rhamnono* epimer **16**. Displacement of the triflate **19** by caesium trifluoroacetate in DMF[16] at 60 °C for 52 h gave the *idono*-lactone **20** (100%). The triflate **21** was unstable and substantially decomposed during isolation and treatment with sodium azide, giving **11** in poor yield (45%). The different behaviour between the *mannono*- **6** and *gulono*- **7** lactones may be ascribed to substantially different conformations of the bicyclic

acetals where the methyl group is, respectively, either axial or equatorial.[15] In both the *rhamnono*- and *gulono*-series, efficient syntheses of the easily separable retained and inverted azides **8**-**11** can be obtained in good yield.

2.1.3 6-Deoxy-L-DGDP 1 and 6-deoxy-L-DMDP 2 from *rhamnono*-azides 8 and 9

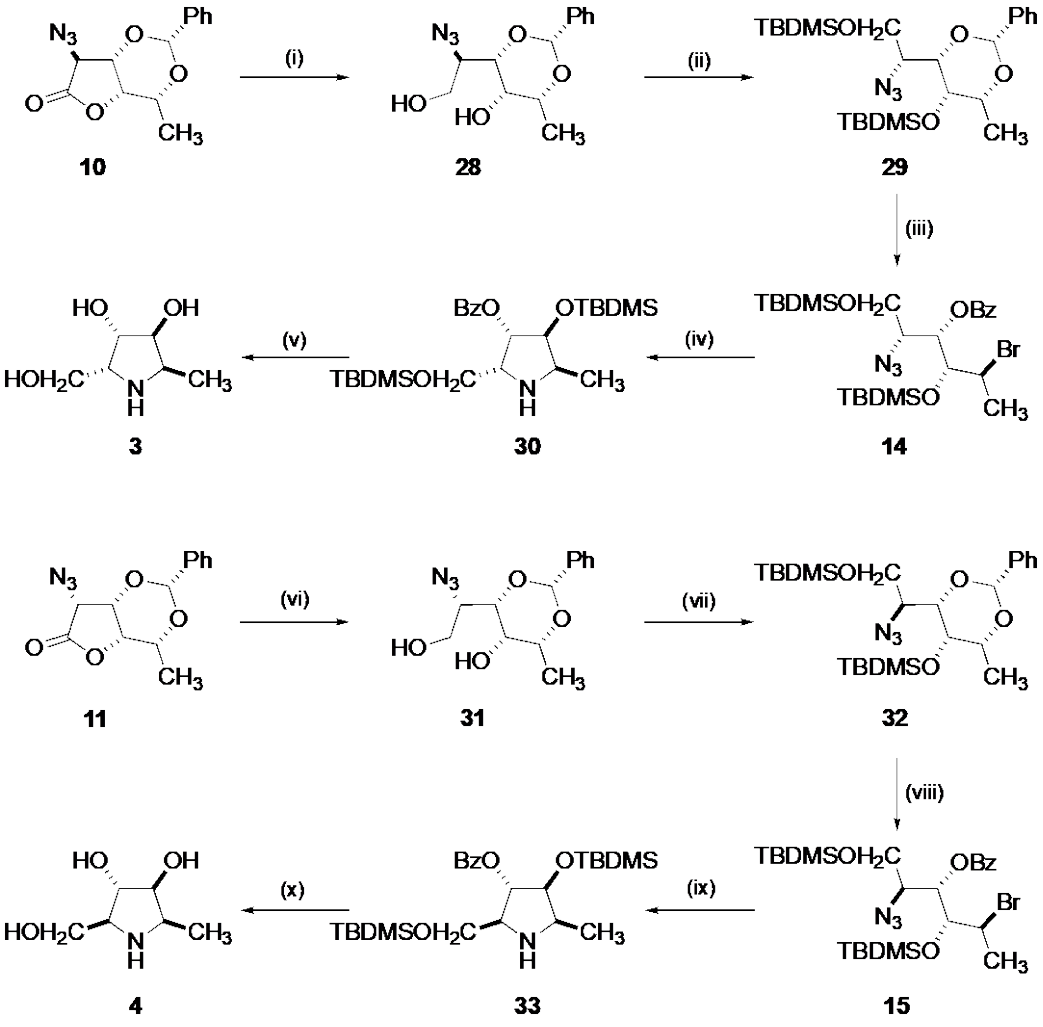


Scheme 4: (i) DIBALH, DCM, -78 °C, then $NaBH_4$, MeOH, 92% (2 steps); (ii) TBDMSOTf, pyridine, DCM, 98%; (iii) NBS, $BaCO_3$, CCl_4, reflux, 86%; (iv) Pd/C, H_2, NaOAc, EtOH, 72%; (v) TFA/water/1,4-dioxane, 50 °C, then NaOH (2 M, aq), 50 °C, 81% (2 steps); (vi) DIBALH, DCM, -78 °C, then $NaBH_4$, MeOH, 89% (2 steps); (vii) TBDMSOTf, pyridine, DCM, 94%; (viii) NBS, $BaCO_3$, CCl_4, reflux, 92%; (ix) Pd/C, H_2, NaOAc, EtOH, 71%; (x) TFA/water/1,4-dioxane, 50 °C, then NaOH (2 M, aq.), 50 °C, 64% (2 steps);

The epimeric azides **8** and **9** derived from rhamnose were used for the synthesis of the α- **1** and β-**2** iminosugar analogues of β-rhamnulose respectively [Scheme 4]. Reduction of **8** with DIBALH followed by *in situ* treatment with sodium borohydride gave the diol **22** (92%) which, with *tert*-butyldimethylsilyl (TBDMS) triflate in dichloromethane in the presence of pyridine, afforded the *bis*-silyl ether **23** (98%). The benzylidene acetal **23** with *N*-bromosuccinimide

(NBS) in the presence of barium carbonate in carbon tetrachloride at reflux underwent a Hanessian-Hullar reaction to produce the bromide **12** in 1 h with inversion of configuration at C5 (86%). Hydrogenation of azide **12** in ethanol in the presence of sodium acetate gave the protected pyrrolidine **24** (72%), formed by closure of the resulting amine with a second inversion at C5. Removal of the silyl groups in **24** by trifluoroacetic acid, followed by hydrolysis of the benzoyl ester with aqueous sodium hydroxide and ion exchange purification, gave the unprotected L-*gluco*-pyrrolidine **1** (81%); no efficient conditions for global deprotection of **24** were found. The overall yield of 6-deoxy-L-DGDP **1** from benzylidene rhamnonolactone **6**, with inversion at C2 and overall retention at C5, was 33%. 6-Deoxy-L-DMDP **2** was formed in an identical sequence from benzylidene rhamnonolactone **6**, with retention of configuration at both C2 and C5, in 29% overall yield [Scheme 4].

2.1.4 6-Deoxy-D-*ido*-DMDP 3 and 6-deoxy-D-*gulo*-DMDP 4 from D-*gulono*-azides 10 and 11

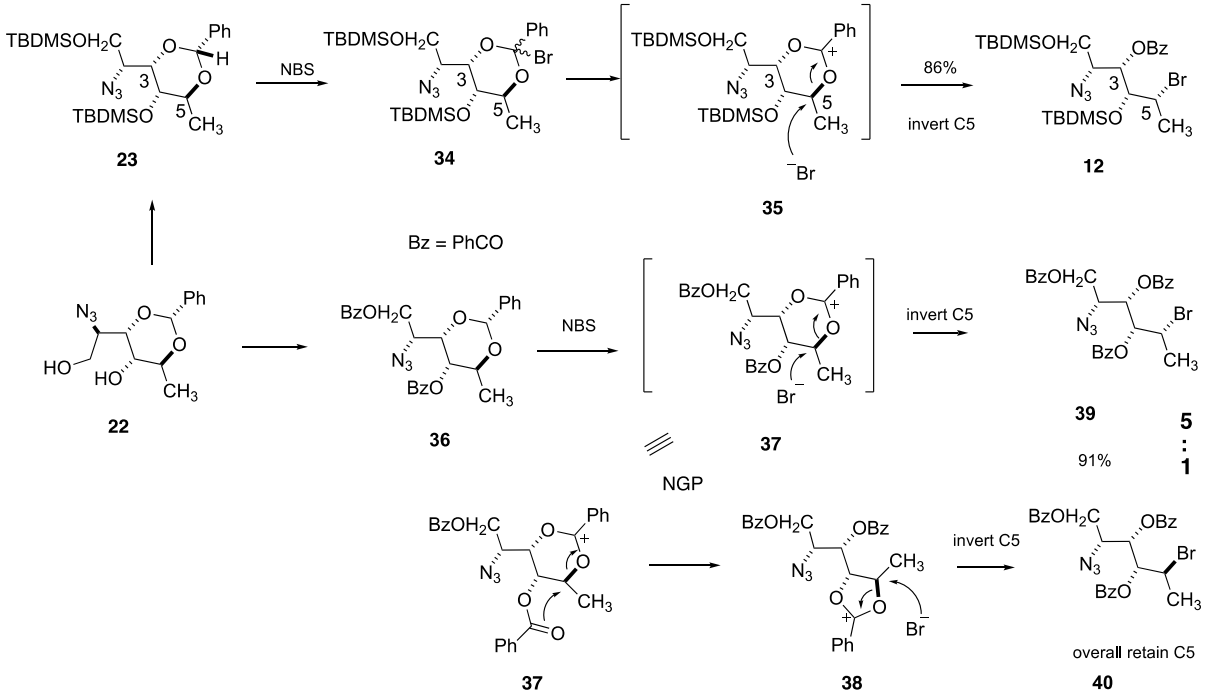


Scheme 5: (i) DIBALH, DCM, -78 °C, then $NaBH_4$, MeOH, 66% (2 steps); (ii) TBDMSOTf, pyridine, DCM, 74%; (iii) NBS, $BaCO_3$, CCl_4, reflux, 99%; (iv) Pd/C, H_2, NaOAc, EtOH; (v) TFA/water/1,4-dioxane, 50 °C, then NaOH (2M, aq), 50 °C, 74% (3 steps from **14**); (vi) $LiBH_4$, THF, -20 °C, 90%; (vii) TBDMSOTf, pyridine, DCM, 84%; (viii) NBS, $BaCO_3$, CCl_4, reflux, 76%; (ix) Pd/C, H_2, NaOAc, EtOH; (x) TFA/water/1,4-dioxane, 50 °C, then NaOH (2M, aq), 50 °C, 51% (3 steps from **15**)

The chemistry developed for the *rhamnono*-azidolactones proceeded equally reliably for the 6-deoxy-*gulonono*-azidolactones and is summarised in Scheme 5. The overall yield of 6-deoxy-D-*ido*-DMDP **3** was 36% from **10**. Although usually the base-sensitivity of 2-azidolactones requires a two step reduction, the lactone **11** on treatment with lithium borohydride in THF gave the diol **31** in 90% yield; 6-deoxy-D-*gulo*-DMDP **4** was obtained in 29% overall yield from **11**.

2.1.4 Benzoate protection: neighbouring group participation (NGP) in the Hanessian-Hullar Reaction

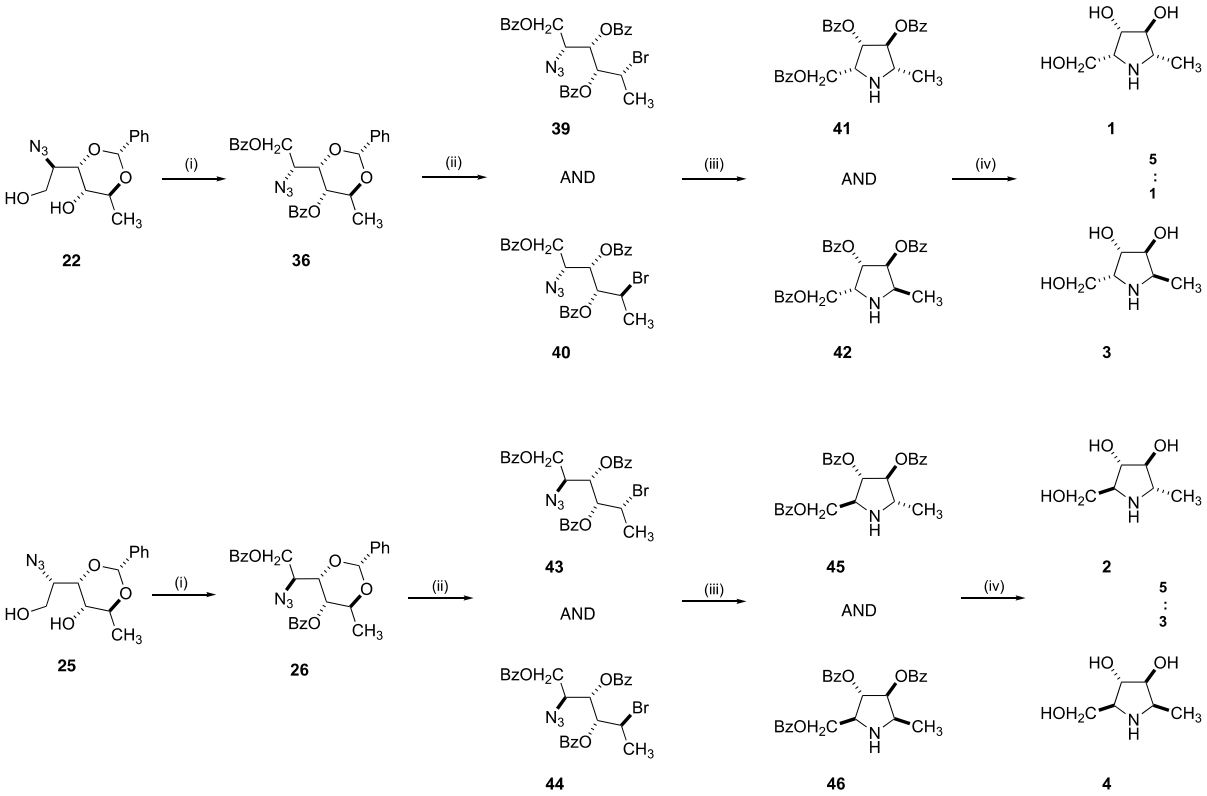
The Hanessian-Hullar reaction of either the benzylidene lactone **8** or the unprotected diol **22** gave complex mixtures of products. As described above, treatment of the silyl ether **23** with *N*-bromosuccinimide (NBS) in carbon tetrachloride in the presence of barium carbonate gave the bromide **12** in 86% yield [Scheme 6]. There is some uncertainty in the mechanism of the formation of the bromide **34**.[8] However, nucleophilic attack at C5 of the cation **35** is less hindered than attack at C3; additionally there are both β-oxygen and β-nitrogen substituents which slow S_N2 displacement at C3. All the four diastereomeric silyl-protected ethers at C2 and C5 - **23**, **26**, **29** and **32** - undergo exclusive attack by bromide at C5 with inversion of configuration.



Scheme 6: Neighbouring group participation (NGP) in Hanessian-Hullar reaction

Benzoate was studied as an alternative protecting group. NBS oxidation of the dibenzoate **36** [obtained by benzolation of the diol **22** (86%)] gave a mixture of the D-*ido* **39** and L-*gluco*- **40** bromides in a 5:1 ratio and 91% yield. The cation **37** is thus mainly trapped by bromide in an S_N2 *inversion* at C5 to give the *ido*-bromide **39**. Competitive NGP by the benzoate at C4 in **37** formed the cation **38** which undergoes attack by bromide to give a second inversion at C5 to form the *gluco*-bromide **40** with overall *retention* at C5; this may be the first report of NGP in

a Hanessian-Hullar reaction. Both cations **37** and **38** undergo regiospecific nucleophilic displacement at C5.



Scheme 7: (i) BzCl, Pyridine, DCM, 86%; (ii) NBS, $BaCO_3$, CCl_4, reflux, **39**:**40** 5:1, 91%; (iii) Pd/C, H_2, NaOAc, EtOH, **41**:**42** 4:1, 82%; (iv) NaOH (aq., 2M), 50 °C, **1**:**3** 5:1, 73%. (v) BzCl, Pyridine, DCM, 97%; (vi) NBS, $BaCO_3$, CCl_4, reflux, **43**:**44** 3:1, 94%; (vii) Pd/C, H_2, NaOAc, EtOH, **45:46** 10:7, 89%; (viii) NaOH (aq., 2M), 50 °C, **2**:**4** 5:3, 70%.

The inseparable bromides **39** and **40** [5:1] (91% from **36**) on hydrogenation in the presence of palladium on charcoal in ethanol gave an inseparable epimeric mixture of the pyrrolidine tribenzoates **41** and **42** [4:1] (82%) [Scheme 7]. Removal of the benzoate protecting groups gave **1** and **3** (73%) in a ratio of 5:1, determined by comparison with ^{1}H NMR of pure samples of **1** and **3** prepared as above.

Benzoylation of the epimeric azidodiol **25** afforded the dibenzoate **26** (97%) which on treatment with NBS gave a mixture of the epimeric bromides **43** : **44**, 3:1 (94%) which on hydrogenation gave the tribenzoates **45** : **46** (94%). Deprotection with aqueous sodium hydroxide gave a mixture of **2** : **4**, 5:3 (94%). Again, none of the intermediate mixtures were separable. The use of silyl protection in Hanessian-Hullar reactions ensures there is no NGP, whereas other protecting groups may give epimeric bromides as products.

3. Biological assays

Compounds that affect enzymes in the biosynthesis and metabolism of L-rhamnose, a sugar that has no role in mammalian metabolism,[17] have potential to affect pathogens and to provide

novel antibiotics.[18] The effects of the rhamnulose mimics **1-4** on glycosidases, rhamnose isomerase and the rhamnose operon were investigated.

3.1 Glycosidase Inhibition Profile

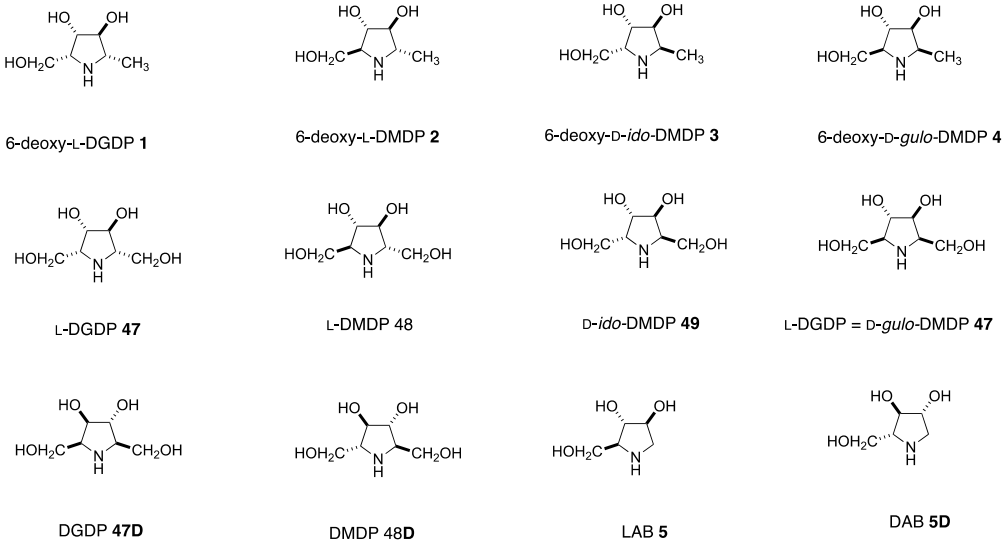


Figure 2: Iminosugar structural relationships

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Table 1. Concentration of iminosugars giving 50 % inhibition of various glycosidases

	IC_{50} (μM)							
enzyme	6-deoxy-L-DGDP **1**	L-DGDP **47**	6-deoxy-D-guloDMDP **4**	6-deoxy-L-DMDP **2**	L-DMDP **48**	LAB **5**	6-deoxy-D-idoDMDP **3**	D-idoDMDP **49**
α-glucosidase								
yeast	NI [a](1.6%)	**60**	NI (2.4%)	NI (11.3%)	NI (34.8%)	**70**	NI (0.8%)	**792**
rice	**300**	NI (16.0%)	**137**	**3.1**	**5.8**	**3.2**	NI (5.8%)	NI (4.1%)
rat intestinal maltase	**116**	**48**	**65**	**5.1**	**1.2**	**0.93**	NI (27.4%)	**654**
rat intestinal sucrase	**115**	**13**	**66.9**	**0.84**	**1.0**	**1.0**	NI (32.0%)	**121**
β-glucosidase								
almond	NI (6.2%)	NI (32.4%)	NI (7.7%)	NI (12.4%)	NI (12.1%)	NI [a](23.1%)	NI (13.3%)	NI (44.4%)
bovine liver	NI (10.0%)	NI (5.4%)	NI (39.5%)	NI (14.7%)	NI (4.6%)	NI (12.9%)	NI (19.0%)	NI (41.2%)
α-galactosidase								
coffee beans	NI (2.1%)	**216**	NI (11.1%)	NI (6.0%)	NI (13.8%)	NI (2.0%)	NI (8.6%)	**419**
β-galactosidase								
bovine liver	NI (5.9%)	NI (12.0%)	NI (28.8%)	NI (10.5%)	NI (0%)	NI (15.7%)	NI (18.1%)	**655**
α-mannosidase								
jack bean	NI (0%)	NI (0%)	NI (1.0%)	NI (1.0%)	NI (17.3%)	NI (0%)	NI (2.0%)	NI (0%)
β-mannosidase								
Snail	NI (0%)	NI (0%)	NI (2.9%)	NI (0%)	NI (12.6%)	NI (1.3%)	NI (0%)	NI (9.5%)
α-L-fucosidase								
bovine kidney	NI (8.0%)	NI (0.3%)	NI (2.1%)	NI (17.5%)	NI (0%)	NI (9%)	NI (10.1%)	NI (10.1%)
α,α-trehalase								
porcine kidney	NI (3.9%)	NI (40.1%)	NI (6.9%)	NI (6.8%)	**48**	**131**	NI (4.3%)	NI (13.1%)
amyloglucosidase								
Aspergillus niger	NI (0%)	NI (5.3%)	NI (7.1%)	NI (2.0%)	NI (0.9%)	NI (41.1%)	NI (1.3%)	NI (0%)
α-L-rhamnosidase								
Penicillium decumbens	**242**	NI (16.1%)	NI (18.4%)	NI (49.1%)	NI (45.6%)	**803**	NI (45.0%)	NI (12.2%)
β-glucuronidase								
E.coli	NI (0.8%)	NI (1.4%)	NI (6.5%)	NI (3.6%)	NI (0.9%)	NI (0%)	NI (0%)	NI (3.6%)
bovine liver	NI (3.7%)	NI (10.0%)	NI (6.0%)	NI (8.9%)	NI (8.0%)	NI (0%)	NI (1.4%)	NI (8.1%)

[a] NI : No inhibition (less than 50% inhibition at 1000 μM).

[b] ( ) : inhibition % at 1000 μM

The inhibition of glycosidases by iminosugar furanose analogues is difficult to predict.[2,19] The four *trans*-3,4-dihydroxypyrrolidines **1-4** prepared in this paper were compared with the corresponding iminosugars **47-49** in which the methyl group is replaced by a hydroxymethyl

group[20] [D-*gulo*DMDP is identical by rotation to L-DGDP **47**] as inhibitors of the following glycosidases[21]: α- and β-glucosidases (from various sources), α- and β-galactosidase, α- and β-mannosidase, α- L-fucosidase, α,α-trehalase, amyloglucosidase, α-L-rhamnosidase, and β-glucuronidase (Table 1). L-DGDP **47** and L-DMDP **48** are the enantiomers of the natural products DGDP **47D** [isolated from the Thai traditional medicine *Non tai yak*[22] and a weak inhibitor of α-glucosidases] and DMDP **48D** [a most abundant natural iminosugar[23] and a potent inhibitor of β-galactosidase [2,24]]. In contrast, their enantiomers L-DGDP **47** and L-DMDP **48** are both specific and potent inhibitors of α-glucosidases;[25] there are many cases in which enantiomers of iminosugars are more potent inhibitors of the *same* enzyme than the natural product. As **1** and **2** are the iminosugar mimics of α- and β-L-rhamnulose, L-DGDP **47** and L-DMDP **48** are the corresponding mimics of α- and β-D-fructose.

1. Only the α-rhamnulose mimic, 6-deoxy-L-DGDP, **1** showed moderate inhibition of α-rhamnosidase. None of the other iminosugar hexose analogues – including the β-rhamnulose mimic **2** – showed any rhamnosidase inhibition. 6-Deoxy-L-DGDP **1** was also a moderate inhibitor of α-glucosidases; the substitution of Me in **1** for the CH_2OH group in L-DGDP **47** considerably reduced glucosidase and galactosidase inhibition. 6-deoxy-D-*ido*-DMDP **3**, in which the methyl group is epimeric to that in **1**, did not show significant inhibition of any glycosidase.

2. 6-Deoxy-L-DMDP **2** was a potent and highly specific inhibitor of α-glucosidases. Comparison of 6-deoxy-L-DMDP **2** and L-DMDP **48** revealed that deoxygenation of C6-OH group slightly increased the inhibition of rice and rat intestinal sucrase. Furthermore, 6-deoxy-L-DMDP **2** lost inhibition of porcine kidney α,α-trehalase, showing more selectivity.

3. 6-Deoxy-L-DMDP **2** was also compared to the potent and α-glucosidase inhibitor LAB **5**. Its enantiomer DAB **5D**, isolated from *Angylocalyx boutiqueanus*[26] is a good inhibitor of α-glucosidase and glycogen phosphorylase as a potential drug for the treatment of diabetes.[27] Although LAB **5** was 10-times better as an inhibitor of rat intestinal maltase than 6-deoxy-L-DMDP **2**, LAB **5** also showed broad inhibition toward α,α-trehalase and α-L-rhamnosidase.

4. 6-Deoxy-D-*gulo*-DMDP **4**, with its methyl group epimeric to that in **2**, was a moderate [and highly specific] inhibitor of α-glucosidase. **2** and **4** may be viewed as the α- and β-1-*C*-methyl-LAB derivatives. α-1-*C*-methyl-LAB **2** is a significantly more potent glucosidase inhibitor than its β-anomer **4**. Broussonetines, a large family of natural glucosidase and galactosidase inhibitors, are α-1-*C*-alkyl-DAB derivatives.[28]

3.2 Rhamnose Isomerase

The only previous report of iminosugar inhibition of aldose isomerases is a crystallographic study of mimics of the substrates and products in the xylose isomerase catalyzed isomerization of glucose to fructose; DGDP **47D** (an α-fructose mimic) was a weak inhibitor whereas DMDP **48D** (β-fructose mimic) showed no inhibition.[29] There are no aldose isomerases in mammalian metabolism; no inhibitors of rhamnose isomerase have been described.[30] L-Rhamnose isomerase activity was measured by the conversion of L-rhamnose as substrate to L-rhamnulose as previously described.[31] None of the four pyrrolidines **1-4** had any significant effect on the activity of rhamnose isomerase (for details, see Supplementary Material).

3.3 Rhamnose Operon

In synthetic biology, a precisely-controlled gene expression system based on the regulatory elements (transcriptional promoter and activator) of the L-rhamnose catabolism gene operon in *E. coli*, *rhaBAD*, has been frequently used for the production of various proteins.[32] Free L-rhamnose is an inducer of *rhaBAD* but has the significant disadvantage of being metabolized to rhamnulose, which causes induction of gene expression to cease. The performance of this promoter system would therefore be enhanced by the development of a non-metabolizable rhamnose substitute; some 35 rare sugars have been studied as potential alternative inducers to rhamnose.[33]

The four iminosugars **1**-**4**, tested for their ability to induce expression of the *rhaBAD* promoter in *Escherichia coli* cells using a reporter assay system[33] showed much weaker induction than the nature inducer, L-rhamnose; the rhamnulose **1, 2** and 6-deoxy-L-sorbose **3** mimics had low but statistically significant induction of the *rhaBAD* promoter system ($P < 0.05$) relative to no inducer (see supplementary material). L-Rhamnose is easily metabolized in *E. coli*, causing gene expression to cease and a much reduced protein production. To overcome this problem, a non-metabolizable inducer is of both commercial and academic interest. The rhamnulose iminosugar analogues **1**, **2** and **3**, with no 6-hydroxyl group, are unlikely to be metabolized by rhamnose metabolic pathways and thus might be suitable to induce sustainable gene expression.

4. Conclusion

The high yield syntheses of iminosugar mimics of L-rhamnulose and 6-deoxy-D-sorbose depended on (i) azide substitution of 2-*O*-triflates of lactones with *either retention or inversion* in consistent yields of >80%; and (ii) efficient Hanessian Hullar NBS oxidation of benzylidene acetals – silyl ether protection ensured bromide was introduced at C5 of the sugar with complete *regio*- and *stereo*-specificity whereas using benzoate as an alternative protecting group lead to a mixture arising from NGP. Only the α-L-rhamnulose mimic **1** showed moderate inhibition of rhamnosidase whereas **2** and **4** were good inhibitors of α-glucosidases; **2** and **4** may be viewed as α- and β-1-*C*-methyl analogues of LAB **5**, a potent α-glucosidase inhibitor. None inhibited rhamnose isomerase and they had only a small effect as synthetic inducers of the rhamnose catabolic operon in *E. coli*.

5. Experimental

5.1 General Experimental

All commercial reagents were used as supplied. Solvents were used as supplied (Analytical or HPLC grade), without prior purification. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 F_{254} silica. Plates were visualised using a 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate solution in 2 M sulfuric acid. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations of the protected sugars were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm; concentrations are quoted in g 100 mL^{-1}. Optical rotations were recorded on a Jasco R1030 polarimeter, Na^+ lamp, (Jasco, Tokyo, Japan) at 20 °C, polarimeter with a path length of 1 dm. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using thin films on a diamond ATR surface (thin film). Only the characteristic peaks are quoted. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.7 MHz) or Bruker AVIII 400 HD nanobay and Bruker DQX 400 (^{1}H: 400 MHz, ^{13}C: 100.6 MHz) spectrometers in the deuterated solvent stated. ^{1}H and ^{13}C NMR spectra were assigned by utilizing 2D COSY, HSQC and HMBC spectra. All chemical shifts (δ) are quoted in ppm and coupling

constants (*J*) in Hz. Residual signals from the solvents were used as an internal reference. For solutions in D_2O acetonitrile was used as an internal reference. HRMS measurements were made using a microTOF mass analyzer using electrospray ionization (ESI) or an HP 5988A mass spectrometer using chemical ionization (CI).

5.2 Azidogulonolactones 10 and 11

***(R)*-3,5-*O*-Benzylidene-6-deoxy-D-*gulono*-1,4-lactone 7**

Concentrated hydrochloride acid (37%, 4 mL) was added to a suspension of 6-deoxy-D-gulono-1,4-lactone **18**[12] (887 mg, 5.5 mmol) in benzaldehyde (15 mL). The reaction mixture was stirred at room temperature for 15 h during which time a solid product separated. The solid was collected by filtration and washed with diethyl ether (20 mL) to yield the benzylidene acetal **7** (1.2 g, 92%) as white crystals. HRMS (ESI+ve): found 273.0733 $[M + Na]^+$; $C_{13}H_{14}O_5Na^+$ requires 273.0733; m.p. 226 - 230 °C; $[\alpha]_D^{25}$ -54 (*c* 0.8, MeCN); ν_{max} (thin film): 1785 (s, C=O); δ_H (CD_3CN, 500 MHz): 1.36 (3H, d, H6, $J_{6,5}$ 6.7), 3.80 (1H, br-d, OH, $J_{OH,2}$ 8.9), 4.19 (1H, t, H4, $J_{4,3} = J_{4,5}$ 2.0), 4.25 (1H, dq, H5, $J_{5,4}$ 1.9, $J_{5,6}$ 6.6), 4.58 (1H, dd, H2, $J_{2,3}$ 4.1, $J_{2,OH}$ 8.2), 4.68 (1H, dd, H3, $J_{3,4}$ 2.0, $J_{3,2}$ 4.1), 5.68 (1H, s, H7), 7.38 - 7.48 (5H, m, -Ar); δ_C (CD_3CN, 100 MHz): 15.8 (C6), 71.4 (C2), 72.8 (C5), 72.1 (C4), 74.5 (C3), 98.9 (C7), 126.3, 128.2, 129.1, 137.9 (-Ar), 175.4 (C=O); *m/z* (ESI+ve): 273 ($[M + Na]^+$, 100%).

***(R)*-3,5-*O*-Benzylidene-6-deoxy-2-*O*-trifluoromethanesulfonyl-D-*gulono*-1,4-lactone 19**

Anhydrous pyridine (0.3 mL, 0.36 mmol) and triflic anhydride (0.05 mL, 0.31 mmol) were sequentially added dropwise to a solution of the benzylidene lactone **7** (600 mg, 2.40 mmol) in anhydrous THF (10 mL) at -20 °C. After 3 h, TLC (cyclohexane/ethyl acetate, 1:1) indicated the formation of one product (R_f 0.57). The reaction mixture was diluted with dichloromethane (10 mL) and washed with HCl (2 M, aq, 2 x 10 mL). The organic layer was dried ($MgSO_4$); the solvent was removed *in vacuo* to give a residue that was purified by flash chromatography (ethyl acetate/cyclohexane, 1:5 to 1:2) to obtain pure triflate **19** (898 mg, 98%) as a white solid.

HRMS (ESI+ve): Found 405.2226 $[M + Na]^+$; $C_{13}H_{14}O_5Na^+$ requires 405.2226; m.p. 198 - 200 °C (decomp); $[\alpha]_D^{25}$ -64 (*c* 0.79, MeCN); ν_{max} (thin film): 1795 (s, C=O); δ_H (CD_3CN, 400 MHz): 1.44 (3H, d, H6, $J_{6,5}$ 6.6), 4.36 (1H, dq, H5, $J_{5,4}$ 1.4, $J_{5,6}$ 6.6), 4.44 (1H, br-t, H4, $J_{5,4} = J_{3,4}$ 1.5), 5.12 (1H, dd, H3, $J_{3,4}$ 1.9, $J_{3,2}$ 4.0), 5.77 (1H, s, H7), 5.91 (1H, d, H2, $J_{2,3}$ 4.0), 7.44 - 7.46 (5H, m, -Ar); δ_C (CD_3CN, 100 MHz): 15.6 (C6), 71.4 (C5), 72.7, 72.8 (C3, C4), 80.2 (C2), 98.9 (C7), 126.1, 128.3, 129.3, 137.1 (-Ar), 168.2 (C1); *m/z* (ESI+ve): 405 ($[M + Na]^+$, 100%).

2-Azido-*(R)*-3,5-*O*-benzylidene-2,6-dideoxy-D-*idono*-1,4-lactone 10

Sodium azide (168 mg, 2.58 mmol) was added to a solution of triflate **19** (898 mg, 2.35 mmol) in anhydrous DMF (10 mL). The resulting solution was stirred at -10 °C for 20 h until TLC (cyclohexane/ethyl acetate, 1:1) indicated the formation of a major product (R_f 0.70). After dilution with ethyl acetate (10 mL), the reaction mixture was washed with half saturated brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to obtain a residue that was purified by flash chromatography (ethyl acetate/cyclohexane, 1:7 to 1:5) to yield the *idono*-azide **10** (500 mg, 77%) as a white solid.

HRMS (ESI+ve): found 276.0980 $[M + H]^+$; $C_{13}H_{14}O_4N_3^+$ requires 276.0979; m.p.: 68 - 69 °C; $[\alpha]_D^{25}$ -89 (*c* 0.88, $CHCl_3$); ν_{max} (thin film): 2112 (s, N_3), 1780 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.51 (3H, d, H6, $J_{6,5}$ 6.6), 4.20 (1H, dq, H5, $J_{5,4}$ 1.8, $J_{5,6}$ 6.6), 4.21 (1H, br-s, H4), 4.35 (1H, dd, H3, $J_{3,4}$ 1.9, $J_{3,2}$ 2.2), 4.44 (1H, d, H2, $J_{2,3}$ 2.2), 5.65 (1H, s, H7), 7.37 - 7.45 (5H, m, -Ar); δ_C ($CDCl_3$, 100 MHz): 17.5 (C6), 63.3 (C5), 72.4 (C4), 76.1, 76.2 (C2, C3), 100.1 (C7), 126.5, 128.8, 129.9, 136.9 (-Ar), 171.4 (C1); *m/z* (ESI+ve): 298 ($[M + Na]^+$, 100%).

***(R)*-3,5-*O*-Benzylidene-6-deoxy-D-*idono*-1,4-lactone 20**

Caesium trifluoroacetate (48 mg, 0.19 mmol) was added to a solution of **10** (50 mg, 0.13 mmol) in anhydrous DMF (1.5 mL). The solution was then stirred at 60 °C for 50 h until TLC (ethyl acetate/cyclohexane, 2:1) indicated the disappearance of the starting material (R_f 0.68) and the formation of one product (R_f 0.62). After dilution with ethyl acetate (5 mL), the reaction mixture was washed with half saturated brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and the

solvent was removed *in vacuo* to give a residue that was purified by flash chromatography (ethyl acetate/cyclohexane, 1:5 to 1:3) to obtain **20** (32.5 mg, 100%) as a white solid.
HRMS (ESI+ve): found 273.0734 $[M + Na]^+$; $C_{13}H_{14}O_5Na^+$ requires 273.0733; m.p. 82 - 84 °C; $[\alpha]_D^{25}$ -39 (*c* 0.78, CH_3CN); ν_{max} (thin film): 3220 (br, OH), 1776 (s, C=O); δ_H (CD_3CN, 400 MHz): 1.39 (3H, d, H6, $J_{6,5}$ 6.6), 4.10 (1H, br-s, H3), 4.29 (1H, dq, H5, $J_{5,4}$ 1.7, $J_{5,6}$ 6.6), 4.51 – 4.53 (1H, m, H4), 5.68 (1H, s, H7), 5.87 (1H, d, H2, $J_{2,3}$ 4.0), 7.37 - 7.44 (5H, m, -Ar); δ_C (CD_3CN, 100 MHz): 17.3 (C6), 72.7 (C5), 73.7 (C3), 76.9 (C4), 78.1 (C2), 99.8 (C7), 127.0, 129.1, 130.0, 138.8 (-Ar), 175.7 (C1); *m/z* (ESI+ve): 273 ($[M + Na]^+$, 100%).

2-Azido-*(R)*-3,5-*O*-benzylidene-2,6-dideoxy-D-*gulono*-1,4-lactone 11
Method 1: from *gulono*-triflate **19**
Sodium azide (228 mg, 3.36 mmol) was added to a solution of the *gulono*-triflate **19** (838 mg, 2.19 mmol) in anhydrous DMF (10 mL). The mixture was stirred at rt for 42 h until TLC (ethyl acetate/cyclohexane, 1:1) indicated the formation of major product (R_f 0.20). After being diluted with ethyl acetate (10 mL), the mixture was washed with half saturated brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to obtain a residue that was purified by flash chromatography (ethyl acetate/cyclohexane, 1:5 to 1:1) to yield the *gulono*-azide **11** (470 mg, 78%) as a white solid, identical to material obtained by Method 2 below.
Method 2: *idono*-lactone from **20**
Anhydrous pyridine (0.3 mL, 0.36 mmol) and triflic anhydride (0.5 mL, 0.31 mmol) were sequentially added dropwise to a solution of the *idono*-lactone **20** (60 mg, 0.24 mmol) in anhydrous THF (3 mL) at -20 °C. After 4 h, TLC (ethyl acetate/cyclohexane, 1:1) indicated the formation of the only product (R_f 0.83). The reaction mixture was diluted with dichloromethane (5 mL) and washed with HCl (2 M, aq, 2 x 5 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the residue (~100 mg) that was used without further purification; in contrast to *gulono*-triflate **21**, this triflate was not stable.
Sodium azide (23 mg, 0.36 mmol) was added to a solution of the crude triflate (~100 mg) in anhydrous DMF (2 mL). The mixture was stirred at rt for 30 h until TLC (ethyl acetate/cyclohexane, 1:1) indicated the formation of the product (R_f 0.20). After being diluted with ethyl acetate (5 mL), the mixture was washed with half saturated brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to obtain a crude that was purified by flash chromatography (ethyl acetate/cyclohexane 1:5 to 1:1) to yield the azido lactone **11** as a white solid (30 mg, 45%).
HRMS (ESI+ve): Found 298.0799 $[M + Na]^+$; $C_{13}H_{13}O_4N_3Na^+$ requires 298.0798; m.p. 144 - 148 °C; $[\alpha]_D^{25}$ -76 (*c* 0.70, $CHCl_3$); ν_{max} (thin film): 2108 (s, N_3), 1775 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.49 (3H, d, H6, $J_{6,5}$ 6.6), 4.04 (1H, d, H2, $J_{2,3}$ 3.8), 4.14 (1H, br-s, H4), 4.22 (1H, dq, H5, $J_{5,4}$ 1.2, $J_{5,6}$ 6.6), 4.78 (1H, dd, H3, $J_{3,4}$ 1.8, $J_{3,2}$ 3.8), 5.61 (1H, s, H7), 7.37 - 7.49 (5H, m, -Ar); δ_C ($CDCl_3$, 100 MHz): 17.0 (C6), 62.1 (C2), 72.5 (C5), 73.7 (C4), 75.2 (C3), 100.1 (C7), 126.5, 128.8, 129.8, 136.8 (-Ar), 170.9 (C1); *m/z* (ESI+ve): 298 ($[M + Na]^+$, 100%).

5.3 6-Deoxy-L-DGDP 1 and 6-deoxy-L-DMDP 2 from *rhamnono*-azides 8 and 9

2-Azido-*(R)*-3,5-*O*-benzylidene-2,6-dideoxy-L-glucitol 22
Diisobutylaluminum hydride (25% w/v in toluene, 0.31 ml, 0.54 mmol) was added dropwise to a solution of the lactone **8** (100 mg, 0.36 mmol) in anhydrous dichloromethane (3.6 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 1 h until mass spectrometry showed the formation of desired product peak ($[M + Na]^+$ 300) and disappearance of the starting material peak ($[M + Na]^+$ 298). The reaction mixture was diluted with ethyl acetate (15 mL) and potassium sodium tartrate (sat. aq., ~1 mL) was added. The reaction mixture was stirred for 8 h, then diluted with water (15 mL) and extracted with ethyl acetate (3 x 15 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo*; the residue was dissolved in methanol (3.6 mL) and then sodium borohydride (14 mg, 0.36 mmol) was added. After stirring the reaction mixture at rt for one h, TLC (ethyl acetate/cyclohexane, 2:3) showed the formation of a single spot (R_f 0.18). Acetic acid was added to neutralize the reaction mixture. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 3:7 to 1:1) to afford the diol **22** (93.6 mg, 92 %) as a white solid.

HRMS (ESI+ve): found 302.1111 $[M + Na]^+$; $C_{13}H_{17}N_3O_4Na^+$ requires 302.1111; m.p. 105 - 106 °C; $[\alpha]_D^{25}$ -5.2 (*c* 1.0, CH_3CN); ν_{max} (thin film): 3395 (br, OH), 2102 (s, N_3); δ_H (CD_3CN, 400 MHz): 1.49 (3H, d, H6, $J_{5,6}$ 7.2), 3.42 (1H, br-t, OH, $J_{OH,1} = J_{OH,1'}$ 5.5), 3.39 (1H, dt, H4, $J_{4,3} = J_{4,5}$ 1.2, $J_{4,OH}$ 9.5), 3.53 (1H, d, OH, $J_{OH,4}$ 9.5), 3.57 - 3.66 (1H, m, H1), 3.68 - 3.78 (2H, m, H1', H3), 4.17 - 4.27 (2H, m, H2, H5), 5.93 (1H, s, H7), 7.26 - 7.54 (5H, m, Ar); δ_C (CD_3CN, 100 MHz): 15.4 (C6), 61.2 (C1), 65.5 (C3), 67.2 (C4), 76.2 (C2), 76.8 (C5), 94.9 (C7), 127.3, 129.1, 129.7, 139.8 (-Ar); *m/z* (ESI+ve): 302 ($[M + Na]^+$, 100%).

2-Azido-*(R)*-3,5-*O*-benzylidene-1,4-*bis*-(*O*-*tert*-butyldimethylsilyl)-2,6-dideoxy-L-glucitol 23

tert-Butyldimethylsilyl triflate (0.51 mL, 2.2 mmol) and anhydrous pyridine (0.22 mL, 2.7 mmol) were added to a solution of diol **22** (250 mg, 0.90 mmol) in anhydrous dichloromethane (6 mL) at 0 °C. After stirring at 0 °C for 1 h, the mixture was stirred at rt for another 3 h. TLC (ethyl acetate/cyclohexane, 1:19) showed the formation of one spot (R_f 0.27). The solvent was removed *in vacuo*; the residue was dissolved in cyclohexane (25 mL) and washed with water (2 x 25 mL). Organic phase was dried ($MgSO_4$), filtered and the solvent removed to obtain a residue that was purified by flash column chromatography (ethyl acetate/cyclohexane, 0:10 to 1:24) to afford the silyl ether **23** (444 mg, 98 %) as a white solid.

HRMS (ESI+ve): found 530.2843 $[M + Na]^+$; $C_{25}H_{45}N_3O_4Si_2Na^+$ requires 530.2841; m.p. 61 - 62 °C; $[\alpha]_D^{25}$ -33.2 (*c* 1.0, MeCN); ν_{max} (thin film): 2098 (s, N_3); δ_H (CD_3CN, 400 MHz): 0.13 (3H, s, CH_3), 0.14 (3H, s, CH_3), 0.15 (3H, s, CH_3), 0.18 (3H, s, CH_3), 0.95 (9H, s, 3 x CH_3), 0.96 (9H, s, 3 x CH_3), 1.44 (3H, d, H6, $J_{6,5}$ 7.2), 3.60 (1H, s, H4), 3.66 (1H, a-dt, H2, $J_{2,1'} = J_{2,1}$ 4.5, $J_{2,3}$ 8.8), 3.79 (1H, dd, H1, $J_{1,2}$ 4.5, J_{gem} 11.1), 3.87 (1H, dd, H1', $J_{1',2}$ 4.5, J_{gem} 11.1), 4.26 - 4.34 (2H, m, H3, H5), 5.94 (1H, s, H7), 7.35 - 7.56 (5H, m, Ar); δ_C (CD_3CN, 100 MHz): -4.9 ($\underline{C}H_3$), -5.0 ($\underline{C}H_3$), -3.9 ($\underline{C}H_3$), -3.2 ($\underline{C}H_3$), 16.1 (C6), 19.2 ($\underline{C}(CH_3)_3$), 19.3 ($\underline{C}(CH_3)_3$), 26.6 ($C(\underline{C}H_3)_3$), 26.7 ($C(\underline{C}H_3)_3$), 63.4 (C1), 65.1 (C2), 69.1 (C4), 75.6 (C3), 76.3 (C5), 95.3 (C7), 127.8, 129.5, 130.2, 140.6 (-Ar); *m/z* (ESI+ve): 530 ($[M + Na]^+$, 100%).

2-Azido-3-*O*-benzoyl-5-bromo-1,4-*bis*-(*O*-*tert*-butyldimethylsilyl)-2,5,6-trideoxy-D-iditol 12

N-Bromosuccinimide (185 mg, 1.0 mmol) and barium carbonate (256 mg, 1.3 mmol) were added to a solution of **23** (440 mg, 0.87 mmol) in carbon tetrachloride (5.8 mL). The stirred reaction mixture was refluxed for 1 h until TLC (ethyl acetate/cyclohexane, 1:19) indicated the disappearance of starting material (R_f 0.27) and the formation of one major product (R_f 0.52). After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (ethyl acetate/hexane, 0:10 to 1:24) to give the bromide **12** (437 mg, 86%) as a colorless oil.

HRMS (ESI+ve): found 586.2127, 588.2107 $[M + H]^+$; $C_{25}H_{45}BrN_3O_4Si_2^+$ requires 586.2127, 588.2106; $[\alpha]_D^{25}$ - 17.5 (*c* 1.0, MeCN); ν_{max} (thin film): 1728 (s, C=O), 2102 (s, N_3); δ_H (400 MHz, CD_3CN): -0.08 (3H, s, CH_3), 0.02 (3H, s, CH_3), 0.04 (3H, s, CH_3), 0.13 (3H, s, CH_3), 0.85 (9H, s, CH_3), 0.88 (9H, s, CH_3), 1.76 (3H, d, H6, $J_{6,5}$ 6.9), 3.77 - 3.86 (2H, m, H1, H2), 3.88 - 3.96 (1H, m, H1'), 4.08 (1H, dd, H4, $J_{4,5}$ 3.0, $J_{4,3}$ 6.6), 4.42 (1H, dq, H5, $J_{5,4}$ 3.0, $J_{5,6}$ 6.9), 5.54 (1H, dd, H3, $J_{3,2}$ 2.9, $J_{3,4}$ 6.6), 7.53 (2H, t, Ar, *J* 7.7), 7.67 (1H, t, Ar, *J* 7.4), 8.03 - 8.10 (2H, m, Ar); δ_C (100 MHz, CD_3CN): -5.0 (CH_3Si), -4.9 (CH_3Si), -3.2 (CH_3Si), -3.1 (CH_3Si), 19.1 ($\underline{C}(CH_3)_3$), 19.2 ($\underline{C}(CH_3)_3$), 23.9 (C6), 26.5 ($C(\underline{C}H_3)_3$), 26.6 ($C(\underline{C}H_3)_3$), 53.3 (C5), 63.4 (C2), 64.8 (C1), 75.3 (C4), 75.8 (C3), 130.0, 131.1, 131.2, 134.8 (Ar), 166.7 (C=O); *m/z* (ESI+ve): 586, 588 ($[M + H]^+$, 100%, 93%).

3-*O*-Benzoyl-1,4-*bis*-(*O*-*tert*-butyldimethylsilyl)-2,5-imino-2,5,6-trideoxy-L-glucitol 24

Palladium on charcoal (10 % wt., 72 mg) and sodium acetate (84 mg, 1.0 mmol) were added to a solution of **12** (399 mg, 0.68 mmol) in ethanol (20 mL). The reaction mixture was flushed sequentially with nitrogen, argon and hydrogen gas and stirred vigorously overnight at rt under a hydrogen atmosphere until TLC (ethyl acetate/cyclohexane, 3:7) showed the formation of one major product (R_f 0.32). After filtration, the solvent was removed *in vacuo* and the residue purified by flash column chromatography (triethylamine/ethyl acetate/cyclohexane, 0.01:3:7) to afford **24** (236 mg, 72%) as a yellow oil.

HRMS (ESI+ve): found 480.2957 $[M + H]^+$; $C_{25}H_{45}NO_4Si_2^+$ requires 480.2960; $[\alpha]_D^{25}$ +17.4 (*c* 1.0, MeCN); ν_{max} (thin film): 1722 (s, C=O); δ_H (CD_3CN, 400 MHz): -0.09 (3H, s, CH_3), -0.05 (3H, s, CH_3), 0.05 (3H, s, CH_3), 0.09 (3H, s, CH_3), 0.82 (9H, s, CH_3), 0.88 (9H, s, 3 x CH_3), 1.18 (3H, d, H6, $J_{6,5}$ 6.4), 2.98 (1H, quintet, H5, $J_{5,4}$ 6.3), 3.45-3.51 (1H, m, H2), 3.60 (1H, dd, H1, $J_{1,2}$ 4.9, J_{gem} 10.1), 3.68 (1H, dd, H1', $J_{1',2}$ 6.6, J_{gem} 10.1), 3.88 (1H, dd, H4, $J_{4,3}$ 4.2, $J_{4,5}$ 6.3), 5.27 (1H, dd, H3, $J_{3,4}$ 4.2, $J_{3,2}$ 6.2), 7.50-

7.56 (2H, m, Ar), 7.59 - 7.64 (1H, m, Ar), 8.05 - 8.07 (2H, m, Ar); δ_C (CD_3CN, 100 MHz): -5.1 ($\underline{C}H_3$), -5.0 ($\underline{C}H_3$), -4.1 ($\underline{C}H_3$), -3.9 ($\underline{C}H_3$), 18.9 $\underline{C}(CH_3)_3$, 19.1 ($\underline{C}(CH_3)_3$), 20.0 (C6), 26.5 ($C(\underline{C}H_3)_3$), 26.6 ($C(\underline{C}H_3)_3$), 60.6 (C5), 61.3 (C2), 63.5 (C1), 82.3 (C3), 84.0 (C4), 129.9, 130.8, 131.6, 134.6 (Ar), 167.0 (C=O); *m/z* (ESI+ve): 480 ($[M + H]^+$, 100%).

2,5-Imino-2,5,6-trideoxy-L-glucitol (6-Deoxy-L-DGDP) 1

24 (236 mg, 0.49 mmol) was dissolved in a mixture of trifluoroacetic acid/water/1,4-dioxane (1:1:1, 6 mL). The solution was stirred at 50 °C for 24 h until mass spectrometry showed the deprotection of the silyl groups ($[M + H]^+$ 252). The solvent was removed *in vacuo*; the residue was dissolved in aqueous sodium hydroxide (aq., 2 M, 10 mL) and stirred at 50 °C for 24 h until mass spectrometry showed the formation of desired product ($[M + H]^+$ 148). After removal of the solvent *in vacuo*, the residue was dissolved in ethanol (5 mL), filtered and then loaded with water (~1 mL) onto a short column of DOWEX® 50WX8-200 resin (pre-washed with water, 1,4-dioxane and water sequentially until the eluent was neutral). The ion exchange column was then washed with water, 1,4-dioxane and then water and the pure product was then eluted with aqueous ammonia (2 M). Removal of the solvent *in vacuo* gave the unprotected pyrrolidine **1** as a yellow oil (58 mg, 81%).
HRMS (ESI+ve): found 148.0967 $[M + H]^+$; $C_6H_{14}NO_3^+$ requires 148.0968; $[\alpha]_D^{25}$ –12.1 (*c* 0.45, water) [lit.[34] for **1D**,the enantiomer of **1**: $[\alpha]_D^{29}$ +5.2 (*c* 1.0, MeOH)]; ν_{max} (thin film): 3300 (br, NH, OH); δ_H (D_2O, 400 MHz): 1.25 (3H, d, H6, $J_{6,5}$ 6.6), 2.92 (1H, quintet, H5, $J_{5,4} = J_{5,6}$ 6.6), 3.05 (1H, q, H2, $J_{2,1} = J_{2,1'} = J_{2,3}$ 6.0), 3.64 (1H, dd, H4, $J_{4,3}$ 3.5, $J_{4,5}$ 6.6), 3.67 (1H, dd, H1, $J_{1,2}$ 6.0, J_{gem} 11.4), 3.79 (1H, dd, H1', $J_{1',2}$ 6.0, J_{gem} 11.4), 4.12 (1H, dd, H3, $J_{3,4}$ 3.5, $J_{3,2}$ 6.0); δ_C (D_2O, 100 MHz): 17.9 (C6), 59.2 (C5), 60.6 (C1), 61.2 (C2), 78.3 (C3), 84.4 (C4); *m/z* (ESI+ve): 148 ($[M + H]^+$, 100%).

2-Azido-*(R)*-3,5-*O*-benzylidene-2,6-dideoxy-L-mannitol 25

Diisobutylaluminium hydride (25% w/v in toluene, 2.33 ml, 4.05 mmol) was added dropwise to a solution of **9** (500 mg, 1.80 mmol) in anhydrous dichloromethane (18 mL) at -78 °C. The solution was stirred at -78°C for 1.5 h until mass spectrometry showed the formation of desired product peak ($[M + Na]^+$ 300) and disappearance of starting material peak ($[M+Na]^+$ 298). Then the mixture was diluted with ethyl acetate (25 mL) and potassium sodium tartrate (sat, aq., ~5 mL) was added and allowed to stand at rt for 8h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). Organic phase was dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to obtain a residue that was dissolved in methanol (18 mL) and sodium borohydride (69 mg, 1.80 mmol) was added. After stirring at rt for one h, TLC (ethyl acetate/cyclohexane, 2:3) showed the formation of a single spot (R_f 0.32). Acetic acid was added to neutralize the reaction mixture. After removing the solvent *in vacuo*, the crude product was purified by flash column chromatography (ethyl acetate/cyclohexane, 3:7 to 1:1) to afford the diol **25** (452 mg, 89 %) as a white solid.
HRMS (ESI+ve): found 302.1111 $[M + Na]^+$; $C_{13}H_{17}N_3O_4Na^+$ requires 302.1111; m.p. 108 - 109 °C; $[\alpha]_D^{25}$ +19.8 (*c* 1.0, MeCN); ν_{max} (thin film): 3406 (br, OH), 2102 (s, N_3); δ_H (CD_3CN, 400 MHz): 1.44 (3H, d, H6, $J_{6,5}$ 7.2), 3.11 (1H, br-t, OH, $J_{OH,1} = J_{OH,1'}$ 5.7), 3.43 - 3.51 (2H, m, H4, OH), 3.65 (1H, dt, H1, $J_{1,2}$ 5.9, J_{gem} 11.8), 3.73 (1H, ddd, H2, $J_{2,1'}$ 2.6, $J_{2,1}$ 5.9, $J_{2,3}$ 9.1), 3.88 (1H, ddd, H1', $J_{1',2}$ 2.6, $J_{1',OH}$ 5.7, J_{gem} 11.8), 4.01 (1H, d, H3, $J_{3,2}$ 9.1), 4.26 (1H, q, H5, $J_{5,6}$ 7.2), 5.85 (1H, s, H7), 7.33 - 7.53 (5H, m, Ar); δ_C (CD_3CN, 100 MHz): 15.2 (C6), 62.4 (C1), 63.4 (C2), 66.8 (C4), 73.9 (C3), 76.9 (C5), 94.7 (H7), 127.2, 129.1, 129.7, 139.8 (Ar); *m/z* (ESI+ve): 302 ($[M + Na]^+$, 100%).

2-Azido-*(R)*-3,5-*O*-benzylidene-1,4-*bis*-(*O*-*tert*-butyldimethylsilyl)-2,6-dideoxy-L-mannitol 26

tert-Butyldimethylsilyl triflate (1.0 mL, 4.50 mmol) and anhydrous pyridine (0.45 mL, 5.4 mmol) were added to a solution of **25** (500 mg, 1.80 mmol) in anhydrous dichloromethane (12 mL) at 0 °C. After stirring at 10 °C for 3 h, TLC (ethyl acetate/cyclohexane, 1:4) showed the formation of a new spot (R_f 0.73) but reaction was not complete. Further *tert*-butyldimethylsilyl triflate (0.33 mL, 1.49 mmol) and anhydrous pyridine (0.15 mL, 1.80 mmol) were added to the reaction mixture which was stirred at -18 °C for 16 h until TLC indicated the completion of reaction. After removing the solvent *in vacuo*, the residue was dissolved in ethyl acetate (50 mL) and washed with half saturated brine (50 mL) and then brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and solvent was removed to obtain a residue that was purified by flash column chromatography (ethyl acetate/cyclohexane, 0:10 to 1:4) to afford **26** (852 mg, 94 %) as a colorless oil.

HRMS (ESI+ve): found 530.2838 $[M + Na]^+$; $C_{25}H_{45}N_3O_4Si_2Na^+$ requires 530.2841; $[\alpha]_D^{25}$ +7.6 (*c* 1.0, MeCN); ν_{max} (thin film): 2099 (s, N_3); δ_H (CD_3CN, 400 MHz): 0.08 (6H, s, CH_3), 0.150 (3H, s, CH_3), 0.153 (3H, s, CH_3), 0.92 (9H, s, 3 x CH_3), 0.95 (9H, s, 3 x CH_3), 1.41 (3H, d, H6, $J_{6,5}$ 7.2), 3.63 (1H, br-s, H4), 3.66 (1H, ddd, H2, $J_{2,1'}$ 1.9, $J_{2,1}$ 5.0, $J_{2,3}$ 7.5), 3.87 (1H, dd, H1, $J_{1,2}$ 5.0, J_{gem} 10.9), 4.01 (1H, dd, H3, $J_{3,4}$ 1.1, $J_{3,2}$ 7.5), 4.06 (1H, dd, H1', $J_{1',2}$ 1.9, J_{gem} 10.9), 4.25 (1H, q, H5, $J_{5,6}$ 7.2), 5.80 (1H, s, H7), 7.32 - 7.47 (5H, m, Ar); δ_C (CD_3CN, 100 MHz): -5.3 (CH_3Si), -5.3 (CH_3Si), -4.7 (CH_3Si), -4.2 (CH_3Si), 15.4 (C6), 18.79 ($\underline{C}(CH_3)_3$), 18.84 ($\underline{C}(CH_3)_3$), 26.1 ($C(\underline{C}H_3)_3$), 26.2 ($C(\underline{C}H_3)_3$), 62.1 (C2), 64.1 (C1), 67.8 (C4), 73.3 (C3), 76.2 (C5), 94.5 (C7), 127.2, 129.0, 129.7, 140.1 (Ar); *m/z* (ESI+ve): 530 ($[M + Na]^+$, 100%).

2-Azido-3-*O*-benzoyl-5-bromo-1,4-*bis*-(*O*-*tert*-butyldimethylsilyl)-2,5,6-trideoxy-D-gulitol 13

N-Bromosuccinimide (358 mg, 2.0 mmol) and barium carbonate (496 mg, 2.5 mmol) were added to a solution of **26** (851 mg, 1.70 mmol) in carbon tetrachloride (11.2 mL). The mixture was refluxed with stirring for 50 min until TLC (ethyl acetate/cyclohexane, 1:19) indicated the disappearance of starting material (R_f 0.50) and the formation of one major product (R_f 0.62). After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (ethyl acetate/hexane 0:10 to 1:24) to afford **13** (909 mg, 92%) as a colorless oil.

HRMS (ESI+ve): found 608.1944, 610.1924 $[M + Na]^+$; $C_{25}H_{44}BrN_3O_4Si_2Na^+$ requires 608.1946, 608.1926; $[\alpha]_D^{25}$ -22.2 (*c* 1.0, MeCN); ν_{max} (thin film): 2098 (s, N_3), 1728 (s, C=O); δ_H (CD_3CN, 400 MHz): 0.05 (3H, s, CH_3), 0.06 (3H, s, CH_3), 0.08 (3H, s, CH_3), 0.16 (3H, s, CH_3), 0.91 (9H, s, 3 x CH_3), 0.93 (9H, s, 3 x CH_3), 1.66 (3H, d, H6, $J_{6,5}$ 6.9), 3.79 - 3.91 (2H, m, H1, H2), 3.96 (1H, dd, H1', $J_{1',2}$ 3.7, J_{gem} 10.0), 4.21 (1H, t, H4, $J_{4,3} = J_{4,5}$ 4.0), 4.34 (1H, dq, H5, $J_{5,4}$ 4.0, $J_{5,6}$ 6.9), 5.60 (1H, dd, H3, $J_{3,4}$ 4.0, $J_{3,2}$ 6.3), 7.49 - 7.57 (2H, m, -Ar), 7.63 - 7.70 (1H, m, -Ar), 8.01 - 8.09 (2H, m, -Ar); δ_C (CD_3CN, 100 MHz): -5.1 (CH_3Si), -5.0 (CH_3Si), -3.5 (CH_3Si), -3.3 (CH_3Si), 19.1 ($\underline{C}(CH_3)_3$), 22.5 (C6), 26.4 ($C(\underline{C}H_3)_3$), 26.5 ($C(\underline{C}H_3)_3$), 52.9 (C5), 63.5 (C2), 64.0 (C1), 73.8 (C3), 74.6 (C4), 130.0, 130.9, 131.2, 134.8 (-Ar), 166.4 (C=O); *m/z* (ESI+ve): 586, 588 ($[M + H]^+$, 100%, 97%).

3-*O*-Benzoyl-1,4-*bis*-(*O*-*tert*-butyldimethylsilyl)-2,5-imino-2,5,6-trideoxy-L-mannitol 27

Palladium on charcoal (10 % wt., 165 mg) and sodium acetate (191 mg, 2.3 mmol) were added to a solution of **13** (909 mg, 1.5 mmol) in ethanol (45 mL). The reaction mixture was flushed with nitrogen, argon and hydrogen gas sequentially. Then the reaction mixture was stirred vigorously overnight at rt under a hydrogen atmosphere for 12 h until TLC (ethyl acetate/cyclohexane, 1:4) showed the formation of one major product (R_f 0.17). Filtration and evaporation *in vacuo* gave a crude bromide salt (~1.2 g). Part of the salty residue (120 mg) was purified by flash column chromatography (triethylamine/ethyl acetate/cyclohexane, 0.01:3:7) to give a pure sample of **27** (64 mg, 71%) as a yellow oil for full characterization. The crude salt was used in the next step.

HRMS (ESI+ve): found 480.2959 $[M + H]^+$; $C_{25}H_{45}NO_4Si_2^+$ requires 480.2960; $[\alpha]_D^{25}$ +10.6 (*c* 1.0, MeCN); ν_{max} (thin film): 3350 (br, NH), 1722 (s, C=O); δ_H (CD_3OD, 400 MHz): 0.00 (3H, s, CH_3), 0.09 (3H, s, CH_3), 0.09 (3H, s, CH_3), 0.13 (3H, s, CH_3), 0.84 (9H, s, 3 x CH_3), 0.91 (9H, s, 3 x CH_3), 1.29 (3H, d, H6, $J_{6,5}$ 6.6), 3.32 - 3.46 (2H, m, H2, H5), 3.81 (1H, dd, H1, $J_{1,2}$ 3.9, J_{gem} 10.6), 4.00 (1H, dd, H1', $J_{1',2}$ 4.4, J_{gem} 10.6), 4.13 (1H, dd, H4, $J_{4,3}$ 5.2, $J_{4,5}$ 7.3), 5.29 (1H, t, H3, $J_{3,2} = J_{3,4}$ 4.6), 7.48 (2H, t, -Ar, *J* 7.7), 7.61 (1H, t, -Ar, *J* 7.4), 8.04 (2H, d, -Ar, *J* 7.4); δ_C (CD_3OD, 100 MHz): -5.3 (CH_3Si), -5.2 (CH_3Si), -4.6 (CH_3Si), -4.2 (CH_3Si), 17.1 (C6), 18.7 ($\underline{C}(CH_3)_3$), 19.1 ($\underline{C}(CH_3)_3$), 26.2 ($C(\underline{C}H_3)_3$), 26.4 ($C(\underline{C}H_3)_3$), 60.2 (C5), 64.0 (C2), 64.7 (C1), 82.8 (C3), 83.3 (C4), 129.7, 130.7, 130.8, 134.6 (Ar), 167.4 (C=O); *m/z* (ESI+ve): 480 ($[M + H]^+$, 100%).

2,5-Imino-2,5,6-trideoxy-L-mannitol (6-Deoxy-L-DMDP) 2

The crude product **27** (617 mg) was dissolved in a solution of trifluoroacetic acid/water/1,4-dioxane (2:1:1, 20 mL). The solution was stirred at 50 °C for 18 h until mass spectrometry showed the deprotection of the silyl groups ($[M + H]^+$ 252). After the solvent was removed *in vacuo*, the residue was dissolved into sodium hydroxide solution (aq, 2M, 5 mL) and stirred at 50 °C for 24 h until mass spectrometry showed the formation of desired product ($[M + H]^+$ 148). The mixture was neutralized with HCl (2M, aq) and the solvent removed *in vacuo*. The residue was dissolved in ethanol (5 mL) and filtered (glass microfiber) to afford a crude salt that was then loaded with water (~1 mL) onto a short column of DOWEX® 50WX8-200 resin. The ion exchange column was then washed with water, 1,4-

dioxane and then water; the pure product was then eluted with aqueous ammonia (2 M). Removal of solvent *in vacuo* gave a residue which was subjected to a further purification cycle by resin column to yield 6-deoxy-L-DMDP **2** as a yellow oil (121 mg, 64% from crude salt of **27**).
HRMS (ESI+ve): found 148.0968 $[M + H]^+$; $C_6H_{13}NO_3^+$ requires 148.0968; $[\alpha]_D^{25}$ -42 (*c* 1.0, MeOH) [lit.[35] $[\alpha]_D^{25}$ -33 (*c* 1.2, MeOH)]; ν_{max} (thin film): 3277 (br, NH, OH); δ_H (D_2O, 400 MHz): 1.19 (3H, d, H6, $J_{6,5}$ 6.4), 2.96 (1H, dq, H5, $J_{5,6}$ 6.4, $J_{5,4}$ 7.3), 3.05 (1H, br-q, H2, *J* 6.5), 3.58 – 3.64 (2H, m, H4, H1), 3.68 (1H, dd, H1', $J_{1',2}$ 4.6, J_{gem} 11.4), 3.81 (1H, t, H3, $J_{3,4} = J_{3,2}$ 6.8); δ_C (D_2O, 100 MHz): 17.8 (C6), 58.2 (C5), 62.0, 63.0 (C1, C2), 78.7 (C3), 83.3 (C4); *m/z* (ESI+ve): 148 ($[M + H]^+$, 100%); *m/z* (ESI+ve): 148 ($[M + H]^+$, 100%).

5.4 6-Deoxy-D-*ido*-DMDP 3 and 6-deoxy-D-*gulo*-DMDP 4 from D-*gulono*-azides 10 and 11

2-Azido-*(R)*-3,5-*O*-benzylidene-2,6-dideoxy-D-iditol 28
Diisobutylaluminium hydride (25% w/v in toluene, 4.83 ml, 8.50 mmol) was added dropwise to a solution of **10** (467 mg, 1.70 mmol) in anhydrous dichloromethane (15 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 3 h until mass spectrometry showed the formation of desired product peak ($[M+Na]^+$ 300) and disappearance of starting material peak ($[M + Na]^+$ 298). Then the mixture was diluted with ethyl acetate (20 mL) and potassium sodium tartrate (sat, aq., ~2 mL) was added. After stirring for 12 h, the mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 20 mL). Organic phase was dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to obtain a residue that was dissolved in methanol (15 mL) and sodium borohydride (84 mg, 2.20 mmol) was added. After stirring at rt for one h, TLC (ethyl acetate/cyclohexane, 1:1) showed the formation of a new spot (R_f 0.32). Acetic acid was added to neutralize the reaction mixture. The solvent was removed *in vacuo*, the resulting crude was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:4 to 1:1) to afford the *ido*-diol **28** (312 mg, 66 %) as a pale syrup.
HRMS (ESI+ve): Found 302.1111 $[M + Na]^+$; $C_{13}H_{17}O_4N_3Na^+$ requires 302.1111; $[\alpha]_D^{25}$ +5.2 (*c* 0.78, $CHCl_3$); ν_{max} (thin film): 3400 (br, OH), 2108 (s, N_3); δ_H ($CDCl_3$, 400MHz): 1.37 (3H, d, H6, $J_{6,5}$ 6.4), 2.24 (1H, br-s, OH), 3.48 (1H, br-s, H4), 3.76 (1H, dd, H1, $J_{1,2}$ 4.2, J_{gem} 12.0), 3.82 (1H, dd, H1', $J_{1',2}$ 3.1, J_{gem} 12.0), 3.90 (1H, ddd, H2, $J_{2,1'}$ 3.1, $J_{2,1}$ 4.2, $J_{2,3}$ 8.5), 4.06 (1H, dq, H5, $J_{5,4}$ 0.6, $J_{5,6}$ 6.5), 4.35 (1H, dd, H3, $J_{3,4}$ 0.6, $J_{3,2}$ 8.5), 5.69 (1H, s, H7), 7.36 - 7.56 (5H, m, -Ar); δ_C ($CDCl_3$, 100MHz): 17.2 (C6), 61.2 (C1), 64.3 (C2), 66.6 (C4), 76.6 (C5), 81.5 (C3), 101.4 (C7), 126.1, 128.6, 129.3, 137.6 (-Ar); *m/z* (ESI+ve): 302 ($[M + Na]^+$, 100%).

2-Azido-*(R)*-3,5-*O*-benzylidene-1,4-*bis*-(*O*-*tert*-butyldimethylsilyl)-2,6-dideoxy-D-iditol 29
tert-Butyldimethylsilyl triflate (1.03 mL, 4.5 mmol) and anhydrous pyridine (0.59 mL, 7.2 mmol) were added to a solution of **28** (250 mg, 0.90 mmol) in anhydrous dichloromethane (6 mL) at 0 °C. Then the mixture was stirred at rt for 18 h until TLC (ethyl acetate/cyclohexane, 1:4) showed the formation of a major spot (R_f 0.78). Removal of the solvent *in vacuo* gave a residue that was dissolved in cyclohexane (25 mL) and washed with water (2 x 25 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent removed to obtain a residue that was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:9) to afford the fully protected **29** (334 mg, 74 %) as a colorless oil.
HRMS (ESI+ve): found 530.2840 $[M + Na]^+$; $C_{25}H_{45}N_3O_4Si_2Na^+$ requires 530.2841; $[\alpha]_D^{25}$ -35 (*c* 0.81, $CHCl_3$); ν_{max} (thin film): 2100 (s, N_3); δ_H ($CDCl_3$, 400 MHz): 0.10 (3H, s, CH_3), 0.11 (6H, s, 2 x CH_3), 0.15 (3H, s, CH_3), 0.92 (9H, s, 3 x CH_3), 0.97 (9H, s, 3 x CH_3), 1.31 (3H, d, H6, $J_{6,5}$ 6.4), 3.56 (1H, br-s, H4), 3.60 (1H, ddd, H2, $J_{2,1'}$ 3.2, $J_{2,1}$ 4.6, $J_{2,3}$ 9.0), 3.75 (1H, dd, H1, $J_{1,2}$ 4.6, J_{gem} 10.7), 3.82 (1H, dd, H1', $J_{1',2}$ 3.1, J_{gem} 10.7), 3.92 (1H, q, H5, $J_{5,6}$ 6.5), 4.00 (1H, d, H3, $J_{3,2}$ 9.0), 5.62 (1H, s, H7), 7.33 - 7.55 (5H, m, -Ar); δ_C ($CDCl_3$, 100 MHz): -5.2 (CH_3Si), -5.1 (CH_3Si), -2.8 (2 x CH_3Si), 18.6 (2 x ($\underline{C}(CH_3)_3$)), 19.1 (C6), 26.1 ($C(\underline{C}H_3)_3$), 26.5 ($C(\underline{C}H_3)_3$), 62.4, 62.5 (C1, C2), 68.4 (C4), 76.9 (C5), 79.8 (C3), 102.2 (C7), 126.8, 128.6, 129.2, 138.6 (-Ar); *m/z* (ESI+ve): 530 ($[M + Na]^+$, 100%).

2-Azido-3-*O*-benzoyl-5-bromo-1,4-*bis*-(*O*-*tert*-butyldimethylsilyl)-2,5,6-trideoxy-L-glucitol 14
N-Bromosuccinimide (146 mg, 0.83 mmol) and barium carbonate (205 mg, 1.04 mmol) were added into a solution of **29** (350 mg, 0.69 mmol) in carbon tetrachloride (5 mL). The reaction mixture was refluxed with stirring for 1 h until TLC (ethyl acetate/cyclohexane, 1:19) indicated the disappearance of the starting material (R_f 0.52) and the formation of one major product (R_f 0.71). After removing the

solvent *in vacuo*, the residue was purified by flash column chromatography (ethyl acetate/hexane, 1:9) to afford the bromide **14** (400 mg, 99%) as a yellow oil.
HRMS (ESI+ve): found 586.2127, 588.2105 $[M + H]^+$; $C_{25}H_{45}BrN_3O_4Si_2^+$ requires 586.2127, 588.2106; $[\alpha]_D^{25}$ -11 (*c* 0.66, $CHCl_3$); ν_{max} (thin film): 2098 (s, N_3), 1728 (s, C=O); δ_H (400 MHz, $CDCl_3$): 0.03 (3H, s, CH_3), 0.04 (3H, s, CH_3), 0.08 (3H, s, CH_3), 0.18 (3H, s, CH_3), 0.86 (9H, s, 3 x CH_3), 0.87 (9H, s, 3 x CH_3), 1.74 (3H, d, H6, $J_{6,5}$ 6.9), 3.69 – 3.73 (1H, m, H2), 3.79 (1H, dd, H1, $J_{1,2}$ 7.0, J_{gem} 10.3), 3.87 (1H, dd, H1', $J_{1',2}$ 4.9, J_{gem} 10.2), 4.26 (1H, t, H4, $J_{4,3} = J_{4,5}$ 5.0), 4.41 (1H, dq, H5, $J_{5,4}$ 4.8, $J_{5,6}$ 6.7), 5.28 (1H, dd, H3, $J_{3,2}$ 3.7, $J_{3,4}$ 5.2), 7.46 (2H, t, -Ar, *J* 7.7), 7.60 (1H, t, -Ar, *J* 7.3), 8.08 – 8.10 (2H, m, -Ar); δ_C (100 MHz, $CDCl_3$): -5.3 (2 x CH_3Si), -3.9 (CH_3Si), -3.8 (CH_3Si), 18.5 ($\underline{C}(CH_3)_3$), 18.6 ($\underline{C}(CH_3)_3$), 22.1 (C6), 26.1 ($C(\underline{C}H_3)_3$), 26.2 ($C(\underline{C}H_3)_3$), 49.5 (C5), 62.2 (C2), 63.8 (C1), 73.8 (C4), 75.9 (C3), 128.6, 129.9, 130.4, 133.7 (-Ar), 165.9 (C=O); *m/z* (ESI+ve): 586, 588 ($[M + H]^+$, 100%, 98%).

3-*O*-Benzoyl-1,4-*bis*-(*O*-*tert*-butyldimethylsilyl)-2,5-imino-2,5,6-trideoxy-L-glucitol 30
Palladium on charcoal (10 % wt., 60 mg) and sodium acetate (82 mg, 0.99 mmol) were added to a solution of the bromide **14** (385 mg, 0.66 mmol) in ethanol (20 mL). The solution was flushed with nitrogen, argon and hydrogen gas sequentially, and then stirred vigorously at rt under hydrogen atmosphere for 2 h until TLC (ethyl acetate/cyclohexane, 1:4) showed the formation of one major product (R_f 0.30). The reaction mixture was filtered, the solvent removed and the resultant crude product **30** (400 mg) was used for the next step without further purification. A small portion of the crude material was purified for characterization by flash column chromatography (triethylamine/ethyl acetate/cyclohexane, 0.01:3:7) to afford **30** as a yellow oil.
HRMS (ESI+ve): found 480.2955 $[M + H]^+$; $C_{25}H_{45}BrNO_4Si_2^+$ requires 480.2960; $[\alpha]_D^{25}$ -13 (*c* 1.45, MeOH); ν_{max} (thin film): 1723 (s, C=O); δ_H (CD_3OD, 400 MHz): -0.09 (3H, s, CH_3), 0.01 (3H, s, CH_3), 0.17 (3H, s, CH_3), 0.26 (3H, s, CH_3), 0.82 (9H, s, 3 x CH_3), 0.99 (9H, s, 3 x CH_3), 1.20 (3H, d, H6, $J_{6,5}$ 6.6), 3.44 (1H, dq, H5, $J_{5,4}$ 3.5, $J_{5,6}$ 6.6), 3.74 – 3.85 (3H, m, H1, H1', H2), 4.10 (1H, br-d, H4, *J* 2.0), 5.39 (1H, br-d, H3, *J* 2.1), 7.52 (2H, t, -Ar, *J* 7.7), 7.65 (1H, t, -Ar, *J* 7.4), 8.08 (2H, d, -Ar, *J* 7.3); δ_C (CD_3OD, 100 MHz): -4.6 (CH_3Si), -4.5 (CH_3Si), -4.1 (CH_3Si), -3.6 (CH_3Si), 15.5 (C6), 19.8 ($\underline{C}(CH_3)_3$), 19.7 ($\underline{C}(CH_3)_3$), 27.1 ($C(\underline{C}H_3)_3$), 27.2 ($C(\underline{C}H_3)_3$), 58.3 (C5), 62.1 (C2), 63.3 (C1), 79.6 (C4), 81.5 (C3), 130.5, 131.5, 132.2, 135.3 (-Ar), 167.7 (C=O); *m/z* (ESI+ve): 480 ($[M + H]^+$, 100%).

2,5-Imino-2,5,6-trideoxy-D-iditol 3
The crude protected pyrrolidine **30** (400 mg) was dissolved in a solution of trifluoroacetic acid/water/1,4-dioxane (2:1:1, 10 mL). The solution was stirred at 50 °C for 24 h until mass spectrometry showed the deprotection of the silyl groups ($[M + H]^+$ 252). The solvent was removed and the residue dissolved in sodium hydroxide solution (aq., 2M, 8 mL); the resulting solution was then stirred at 50 °C for 24 h until mass spectrometry showed the formation of the desired product ($[M + H]^+$ 148). The reaction mixture was neutralized with HCl (2M, aq) and the solvent removed *in vacuo*. The residue was dissolved in ethanol (5 mL) and filtered (glass microfiber) to afford a crude salt that was then loaded with water (~1 mL) onto a short column of DOWEX® 50WX8-200 resin. The ion exchange column was then washed with water, 1,4-dioxane and then water; the pure product was then eluted with aqueous ammonia (2 M). Removal of solvent *in vacuo* gave a residue which was subjected to a further purification cycle by resin column to give the title compound **3** (72 mg, 74% 3 steps from **14**) as a yellow oil.
HRMS (ESI+ve): found 148.0968 $[M + H]^+$; $C_6H_{14}N_3O_3^+$ requires 148.0968; $[\alpha]_D^{25}$ +2.4 (*c* 0.17, water); ν_{max} (thin film): 3300 (br, NH, OH); δ_H (D_2O, 400 MHz): 1.15 (3H, d, H6, $J_{6,5}$ 6.7), 3.43 (1H, dq, H5, $J_{5,4}$ 3.7, $J_{5,6}$ 6.7), 3.05 (1H, ddd, H2, $J_{2,3}$ 4.9, $J_{2,1'}$ 6.6, $J_{2,1}$ 7.2), 3.65 (1H, dd, H1, $J_{1,2}$ 7.2, J_{gem} 11.4), 3.77 (1H, dd, H1', $J_{1',2}$ 6.6, J_{gem} 11.4), 3.98 (1H, dd, H4, $J_{4,3}$ 1.5, $J_{4,5}$ 3.6), 4.24 (1H, dd, H3, $J_{3,4}$ 1.4, $J_{3,2}$ 4.9); δ_C (D_2O, 100 MHz): 13.2 (C6), 55.5 (C5), 60.7, 60.8 (C1, C2), 77.2 (C3), 78.9 (C4); *m/z* (ESI+ve): 148 ($[M + H]^+$, 100%).

2-Azido-*(R)*-3,5-*O*-benzylidene-2,6-dideoxy-D-gulitol 31
Lithium borohydride (2M in THF, 0.74 mL, 1.47 mmol) was added to a solution of lactone **11** (270 mg, 0.98 mmol) in anhydrous THF at -20 °C. The reaction mixture was stirred at -20 °C for 2 h when TLC (ethyl acetate/cyclohexane, 2:1) showed the consumption of starting material (R_f 0.51) and the formation of a new spot (R_f 0.71). After addition of acetic acid (0.4 mL) to the mixture at -20 °C with

stirring, the solvent was removed *in vacuo* to obtain a residue that was re-dissolved in ethyl acetate (20 mL) and washed with water (20 mL). The aqueous layer was back extracted with ethyl acetate (2 x 15 mL). The organic phase was combined, dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield a residue that was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:2 to 2:1) to afford the diol **31** (246 mg, 90%) as a white solid.
HRMS (ESI+ve): Found 302.1112 $[M + Na]^+$; $C_{13}H_{17}N_3O_4Na^+$ requires 302.1113; m.p.: 100 – 102 °C; $[\alpha]_D^{25}$ +19 (*c* 0.69, $CHCl_3$); ν_{max} (thin film): 2102 (s, N_3); δ_H ($CDCl_3$, 400 MHz): 1.40 (3H, d, H6, $J_{6,5}$ 6.4), 3.58 (1H, s, H4), 3.82 (1H, dd, H1, $J_{1,2}$ 4.9, J_{gem} 11.4), 3.85 (1H, d, H3, $J_{3,2}$ 9.1), 3.88 – 3.92 (1H, m, H4), 3.98 (1H, dd, H1', $J_{1',2}$ 3.2, J_{gem} 12.0), 3.90 (1H, ddd, H2, $J_{2,1'}$ 3.1, $J_{2,1}$ 4.2, $J_{2,3}$ 8.5), 4.07 (1H, q, H5, $J_{5,6}$ 6.4), 5.60 (1H, s, H7), 7.37 - 7.48 (5H, m, -Ar); δ_C ($CDCl_3$, 100 MHz): 17.5 (C6), 62.4, 62.5 (C1, C2), 66.2 (C4), 76.9 (C5), 79.1 (C3), 101.5 (C7), 126.2, 128.7, 129.5, 137.6 (-Ar); *m/z* (ESI+ve): 302 ($[M + Na]^+$, 100%).

2-Azido-*(R)*-3,5-*O*-benzylidene-1,4-*bis*-(*O*-*tert*-butyldimethylsilyl)-2,6-dideoxy-D-gulitol 32
tert-Butyldimethylsilyl triflate (0.27 mL, 1.18 mmol) and anhydrous pyridine (0.11 mL, 1.41 mmol) were added to a solution of **31** (130 mg, 0.47 mmol) in anhydrous dichloromethane (6 mL) at 0 °C. The reaction mixture was stirred at rt for 15 h until TLC (ethyl acetate/cyclohexane, 1:9) showed the formation of a major spot (R_f 0.73). Removal of solvent *in vacuo* gave a residue that was dissolved in cyclohexane (20 mL) and washed with water (2 x 15 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent was removed to obtain a residue that was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:9) to afford the silyl ether **32** (200 mg, 84%) as a colorless oil.
HRMS (ESI+ve): found 530.2840 $[M + Na]^+$; $C_{25}H_{45}N_3O_4Si_2Na^+$ requires 530.2841; $[\alpha]_D^{25}$ +6.6 (*c* 0.80, $CHCl_3$); ν_{max} (thin film): 2103 (s, N_3); δ_H (400 MHz, $CDCl_3$): 0.04 (3H, s, CH_3), 0.05 (3H, s, CH_3), 0.14 (3H, s, CH_3), 0.17 (3H, s, CH_3), 0.90 (9H, s, 3 x CH_3), 0.99 (9H, s, 3 x CH_3), 1.30 (3H, d, H6, $J_{6,5}$ 6.4), 3.53 (1H, ddd, H2, $J_{2,1'}$ 2.3, $J_{2,1}$ 4.9, $J_{2,3}$ 10.0), 3.66 (1H, s, H4), 3.76 (1H, d, H3, $J_{3,2}$ 10.0), 3.89 – 3.95 (2H, m, H1, H5), 4.01 (1H, dd, H1', $J_{1',2}$ 2.4, J_{gem} 10.7), 5.51 (1H, s, H7), 7.32 - 7.47 (5H, m, -Ar); δ_C (100 MHz, $CDCl_3$): -5.3 (CH_3Si), -5.2 (CH_3Si), -3.6 (CH_3Si), -3.4 (CH_3Si), 18.6 ($\underline{C}(CH_3)_3$), 18.8 ($\underline{C}(CH_3)_3$), 22.3 (C6), 19.0 ($\underline{C}(CH_3)_3$), 26.1 ($C(\underline{C}H_3)_3$), 26.6 ($C(\underline{C}H_3)_3$), 59.9 (C2), 63.2 (C1), 66.7 (C4), 76.9 (C5), 78.1 (C3), 102.1 (C7), 126.9, 128.6, 129.3, 138.8 (-Ar); *m/z* (ESI+ve): 530 ($[M + Na]^+$, 100%).

2-Azido-3-*O*-benzoyl-5-bromo-1,4-*bis*-(*O*-*tert*-butyldimethylsilyl)-2,5,6-trideoxy-L-mannitol 15
N-Bromosuccinimide (55 mg, 0.47 mmol) and barium carbonate (115 mg, 0.59 mmol) were added to a solution of **32** (200 mg, 0.39 mmol) in carbon tetrachloride (6 mL). The reaction mixture was refluxed for 1 h until TLC (ethyl acetate/cyclohexane, 1:19) indicated the disappearance of starting material (R_f 0.70) and the formation of one major product (R_f 0.62). After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (ethyl acetate/hexane, 1:9) to give the *manno*-bromide **15** (173 mg, 76%) as a yellow oil.
HRMS (ESI+ve): found 586.2128, 588.2107 $[M + H]^+$; $C_{25}H_{45}BrN_3O_4Si_2^+$ requires 586.2127, 588.2106; $[\alpha]_D^{25}$ -8.1 (*c* 0.93, $CHCl_3$); ν_{max} (thin film): 2103 (s, N_3), 1730 (s, C=O); δ_H ($CDCl_3$, 400 MHz): -0.01 (3H, s, CH_3), 0.01 (3H, s, CH_3), 0.21 (3H, s, CH_3), 0.22 (3H, s, CH_3), 0.87 (9H, s, 3 x CH_3), 0.98 (9H, s, 3 x CH_3), 1.69 (3H, d, H6, $J_{6,5}$ 6.9), 3.70 – 3.81 (2H, m, H1, H2), 3.86 (1H, dd, H1', $J_{1',2}$ 2.7, J_{gem} 10.4), 4.16 (1H, dq, H5, $J_{5,4}$ 5.7, $J_{5,6}$ 6.7), 4.29 (1H, dd, H4, $J_{4,3}$ 1.7, $J_{4,5}$ 5.7), 5.41 (1H, dd, H3, $J_{3,4}$ 1.7, $J_{3,2}$ 9.2), 7.46 (2H, t, -Ar, *J* 7.6), 7.59 (1H, t, -Ar, *J* 7.5), 8.05 (2H, d, -Ar, *J* 7.3); δ_C ($CDCl_3$, 100 MHz): -5.3 (2 x CH_3Si), -3.9 (CH_3Si), -3.8 (2 x CH_3Si), 18.5 ($\underline{C}(CH_3)_3$), 18.8 ($\underline{C}(CH_3)_3$), 22.3 (C6), 26.1 ($C(\underline{C}H_3)_3$), 26.4 ($C(\underline{C}H_3)_3$), 50.3 (C5), 61.9 (C2), 64.0 (C1), 71.9 (C3), 75.4 (C4), 128.9, 130.0, 130.3, 133.7 (-Ar), 165.7 (C=O); *m/z* (ESI+ve): 586, 588 ($[M + H]^+$, 100%, 98%).

3-*O*-Benzoyl-1,4-*bis*-(*O*-*tert*-butyldimethylsilyl)-2,5-imino-2,5,6-trideoxy-D-gulitol 33
Palladium on charcoal (10 % wt., 40 mg) and sodium acetate (49 mg, 0.60 mmol) was added to a solution of **15** (233 mg, 0.40 mmol) in ethanol (15 mL). The reaction mixture was flushed with nitrogen, argon and hydrogen gas sequentially. Then the reaction mixture was stirred vigorously at rt under hydrogen atmosphere for 5 h until TLC (ethyl acetate/cyclohexane, 1:4) showed the formation of one major product (R_f 0.14). Filtration and evaporation to dryness *in vacuo* gave the crude protected

pyrrolidine **33** (170 mg) which was used for the next step without further purification. A small portion was purified for characterization by flash column chromatography (triethylamine/ethyl acetate/cyclohexane, 0.01:2:1) to produce a pure sample of **33** as a yellow oil.
HRMS (ESI+ve): found 480.2958 $[M + H]^+$; $C_{25}H_{45}BrNO_4Si_2^+$ requires 480.2960; $[\alpha]_D^{25}$ -23 (*c* 0.90, MeOH); ν_{max} (thin film): 1721 (s, C=O); δ_H (CD_3OD, 400 MHz): 0.13 (6H, s, 2 x CH_3), 0.15 (3H, s, CH_3), 0.23 (3H, s, CH_3), 0.93 (9H, s, 3 x CH_3), 0.98 (9H, s, 3 x CH_3), 1.23 (3H, d, H6, $J_{6,5}$ 6.6), 3.25 (1H, dt, H2, $J_{2,3}$ 3.2, $J_{2,1} = J_{2,1'}$ 6.0), 3.31 (1H, dq, H5, $J_{5,4}$ 3.5, $J_{5,6}$ 6.6), 3.85 (1H, dd, H1, $J_{1,2}$ 6.4, J_{gem} 10.1), 3.92 3.85 (1H, dd, H1', $J_{1',2}$ 6.0, J_{gem} 10.1), 4.15 (1H, br-d, H4, $J_{4,5}$ 3.2), 5.19 (1H, br-d, H3, $J_{3,2}$ 2.8), 7.52 (2H, t, -Ar, *J* 7.6), 7.65 (1H, t, -Ar, *J* 7.3), 8.06 (2H, d, -Ar, *J* 7.2); δ_C (CD_3OD, 100 MHz): -4.4 (CH_3Si), -4.3 (CH_3Si), -4.1 (CH_3Si), -3.5 (CH_3Si), 15.0 (C6), 19.9 ($\underline{C}(CH_3)_3$), 20.0 ($\underline{C}(CH_3)_3$), 27.2 ($C(\underline{C}H_3)_3$), 27.3 ($C(\underline{C}H_3)_3$), 59.9 (C5), 65.3 (C2), 67.7 (C1), 80.9 (C4), 84.7 (C3), 130.5, 131.5, 132.0, 135.3 (-Ar), 167.9 (C=O); *m/z* (ESI+ve): 480 ($[M + H]^+$, 100%).

2,5-Imino-2,5,6-trideoxy-D-gulitol [2,5-Imino-1,2,5-trideoxy-D-glucitol] 4
A solution of the protected pyrrolidine **33** (170 mg) in trifluoroacetic acid/water/1,4-dioxane (2:1:1, 4 mL) was stirred at 50 °C for 24 h until mass spectrometry showed the deprotection of the silyl groups ($[M + H]^+$ 252). The solvent was removed and the residue dissolved in sodium hydroxide solution (aq, 2M, 3 mL) and stirred at 50 °C for 24 h until mass spectrometry showed the formation of desired product ($[M + H]^+$ 148). The mixture was neutralized with HCl (2M, aq) and the solvent removed *in vacuo*. The residue was dissolved in ethanol (5 mL) and filtered (glass microfiber) to afford a crude salt that was then loaded with water (~1 mL) onto a short column of DOWEX® 50WX8-200 resin. The ion exchange column was then washed with water, 1,4-dioxane and then water; the pure product was then eluted with aqueous ammonia (2 M). Removal of solvent *in vacuo* gave a residue which was subjected to a further purification by ion exchange column chromatography to yield the *gulo*-pyrrolidine **4** (30 mg, 51% 3 steps from **15**) as a light yellow gum.
HRMS (ESI+ve): found 148.0968 $[M + H]^+$; $C_6H_{14}N_3O_3^+$ requires 148.0968; $[\alpha]_D^{25}$ -8.9 (*c* 0.57, water) [lit.[36] for **4L** the enantiomer of **4**: $[\alpha]_D^{24}$ +17 (*c* 0.50, water)]; ν_{max} (thin film): 3290 (br, NH, OH); δ_H (D_2O, 400 MHz): 1.21 (3H, d, H6, $J_{6,5}$ 6.7), 3.13 (1H, ddd, H2, $J_{2,3}$ 4.4, $J_{2,1'}$ 4.9, $J_{2,1}$ 6.7), 3.45 (1H, dq, H5, $J_{5,4}$ 4.3, $J_{5,6}$ 6.7), 3.71 (1H, dd, H1, $J_{1,2}$ 7.0, J_{gem} 11.8), 3.80 (1H, dd, H1', $J_{1',2}$ 4.9, J_{gem} 11.8), 3.93 (1H, dd, H3, $J_{3,4}$ 1.8, $J_{3,2}$ 4.4), 3.99 (1H, dd, H4, $J_{4,3}$ 1.8, $J_{4,5}$ 4.3); δ_C (D_2O, 100 MHz): 12.6 (C6), 57.1 (C5), 61.9 (C1), 66.7 (C2), 78.9 (C3), 79.4 (C4); *m/z* (ESI+ve): 148 ($[M + H]^+$, 100%).

5.5 Benzoyl protection: NGP in the Hanessian-Hullar reaction

2-Azido-*(R)*-3,5-*O*-benzylidene-1,4-di-*O*-benzoyl-2,6-dideoxy-L-glucitol 36
Benzoyl chloride (0.24 mL, 2.2 mmol) and pyridine (0.24 mL, 2.8 mmol) were added to a solution of the diol **22** (200 mg, 0.72 mmol) in anhydrous dichloromethane (7 mL). The reaction mixture was stirred at rt for 16 h until TLC (ethyl acetate/cyclohexane, 1:4) showed the formation of one major product (R_f 0.41). The solvent was removed *in vacuo* and the residue purified by flash column chromatography (ethyl acetate/cyclohexane, 1:19 to 1:4) to form the dibenzoate **36** (300 mg, 86%) as a clear oil; trituration of the oil with acetonitrile gave a white crystalline solid.
HRMS (ESI+ve): found 510.1634 $[M + Na]^+$; $C_{27}H_{25}N_3O_6Na^+$ requires 510.1636; m.p. 111 - 114 °C; $[\alpha]_D^{25}$ -29.6 (*c* 1.0, MeCN); ν_{max} (thin film): 1716 (s, C=O), 2104 (s, N_3); δ_H (CD_3CN, 400 MHz): 1.58 (3H, d, H6, $J_{6,5}$ 7.2), 4.14 - 4.21 (1H, m, H2), 4.35 (1H, dd, H1, $J_{1,2}$ 5.8, J_{gem} 12.1), 4.46 (1H, br-q, H5, $J_{5,6}$ 7.2), 4.50 (1H, dd, H1', $J_{1',2}$ 3.3, J_{gem} 12.1), 4.68 (1H, dd, H3, $J_{3,4}$ 1.4, $J_{3,2}$ 7.9), 5.02 (1H, br-s, H4), 6.11 (1H, s, H7), 7.37 - 7.68 (10H, m, Ar x 2), 7.95 - 8.01 (2H, m, Ar), 8.09 - 8.15 (2H, m, Ar); δ_C (CD_3CN, 100 MHz): 15.4 (C6), 60.8 (C2), 64.0 (C1), 69.8 (C4), 73.8 (C5), 74.5 (C3), 95.1 (C7), 127.3, 129.2, 129.6, 129.7, 129.9, 130.4, 130.6, 130.9, 134.4, 134.5, 139.5 (-Ar), 166.7 (C=O), 166.8 (C=O); *m/z* (ESI+ve): 510 ($[M + Na]^+$, 100%).

2-Azido-5-bromo-1,3,4-tri-*O*-benzoyl-2,5,6-trideoxy-D-iditol 39 and **2-Azido-5-bromo-1,3,4-tri-*O*-benzoyl-2,5,6-trideoxy-L-glucitol 40**
N-Bromosuccinimide (116 mg, 0.65 mmol) and barium carbonate (160 mg, 0.81 mmol) were added to a solution of **36A/B** (265 mg, 0.54 mmol) in carbon tetrachloride (3.5 mL). The stirred reaction mixture was refluxed for 1 h until TLC (ethyl acetate/cyclohexane, 1:4) indicated the disappearance of starting

material (R_f 0.39) and the formation of two products (R_f 0.45, 0.5). After removal of the solvent, the residue was purified by flash column chromatography (ethyl acetate/hexane, 0:10 to 1:4) to give a mixture of the inseparable epimeric bromides **39** and **40** (5:1, 280 mg, 91%) as a light yellow syrup.
39: δ_H (CD_3CN, 400 MHz): 1.76 (3H, d, H6, $J_{6,5}$ 6.8), 4.29 (1H, ddd, H2, $J_{2,3}$ 3.0, $J_{2,1'}$ 5.2, $J_{2,1}$ 6.6), 4.35 (1H, dd, H1, $J_{1,2}$ 6.6, J_{gem} 11.4), 4.63 - 4.71 (2H, m, H1', H5,), 5.72 (1H, dd, H4, $J_{4,5}$ 3.1, $J_{4,3}$ 7.3), 5.95 (1H, dd, H3, $J_{3,2}$ 3.1, $J_{3,4}$ 7.3), 7.39 - 7.72 (15H, m, -Ar x 3), δ_C (CD_3CN, 100 MHz): 24.8 (C6), 50.4 (C5), 60.9 (C2), 66.0 (C1), 75.4 (C3), 76.5 (C4), 130.9 – 136.1 (-Ar x 3), 167.7 (C=O), 167.8 (C=O), 167.9 (C=O);
40: δ_H (CD_3CN, 400 MHz): 1.79 (3H, d, H6, $J_{6,5}$ 6.7), 4.20 (1H, dt, H2, $J_{2,3} = J_{2,1'}$ 4.2, $J_{2,1}$ 6.2), 4.54 - 4.71 (3H, m, H1, H1', H5,), 5.89 (1H, t, H4, $J_{4,5} = J_{4,3}$ 5.4), 5.98 (1H, dd, H3, $J_{3,2}$ 4.5, $J_{3,4}$ 5.4), 7.39 - 7.72 (15H, m, -Ar x 3), δ_C (CD_3CN, 100 MHz): 22.9 (C6), 48.1 (C5), 62.3 (C2), 66.3 (C1), 73.4 (C3), 77.4 (C4), 131.1 – 136.4 (-Ar x 3);

1,3,4-Tri-*O*-benzoyl-2,5-imino-2,5,6-trideoxy-L-glucitol 41 and **1,3,4-Tri-*O*-benzoyl-2,5-imino-2,5,6-trideoxy-D-iditol 42**
Palladium on charcoal (10 % wt., 30 mg) and sodium acetate (49 mg, 0.6 mmol) were added to a solution of the mixture of **39** and **40** (260 mg, 0.46 mmol) in ethanol (15 mL). The reaction mixture was flushed sequentially with nitrogen, argon and hydrogen and then stirred overnight at rt under a hydrogen atmosphere for 12 h when TLC (ethyl acetate/cyclohexane, 1:1) showed the formation of two products (R_f 0.14, 0.17). The solvent was removed and the residue purified by flash column chromatography (triethylamine/ethyl acetate/cyclohexane, 0.01:1:5 to 0.01:2:1) to afford a mixture of 5-epimers **41** and **42** (4:1, 173 mg, 82%) as a white solid. The mixture was not clean enough for assignment of the tribenzoates by NMR; this crude product was directly used in the deprotection step.

2,5-Imino-2,5,6-trideoxy-L-glucitol 1 and **2,5-Imino-2,5,6-trideoxy-D-iditol 3**
The mixture of **41** and **42** (100 mg, 0.22 mmol) was dissolved in sodium hydroxide (aq, 2M, 10 mL) and stirred at 50 °C for 48 h until mass spectrometry showed the formation of desired product ($[M+H]^+$ 148). The solvent was removed *in vacuo*; the residue was dissolved in ethanol (5 mL) and passed through glass fiber to afford a crude salt that was then loaded with water (~1 mL) onto a short column of DOWEX® 50WX8-200 resin. The ion exchange column was then washed with water, 1,4-dioxane and then water; the pure product was then eluted with aqueous ammonia (2 M). Removal of solvent *in vacuo* gave a mixture of the unprotected pyrrolidines **1** and **3** as a yellow oil (5 :1 according to ^1H spectrum, 23 mg, 73%).

2-Azido-*(R)*-3,5-*O*-benzylidene-1,4-di-*O*-benzoyl-2,6-dideoxy-L-mannitol 26
Benzoyl chloride (0.12 mL, 1.1 mmol) and pyridine (0.12 mL, 1.4 mmol) were added into a solution of diol **25** (100 mg, 0.36 mmol) in anhydrous dichloromethane (7 mL). The mixture was stirred at rt for 18 h until TLC (ethyl acetate/cyclohexane, 1:4) showed the formation of one major product (R_f 0.42). The solvent was *in vacuo* and the residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:8 to 1:4) to afford the dibenzoate **26** (196 mg, 97%) as a white solid.
HRMS (ESI+ve): found 510.1633 $[M + Na]^+$; $C_{27}H_{25}N_3O_6Na^+$ requires 510.1636; m.p. 79 - 85 °C; $[\alpha]_D^{25}$ +37.9 (*c* 1.0, MeCN); ν_{max} (thin film): 2103 (s, N_3), 1719 (s, C=O); δ_H (CD_3CN, 400 MHz): 1.59 (3H, d, H6, $J_{6,5}$ 7.2), 4.23 (1H, ddd, H2, $J_{2,1'}$ 2.7, $J_{2,1}$ 7.4, $J_{2,3}$ 9.7), 4.43 (1H, dd, H3, $J_{3,4}$ 1.5, $J_{3,2}$ 9.7), 4.50 (1H, dd, H1, $J_{1,2}$ 7.4, J_{gem} 11.7), 4.51 (1H, dq, H5, $J_{5,4}$ 1.5, $J_{5,6}$ 7.2), 4.80 (1H, dd, H1', $J_{1',2}$ 2.7, J_{gem} 11.7), 5.05 (1H, t, H4, $J_{4,3} = J_{4,5}$ 1.5), 6.01 (1H, s, H7), 7.34 - 7.69 (10H, m, -Ar x 2), 8.02 - 8.18 (4H, m, -Ar); δ_C (CD_3CN, 100 MHz): 15.4 (C6), 60.7 (C2), 65.2 (C1), 69.3 (C4), 72.8 (C3), 73.7 (C5), 94.7 (C7), 127.2, 129.2, 129.6, 129.7, 129.9, 130.47, 130.52, 130.7, 130.9, 134.3, 134.5, 139.4 (-Ar x 2), 166.6, 166.8 (C=O); *m/z* (ESI+ve): 510 ($[M + Na]^+$, 100%).

2-Azido-1,3,4-tri-*O*-benzoyl-5-bromo-2,5,6-trideoxy-D-gulitol 43 and **2-Azido-1,3,4-tri-*O*-benzoyl-5-bromo-2,5,6-trideoxy-L-mannitol 44**
N-Bromosuccinimide (156 mg, 0.88 mmol) and barium carbonate (217 mg, 1.1 mmol) were added into a solution of **26** (357 mg, 0.73 mmol) in carbon tetrachloride (5.0 mL). The mixture was refluxed with stirring for 1 h until mass spectrometry indicated the completion of reaction ($[M + Na]^+$ 588, 590) The solvent was removed *in vacuo* and the residue purified by flash column chromatography (ethyl

acetate/hexane, 1:9 to 3:7) to give a mixture of the bromide epimers **43** and **44** (4:1, 388 mg, 94%) as a colorless oil. Separation of the epimers **43** and **44** by flash column chromatography was not efficient. HRMS (ESI+ve): found 588.0740, 590.0719; $C_{27}H_{24}BrN_3O_6Na^+$ requires 588.0741, 590.0720; ν_{max} (thin film): 2108 (s, N_3), 1722 (s, C=O); *m/z* (ESI+ve): 588, 590 ($[M + Na]^+$, 100%, 95%)
43: δ_H (CD_3CN, 400 MHz): 1.76 (3H, d, H6, $J_{6,5}$ 6.8), 4.31 (1H, dt, H2, $J_{2,1'}$ 3.7, $J_{2,1} = J_{2,3}$ 6.7), 4.46 (1H, dd, H1, $J_{2,1}$ 6.7, J_{gem} 12.0), 4.55 - 4.63 (1H, m, H5), 4.70 (1H, dd, H1', $J_{1',2}$ 3.7, J_{gem} 12.0), 5.72 (1H, t, H4, $J_{4,3} = J_{4,5}$ 5.0), 5.78 (1H, dd, H3, $J_{4,3}$ 5.0, $J_{3,2}$ 6.7), 7.41 - 7.71 (9H, m, -Ar), 7.95 - 7.17 (6H, m, -Ar); δ_C (CD_3CN, 100 MHz): 23.1 (C6), 49.4 (C5), 61.0 (C2), 64.3 (C1), 72.4 (C3), 75.1 (C4), 129.6-130.8, 134.5, 134.7, 134.8 (-Ar), 166.1 (C=O), 166.4 (C=O), 166.7 (C=O).
44: δ_H (CD_3CN, 400 MHz): 1.72 (3H, d, H6, $J_{6,5}$ 6.7), 4.25 (1H, ddd, H2, $J_{2,1'}$ 3.7, $J_{2,1}$ 6.7, $J_{2,3}$ 7.8), 4.42 (1H, dd, H1, $J_{1,2}$ 6.7, J_{gem} 11.9), 4.41 - 4.49 (1H, m, H5), 4.63 (1H, dd, H1', $J_{2,1'}$ 3.7, J_{gem} 11.9), 5.82 (1H, dd, H4, $J_{3,4}$ 2.7, $J_{4,5}$ 7.7), 5.87 (1H, dd, H3), 7.41 - 7.71 (9H, m, -Ar), 7.95 - 7.17 (6H, m, -Ar); δ_C (CD_3CN, 100 MHz): 22.1 (C6), 46.8 (C5), 61.1 (C2), 64.4 (C1), 71.2 (C3), 75.5 (C4), 129.6 - 130.8, 134.4, 134.87, 134.92 (-Ar), 166.1 (C=O), 166.4 (C=O), 166.6 (C=O).

1,3,4-Tri-*O*-benzoyl-2,5-imino-2,5,6-trideoxy-L-mannitol 45 and **1,3,4-Tri-*O*-benzoyl-2,5-imino-2,5,6-trideoxy-D-gulitol 46**
Palladium on charcoal (10 % wt., 73 mg) and sodium acetate (84 mg, 0.6 mmol) were added to a solution of **43** and **44** (388 mg, 0.69 mmol) in ethanol (15 mL). The reaction mixture was flushed sequentially with nitrogen, argon and hydrogen, stirred at rt under hydrogen atmosphere for 16 h until TLC (ethyl acetate/cyclohexane, 3:7) showed the formation of two products (R_f 0.12, 0.14). The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (triethylamine/ethyl acetate/ petroleum ether, 0.01:1:8 to 0.01:2:1) to obtain a mixture of 5-epimers **45** and **46** (10:7, 280 mg, 89%) as a yellow oil. Attempted separation of **45** and **46** by flash column chromatography was not successful.
45: δ_H (CD_3CN, 400 MHz): 1.34 (3H, d, H6, $J_{6,5}$ 6.6), 3.57 (1H, br-dq, H5, $J_{5,4}$ 4.2, $J_{5,6}$ 6.6), 3.82 (1H, dt, H2, $J_{2,3}$ 4.2, $J_{2,1} = J_{2,1'}$ 5.6), 4.50 (1H, dd, H1, $J_{1,2}$ 5.6, J_{gem} 10.9), 4.53 - 4.60 (1H, m, H1'), 5.72 (1H, dd, H4, $J_{4,3}$ 3.7, $J_{4,5}$ 4.2), 5.58 (1H, dd, H3, $J_{3,4}$ 3.7, $J_{3,2}$ 4.1), 7.34 – 7.78 (15H, -Ar x 3); δ_C (CD_3CN, 100 MHz): 20.3 (C6), 60.2 (C5), 63.4 (C2), 67.7 (C1), 83.4 (C3), 86.9 (C4), 120.7 – 135.8 (-Ar x 3), 168.0 (C=O), 168.1 (C=O), 168.4 (C=O).
46: δ_H (CD_3CN, 400 MHz): 1.21 (3H, d, H6, $J_{6,5}$ 6.3), 3.61 – 3.68 (2H, m, H2, H5), 4.45 – 4.60 (2H, m, H1, H1'), 5.42 (1H, dd, H4, *J* 1.9, *J* 4.9), 4.48 (1H, dd, H3, *J* 1.9, *J* 4.5), 7.34 – 8.08 (15H, m, -Ar x 3); δ_C (CD_3CN, 100 MHz): 16.0 (C6), 58.6 (C5), 64.8 (C2), 67.6 (C1), 82.8 (C3), 83.3 (C4), 120.7 – 135.8 (-Ar x 3), 167.8 (C=O), 167.9 (C=O), 168.3 (C=O).

2,5-Imino-2,5,6-trideoxy-L-mannitol 2 and **2,5-Imino-2,5,6-trideoxy-D-gulitol 4**
The epimeric mixture of the tribenzoates **45** and **46** (200 mg, 0.44 mmol) was dissolved into sodium hydroxide solution (aq., 2 M, 15 mL) and stirred at 50 °C for 48 h until mass spectrometry showed the formation of desired product ($[M + H]^+$ 148). The solvent was removed *in vacuo*, the residue was dissolved in ethanol (5 mL) and filtered (glass fiber) to afford a crude salt that was then loaded with water (~1 mL) onto a short column of DOWEX® 50WX8-200 resin. The ion exchange column was then washed with water, 1,4-dioxane and then water; the pure product was then eluted with aqueous ammonia (2 M). Removal of solvent *in vacuo* yielded a mixture of **2** and **4** as a yellow oil (5:3 according to ^1H spectrum, 46 mg, 70%).

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7. Conflict of interest

None of the authors have any conflict of interest arising from this work.

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