Regioselective intramolecular ring closure of 2-amino-6-bromo-2,6-dideoxyhexono-1,4-lactones to 5- or 6-membered iminuronic acid analogues: synthesis of 1-deoxymannojirimycin and 2,5-dideoxy-2,5-imino-D-glucitol

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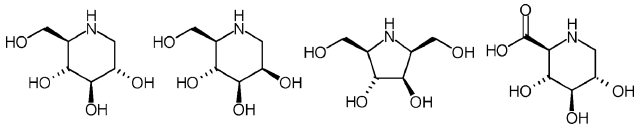
1-Deoxymannojirimycin (**8c**) was synthesised from 2-amino-6-bromo-2,6-dideoxy-D-mannono-1,4-lactone (**7**) by intramolecular direct displacement of the C-6 bromine employing non-aqueous base treatment followed by reduction of the intermediate methyl ester. Likewise, using aqueous base at pH 12, ring closure took place by 5-*exo* attack on the 5,6-epoxide leading to 2,5-dideoxy-2,5-imino-L-gulonic acid (**9b**), which was reduced to 2,5-dideoxy-2,5-imino-D-glucitol (**9c**). The method was further applied to 2-amino-6-bromo-2,6-dideoxy-D-*galacto*- as well as D-*talo*-1,4-lactones (**14** and **15**). However, only the corresponding six-membered ring 1,5-iminuronic acid mimetics, namely (2*R*,3*R*,4*S*,5*R*)-3,4,5-trihydroxypipecolic acid (2,6-dideoxy-2,6-imino-D-galactonic acid, **16**) and (2*S*,3*R*,4*S*,5*R*)-3,4,5-trihydroxypipecolic acid (2,6-dideoxy-2,6-imino-D-talonic acid, **17**), were obtained. The corresponding enantiomers, L-*galacto*- as well as L-*talo*-2-amino-6-bromo-2,6-dideoxy-1,4-lactones *ent*-**14** and *ent*-**15**, reacted accordingly to give the D-*galacto*- and L-*altro*-1,5-iminuronic acid mimetics, (2*S*,3*S*,4*R*,5*S*)-3,4,5-trihydroxypipecolic acid (2,6-dideoxy-2,6-imino-L-galactonic acid, *ent*-**16**) and (2*R*,3*S*,4*R*,5*S*)-3,4,5-trihydroxypipecolic acids (2,6-dideoxy-2,6-imino-L-talonic acid, *ent*-**17**), respectively.

Introduction

Iminoalditols, such as **1**, **2** and **3** (Fig. 1), are sugar analogues featuring a basic nitrogen instead of the oxygen in the endocyclic position. Such compounds have gained immense importance[1] due to the fact that they have been found to inhibit glycosidases and other carbohydrate-processing enzymes. Consequently, they are of great interest for a number of quite different applications, which include mechanistic investigations[2] of this class of enzyme as well as medical purposes. Today their anti-viral, anti-cancer and anti-diabetes properties are well known, and emphasis has moved towards their use as analytical tools and diagnostics as well as pharmaceutical drug candidates.[3] A few compounds are available on the market,[4] while others are undergoing clinical trials against various diseases.[5] In order to further elucidate their potential regarding such applications, there is the need for short, efficient and reliable synthetic methods that allow the production of sufficient amounts for study.

Iminosugars having a carboxyl group as side chain at C-2 can be considered mimetics of uronic acids, thereby possessing potential as glycuronidase inhibitors. The glucuronic acid analogue, (2*S*,3*R*,4*R*,5*S*)-3,4,5-trihydroxypipecolic acid (2,6-dideoxy-2,6-imino-L-gulonic acid, **4**), isolated from seeds of *Baphia racemosa*[6] and leaves of *Baphiopsis parviflora*[7] and synthesised by several groups,[8] has been shown to inhibit[9] human liver β-D-glucuronidase and α-L-iduronidase and to have anti-HIV[10] as well as anti-metastatic properties.[11] The corresponding mannuronic acid mimic, (2*S*,3*R*,4*R*,5*R*)-3,4,5-trihydroxypipecolic acid (2,6-dideoxy-2,6-imino-D-mannonic acid, **8b**) was synthesised by Fleet and co-workers[8g,12] from D-glucose in 11 steps and 33% yield, as well as by Lee who started from D-glucono-δ-lactone.[13] This iminoacid has not been isolated from Nature and no biological activity has been assigned to this compound in the literature thus far. Likewise, the D-*galacto* iminoacid analogue *ent*-**16**, (2*S*,3*S*,4*R*,5*S*)-3,4,5-trihydroxypipecolic acid (2,6-dideoxy-2,6-imino-L-galactonic acid), was synthesised by Ganem and co-workers[14] by chemoselective oxidation at C-6 of the corresponding D-*galacto*-configured iminoalditol. Additionally, a *de novo* approach[15] to *ent*-**16** starting from building blocks derived from glycine, D-valine and L-tartaric acid was introduced. Furthermore, the synthesis of non-natural (2*R*,3*R*,4*R*,5*R*)-3,4,5-trihydroxypipecolic acid with an L-*ido* configuration is known in the literature.[8h,16] The synthesis of a five-membered ring species, a polyhydroxylated pyrrolidine iminoacid derivative with the D-*allo* configuration, has been reported by Davies and co-workers.[17]



1 **2** **3** **4**

Fig. 1

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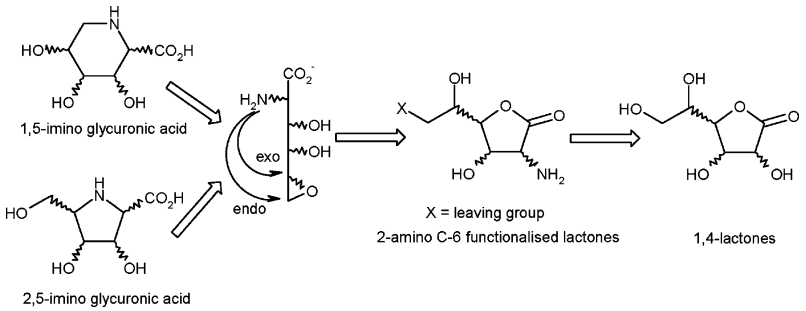


Scheme 1 Retrosynthetic strategy towards iminuronic acid derivatives by regioselective intramolecular ring closure reactions.

In connection with our work exploiting aldonolactones as starting materials *en route* to various iminoalditols, we turned our interest to investigating the options of synthesising six-membered imino-2-carboxylic acids, which additionally allow for access to the corresponding iminoalditols by simple reduction of the carboxylic acid function.

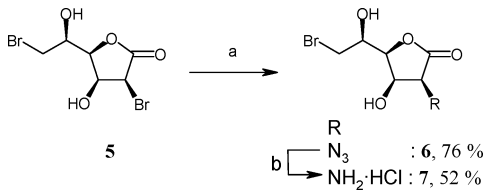
Previously, the synthesis of 1,4-dideoxy-1,4-iminohexitols was accomplished from 2,6-dibromohexonolactones by treatment with ammonia.[18] The favoured product was formed by an intramolecular 5-*exo* opening at C-3 by attack of the primary C-6 amino group on the intermediary 2,3-epoxide. This way, the nitrogen was introduced exclusively at C-3, affording the 3,6-cyclised products in high stereoselectivities.

In order to synthesise 2,6- or 2,5-iminoacids along with the corresponding iminoalditols, we investigated the regioselective ring closure of 2-amino-6-bromo-2,6-dideoxy-1,4-lactones (Scheme 1).[19] The retrosynthetic strategy was based on regioselective introduction of a nitrogen function at C-2 in the readily available 1,4-aldonolactones. It was clear that we could start from 2,6-dibromo-2,6-dideoxyhexonolactones (available from aldonolactones by treatment with HBr-HOAc), following the discovery of a regiospecific introduction of an azide at C-2, avoiding substitution of the primary bromine.[20] This gave access to 2-amino-6-bromo-2,6-dideoxy-1,4-lactones as a suitable starting material. From our experience with the reaction of bromolactones with base,[21] we expected rapid formation of the terminal oxirane, which could either migrate (Payne rearrangement) or be opened by an intramolecular nucleophile. In compounds having a 2-amino group, the epoxide might be opened at C-5 by the amino group by a 5-*exo* opening according to Baldwin's rules or at the primary C-6 (6-*endo* attack) by a direct displacement reaction, depending on the reaction conditions employed.

This concept was used for the 2-amino-6-bromo-2,6-dideoxy-D-1,4-mannonolactone (**7**), with the aim of extending it to other lactones for the stereoselective synthesis of specific molecules such as the interesting 2,6-dideoxy-2,6-imino-L-galactonic acid (*ent*-**16**), a mimic of the pectin monomer D-galacturonic acid.

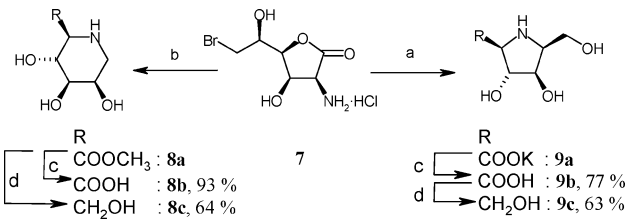
Results and discussion

2-Azido-6-bromo-2,6-dideoxy-D-mannono-1,4-lactone (**6**) was prepared from easily accessible 2,6-dibromo-2,6-dideoxy-D-mannono-1,4-lactone (**5**, 40% in one step from D-glucono-δ-lactone)[22] with retention of configuration at C-2.[20] Catalytic hydrogenation in the presence of hydrochloric acid gave the 2-amine hydrochloride **7**, which could be obtained crystalline (52%) (Scheme 2).



Scheme 2 *Reagents and conditions*: a) NaN_3, acetone, reflux;[20] b) H_2 (1 atm, rt), Pd/C, MeOH, H^+.

Treatment of **7** with strong aqueous base (5 eq. of KOH, pH 12) resulted in regioselective ring closure at C-5. The reaction proceeds *via* the 2-amino-5,6-epoxide, by an intramolecular nucleophilic *exo*-opening according to Baldwin's rules[23] to give the pyrrolidine ring **9a**, which was obtained as the corresponding potassium salt as the only product according to ^{13}C NMR spectroscopy. Purification by ion-exchange chromatography gave the crystalline 2,5-dideoxy-2,5-imino-L-gulonic acid (**9b**) in 77% yield. Formation of the pyrrolidine product was in agreement with previous results, where the five-membered ring was favoured over the six-membered ring.[18] Reduction of the corresponding carboxylic ethyl ester to the primary alcohol employing sodium borohydride in ethanol gave the known glucosidase inhibitor 2,5-dideoxy-2,5-imino-D-glucitol **9c**[24,25] in 63% yield (Scheme 3). This method allows one to obtain **9c** in gram amounts from dibromomannonolactone **5** using inexpensive reagents without the need for protecting group manipulations.



Scheme 3 *Reagents and conditions*: a) 5 eq. KOH, H_2O, 0 °C; b) 3 eq. Et_3N, MeOH, 0 °C; c) Amberlite IR-120 H^+, aq. NH_3; d) $NaBH_4$, EtOH, 0 °C.

In order to form the piperidine product **8b** regioselectively, it was necessary to avoid formation of the 5,6-epoxide. This was achieved by keeping the pH value below 8 by addition of $Ba(OH)_2$ in H_2O. Under these conditions direct substitution of the C-6

bromide by the C-2 amine can take place. However, the reaction was difficult: in order to maintain the pH value below 8 during the whole reaction, addition of the base had to be slow and in small portions, requiring three days for the completion of the reaction. Even minor deviations from the procedure resulted in formation of the pyrrolidine product **9b**. The piperidine/pyrrolidine products were obtained in a ratio of 7 : 1 as evident from ^{13}C NMR data. Changing the base to KOH and slow addition, keeping the pH at 8, favoured the piperidine in a ratio of 6 : 1, with no significant difference between the two bases. The product formation turned out to be solely dependent on the pH, and to achieve full conversion it was difficult to eliminate formation of the pyrrolidine as minor side product.

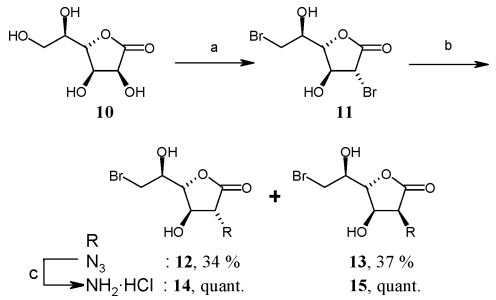
Therefore, a new method using a non-aqueous base was applied: addition of three equivalents of Et_3N to a solution of the aminolactone **7** in MeOH at 0 °C afforded the 2,6-dideoxy-2,6-imino-D-mannonic acid methyl ester (**8a**) as the only product according to ^{13}C NMR spectroscopy (Scheme 3). Purification of the ester by acidic ion exchange chromatography gave the 2,6-dideoxy-2,6-imino-D-mannonic acid (**8b**) in 93% yield, the methyl ester being quantitatively hydrolysed under the acidic conditions of the column. The NMR data were in accordance with those reported.[12] When sodium methoxide was added to the crude methyl ester, triethylamine was liberated and could be evaporated off. This left pure **8a** (as seen by ^{13}C NMR), contaminated only with sodium chloride and sodium bromide. The product was used directly for reduction to 1-deoxymannojirimycin **8c**, which was isolated in 64% yield; no protecting group manipulations were needed during this synthetic approach.

Next we wanted to apply the concept of basic regioselective ring closure to other configurations, such as 2-amino-6-bromo-2,6-dideoxy-D-galactono- as well as -D-talono-1,4-lactones (**14** and **15**), easily available from 2,6-dibromo-2,6-dideoxy-D-galactono-1,4-lactone (**11**), in order to obtain the 1,5-iminuronic acid analogues **16** and **17b** with L-*galacto*- and D-*altro* configuration, as well as the five-membered 2,5-iminuronic acid mimetics **18** and **19** with the L-*talo* and D-*allo* configurations. Treatment of D-talonolactone (**10**)[26] (obtained in quantitative yield by oxidation of D-talose with Br_2) with HBr in acetic acid by standard procedures gave 2,6-dibromo-2,6-dideoxy-D-galactono-1,4-lactone (**11**, 72% in two steps from D-talose).[26] Regioselective introduction of the azido group at C-2 was performed by treatment of **11** with NaN_3 in refluxing acetone. The obtained product was an equilibrium mixture of the C-2 epimers **12** and **13** (1.1 : 1), due to epimerisation at C-2 in aldonolactones in the presence of base.[19] The product mixture differs from the results obtained for the D-*gluco*- and D-*manno*-isomers, which in both cases gave the D-*manno*-configured 2-azidolactone only.[19]

The azidolactones **12** and **13** were easy to separate by crystallisation of the D-*talo* lactone (**13**) from the mixture. Pure D-*galacto* lactone **12** was obtained by column chromatography of the mother liquor. The azidolactones **12** and **13** were thus obtained in 34% and 37% yield, respectively (Scheme 4).[27]

The azidolactones **12** and **13** were reduced to the aminolactones **14** and **15**, respectively, by catalytic hydrogenation in MeOH and aqueous hydrochloric acid in quantitative yield.

The 2-amino-2-deoxy-D-galactonolactone **14** was subjected to strong aqueous base to investigate the favoured products. The reaction was regioselective, giving the six-membered ring as the only

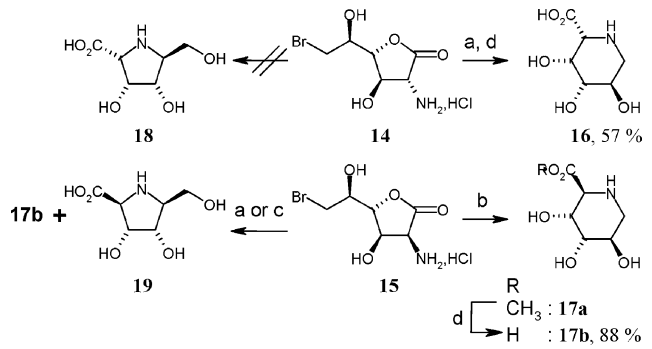


Scheme 4 *Reagents and conditions*: a) HBr, AcOH, rt;[26] b) NaN_3, acetone, reflux; c) H_2, Pd/C, MeOH, HCl.

product. Reaction of 2-amino-6-bromo-2,6-dideoxy-D-galactono-1,4-lactone (**14**) with 5 eq. of KOH in H_2O at 0 °C afforded the potassium salt of **16** within 5 min. The product 2,6-dideoxy-2,6-imino-D-galactonic acid (**16**) was purified by acidic ion-exchange chromatography and crystallised as colourless crystals in 57% yield. Formation of the six-membered ring in strong aqueous base limits formation of the five-membered ring **18** by this simple method; thus no further efforts have been made to synthesise the pyrrolidine 2,5-dideoxy-2,5-imino-L-altronic acid (**18**).

Similar reaction conditions applied to 2-amino-6-bromo-2,6-dideoxy-D-talono-1,4-lactone (**15**) gave a mixture of the piperidine and the pyrrolidine in the ratio 1 : 1. The reaction was complete within 5 minutes and it was impossible to detect any intermediate epoxide by ^{13}C NMR spectroscopy. In an attempt to synthesise the five-membered ring 2,5-dideoxy-2,5-imino-L-allonic acid (**19**) exclusively, various basic conditions were tried in order to control the epoxide formation. Despite all efforts (*viz.* using KOH, allowing the pH to rise from 8 to 12 over time, or employing liquid NH_3 as base), mixtures of the piperidine and the pyrrolidine were obtained. In our hands, it turned out to be impossible to achieve good selectivity for one of the three modes of ring formation: 5-*exo*, 6-*endo* or direct substitution at C-6 in the different experiments.

Consequently, we decided to synthesise the six-membered ring exclusively. Treatment of **15** with Et_3N in MeOH at 0 °C resulted in regioselective formation of the corresponding methyl ester of 2,6-dideoxy-2,6-imino-D-talonic acid **17a**. The crude product was purified by ion-exchange chromatography to remove the halide salts of triethylamine and crystallised to give (2*S*,3*R*,4*S*,5*R*)-3,4,5-trihydroxypipecolic acids (**17b**) in 88% overall yield from **13** (Scheme 5).



Scheme 5 *Reagents and conditions*: a) 5 eq. KOH, H_2O, 0 °C; b) 3 eq. Et_3N, MeOH, 0 °C; c) 25% NH_3, rt; d) Amberlite IR-120 H^+, aq. NH_3.

We concluded that steric crowding of 2,3,4-*cis*-arranged substituents in the D-*galacto* open-chain transition state (**21**) for a 5-*exo* opening of the primary epoxide ring closure is much less favourable than for the corresponding reaction in the D-*manno* series (**20**), which has a 2,3,4-all-*trans* substituent pattern (Fig. 2). Such unfavourable interactions in five-membered ring systems were first described by Angyal and co-workers, who postulated that substantial interaction of vicinal *cis* substituents in furanoses cause disadvantageous dipolar interactions.[28] Therefore, in the transition state **21**, such unfavourable interactions could be considered to be responsible for the 2,6-*endo* attack upon the six-membered 1,5-iminuronic acid analogues **16**. For the D-*talo* open-chain transition state of substrate **15**, the substituents at positions 2, 3 and 4 show a *trans*-*cis* pattern, which might allow for a 5-*exo* opening, but due to one unfavourable *cis* orientation no selectivity could be achieved for formation of the corresponding pyrrolidine iminoacid derivative. The relative substituent pattern might be a means of predicting the outcome of such ring closure reactions.

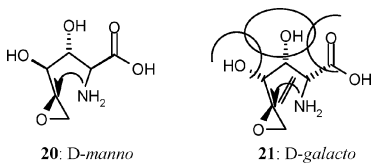
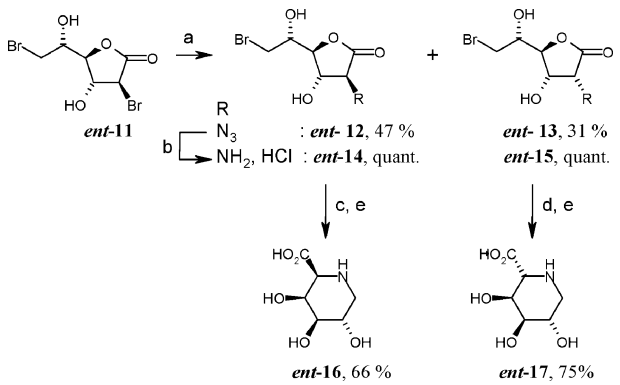


Fig. 2 Steric crowding in the transition state of 2,3,4-*cis*-arranged substituents in D-*galacto* compound **21** compared to the 2,3,4-all-*trans*-D-*manno* compound **20**.

Finally, the commercially available L-galactono-1,4-lactone[18] was isomerised at C-2 and brominated with HBr in acetic acid; the azido group was then introduced at C-2, and subsequently reduced to the corresponding C-2 amine, in order to obtain *ent*-**14** and *ent*-**15**, which were obtained in yields of 47% and 31% respectively from *ent*-**11** (obtained in 55% in two steps from L-talono-1,4-lactone). These chiral starting materials resulted, after regioselective intramolecular ring closure, in the enantiomeric products (2*S*,3*S*,4*R*,5*S*)-3,4,5-trihydroxypipecolic acid (2,6-dideoxy-2,6-imino-L-galactonic acid, *ent*-**16**, 66%) and (2*R*,3*S*,4*R*,5*S*)-3,4,5-trihydroxypipecolic acid (2,6-dideoxy-2,6-imino-L-talonic acid, *ent*-**17**, 75%), respectively (Scheme 6).



Scheme 6 *Reagents and conditions*: a) NaN_3, acetone, reflux; b) H_2 (1 atm), rt, Pd/C, MeOH, H^+; c) 5 eq. KOH, H_2O, 0 °C; d) 3 eq. Et_3N, MeOH, 0 °C → rt; e) Amberlite IR-120 H^+, aq. NH_3.

Conclusions

The syntheses of the 1,5-dideoxy-1,5-iminuronic acid mimetics with D-*altro*, L-*altro*, D-*galacto*, L-*galacto* and D-*manno* configurations and the regioselective synthesis of 2,5-dideoxy-2,5-imino-L-gulonic acid from dibromoaldonolactones is reported. The dibromohexonolactones were shown to be valuable precursors for obtaining the iminoacid derivatives in only three steps without any need for protecting groups.

The favoured mode of the ring closure reaction using strong aqueous base was shown to be dependent on the relative configuration of the respective 2-amino-6-bromo-2,6-dideoxy-1,4-lactone. An all-*trans* pattern of the C-2,3,4 substituents, as in lactone **7**, gave the five-membered ring structure 2,5-dideoxy-2,5-imino-L-gulonic acid (**9b**), in contrast to the lactone **14**, which afforded the six-membered ring iminoacid with an all-*cis* orientation of the C-2,3,4 substituents. 2-Amino-6-bromo-2,6-dideoxy-1,4-lactones having a *cis*-*trans* pattern of C-2,3,4 substituents (such as **15**) did not show selectivity for the pyrrolidine ring formation with the reaction conditions employed. However, no general rule to predict the outcome of this reaction can be outlined. Employing Et_3N in MeOH, the formation of the epoxide was avoided, and the six-membered rings were formed regioselectively by direct nucleophilic substitution of the bromine at C-6. In this case the competition between the 5-*exo* and the 6-*endo* mode of reaction was eliminated. Furthermore, by simple reduction of the terminal carboxylic acid function, iminoalditols can easily be obtained, which was demonstrated by the synthesis of 1-deoxymannojirimycin (**8c**) and 2,5-dideoxy-2,5-imino-D-glucitol (**9c**) as representative examples.

Experimental

^1H NMR spectra were recorded on a Bruker AM 500 instrument and ^{13}C NMR spectra on a Varian Mercury 300 instrument. Chemical shifts were measured in δ (ppm) and coupling constants J in Hz. For NMR spectra in deuterated solvents, the solvent peak was used as the reference ($CDCl_3$: $\delta = 7.26$ Hz for ^1H, 76.93 for ^{13}C; MeOH-d_4: $\delta = 3.31$ for ^1H, 49.00 for ^{13}C). When necessary, NMR data were assigned using H–H- and C–H-correlated spectra. Melting points are uncorrected. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Institute of Physical Chemistry, Vienna. HR-MS was performed by BioCentrum, DTU. TLC was performed on Merck 60 F_{254} precoated silica plates, and spots were generally detected by spraying with a solution of 15% $NH_4Mo_2O_2$, 1% $Ce(SO_4)_2$ and 10% H_2SO_4, followed by charring. Flash chromatography was performed with silica gel 60 (Merck, 40–63 μm). Concentrations were performed on a rotary evaporator at a temperature below 40 °C. All solvents were distilled before use. Celite refers to Filter Aid from Celite Corporation.

2-Azido-6-bromo-2,6-dideoxy-D-mannono-1,4-lactone (6)

2,6-Dibromo-2,6-dideoxy-D-mannono-1,4-lactone (**5**)[22,29] (4.02 g, 13.22 mmol) and NaN_3 suspended in dry acetone ($MgSO_4$) was heated at reflux for 24 h. The suspension was cooled, filtered and concentrated to a semicrystalline orange residue. Purification by column chromatography (EtOAc–pentane 1 : 2) gave **6** as a

colorless oil (2.67 g, 76%). Analytical data were in accordance with the literature.[20,18]

2-Amino-6-bromo-2,6-dideoxy-D-mannono-1,4-lactone (7), hydrochloride salt

2-Azido-6-bromo-2,6-dideoxy-D-mannono-1,4-lactone (**6**) (0.72 g, 2.71 mmol) was hydrogenated in MeOH (15 mL) in the presence of 60 mg Pd/C (5%) and 1.5 mL conc. HCl at 1 atm for 24 h. The catalyst was filtered off and the filtrate was concentrated and co-evaporated with conc. HCl (10 mL) and toluene (3 × 10 mL) to give the hydrochloride salt of **7** as a crystalline residue in quantitative yield. Recrystallisation from EtOH afforded an analytical sample (52% yield); mp 208–210 °C (decomp.); $[a]_D^{20}$ EQ/S +48.6 (*c* 1.0, H_2O); found; C, 26.06; H, 4.01; N, 5.07; Cl 12.70; Br 57.97 (total halogen calc. as Br). Calc. for $C_6H_{11}NClBrO_4$; C, 26.10; H, 4.07; N, 5.00; Br 28.90; Cl 12.82 (total halogen calc. as Br 57.80).[30] ^{13}C NMR (50 MHz, D_2O): δ_C 36.6 (C-6), 53.0 (C-2), 65.7, 67.0 (C-3, C-5), 81.8 (C-4), 171.9 (C-1).

2,5-Dideoxy-2,5-imino-L-gulonic acid (9b)

The 2-amino-1,4-lactone **7** (0.74 g, 2.68 mmol) was dissolved in H_2O (5 mL) and cooled to 0 °C. KOH (1.11 g, 19.78 mmol, 150 w%) was dissolved in H_2O (5 mL) and cooled to 0 °C. The two solutions were mixed and stirred vigorously overnight. The solution was acidified with conc. HCl and concentrated. The crude product **9a** was dissolved in H_2O (30 mL) and applied to a column of ion-exchange resin (Amberlite IR-120, H^+, 36 mL), which was eluted with aq. NH_3 (12.5%, 200 mL) and concentrated to give crystalline **9b** (0.36 g, 77%) and recrystallised from H_2O–EtOH; mp 216 °C (decomp.); $[a]_D^{20}$ EQ/S −14.3 (*c* 1.0, H_2O); found; C, 40.68; H, 6.22; N, 7.86. Calc. for $C_6H_{11}O_5N$; C, 40.68; H, 6.26; N, 7.91. ^1H NMR (500 MHz, D_2O, HCl, pH 1): δ_H 3.98–4.05 (3H, m, H-1, H-1′, H-5), 4.12 (1H, br s, H-4), 4.28 (1H, br s, H-2), 4.53 (1H, br s, H-3); ^{13}C NMR (125 MHz, D_2O, HCl, pH 1): δ_C 58.1 (C-1), 64.2, 68.0 (C-2, C-5), 75.1, 79.2 (C-3, C-4), 171.4 (C-6).

2,5-Dideoxy-2,5-imino-D-glucitol (9c)

Ethyl 2,5-dideoxy-2,5-imino-L-gulonate[31] (2.5 g, 12.2 mmol) was dissolved in EtOH (50 mL), and $NaBH_4$ (1.5 g, 39.6 mmol) was added at 0 °C followed by stirring at room temperature overnight. For destruction of the excess $NaBH_4$, the pH was adjusted to 5–6 by addition of 4 N HCl. The reaction mixture was concentrated to a syrup, which was dissolved in water (50 mL), poured onto a column of IR-120 H^+, and eluted with aq. NH_3, giving after concentration of the eluent compound **9c** in 63% yield. Analytical data were in accordance with the literature.[24,25]

(2*S*,3*R*,4*R*,5*R*)-3,4,5-Trihydroxypipecolic acid (2,6-dideoxy-2,6-imino-D-mannonic acid) (8b)

The 2-amino-D-mannono-1,4-lactone **7** (2.01 g, 7.27 mmol) was dissolved in MeOH (30 mL) and cooled to 0 °C. Et_3N (3.0 mL, 21.28 mmol) was added at 0 °C and stirring was continued overnight at rt. Concentration afforded a semicrystalline residue of **8a**, which was dissolved in H_2O (30 mL) and poured onto a column of ion-exchange resin (Amberlite 120 H^+, 30 mL). The column was washed with H_2O until neutral followed by eluting with aq. NH_3 (6%, 300 mL). Treatment with active charcoal, concentration and co-concentration with toluene afforded semicrystalline **8b** (1.20 g, 93%): NMR data were identical with those reported in literature.[12] ^1H NMR (300 MHz, D_2O, pH 8): δ_H 3.08 (1H, dd, $J = 13.6$, 1.3 Hz, H-1), 3.31 (1H, dd, $J = 13.6$, 4.0 Hz, H-1′), 3.35 (1H, d, $J = 9.4$ Hz, H-5), 3.71 (1H, dd, $J = 8.8$, 3.1 Hz, H-3), 3.99 (1H, dd, $J = 9.4$, 8.8 Hz, H-4), 4.16 (1H, m, H-2); ^{13}C NMR (75 MHz, D_2O, pH 8): δ_C 47.0 (C-1), 62.7 (C-5), 67.0, 69.3, 73.1 (C-2, C-3, C-4), 174.1 (C-6).

Methyl 2,6-dideoxy-2,6-imino-D-mannonate (8a)

The 2-amino-1,4-lactone hydrochloride **7** (1.0 g, 3.62 mmol) was dissolved in MeOH (10 mL) and cooled to 0 °C. Et_3N (2.0 mL, 14.2 mmol) was added at 0 °C and stirring was continued overnight at rt. Then a solution of sodium methoxide in methanol (0.7 M, 5 mL) was added and stirred for 15 min. The reaction mixture was concentrated to give quantitatively the methyl ester and sodium bromide. The product was used directly for the reduction to 1-deoxymannojirimycin (**8c**). ^{13}C NMR: δ_C 49.0 (C-1), 56.3 (CH_3O), 61.0 (C-5), 66.1, 70.0, 73.2 (C-2, C-3, C-4), 170.6 (C-6).

1,5-Dideoxy-1,5-imino-D-mannitol (8c)

The methyl ester **8a** (0.69 g, 3.62 mmol) was dissolved in ethanol (15 mL) and cooled to 0 °C. Then $NaBH_4$ (1.0 g, 26.5 mmol) was added over 5–10 minutes at 0 °C and stirring was continued overnight at room temperature. Addition of methanol, filtration, and concentration left a product which was co-concentrated with MeOH–HCl three times. Column chromatography (EtOH–conc. NH_3 7 : 1) gave **8c** (380 mg, 2.33 mmol, 64%). Analytical data were found to be in agreement with the literature.[12]

2-Azido-6-bromo-2,6-dideoxy-D-galactono-1,4-lactone (12) and -D-talono-1,4-lactone (13)

2,6-Dibromo-2,6-dideoxy-D-galactono-1,4-lactone (**11**)[26] (5.75 g, 18.92 mmol) was dissolved in dry acetone (130 mL, $MgSO_4$). NaN_3 (17.25 g, 3 w%) was added and the mixture was stirred vigorously at reflux for 17 h. The mixture was cooled to r.t., filtered and concentrated *in vacuo* (T_{max} 30 °C). The residue was dissolved in acetone (10 mL) and eluted through a short column of silica. The combined fractions were treated with active charcoal, filtered and concentrated to give a semicrystalline residue in quantitative yield (C-2 epimers **12** and **13** in the ratio 5 : 4). Crystallisation from 4 mL EtOAc afforded 1.37 g of **13** as colourless crystals. The mother liquor was concentrated and further purified by flash chromatography (EtOAc–pentane 1 : 2) to give the two crystalline compounds: **12** (1.73 g, 34%, $R_f = 0.28$) and **13** (0.43 g, $R_f = 0.18$, total 37%). Overall yield 71%.

D-*galacto* epimer **12**: mp 114–115 °C; $[a]_D^{20}$ EQ/S +31.2 (*c* 1.0, EtOAc); Found; C, 27.41; H, 2.82; N, 16.01, Br; 29.22. Calc. for $C_6H_8BrO_4N_3$; C, 27.09; H, 3.03; N, 15.79; Br, 30.03; ^1H NMR (250 MHz, acetone-d_6): δ_H 3.55 (1H, dd, $J = 10.0$, 6.5 Hz, H-6), 3.61 (1H, dd, $J = 10.0$, 7.0 Hz, H-6′), 4.06 (1H, ddd, $J = 7.0$, 2.0 Hz, H-5), 3.44 (1H, ddd, $J = 9.0$, 8.0, 5.5 Hz, H-3), 4.50 (1H, dd, $J = 8.0$, 2.0, H-4), 4.70 (1H, d, $J = 9.0$ Hz, H-2), 4.94 (1H, d, $J = 7.0$ Hz, OH-5), 5.50 (1H, d, $J = 5.5$ Hz, OH-3); ^{13}C NMR (62.5 MHz, MeOH-d_4): δ_C 33.2 (C-6), 66.2 (C-2), 69.7, 73.0 (C-3, C-5), 82.5 (C-4), 172.2 (C-1).

D-*talo* epimer **13**: mp 154–155 °C; $[\alpha]_D^{20}$ EQ/S −49.5 (*c* 1.02, EtOAc); Found; C, 27.32; H, 2.77; N, 16.04; Br, 29.18. Calc. for $C_6H_8BrO_4N_3$; C, 27.09; H, 3.03; N, 15.79; Br, 30.03; ^{1}H NMR (500 MHz, acetone-d_6): δ_H 3.47 (1H, dd, J = 10.0, 6.5 Hz, H-6), 3.59 (1H, dd, J = 10.0, 7.0 Hz, H-6′), 4.22 (1H, dddd, J = 7.0, 6.5, 5.5, 1.5 Hz, H-5), 4.50 (1H, d (br), J = 5.5 Hz, H-4), 4.68 (1H, ddd, J = 5.5, 4.0, 0.5 Hz, H-3), 4.74 (1H, m, H-2), 5.25 (1H, d, J = 5.5 Hz, OH-5), 5.33 (1H, d, J = 4.0 Hz, OH-3); ^{13}C NMR (62.5 MHz, MeOH-d_4): δ_C 32.6 (C-6), 61.8 (C-2), 71.9, 72.9 (C-3, C-5), 87.5 (C-4), 174.3 (C=O).

1,3,4-Tri-*O*-acetyl-2-azido-6-bromo-2,6-dideoxy-D-galactose (12a)

2-Azido-6-bromo-2,6-dideoxy-D-galactono-1,4-lactone (**12**) (0.20 g, 0.75 mmol) was dissolved in EtOH and H_2O (1.5 and 3.5 mL) and ion-exchange resin (Amberlite IR-120, H^+, 5 mL) was added. The solution was cooled to 0 °C and $NaBH_4$ (*ca.* 5 eq.) was then added in small portions over 30 min, keeping the pH at 5–6 by adding IR-120. Stirring was continued overnight. The resin was filtered off and washed with MeOH. The filtrate was concentrated and co-evaporated with MeOH (3 × 5 mL). The residue was dissolved in Ac_2O (2 mL) and pyridine (2 mL) and stirred at r.t. overnight followed by concentration. The residue was diluted with CH_2Cl_2 (5 mL) and washed with H_2O (6 × 5 mL). The organic phase was dried ($NaSO_4$), treated with active charcoal, filtered over Celite and concentrated to give a product mixture (166 mg), which was isolated by flash chromatography (EtOAc–pentane 1 : 3), allowing separation of the α- and β-pyranoses. NMR spectroscopy indicated an α/β ratio of 1 : 2.

α-**12a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.05–2.20 (3 × CH_3), 3.23 (1H, dd, J = 11.0, 8.0 Hz, H-6), 3.32 (1H, dd, J = 11.0, 6.0 Hz, H-6′), 3.91 (1H, dd, J = 11.0, 3.5 Hz, H-2), 4.23 (1H, ddd, J = 8.0, 6.0, 1.0 Hz, H-5), 5.33 (1H, dd, J = 11.0, 3.0 Hz, H-3), 5.66 (1H, dd, J = 3.0, 1.0 Hz, H-4), 6.30 (1H, d, J = 3.5 Hz, H-1); ^{13}C NMR (62.50 MHz, $CDCl_3$): δ_C 20.7 (3 × CH_3), 27.2 (C-6), 56.5 (C-2), 67.1, 68.8, 71.0 (C-3, C-4, C-5), 90.3 (C-1), 168.4, 169.6 (3 × C=O).

β-**12**: ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.05–2.20 (3 × CH_3), 3.29 (1H, dd, J = 11.0, 8.0 Hz, H-6), 3.38 (1H, dd, J = 11.0, 6.0 Hz, H-6′), 3.82 (1H, dd, J = 11.0, 8.5 Hz, H-2), 3.98 (1H, ddd, J = 8.0, 6.0, 1.0 Hz, H-5), 4.92 (1H, dd, J = 11.0, 3.0 Hz, H-3), 5.55 (1H, d, J = 8.5 Hz, H-1), 5.57 (1H, dd, J = 3.0, 1.0 Hz, H-4); ^{13}C NMR (62.50 MHz, $CDCl_3$): δ_C 20.5 (3 × CH_3), 26.7 (C-6), 59.3 (C-2), 66.5, 71.2, 73.8 (C-3, C-4, C-5), 92.6 (C-1), 168.4, 169.7 (3 × C=O).

2-Amino-6-bromo-2,6-dideoxy-D-galactono-1,4-lactone (14), hydrochloride salt

2-Azido-D-galactono-1,4-lactone **12** (0.50 g, 1.88 mmol) was hydrogenated in MeOH (10 mL) in the presence of 50 mg Pd/C (5%) and 1 mL conc. HCl at 1 atm for 24 h. The catalyst was filtered off and the filtrate was concentrated and co-evaporated with toluene (3 × 10 mL) to give the hydrochloride salt of **14** in quantitative yield; ^{13}C NMR (62.50 MHz, D_2O): δ_C 34.9 (C-6), 57.7 (C-2), 70.1, 71.8 (C-3, C-5), 84.6 (C-4), 171.8 (C-1).

(2*R*,3*R*,4*S*,5*R*)-3,4,5-Trihydroxypipecolic acid (2,6-dideoxy-2,6-imino-D-galactonic acid, 16)

2-Amino-D-galactono-1,4-lactone **14** (1.13 g, 4.09 mmol) was dissolved in H_2O (10 mL) and cooled to 0 °C. A solution of 5 eq. of KOH was added in 1.2 mL H_2O (1.17 g, 20.43 mmol) and stirring was continued for 2 h. The solution was acidified with 4 N HCl and concentrated. The residue was dissolved in H_2O (10 mL) and poured onto a column of ion-exchange resin (Amberlite IR-120, H^+, 200 mL), which was eluted with H_2O until pH 7, followed by 12.5% aq. NH_3 (250 mL). The NH_3-eluate was concentrated to give a crystalline residue in quantitative yield, which on recrystallization from H_2O–MeOH gave **16** (412 mg, 57%): mp 292 °C (decomp.); $[\alpha]_D^{20}$ EQ/S −16.9 (*c* 0.6, H_2O); found; C, 36.88; H, 6.68; N, 7.10. Calc. for $C_6H_{11}O_5N{\cdot}H_2O$; C, 36.92; H, 6.71; N, 7.18; MS (FAB+); *m*/*z* 178.0709 (M + H+) ($C_6H_{12}O_5N$ requires 178.0715); ^{1}H NMR (500 MHz, D_2O): δ_H 2.67 (1H, dd, J = 12.5, 11.5 Hz, H-1_{ax}), 3.30 (1H, dd, J = 12.5, 5.5 Hz, H-1_{eq}), 3.50 (1H, dd, J = 10.0, 3.0 Hz, H-3), 3.66 (1H, d, J = 2.0 Hz, H-5), 3.88 (1H, ddd, J = 11.5, 10.0, 5.5 Hz, H-2), 4.29 (1H, dd, J = 3.0, 2.0 Hz, H-4); ^{13}C NMR (62.50 MHz, D_2O, pH 7): δ_C 44.7 (C-1), 61.5 (C-5), 63.9, 68.1, 72.7 (C-2, C-3, C-4), 170.6 (C-6).

2-Amino-6-bromo-2,6-dideoxy-D-talono-1,4-lactone (15), hydrochloride salt

2-Azido-D-talono-1,4-lactone **13** (0.50 g, 1.88 mmol) was hydrogenated in MeOH (10 mL) in the presence of 50 mg Pd/C (5%) and 1 mL conc. HCl at 1 atm for 24 h. The catalyst was filtered off and the filtrate was concentrated and co-evaporated with toluene (3 × 10 mL) to give the hydrochloride salt of **15** in quantitative yield: ^{13}C NMR (62.50 MHz, D_2O): δ_C 34.4 (C-6), 53.2 (C-2), 70.5, 72.0 (C-3, C-5), 90.6 (C-4), 174.9 (C-1).

Methyl 2,6-dideoxy-2,6-imino-D-talononate (17a)

2-Amino-D-talono-1,4-lactone **15** (0.47 g, 1.70 mmol) was dissolved in MeOH (8 mL) and cooled to 0 °C. Et_3N (0.7 mL, 5.11 mmol) was added at 0 °C and stirring was continued overnight at rt. Concentration gave a residue, which was characterised by ^{13}C NMR as the methyl ester **17a**: ^{13}C NMR (62.5 MHz, D_2O): δ_C 45.7 (C-6), 53.5 (CO_2CH_3), 59.9 (C-2), 69.2, 69.3, 71.8 (C-3, C-4, C-5), 174.0 (CO_2CH_3).

(2*S*,3*R*,4*S*,5*R*)-3,4,5-Trihydroxypipecolic acid (2,6-Dideoxy-2,6-imino-D-talonic acid) (17b)

A test sample of crude **17a** was treated with KOH to remove the hydrochloride salts of triethylamine. Evaporation gave pure compound without Et_3N but caused epimerisation of the product according to ^{13}C NMR. The residue was dissolved in H_2O and acidified with 4 N HCl and poured onto a column of ion-exchange resin (Amberlite IR-120, H^+, 5 mL). The resin was eluted with H_2O until neutral followed by 12.5% NH_3 (2 × 20 mL). Evaporation of the NH_3-eluate gave colourless crystals of **17b** (30 mg, 88% yield). ^{13}C NMR (62.5 MHz, D_2O): δ 45.0 (C-6), 60.6 (C-2), 66.2, 68.5, 70.8 (C-3, C-4, C-5), + signals for epimer. According to ^{13}C NMR epimerisation had occurred. The ratio of the two C-2 epimers was 3 : 1.

Compound **17b** was also prepared from 2-azido-D-talono-1,4-lactone **15** as described for the enantiomer *ent*-**17**: mp 155 °C; $[\alpha]_D^{20}$ EQ/S −9.48 (*c* 1.1, H_2O); found; C, 36.91; H, 6.67; N, 7.06; Calc. for $C_6H_{11}O_5N,H_2O$; C, 36.92; H, 6.71, N, 7.18; ^{1}H NMR (500 MHz, D_2O): δ_H 3.16 (1H, dd, J = 13.2, 7.7 Hz, H-1), 3.36 (1H, dd, J = 13.2, 3.8 Hz, H-1′), 3.71 (1H, dd, J = 7.3, 2.6 Hz, H-3), 3.89 (1H, d, J = 6.4 Hz, H-5), 4.05 (1H, ddd, J = 7.7, 7.3, 3.8 Hz, H-2), 4.34 (1H, dd, J = 6.4, 2.6 Hz, H-4); ^{13}C NMR (75 MHz, D_2O): δ_C 44.8 (C-6), 60.3 (C-2), 65.7, 68.2, 70.6 (C-3, C-4, C-5), 171.6 (C-1).

2-Azido-6-bromo-2,6-dideoxy-L-galactono-1,4-lactone (*ent*-12) and -L-talono-1,4-lactone (*ent*-13)

2,6-Dibromo-2,6-dideoxy-L-galactono-1,4-lactone (*ent*-**11**)[18] (3.12 g, 10.27 mmol) and NaN_3 (9.3 g, 3 w%) in dry acetone (60 mL, $MgSO_4$) were stirred vigorously under reflux for 17 h. Work-up as described for the enantiomers **12** and **13** gave a semicrystalline product in quantitative yield (*ent*-**12** and *ent*-**13** in the ratio 1 : 1.2 according to ^{13}C NMR). Crystallisation from 5 mL EtOAc afforded 0.49 g of *ent*-**13** as colourless crystals. Flash chromatography (EtOAc–pentane 1 : 2) of the residue gave: *ent*-**12** (1.27 g, 47%, R_f = 0.28) and *ent*-**13** (0.36 g, R_f = 0.18, total 31%). Overall yield 78%. *ent*-**12**: mp 110–112 °C; found; C, 27.36; H, 2.87; N, 15.58; Br, 29.94; Calc. for $C_6H_8BrO_4N_3$; C, 27.09; H, 3.03; N, 15.79; Br, 30.03; NMR data were identical with those reported for the enantiomer: ^{13}C NMR (62.5 MHz, acetone-d_6): δ_C 33.5 (C-6), 65.2 (C-2), 69.1, 72.5 (C-3, C-5), 81.7 (C-4), 170.9 (C=O). *ent*-**13**: mp 153–155 °C; NMR data were identical with those reported for the enantiomer: ^{13}C NMR (62.5 MHz, acetone-d_6): δ_C 33.2 (C-6), 61.2 (C-2), 71.6, 72.6 (C-3, C-5), 86.7 (C-4), 172.7 (C=O).

(2*S*,3*S*,4*R*,5*S*)-3,4,5-Trihydroxypipecolic acid (2,6-dideoxy-2,6-imino-L-galactonic acid) (*ent*-16)

2-Azido-6-bromo-L-galactono-1,4-lactone (*ent*-**12**) (0.53 g, 1.97 mmol) was hydrogenated in MeOH (10 mL) in the presence of 50 mg Pd/C (5%) and 0.5 mL conc. HCl at 1 atm for 16 h. The catalyst was filtered off and the filtrate was concentrated and co-evaporated with conc. HCl and toluene (3 × 5 mL) to give the hydrochloride salt of *ent*-**14** in quantitative yield. 2-Amino-L-galacto-1,4-lactone *ent*-**14** (0.78 g, 2.82 mmol) was treated with KOH and worked up as described above for the enantiomer to give *ent*-**16** (0.33 g, 66%) after crystallisation; mp 270 °C (decomp.); $[\alpha]_D^{20}$ EQ/S +18.7 (*c* 1.0, H_2O); found; C, 37.03; H, 6.71; N, 7.08; Calc. for $C_6H_{11}O_5N,H_2O$; C, 36.92; H, 6.71; N, 7.18; (FAB+): *m*/*z* 178.0717 (M + H^+) ($C_6H_{12}O_5N$ requires 178.0715); NMR data were identical with those reported for the enantiomer **16**. The compound has been reported,[14] but no spectral and analytical data were given.

(2*R*,3*S*,4*R*,5*S*)-3,4,5-Trihydroxypipecolic acid (2,6-dideoxy-2,6-imino-L-talonic acid) (*ent*-17)

2-Azido-6-bromo-L-talonolactone *ent*-**13** (0.38 g, 1.41 mmol) was hydrogenated in MeOH (8 mL) in the presence of 40 mg Pd/C (5%) and 0.8 mL conc. HCl at 1 atm for 16 h. The catalyst was filtered off and the filtrate was concentrated and co-evaporated with conc. HCl and toluene (3 × 5 mL) to give the hydrochloride salt of *ent*-**15** in quantitative yield. The 2-amino-L-talo-1,4-lactone *ent*-**15** was dissolved in MeOH (3 mL) and cooled to 0 °C. Et_3N (0.6 mL, 4.23 mmol) was added at 0 °C and stirring was continued overnight at rt. Concentration gave a light yellow crude product, which was dissolved in H_2O (5 mL) and poured onto a column of ion-exchange resin. The column was eluted with aq. NH_3 (6%, 80 mL, 12.5%, 60 mL) and the eluate concentrated to give crystalline *ent*-**17** (0.19 g, 75%). Recrystallisation from H_2O–EtOH afforded an analytical sample of *ent*-**17** (79 mg, 32% yield): mp 208–210 °C (decomp.); $[\alpha]_D^{20}$ +10.3 (*c* 0.57, H_2O); found: C, 36.96; H, 6.63; N, 7.11; Calc. for $C_6H_{11}O_5N{\cdot}H_2O$; C, 36.92; H, 6.71, N, 7.18; ^{1}H NMR (500 MHz, D_2O, pH 7): δ_H 3.21 (1H, dd, J = 12.8, 7.7 Hz, H-1), 3.40 (1H, dd, J = 12.8, 3.8 Hz, H-1′), 3.76 (1H, dd, J = 7.3, 2.4 Hz, H-3), 3.94 (1H, d, J = 6.0 Hz, H-5), 4.10 (1H, ddd, J = 7.7, 7.3, 3.8 Hz, H-2), 4.39 (1H, dd, J = 6.0, 2.4 Hz, H-4); ^{13}C NMR (75 MHz, D_2O, pH 7): δ_C 44.6 (C-1), 60.1 (C-5), 65.5, 68.0, 70.4 (C-2, C-3, C-4), 171.4 (C-6).

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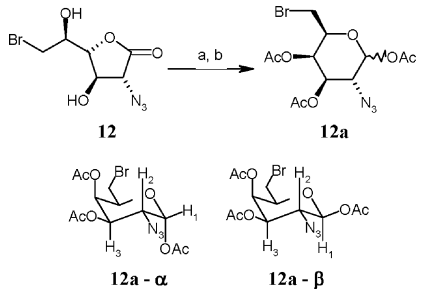
27 The configuration of **12** was determined by ^{1}H NMR of the acetylated pyranose **12a**, which was formed upon reduction of the lactone with $NaBH_4$ in the presence of acidic ion-exchange resin. The ^{13}C and ^{1}H NMR spectra showed signals from two anomeric pyranoses in the ratio α:β 1 : 2 with the coupling constants $J_{1,2}$ 3.5 Hz and $J_{2,3}$ 11.0 Hz assigned to $H_1\alpha$ (δ 6.30) and $J_{1,2}$ 8.5 Hz and $J_{2,3}$ 11.0 Hz assigned to $H_1\beta$ (δ 5.55). Thus, the configuration of **12** was unambiguously determined to be D-*galacto*.



Reagents and conditions: a) $NaBH_4$, EtOH–H_2O, Amberlite IR-120 H^+, pH 5–6, 0 °C; b) Ac_2O, pyridine, rt.
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