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Polyhydroxyamino-Piperidine-Type Iminosugars and Pipecolic Acid Analogues from a D-Mannose-Derived Aldehyde

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Dedicated to C.I.N.M.P.I.S on the occasion of its 20th anniversary

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A general strategy for the synthesis of diversely substituted 3,4,5-trihydroxypiperidines (including two natural products), 5-amino-3,4-dihydroxypiperidines, 3,4,5-trihydroxypipecolic acids, and 2-(aminomethyl)-3,4,5-trihydroxypiperidines is reported. The procedure used a double reductive amination or a Strecker reaction, starting from differently protected aldehydes readily synthesized on a gram scale from D-mannose. The biological activities of the target compounds were evaluated, and some of them showed moderate inhibition of α-L-fucosidase and β-glucosidase.

Introduction

Polyhydroxylated piperidines such as 1-deoxynojirimycin (**1**) and 1-deoxymannojirimycin (**2**) (Figure 1), also commonly known as iminosugars or iminocyclitols, are natural products widely found in plants and microorganisms, and are among the most attractive carbohydrate mimetics reported to date.[1] In these compounds, an imino group generally replaces the endocyclic oxygen of the parent sugar. Their inhibitory activity against glycosidic enzymes[2] has prompted intense research into the synthesis of the natural products and their unnatural analogues[3] in order to develop new therapies against cancer, viruses, diabetes, and hereditary metabolic disorders.[4] Synthetic amino derivatives such as 6-(acetylamino)-1,6-dideoxymannojirimycin (**3**, Figure 1) also showed very high activities as glycosidase inhibitors.[5] More recently, the antibacterial activity of synthetic (hydroxyamino)-piperidines and other iminosugar derivatives was discovered.[6] Polyhydroxypipecolic acid **4**, the only natural trihydroxypipecolic acid known, was isolated from the seeds of *Bathia racemosa*.[7] It proved to be a specific inhibitor of human liver β-D-glucuronidase,[8] and was found to show anti-HIV[9] and antimetastatic properties.[10]

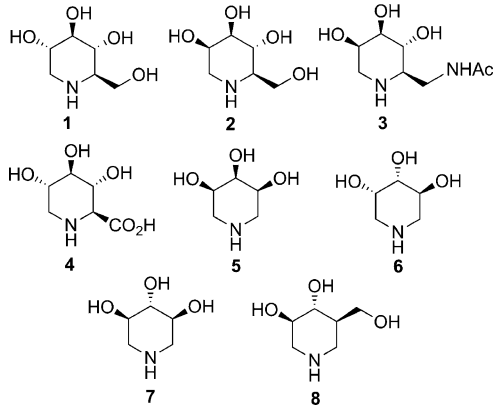

Figure 1. Natural and synthetic piperidine-type iminosugars **1**, **2**, **5**–**8**, amino derivative **3**, and polyhydroxypipecolic acid **4**.

3,4,5-Trihydroxypiperidines **5**–**7** (Figure 1) were isolated from *Eupatorium fortunei* TURZ in 1995,[11] a plant used in folk medicine for the treatment of several pathologies. They, together with their unnatural relative isofagomine (**8**), may be referred to as 1-*N*-iminosugars. Compounds **5**–**7** were synthesized by Ganem[12] and subsequently by several other groups, using either a chiral pool approach[13] or enantioselective synthesis.[14] These molecules were recently found to have potential therapeutic applications for the treatment of energy-utilization diseases, viral infections, and lysosomal storage disorders.[15,16]

Due to our ongoing interest in polyhydroxylated alkaloids and their unnatural analogues,[17] we recently envisaged D-mannose-derived aldehyde **9**[18] as a possible com-

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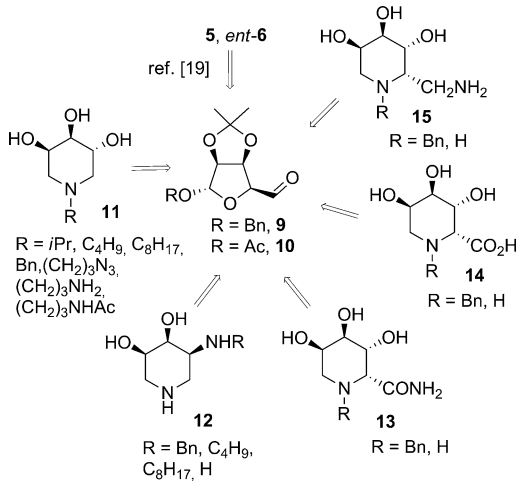
mon building block for the synthesis of natural **5**, *ent*-**6**, and some new unnatural *N*-alkylated analogues (Scheme 1), using a double reductive amination procedure.[19]



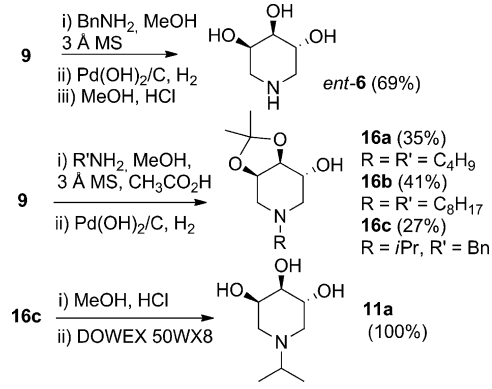
Scheme 1. Retrosynthetic analysis of polyhydroxyamino-piperidines and pipecolic acid analogues from D-mannose-derived aldehydes **9** and **10**.

In this paper, we describe our exploration of the scope of this strategy, which allowed access to 1-*N*-alkyl-substituted polyhydroxypiperidines **11** and aminopiperidines **12** (Scheme 1). A change in the anomeric hydroxy protecting group on aldehyde **9** gave us the opportunity to exploit the Strecker reaction of aldehyde **10** en route to the synthesis of new polyhydroxypipecolic acid analogues **13** and **14**, and 6-(aminomethyl)piperidine iminosugars **15** (Scheme 1). The results of the Strecker reaction of **10** also gave strong evidence about the mechanism proposed for the stereoselective formation of piperidine-2-carbonitriles as by-products of the double reductive amination reaction. The biological evaluation of the compounds synthesized against a panel of commercially available glycosidase enzymes is also reported.

Results and Discussion

Aldehyde **9** was easily synthesized in four steps and 80% overall yield from D-mannose, without the need for any chromatographic purification.[19] Our first aim was the introduction of lipophilic chains onto the nitrogen atom of the target piperidine-type iminosugars, which is expected to improve the pharmacokinetic properties in vivo, and the suitability of such molecules as pharmacological chaperones.[20]

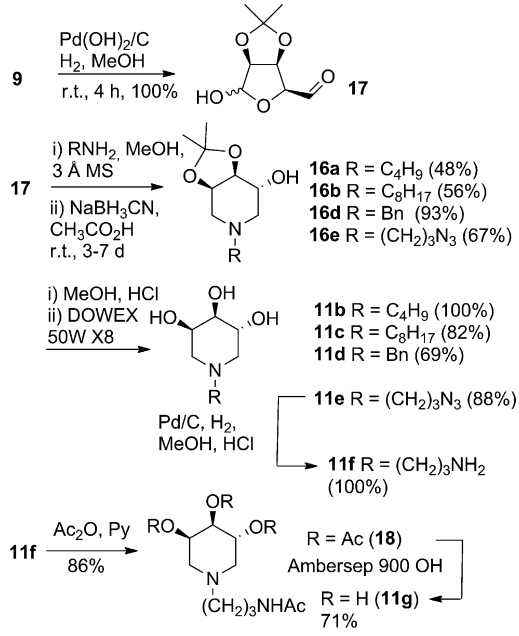
We initially investigated the reductive amination reaction of **9** using different amine sources, and using hydrogen as the reducing agent. This could allow removal of the benzyl protecting group at the anomeric position of **9** in the same step, resulting in the liberation of the second aldehyde moiety necessary to perform the required cyclization. However, in our hands, this reaction was poorly reproducible, it was not versatile, and it also showed unexpected drawbacks. Most of the problems encountered probably derived from the tendency of **9** to undergo quick hydration from air humidity. The results are shown in Scheme 2. Although the reductive amination reaction with benzylamine gave a satisfactory yield, the same protocol with butylamine or octylamine gave **16a** and **16b** in moderate yields after prolonged reaction times.[19] Moreover, upon reaction of **9** with benzylamine and AcOH for 4 d, *N*-isopropyl piperidine **16c** was isolated in 27% yield (Scheme 2), probably as a result of partial acetonide deprotection and subsequent reductive amination of the acetone liberated in situ with the formed piperidine. Therefore, in this case, a one-pot triple reductive amination took place, together with debenzylation and acetonide deprotection. Deprotection of **16c** was carried out as usual to give compound **11a** in quantitative yield.



Scheme 2. The double reductive amination strategy using aldehyde **9** and hydrogen as reducing agent.

Due to the problems encountered with the reductive amination strategy on aldehyde **9**, we sought to perform the same task by working on dialdehyde **17**, obtained quantitatively by catalytic hydrogenation of **9** (Scheme 3).[19] It is worth noting that this compound can be viewed (in its open-chain form) either as a 2,3-di-*O*-protected D-lyxaric aldehyde or a 3,4-di-*O*-protected D-arabinaric aldehyde. In solution, the ^{1}H NMR spectrum of **17** was rather complicated, showing the presence of a complex mixture of different forms. While many examples of reductive amination reactions of diketones or ketoaldehyde derivatives have been reported,[21] the same reaction with dialdehydes has been much less exploited. The reaction was used in Bols's synthesis of isofagomine with ammonia as the nitrogen source,[15a] and a few other recent reports.[22] In particular, Crich and co-workers used a double reductive amination strategy on functionalized 1,5-dialdehydes with various hydroxylamines en route to the synthesis of polyhydroxylated *N*-alkoxypiperidines.[15g,15i] In our hands, the reaction of dialdehyde **17** with different amine sources (0.9 equiv.), $NaBH_3CN$ (3.0 equiv.), and AcOH (2 equiv.)[22b] was much more reliable and reproducible than the hydrogenation procedure on masked dialdehyde **9** described above, giving protected piperidines **16a** and **16b** in slightly higher yields (48 and 56%, respectively). This procedure allowed the prepa-

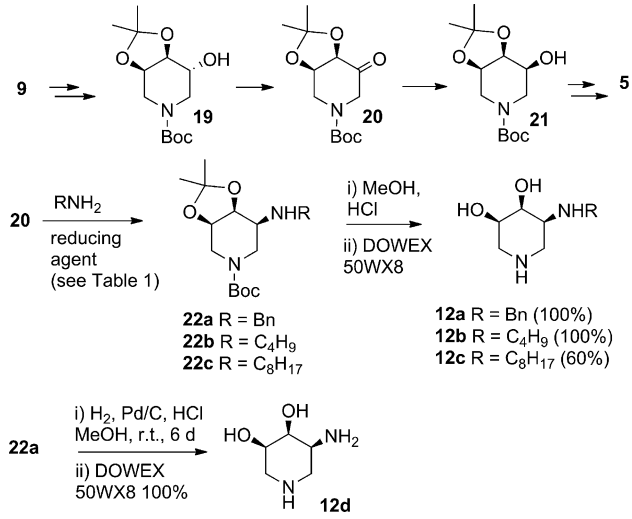
ration of *N*-benzyl-substituted piperidine **16d** in excellent yield (93%). Deprotection of **16a**, **16b**, and **16d** with methanolic HCl, followed by treatment with ion-exchange resin, gave *N*-alkylated piperidines **11b**–**11d** (Scheme 3).[19]



Scheme 3. Double reductive amination strategy using dialdehyde **17** and $NaBH_3CN$ as reducing agent.

The use of $NaBH_3CN$ instead of H_2 as the reducing agent for the double reductive amination of **17** also allowed the synthesis of piperidines functionalized on the alkyl chain. Thus, the reaction of **17** with 3-azidopropyl-1-amine[23] (1 equiv.), $NaBH_3CN$ (3.0 equiv.), and AcOH (2 equiv.) gave *N*-alkylated piperidine **16e** in 67% yield (Scheme 3), which upon conventional deprotection, gave compound **11e** in 88% yield. Catalytic hydrogenation followed by ion-exchange resin treatment, eluting with 15% NH_4OH, gave primary amine **11f**. This compound showed a high tendency to be protonated, possibly through reaction with atmospheric CO_2, as evidenced by the NMR spectra, which showed signals for an HCO_3^- counterion. However, the presence of a single compound was demonstrated by acetylation of **11f** with an excess of acetic anhydride in pyridine, which gave **18** in 86% yield. Treatment of **18** with the strongly basic resin Ambersep 900 OH in MeOH gave trihydroxypiperidine **11g** in 71% yield (Scheme 3).

The inversion of configuration at C5–OH in compound **19** to access natural trihydroxypiperidine **5** (Scheme 4) was achieved through an oxidation–reduction sequence to give alcohol **21**, which was transformed into **5** by deprotection in acidic medium.[19] We envisaged that ketone **20** would be a suitable intermediate to introduce an exocyclic amino moiety into the piperidine skeleton to give piperidines **22**. Indeed, the high stereoselectivity observed in the reduction of **20** to **21** by the hydride anion, deriving from a favoured axial attack on the C-5 carbonyl group *anti* to the vicinal C–O bond, according to a Felkin–Anh model, could be extended to the reduction of C=N bonds formed by the reaction of **20** with different amines (Figure 2).



Scheme 4. The oxidation–reduction procedure. Synthesis of natural **5** and amino piperidines **12**.

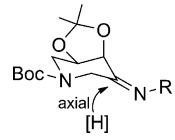


Figure 2. Favoured axial attack of the hydride anion on the C=N bond.

Therefore, we investigated the reductive amination reaction of ketone **20** (Scheme 4). We initially used the best reaction conditions previously found for the synthesis of piperidine **16d** from dialdehyde **17**: dry MeOH, 3 Å molecular sieves, $BnNH_2$ (0.9 equiv.), $NaBH_3CN$ (3.0 equiv.), and AcOH (2.0 equiv.). After 6 d, the conversion was complete, but unexpectedly a 1:2 mixture of the desired aminopiperidine (i.e., **22a**) together with alcohol **21** was recovered (Table 1, entry 1). When a slight excess of $BnNH_2$ (1.1 equiv.) was used, and we waited 40 min before the addition of $NaBH_3CN$ in lower excess (1.5 equiv.), the result was similar (Table 1, entry 2). The critical point in this reaction was the formation of the imine intermediate, since the chemoselectivity of $NaBH_3CN$ in this reaction appeared to be quite low. The formation of alcohol **21** could be completely suppressed by stirring a mixture of **20**, $BnNH_2$ (1.5 equiv.), and AcOH (2 equiv.) for 3 h before the addition of $NaBH_3CN$, thus ensuring complete formation of the imine intermediate (Table 1, entry 3) prior to hydride attack. Under these conditions, amine **22a** could be recovered in 48% yield after purification on silica gel. Due to the low chemoselectivity of $NaBH_3CN$, alkylpiperidines **22b** and **22c** were more easily accessed by using hydrogen as the reducing agent. Ketone **20** was stirred in MeOH with 3 Å molecular sieves and the appropriate amine for 40 min, then

$Pd(OH)_2/C$ was added, and the mixture was stirred under H_2 (1 atm) for 20–24 h. Both reactions (Table 1, entries 4 and 5) gave the desired amines in good yields. Hydrogenation also showed complete diastereofacial selectivity, resulting from the steric hindrance to attack at the opposite face.

Table 1. The reductive amination of ketone **20** in MeOH.

Entry	RNH_2 (equiv.)	Reducing agent (equiv.)	Time [h]	**22/21**[a] ratio	Yield of **22** [%]
1[b]	$BnNH_2$ (0.9)	$NaBH_3CN$ (3.0)	144	1:2	17
2[c]	$BnNH_2$ (1.1)	$NaBH_3CN$ (1.5)	20	1:2	19
3[d]	$BnNH_2$ (1.1)	$NaBH_3CN$ (3.0)	25	>98:2	48
4	$C_4H_9NH_2$ (1.5)	$Pd(OH)_2/C$ H_2	24	>98:2	68
5	$C_8H_{17}NH_2$ (1.5)	$Pd(OH)_2/C$ H_2	20	>98:2	53

[a] Determined by isolation of compounds after flash column chromatography. [b] All reagents, including 3 Å MS and AcOH (2.0 equiv.) were mixed together at the same time. [c] Ketone, amine, and 3 Å MS were stirred for 40 min before addition of $NaBH_3CN$ and AcOH (2.0 equiv.). [d] Ketone, amine, 3 Å MS, and AcOH (2.0 equiv.) were stirred for 3 h before addition of $NaBH_3CN$.

Treatment of **22a–22c** with methanolic HCl, followed by ion-exchange resin treatment, gave new *N*-alkylamino piperidines **12a–12c** (Scheme 4) in good to quantitative yields. Moreover, 5-amino piperidine **12d** was also accessed in quantitative yield by catalytic hydrogenation of compound **22a** under acidic conditions: the acetonide, Boc (*tert*-butoxycarbonyl), and benzyl protecting groups were all removed in the same step.

The structures of aminopiperidines **12** were established on the basis of careful analysis of their ^1H NMR and 1D NOESY spectra. In particular, for **12d**, a strong NOE correlation peak between 3-H and 5-H was observed (Figure 3), which also established the structure of **12a** since both compounds are derived from **22a**. Moreover, the ^1H NMR spectrum of **12d** showed a pseudo triplet with J = 2.5 Hz for 4-H, consistent with two *eq-ax* relationships with both 3-H and 5-H. For piperidines **12b** and **12c**, due to overlapping NMR signals, 1D NOESY spectra could not be used for structural assignment. However, the ^1H NMR spectra of both **12b** and **12c** showed a broad singlet for 4-H, consistent with two *eq-ax* relationships with both 3-H and 5-H. In contrast, the ^1H NMR spectrum of **11a** (with the opposite configuration at C-5) showed a dd for 4-H with J = 8.3 Hz and J = 2.9 Hz, consistent with an *ax-ax* relationship and an *ax-eq* relationship with the vicinal protons (Figure 3).[24]

Another synthetic strategy that could give access to functionalized piperidines from aldehyde **9**, and in particular to compounds **13–15** (Scheme 1), uses a Strecker reaction,[25] followed by deprotection at the anomeric carbon, and cyclization. We envisaged that aldehyde **9** would afford piperidines functionalized at the α-position with a cyano

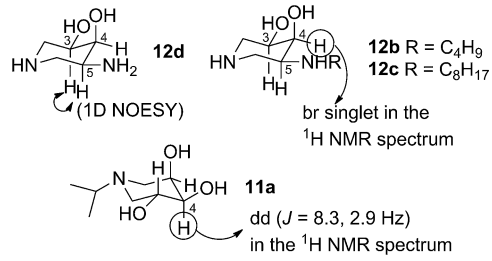
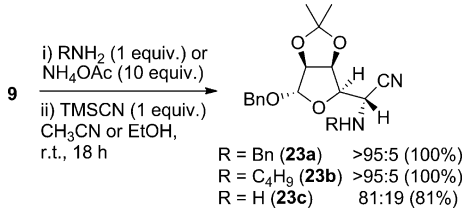


Figure 3. Structural assignments by 1D NOESY and ^1H NMR spectra of piperidines **12** and **11a**.

group,[26,27] a motif that also occurs in natural products with antitumor activity such as Saframycin A, and in related synthetic hybrids.[28]

We reasoned that such compounds could be obtained regioselectively by a Strecker reaction performed on "masked" dialdehyde **9**. Due to the chirality of **9**, we expected to obtain diastereoselective Strecker reaction. The enantioselective version of this reaction has also been widely investigated.[29] The results with different amines (Scheme 5) show that the Strecker reaction of **9** using TMSCN (TMS = trimethylsilyl) as the cyanide source led to major diastereoisomers **23** with high stereoselectivities and in very good yields.[19]



Scheme 5. The Strecker reaction of aldehyde **9**.

The observed stereoselectivities varied from excellent (>95:5, R = Bn, C_4H_9) to good (81:19, R = H), depending on the amine used. Initial experiments were done in the presence of $Cu(OTf)_2$ as a Lewis acid catalyst,[30] but we subsequently found that the addition of copper was not necessary for the reaction to occur, and neither did it improve the stereoselectivity. Without the copper catalyst, the reaction gave very clean products that did not even require purification on silica gel in the case of α-amino nitriles **23a** and **23b** (Scheme 5). The (*S*) configuration at the newly formed stereocentre was unambiguously assigned for **23c** by single-crystal X-ray analysis (Figure 4), and the same configuration was attributed accordingly to **23a** and **23b**.

CCDC-849588 contains the supplementary crystallographic data for **23c**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

This stereochemical outcome was in agreement with our expectations. It can be rationalized by a preferred approach of cyanide through a Cram-chelated transition state (Figure 5), where the chelation involves the iminium proton and the endocyclic oxygen atom of the sugar in a five-membered

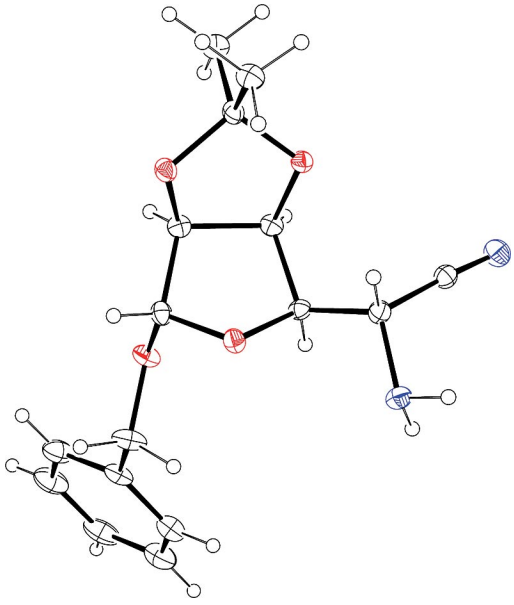


Figure 4. X-ray crystal structure of **23c**.

ring. According to this model, the cyanide anion would attack from the less hindered *Si* face of the double bond, thus giving adducts **23a**–**23c** with the (*S*) absolute configuration at the newly formed stereocentre. This stereochemical outcome is consistent with a recent proposal about nucleophilic attack on acyclic polyhydroxylated aldehydes.[31] Unfortunately, attempted deprotection at the anomeric position by catalytic hydrogenation of α-aminonitriles **23**, which would induce subsequent cyclization, failed under both neutral and acidic conditions and using different solvents (MeOH, EtOH, CH_3CN), probably due to catalyst deactivation by the cyanide group. However, the direct Strecker reaction with benzylamine on dialdehyde **17**, followed by cyclization and in situ reduction of the iminium ion intermediate by $NaBH_3CN$, gave 2-cyano piperidine **24** highly regio- and stereoselectively in 50% isolated yield (Scheme 6). Compound **24** has previously been observed as a by-product formed in the reductive amination of **17** with $NaBH_3CN$ under neutral conditions. Its identity was confirmed by comparison of ^1H NMR spectra of the corresponding acetylated derivative **25** (Scheme 6). The formation of cyano-substituted compounds as by-products during reductive amination reactions with $NaBH_3CN$ under neutral or basic reaction conditions has occasionally been reported.[32]

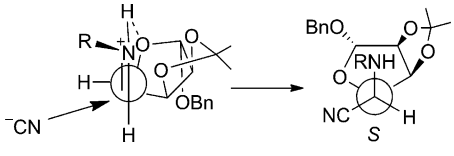
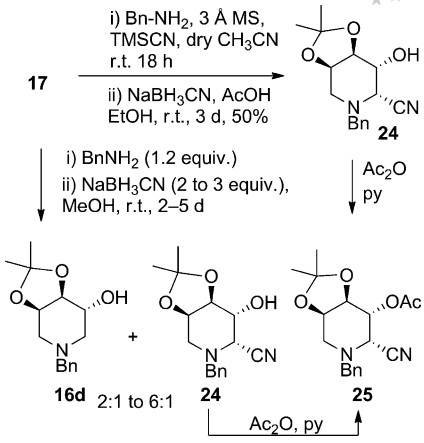
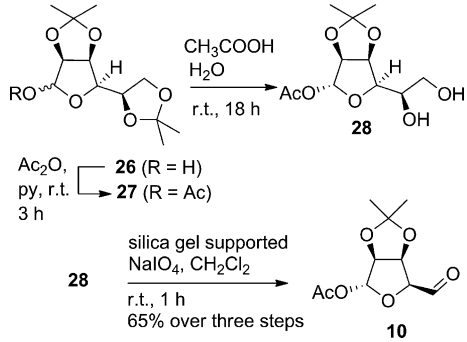


Figure 5. Cram chelate model for the Strecker reaction of **9** to stereoselectively give α-aminonitriles **23**.



Scheme 6. Synthesis of 2-cyano piperidine **24** by Strecker reaction of **17**, and as a by-product in the reductive amination of **17** under neutral conditions.

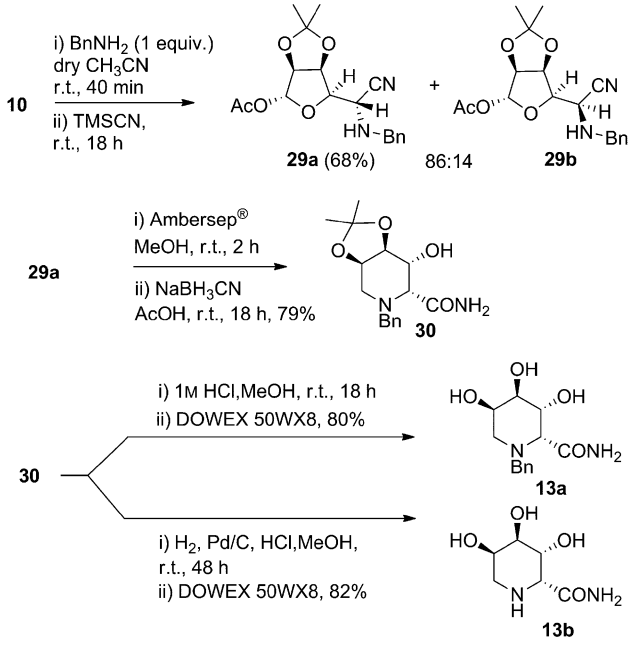
Following these results, we considered that the regio- and stereoselective formation of compound **24** from **17** during the reductive amination was the result of a Strecker reaction occurring at the more reactive aldehyde at C-5, followed by intramolecular reductive amination at C-1. To get solid evidence, we modified the anomeric protecting group of the starting sugar derivative, in order to demonstrate that the product of the Strecker reaction (i.e., **23a**) is transformed into piperidine **24** upon subjection to a reductive amination/ring closure procedure. The use of a different protecting group could enable the cyclization to piperidines functionalized at C-2 that failed starting from α-aminonitriles **23**. The simplest protecting group that could be orthogonally removed with respect to the acetonide moiety was envisaged to be an acetyl group. Therefore, the differently protected "masked" dialdehyde **10** was synthesized in three steps from protected D-mannose **26** (Scheme 7). Compound **26** was acetylated at the anomeric position to give **27**,[33] which was deprotected at the C-5 and C-6 hydroxy groups by treatment with aqueous acetic acid to give **28**.[33a] Subsequent oxidative cleavage of glycol **28** using silica-gel-supported sodium metaperiodate in dichloromethane[34] led to aldehyde **10**[35] in 65% yield over three steps (Scheme 7).



Scheme 7. Synthesis of aldehyde **10**.

We were delighted to observe that the Strecker reaction of **10** was also highly stereoselective. Indeed, the reaction of **10** with $BnNH_2$ in the presence of TMSCN gave the two

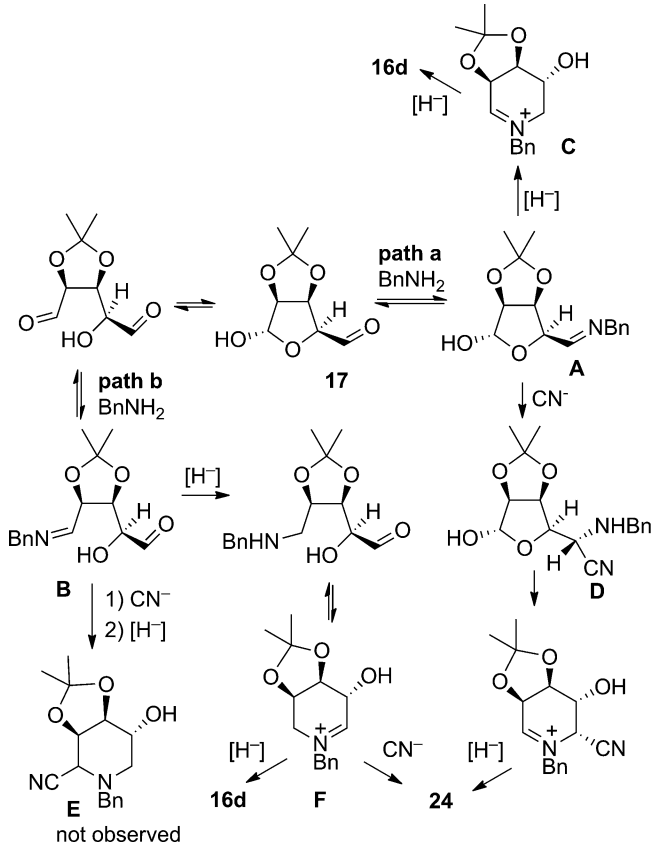
diastereoisomers **29a** and **29b** in an 86:14 ratio. Major isomer **29a** could be isolated in 68% yield after chromatography on silica gel (Scheme 8). The structural assignment of the major product as **29a** was based on the similarity of its spectroscopic data to those of **23a**, but it was unequivocally established by successive transformations (see below). A reason for the lower diastereoselectivity of the Strecker reaction of aldehyde **10** compared to its relative **9** may be due to the presence of the electron-withdrawing acetoxy group, which makes the *anti* lone pair of the endocyclic oxygen less available for intramolecular hydrogen bonding. A solution of **29a** in MeOH was stirred with Ambersep® 900-OH ion-exchange resin at room temperature to remove the acetyl group at the anomeric position. After 2 h, the ion-exchange resin was simply filtered off, and to perform the reductive amination reaction, $NaBH_3CN$ (1.1 equiv.) and AcOH (2.0 equiv.) were added, and the reaction mixture was stirred at room temperature overnight. To our pleasure, the ring closure finally worked, leading to 2-amido-piperidine **30** in 79% yield (Scheme 8). The formation of this compound instead of the expected 2-cyanopiperidine **24** was probably due to concomitant hydrolysis of the cyano group under basic conditions during treatment with the resin.[36] Treatment of **30** with methanolic HCl, or catalytic hydrogenation under acidic conditions, gave the hydrochloride salts of **13a** and **13b**, respectively. Final elution through ion-exchange resin (DOWEX® 50XW8-100) led to the corresponding free amines in 80 and 82% yields, from **30** (Scheme 8).



Scheme 8. The Strecker reaction of aldehyde **10**, and synthesis of piperidine-2-carboxamides **13a** and **13b** by reductive amination.

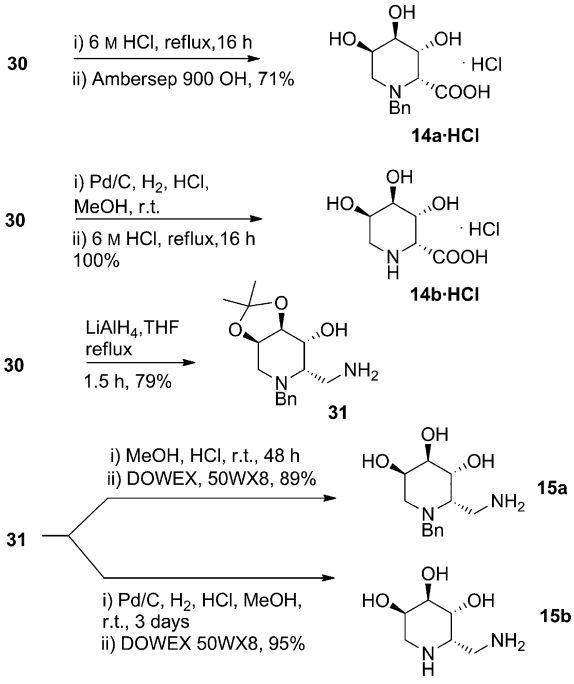
The structure of **30** was assigned on the basis of its 1D and 2D NMR spectra. The ^1H NMR spectrum showed for 2-H a doublet with J = 4.4 Hz, consistent with an *eq-ax* relationship with 3-H, and therefore of a *cis* relationship between the amido group and the free hydroxy group at C-3. Remarkably, the relative stereochemistry of C-2 in **30** is the same as that found for piperidine-2-carbonitrile **24**. This finding supports the hypothesis that the selective formation of **24** during the reductive amination (see Scheme 6) is driven by a Strecker reaction, combined with subsequent double reductive amination, in agreement with our expectations.

On the basis of these data, a plausible mechanism for the regio- and stereoselective formation of compound **24** in the reductive amination of dialdehyde **17** under neutral conditions is shown in Scheme 9. Probably, imine **A**, formed preferentially over imine **B** (path a vs. b, Scheme 9), leads to adduct **C** through attack of the hydride ion, and therefore to piperidine **16d** as the major product. However, imine **A** can undergo stereoselective attack of the cyanide ion according to the Cram chelate model to give α-amino nitrile **D**, and, after cyclization and reduction by the hydride ion, piperidine-2-carbonitrile **24**. The alternative pathway (path b, Scheme 9) would involve reaction of the open-chain form of aldehyde **17** to give imine **B**. Attack of the cyanide ion on **B** can be ruled out, since piperidines **E** were never observed. Alternatively, reduction of imine **B** and formation of iminium ion **F** might lead to piperidine **24** by stereoselective cyanide addition at this level. This seems unlikely, but it cannot be completely excluded.



Scheme 9. Proposed mechanism for the formation of **24** during the reductive amination of **17** via intermediate cyanide **D**.

Amide **30** is also a suitable intermediate for the synthesis of new trihydroxypipecolic acid **14a**, recently synthesized **14b**,[37] and 2-aminomethylpiperidine iminosugars **15a** and **15b** (Scheme 10). Hydrolysis of the amido moiety and concomitant deprotection of the acetonide group of **30** was achieved by heating in HCl (6 M) for 16 h.[38] Purification of this hydrochloride salt was achieved by stirring in an aqueous NaOH solution for 1 h, followed by elution on an anion-exchange resin (Ambersep 900 OH) eluting sequentially with MeOH, H_2O, and HCl (6 M). Concentration of the acidic fractions gave pure **14a**·HCl in 71% yield (Scheme 10). Alternatively, catalytic hydrogenation, followed by heating in HCl (6 M) for 16 h, gave **14b**·HCl in 100% yield. This compound was characterized as the hydrochloride salt, since earlier isolation of the free amine[37] had resulted in great variability in the optical rotation measurement.



Scheme 10. Synthesis of trihydroxypipecolic acids **14a** and **14b** and of aminopiperidines **15a** and **15b**.

On the other hand, reduction of **30** with $LiAlH_4$ in refluxing THF gave diamine **31** in 79% yield. Treatment with methanolic HCl or catalytic hydrogenation under acidic conditions gave the hydrochloride salts of **15a** and **15b**,[39] respectively. Final elution through ion-exchange resin (DOWEX® 50XW8-100) led to the corresponding free amines in 89 and 95% yields, respectively (Scheme 10).

Biological Evaluation

Since natural compounds **5** and *ent*-**6** were reported to be unselective moderate inhibitors of glycosidases,[13f] our aim was to investigate the effect of the introduction of alkyl, aryl, or additional amino moieties on the activity and/or selectivity.[40] Compounds **5**, *ent*-**6**, **11a**–**11g**, **12a**–**12d**, **13a**–**13b**, **14a**–**14b**·HCl, and **15a**–**15b** were assayed as glycosidase inhibitors against a panel of commercially available glycosidases, following well established procedures.[41] The results are summarized in Table 2. The compounds tested did not show significant activity against β-galactosidase from *Escherichia coli*, α-glucosidases from rice, β-mannosidase from snail, and β-*N*-acetylglucosaminidase from Jack bean. In our hands, known compound *ent*-**6**[13f] showed the best activity against α-L-fucosidase, showing moderate inhibition, IC_{50} = 90.3 μM, of this enzyme. Previous results for this compound showed worse results, with an IC_{50} = 450 μM against the same enzyme, and no selectivity.[42] *N*-Substitution of compound *ent*-**6** reduces the inhibitory activity, isopropyl derivative **11a** being affected to a greater extent. *N*-Butyl derivative **11b** showed moderate activity, which is consistent with data reported[13f] for this compound. The presence of a free amino group or an acetamido group at the 1-*N*-alkyl side-chain is detrimental to α-L-fucosidase inhibition, as seen for compounds **11f** and **11g**. These compounds showed weak-to-moderate inhibitory activity against α-galactosidase from coffee beans.

Inversion of configuration at 5-OH, as in epimer **5**, greatly diminished the activity against α-L-fucosidase, and compound **5** also showed weak to moderate inhibition of the other enzymes.[43] The substitution of an OH group in **5** by an amino moiety (to give **12d**) reduced the inhibitory activity against the panel of tested enzymes, and this compound showed only a poor inhibition against amyloglucosidase from *Aspergillus niger*. Interestingly, the introduction of an aromatic moiety (in compound **12a**), increased the inhibitory activity against β-glucosidase from almonds to IC_{50} = 65.3 μM, which is consistent with data reported for other aryl iminosugars.[40,44] Changing the aryl moiety to alkyl chains (in **12b** and **12c**) resulted in a slight reduction of the inhibitory activity against β-glucosidase, and aminopiperidine **12d** did not inhibit this enzyme at all.

The inhibitory activity of the series of 3,4,5-trihydroxypipecolic acids have been evaluated,[37] and they were found to be weak inhibitors. In our hands, known compound **14b**·HCl showed only weak inhibition of α- and β-glucosidases.[37b] Significantly, benzyl derivative **14a**·HCl showed moderate inhibition of α-mannosidases, which is lost in *N*-benzyl aminomethyl derivative **15a**, and somewhat reduced in aminomethyl derivative **15b**. Changing the acid group to an amide group in **13a** and **13b** led to a complete loss of inhibitory activity.

Conclusions

In conclusion, a straightforward strategy for the synthesis of diversely functionalized polyhydroxy and polyhydroxyamino piperidines, including natural products **5** and *ent*-**6**, is presented. The synthesis involves a double reductive amination or a Strecker reaction on D-mannose-derived aldehydes **9** and **10**. This strategy also allowed the synthesis of trihydroxypipecolic acids **14a** and **14b**, and of (aminomethyl)piperidine iminosugars **15a** and **15b**. Bio-

Table 2. Inhibitory activities of compounds **5**, *ent*-**6**, **11a**–**11g**, **12a**–**12d**, **13a**–**13b**, **14a**–**14b**·HCl, and **15a**–**15b** against glycosidases. Percentage inhibition at 1 mM (IC_{50} in parentheses [μM]). Optimal pH, 37 °C.[a,b,c]

	α-L-Fuc-ase	α-Gal-ase	β-Gal-ase	α-Glc-ase	Amylogluc-ase	β-Glc-ase	α-Man-ase
5	38	–	47[d]	–	–	79	17
ent-**6**	89 (90.3)	–	–	–	–	–	–
11a	46	–	–	–	–	–	–
11b	72	22	–	–	–	–	–
11c	77	–	–	50	36	–	–
11d	–	–	–	–	–	48	–
11e	62	–	–	–	27	–	–
11f	–	32	–	–	–	–	–
11g	–	64	–	15	–	–	–
12a	–	–	–	–	24	83 (65.3)	–
12b	–	–	–	–	21	75	35
12c	–	–	–	–	16	66	–
12d	–	–	–	–	35	–	–
13a	–	–	–	–	–	–	–
13b	–	–	–	–	–	–	–
14a·HCl	18	–	–	–	37	–	70
14b·HCl	–	–	–	20	–	35	–
15a	–	–	–	–	–	–	–
15b	37	–	–	–	–	–	51

[a] For conditions of measurements see ref.[41b] and Exp. Section. [b] No inhibition was detected at 1 mM concentration of the corresponding compound. [c] α-L-Fucosidase from bovine kidney, α-galactosidase from coffee beans, β-galactosidase from *Aspergillus oryzae*, α-glucosidase from rice, Amyloglucosidase from *Aspergillus niger*, β-glucosidase from almonds, α-mannosidase from Jack bean. [d] β-Galactosidase from *Aspergillus oryzae* and from *Escherichia coli*.

logical evaluation of all the synthesized compounds against a range of commercially available glycosidases revealed that symmetrical compound **5** is an unselective and moderate-to-weak β-glucosidase inhibitor. Substitution of 5-OH by amino or alkyamino moieties does not greatly affect the inhibitory activity, except for the benzylamino group, which increases its specificity and activity against this enzyme. Compound *ent*-**6** (the C-5 epimer of **5**) is a moderate-to-good inhibitor of α-L-fucosidases; other structural variations of this compound diminish the inhibitory activity. The introduction of a substituent at position 2 of the piperidine skeleton led to a decrease in the inhibitory properties, as observed for amides **13**, trihydroxy pipecolic acids **14**, and aminomethyl derivatives **15**. Although the compounds prepared in this paper are not good inhibitors, significant information can be derived from their structure–activity relationships that will be valuable in the search for better enzyme inhibitors. Further exploitation of the potential of aldehydes **9** and **10** for the synthesis of other iminosugar mimetics is underway.

Experimental Section

General Methods: Commercially sourced reagents were used as received. All reactions were magnetically stirred and monitored by TLC on 0.25 mm silica gel plates (Merck F254). Column chromatography was carried out on silica gel 60 (32–63 μm), yields refer to spectroscopically and analytically pure compounds, unless otherwise stated. ^{1}H NMR spectra were recorded with Varian Mercury-400, Varian INOVA-400, or Bruker AVANCE-500 instruments. ^{13}C NMR spectra were recorded with Varian Gemini-200 or Bruker AVANCE-500 instruments. Infrared spectra were recorded with a Perkin–Elmer Spectrum BX FTIR System spectrophotometer. ESI full MS were recorded with a Thermo LTQ instrument by direct inlet; relative percentages are shown in brackets. Elemental analyses were carried out with a Perkin–Elmer 2400 analyzer. Optical rotation measurements were carried out with a JASCO DIP-370 polarimeter.

(3*R*,4*S*,5*R*)-5-Hydroxy-1-isopropyl-3,4-isopropylidenedioxypiperidine (16c): Aldehyde **9** (570 mg, 2.05 mmol) and benzylamine (220 μL, 2.05 mmol) were dissolved in MeOH (90 mL) under a nitrogen atmosphere, and molecular sieves (3 Å pellets; 300 mg) were added. The reaction mixture was stirred at room temperature for 40 min, then $Pd(OH)_2$/C (285 mg) was added. The mixture was stirred at room temperature under a hydrogen atmosphere for 4 d. The disappearance of benzyl signals was checked by ^{1}H NMR spectroscopy. The catalyst and the molecular sieves were removed by filtration, washing several times with MeOH, and the solvent was evaporated under vacuum. Purification of the residue by flash column chromatography on silica gel gave pure **16c** (121 mg, 0.56 mmol, 27%). R_f = 0.70 [CH_2Cl_2/MeOH/NH_4OH (6%), 10:1:0.1]. $[\alpha]_D^{24}$ = +23.0 (c = 1.04 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30–4.25 (m, 1 H, 3-H), 4.08 (dd, $^3J_{H,H}$ = 5.0, 3.6 Hz, 1 H, 4-H), 3.92 (dd, $^3J_{H,H}$ = 6.4, 3.6 Hz, 1 H, 5-H), 2.84–2.76 (m, 2 H, 2a-H, CH-*i*Pr), 2.61–2.59 (m, 2 H, 6-H), 2.38 (dd, $^2J_{H,H}$ = 11.6, $^3J_{H,H}$ = 8.0 Hz, 1 H, 2b-H), 1.49 (s, 3 H, Me), 1.34 (s, 3 H, Me), 1.00 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3-*i*Pr), 0.99 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3-*i*Pr) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 108.9 (s, acetal), 77.3 (d, C-4), 71.9 (d, C-3), 66.5 (d, C-5), 54.0 [d, N*C*H(CH_3)$_2$], 51.7 (t, C-2), 50.3 (t, C-6), 28.0 (q, Me), 26.1 (q, Me), 18.0 [q, NCH(*C*H_3)$_2$], 17.5 [q, NCH(*C*H_3)$_2$] ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3469, 2938, 2970, 2837, 2249, 1660, 1459, 1405, 1383, 1325, 1291, 1253, 1219, 1163, 1058 cm^{-1}. MS (ESI): *m*/*z* (%) = 216.11 (100) [M + H]$^+$. $C_{11}H_{21}NO_3$ (215.29): calcd. C 61.37, H 9.83, N 6.51; found C 61.57, H 10.02, N 6.31.

(3*R*,4*S*,5*R*)-3,4,5-Trihydroxy-1-isopropylpiperidine (11a): A solution of **16c** (40 mg, 0.19 mmol) in MeOH (10.0 mL) was stirred with HCl (12 M; 8 drops) at room temperature for 24 h. The crude mixture was concentrated to give the hydrochloride salt of **11a**. The corresponding free amine was obtained by passing the hydrochlo-

ride salt through DOWEX® 50XW8-100 ion-exchange resin. Elution with 6% ammonia gave free base **11a** (33 mg, 0.19 mmol, 100%). $[\alpha]_D^{24}$ = –41.9 (*c* = 0.65 in H_2O). ^1H NMR (400 MHz, D_2O): δ = 3.86 (m, 1 H, 3-H), 3.72 (td, $^3J_{H,H}$ = 8.8, 4.4 Hz, 1 H, 5-H), 3.34 (dd, $^3J_{H,H}$ = 8.3, 2.9 Hz, 1 H, 4-H), 2.77–2.64 (m, 3 H, 2a-H, 6a-H, CH-*i*Pr), 2.31 (dd, $^2J_{H,H}$ = 12.4, $^3J_{H,H}$ = 1.7 Hz, 1 H, 2b-H), 2.12 (t, $J_{H,H}$ = 10.0 Hz, 1 H, 6b-H), 0.91 (d, $^3J_{H,H}$ = 9.2 Hz, 3 H, CH_3-*i*Pr), 0.89 (d, $^3J_{H,H}$ = 9.2 Hz, 3 H, CH_3-*i*Pr) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 73.6 (d, C-4), 67.7 (d, C-5), 67.5 (d, C-3), 54.0 [d, N*C*H(CH_3)$_2$], 52.2 (t, C-6), 50.6 (t, C-2), 17.6 [q, NCH(*C*H_3)$_2$], 16.2 [q, NCH(*C*H_3)$_2$] ppm. MS (ESI): *m*/*z* (%) = 198.17 (100) $[M + Na]^+$. $C_8H_{17}NO_3$ (175.23): calcd. C 54.84, H 9.78, N 7.99; found C 55.15, H 9.92, N 7.68.

(3*R*,4*S*,5*R*)-1-(3-Azidopropyl)-5-hydroxy-3,4-(isopropylidenedioxy)-piperidine (16e): Compound **17** (147 mg, 0.78 mmol) was dissolved in dry MeOH (10 mL), and a solution of 3-azidopropyl-1-amine (78 mg, 0.78 mmol) in dry MeOH (13 mL) and molecular sieves (3 Å powdered) were added. The mixture was stirred under a nitrogen atmosphere for 4 h. The disappearence of the aldehyde was checked by ^1H NMR spectroscopy. Then $NaBH_3CN$ (147 mg, 2.34 mmol) and AcOH (90 μL, 1.56 mmol) were added. The reaction mixture was stirred at room temperature for a week, and then it was concentrated under vacuum. The crude product was purified by gradient flash column chromatography (CH_2Cl_2/MeOH, 20:1 to 10:1), to give **16e** (132 mg, 0.52 mmol, 67%) as a pale yellow oil. R_f = 0.26 (CH_2Cl_2/MeOH, 20:1). $[\alpha]_D^{23}$ = +16.3 (*c* = 0.92 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.29 (pq, $^3J_{H,H}$ = 5.9 Hz, 1 H, 3-H), 4.04 (pseudo-t, $^3J_{H,H}$ = 4.7 Hz, 1 H, 4-H), 3.96–3.93 (m, 1 H, 5-H), 3.34 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, 3′-H), 2.73 (ddd, $^2J_{H,H}$ = 12.0, $^3J_{H,H}$ = 6.0, $^4J_{H,H}$ = 1.5 Hz, 1 H, 2a-H), 2.60 (dd, $^2J_{H,H}$ = 11.7, $^3J_{H,H}$ = 2.9 Hz, 1 H, 6a-H), 2.50–2.41 (m, 4 H, 2b-H, 6b-H, 1′-H), 1.75 (quint, $^3J_{H,H}$ = 6.8 Hz, 2 H, 2′-H), 1.50 (s, 3 H, Me), 1.36 (s, 3 H, Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 109.0 (s, acetal), 76.7 (d, C-4), 71.8 (d, C-3), 67.5 (d, C-5), 55.3 (t, C-6), 55.2 (t, C-2), 54.3 (t, C-1′), 49.2 (t, C-3′), 28.0 (q, Me), 26.0 (t, C-2′), 25.9 (q, Me) ppm. MS (ESI): *m*/*z* (%) = 279.14 (100) $[M + Na]^+$, 257.27 (20) $[M + H]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3677, 3608, 3487, 2987, 2944, 2823, 2237, 2099, 1456, 1378, 1219, 1060 cm^{-1}. $C_{11}H_{20}N_4O_3$ (256.30): calcd. C 51.55, H 7.87, N 21.86; found C 51.91, H 7.94, N 21.61.

(3*R*,5*R*)-1-(3-Azidopropyl)-3,4,5-trihydroxypiperidine (11e): A solution of **16e** (44 mg, 0.17 mmol) in MeOH (2.0 mL) was stirred with HCl (12 M; 142 μL, 1.7 mmol) at room temperature for 18 h. The crude mixture was concentrated to give the hydrochloride salt of **11e**. The corresponding free amine was obtained by passing the hydrochloride salt through DOWEX® 50XW8–100 ion-exchange resin. Elution with 6% ammonia gave free base **11e** (33 mg, 0.15 mmol, 88%). $[\alpha]_D^{21}$ = –21.2 (*c* = 0.74 in MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 3.89 (dt, $^3J_{H,H}$ = 5.8, 2.9 Hz, 1 H, 3-H), 3.78 (td, $^3J_{H,H}$ = 7.8, 4.3 Hz 1 H, 5-H), 3.40–3.38 (m, 1 H, 4-H), 3.36 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, 3′-H), 2.82–2.74 (m, 2 H, 6a-H, 2a-H), 2.46 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, 1′-H), 2.31 (d, $^2J_{H,H}$ = 11.2 Hz, 1 H, 2b-H), 2.12–2.09 (m, 1 H, 6b-H), 1.76 (quint, $^3J_{H,H}$ = 6.8 Hz, 2 H, 2′-H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 72.9 (d, C-4), 67.2 (d, C-5), 66.8 (d, C-3), 55.8 (t, C-6), 55.2 (t, C-2), 53.7 (t, C-1′), 48.2 (t, C-3′), 24.8 (t, C-2′) ppm. MS (ESI): *m*/*z* (%) = 217.17 (100) $[M + H]^+$. $C_8H_{16}N_4O_3$ (216.24): calcd. C 44.44, H 7.46, N 25.91; found C 44.29, H 7.79, N 25.71.

(3*R*,5*R*)-1-(3-Aminopropyl)-3,4,5-trihydroxypiperidine (11f): Compound **11e** (40 mg, 0.18 mmol) was dissolved in MeOH (3 mL) and HCl (12 M; 6 drops), and Pd/C (25 mg) was added. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 3 d. The catalyst was filtered through Celite®, and the filtrate was concentrated under vacuum to give the hydrochloride salt of **11f**, which was then passed through ion-exchange resin (DOWEX® 50XW8–100). Elution with MeOH, H_2O, and NH_4OH (15%) gave amine **11f** (34 mg, 0.18 mol, quantitative). $[\alpha]_D^{23}$ = –37.1 (*c* = 0.77 in H_2O). ^1H NMR (500 MHz, CD_3OD): δ = 3.94 (td, $^3J_{H,H}$ = 5.5, 2.6 Hz, 1 H, 3-H), 3.81 (td, $^3J_{H,H}$ = 8.0, 4.1 Hz, 1 H, 5-H), 3.42 (br. s, 1 H, 4-H), 3.11 (t, $^3J_{H,H}$ = 6.6 Hz, 0.5 H, 3′-H of HCO_3^- salt), 2.90 (t, $^3J_{H,H}$ = 6.6 Hz, 1.5 H, 3′-H of free amine), 2.87–2.78 (m, 2 H, 6a-H, 2a-H), 2.59–2.49 (m, 1.5 H, 1′-H of free amine), 2.48–2.41 (m, 0.5 H, 1′-H of HCO_3^- salt), 2.37–2.24 (m, 1 H, 2b-H), 2.21–2.10 (m, 1 H, 6b-H), 1.76 (dquint, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 6.6 Hz, 1.5 H, 2′-H of free amine), 1.68 (quint, $^3J_{H,H}$ = 7.1 Hz, 0.5 H, 2′-H of HCO_3^- salt) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 164.5, 160.1 (s, H*C*O_3^-), 74.0 (d, C-4), 68.3 (d, C-5), 67.9 (d, C-3), 56.9 (t, C-6), 56.0 (t, C-2), 55.8, 55.4 (C-1′, HCO_3^- and free amine), 39.9, 39.6 (C-3′, HCO_3^- salt and free amine), 27.2–26.0 (C-2′, HCO_3^- salt and free amine) ppm. ^1H NMR (400 MHz, D_2O): δ = 3.90–3.87 (m, 1 H, 3-H), 3.77–3.71 (m, 1 H, 5-H), 3.39–3.37 (m, 1 H, 4-H), 2.89 (t, $^3J_{H,H}$ = 6.8 Hz, 0.8 H, 3′-H of HCO_3^- salt), 2.78 (t, $^3J_{H,H}$ = 6.8 Hz, 1.2 H, 3′-H of free amine), 2.80–2.69 (m, 2 H, 6a-H, 2a-H), 2.48–2.26 (m, 2 H, 1′-H), 2.21 [br. d, $^2J_{H,H}$ = 11.7 Hz, 1 H, 2b-H), 2.60–1.94 (m, 1 H, 6b-H), 1.65 (quint, $^3J_{H,H}$ = 7.3 Hz, 1.3 H, 2′-H of free amine), 1.52 (quint, $^3J_{H,H}$ = 7.3 Hz, 0.7 H, 2′-H of HCO_3^- salt) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 73.6 (d, C-4), 67.6 (d, C-3), 67.5 (d, C-5), 56.4 (t, C-6), 55.5 (t, C-2), 54.7 (C-1′, HCO_3^- and free amine), 39.4, 38.8 (C-3′, HCO_3^- salt and free amine), 26.4–25.5 (C-2′, HCO_3^- salt and free amine) ppm. MS (ESI): *m*/*z* (%) = 191.08 (100) $[M + H]^+$.

(3*R*,5*R*)-3,4,5-tri-*O*-Acetyl-1-[3-(acetylamino)propyl]piperidine-3,4,5-trihydroxypiperidine (18): A solution of **11f** (13 mg, 0.07 mmol) in pyridine (0.3 mL) and Ac_2O (0.2 mL) was stirred at room temperature for 18 h, and then concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 15:1) to give **18** (22 mg, 0.06 mmol, 86%) as a colourless oil. R_f = 0.32 (CH_2Cl_2/MeOH, 15:1). $[\alpha]_D^{25}$ = –58.5 (*c* = 0.93 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.65 (br. s, 1 H, NH), 5.30 (dt, $^3J_{H,H}$ = 5.2, 2.7 Hz, 1 H, 3-H), 5.11 (dt, $^3J_{H,H}$ = 8.6, 4.3 Hz, 1 H, 5-H), 4.95 (dd, $^3J_{H,H}$ = 8.6, 3.6 Hz, 1 H, 4-H), 3.46 (td, $^2J_{H,H}$ = 12.1, $^3J_{H,H}$ = 5.8 Hz, 1 H, 3′a-H), 3.20–3.12 (m, 1 H, 3′b-H), 3.04–3.02 (m, 1 H, 6a-H), 2.86–2.83 (m, 1 H, 2a-H), 2.46 (t, $^3J_{H,H}$ = 6.3 Hz, 2 H, 1′-H), 2.44 (d, $^2J_{H,H}$ = 11.7 Hz, 1 H, 2b-H), 2.24–2.18 (m, 1 H, 6b-H), 2.08 (s, 3 H, Me), 2.04 (s, 3 H, Me), 2.02 (s, 3 H, Me), 1.98 (s, 3 H, Me), 1.64 (quint, $^3J_{H,H}$ = 6.3 Hz, 2 H, 2′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.5–169.9 (s, 4 C, *C*OCH_3), 70.7 (d, C-4), 67.9 (d, C-5), 67.7 (d, C-3), 56.0 (t, C-1′), 54.0 (t, C-6), 53.8 (t, C-2), 38.9 (t, C-3′), 25.5 (t, C-2′), 23.2–20.7 (q, 4 C, CO*C*H_3) ppm. MS (ESI): *m*/*z* (%) = 381.41 (100) $[M + Na]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3689, 3606, 3451, 3312, 3950, 2825, 2257, 2245, 1743, 1660, 1522, 1372, 1230, 1050 cm^{-1}. $C_{16}H_{26}N_2O_7$ (358.39): calcd. C 53.62, H 7.31, N 7.82; found C 53.20, H 7.42, N 8.16.

(3*R*,5*R*)-1-[3-(Acetylamino)propyl]-3,4,5-trihydroxypiperidine (11g): Compound **18** (74 mg, 0.21 mmol) was dissolved in MeOH (7 mL), and Ambersep® 900-OH (300 mg) was added. The mixture was stirred at room temperature. After 2 h, the ion-exchange resin was removed by filtration, washing with MeOH. The solvent was evaporated under vacuum to give pure **11g** (48 mg, 0.15 mmol, 71%). $[\alpha]_D^{24}$ = –33.1 (*c* = 1.17 in H_2O). ^1H NMR (400 MHz, D_2O): δ = 3.88–3.86 (m, 1 H, 3-H), 3.73 (td, $^3J_{H,H}$ = 8.8, 4.4 Hz, 1 H, 5-H), 3.37 (dd, $^3J_{H,H}$ = 8.3, 2.4 Hz 1 H, 4-H), 3.06 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, 3′-H), 2.77–2.71 (m, 2 H, 6a-H, 2a-H), 2.36–2.25 (m, 2 H, 1′-H), 2.18 (d, $^2J_{H,H}$ = 12.2 Hz, 1 H, 2b-H), 2.02–1.92 (m, 1 H, 6b-

H), 1.85 (s, 3 H, Me), 1.57 (quint, $^3J_{H,H}$ = 6.8 Hz, 2 H, 2′-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 173.91 (s, *C*OCH$_3$), 75.6 (d, C-4), 67.6 (d, C-3), 67.5 (d, C-5), 56.4 (t, C-1′), 55.5 (t, C-2), 54.5 (t, C-6), 37.6 (t, C-3′), 25.1 (q, CO*C*H$_3$), 21.8 (t, C-2′) ppm. MS (ESI): *m*/*z* (%) = 255.08 (100) [M + Na]$^+$, 233.17 (72) [M + H]$^+$. $C_{10}H_{20}N_2O_4$ (232.28): calcd. C 51.71, H 8.68, N 12.06; found C 51.61, H 8.39, N 12.10.

(3*R*,4*S*,5*S*)-*N*-Boc-5-(Benzylamino)-3,4-(isopropylidenedioxy)piperidine (22a): A solution of ketone **20** (69 mg, 0.25 mmol) in dry MeOH (4.5 mL) was stirred in the presence of molecular sieves (3 Å powder) for 15 min under a nitrogen atmosphere, and then benzylamine (43 μL, 0.39 mmol) and AcOH (22 μL, 0.39 mmol) were added. The reaction mixture was stirred for 3 h, and then $NaBH_3CN$ (49 mg, 0.78 mmol) and more AcOH (8 μL, 0.13 mmol) were added. The mixture was stirred for 25 h under a nitrogen atmosphere. The molecular sieves were removed by filtration through Celite®, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc/NEt_3, 2:1:0.1) to give **22a** (43 mg, 0.12 mmol, 48%). R_f = 0.26 (petroleum ether/EtOAc/NEt_3, 2:1:0.1). $[\alpha]_D^{25}$ = +16.25 (*c* = 0.8 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 5 H, Ar), 4.41 (dd, $^3J_{H,H}$ = 6.8, 2.5 Hz, 1 H, 4-H), 4.27 (br. s, 1 H, 3-H), 3.90 (m, 2 H, Bn), 3.66–3.55 (m, 2 H, 2a-H, 6a-H), 3.28 (dd, $^2J_{H,H}$ = 14.0, $^2J_{H,H}$ = 3.9 Hz, 1 H, 2b-H), 2.98 (t, $J_{H,H}$ = 11.7 Hz, 1 H, 6b-H), 2.84 (m, 1 H, 5-H), 1.45 (s, 12 H, *t*Bu, Me), 1.34 (s, 3 H, Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.2 (s, C=O), 139.9 (s, Ar), 128.4–127.1 (d, 5 C, Ar), 108.8 (s, acetal), 79.7 (s, O*C*tBu), 72.4 (d, 2 C, C-3, C-4), 52.4 (d, C-5), 50.5 (t, Bn), 42.5 (t, 2 C, C-2, C-6), 28.4 (3 C, q, *t*Bu), 26.9 (q, Me), 24.9 (q, Me) ppm. MS (ESI): *m*/*z* (%) = 385.25 (100) [M + Na]$^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3333, 2981, 2933, 2248, 1685, 1454, 1413, 1163 cm^{-1}.

General Procedure for the Synthesis of 5-*N*-Alkylated Aminopiperidines 22b and 22c: Ketone **20** and the appropriate amine (1.5 equiv.) were dissolved in MeOH (0.05 M), and molecular sieves (3 Å pellets; 25 mg) were added. The reaction mixture was stirred at room temperature for 50 min, and when ^{1}H NMR spectroscopy indicated that the conversion into the imine was complete, Pd(OH)$_2$/C (50 wt.-%) was added. The mixture was stirred at room temperature under a hydrogen atmosphere for 24 h. The catalyst and the molecular sieves were removed by filtration, washing several times with MeOH, and the solvent was evaporated under vacuum.

(3*R*,4*S*,5*S*)-*N*-Boc-5-Butylamino-3,4-(isopropylidenedioxy)piperidine (22b): Application of this procedure to **20** (68 mg, 0.25 mmol) with butylamine (37 μL, 0.38 mmol) gave, after purification by flash column chromatography (petroleum ether/EtOAc, 2:1), compound **22b** (57 mg, 0.17 mmol, 68%) as a colourless oil. R_f = 0.16 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.46 (m, 1 H, 4-H), 4.29 (br. s, 1 H, 3-H), 3.59–3.50 (m, 2 H), 3.31, (dd, $^2J_{H,H}$ = 4.3, $^3J_{H,H}$ = 3.7 Hz, 1 H), 2.98–2.65 (m, 4 H), 1.56–1.16 (m, 19 H, *t*Bu, Me, 2′-H, 3′-H), 0.86 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, 4′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.2 (s, C=O), 108.8 (s, acetal), 79.7 (s, O*C*tBu), 72.4 (d, 2 C, C-3, C-4), 53.5, 46.6, 42.8 (4 C, C-2, C-5, C-6, C-1′), 32.4–20.3 (7 C, *t*Bu, Me, C-2′, C-3′), 13.9 (q, C-4′) ppm. MS (ESI): *m*/*z* (%) = 329.25 (100) [M + H]$^+$.

(3*R*,4*S*,5*S*)-*N*-Boc-3,4-(Isopropylidenedioxy)-5-octylaminopiperidine (22c): Application of this procedure to **20** (52 mg, 0.19 mmol) with octylamine (47 μL, 0.28 mmol) gave, after purification by gradient flash column chromatography (petroleum ether/EtOAc, from 5:1 to 2.1), compound **22c** (39 mg, 0.10 mmol, 53%). R_f = 0.39 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.44 (m, 1 H, 4-H), 4.30 (br. s, 1 H, 3-H), 3.79–3.55 (m, 2 H), 3.32 (dd, $^2J_{H,H}$ = 14.1, $^3J_{H,H}$ = 3.5 Hz, 1 H), 2.98–2.68 (m, 4 H), 1.99 (m, 2 H, 2′-H), 1.53–1.13 (m, 25 H, 3′-H–7′-H, Me, *t*Bu), 0.87 (t, *J* = 6.3 Hz, 3 H, 8′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.2 (s, C=O), 108.8 (s, acetal), 79.6 (s, O*C*tBu), 72.4 (d, 2 C, C-3, C-4), 53.5, 46.9 (2 C, C-5, C-1′), 42.4 (t, 2 C, C-2, C-6), 31.8–22.6 (11 C, C-2′–C-7′, Me, *t*Bu), 14.0 (q, C-8′) ppm. MS (ESI): *m*/*z* (%) = 385.33 (100) [M + H]$^+$.

General Procedure for the Synthesis of 5-*N*-Alkylated Aminopiperidines 12a–12c: A solution of **22a**–**22c** in MeOH (0.02 M) was stirred with HCl (12 M; 5 drops) at room temperature overnight. The crude mixture was concentrated to give the hydrochloride salts of **12a**–**12c**. The corresponding free amines were obtained by passing the hydrochloride salts through DOWEX® 50XW8–100 ion-exchange resin. Elution with ammonia (6%) gave free bases **12a**–**12c**.

(3*R*,4*S*,5*S*)-5-(Benzylamino)-3,4-dihydroxypiperidine (12a): Application of this procedure to **22a** (28 mg, 0.08 mmol) gave free amine **12a** (17 mg, 0.08 mmol, 100%). $[\alpha]_D^{25}$ = –3.6 (*c* = 0.74 in MeOH). ^{1}H NMR (400 MHz, D_2O): δ = 7.32–7.22 (m, 5 H, Ar), 4.04 (br. s, 1 H, 4-H), 3.76 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, Bn), 3.69 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, Bn), 3.53 (ddd, $^3J_{H,H}$ = 10.5, 4.7, 1.9 Hz, 1 H, 3-H), 2.77–2.64 (m, 3 H, 6a-H, 2a-H, 5-H), 2.55 (t, $^2J_{H,H}$ = 11.5 Hz, 1 H, 2b-H), 2.43 (t, $^2J_{H,H}$ = 11.5 Hz, 6b-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 137.4 (s, Ar), 127.8–126.6 (d, 5 C, Ar), 67.6 (d, C-3), 67.2 (d, C-4), 54.4 (d, C-5), 48.2 (t, Bn), 43.15 (t, C-2), 41.6 (t, C-6) ppm. MS (ESI): *m*/*z* (%) = 223.17 (100) [M + H]$^+$. $C_{12}H_{18}N_2O_2$ (222.28): calcd. C 64.84, H 8.16, N 12.60; found C 65.15, H 8.34, N 12.36.

(3*R*,4*S*,5*S*)-5-(Butylamino)-3,4-dihydroxypiperidine (12b): Application of this procedure to **22b** (20 mg, 0.06 mmol) gave free amine **12b** (12 mg, 0.06 mmol, 100%) as a colourless oil. $[\alpha]_D^{26}$ = –8.1 (*c* = 0.44 in H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 4.04 (br. s, 1 H, 4-H), 3.56 (m, 1 H, 3-H), 2.77–3.89 (m, 7 H, 2-H, 5-H, 6-H, 1′-H), 1.38 (quint, $^3J_{H,H}$ = 7.4 Hz, 2 H, 2′-H), 1.22 (sext, $^3J_{H,H}$ = 7.3 Hz, 2 H, 3′-H), 0.78 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H, 4′-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 68.6 (d, C-3), 67.9 (d, C-4), 56.2 (d, C-5), 44.9 (t, C-1′), 44.3, (t, C-2), 42.3 (t, C-6), 30.1 (t, C-2′), 19.7 (t, C-3′), 13.1 (q, C-4′) ppm. MS (ESI): *m*/*z* (%) = 189.17 (100) [M + H]$^+$. $C_9H_{20}N_2O_2$ (188.27): calcd. C 57.42, H 10.71, N 14.88; found C 57.68, H 10.98, N 14.56.

(3*R*,4*S*,5*S*)-3,4-Dihydroxy-5-(octylamino)piperidine (12c): Application of this procedure to **22c** (38 mg, 0.10 mmol) gave free amine **12c** (14 mg, 0.06 mmol, 60%) as a colourless oil. $[\alpha]_D^{24}$ = –2.5 (*c* = 0.36 in MeOH). ^{1}H NMR (400 MHz, D_2O): δ = 4.03 (br. s, 1 H, 4-H), 3.57 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, 3-H), 2.78–2.47 (m, 7 H, 2-H, 5-H, 6-H, 1′-H), 1.42 (br. s, 2 H, 2′-H), 1.17 (m, 10 H, 3′-H–7′-H), 0.74 (t, $^3J_{H,H}$ = 6.8 Hz, 3 H, 8′-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = ppm = 67.7 (d, C-3), 66.8 (d, C-4), 55.6 (d, C-5), 44.8 (t, C-1′), 43.7 (t, C-2), 41.4 (t, C-6), 30.6–21.4 (t, 6 C, C-2′–C-7′), 12.8 (q, C-8′) ppm. MS (ESI): *m*/*z* (%) = 245.25 (100) [M + H]$^+$. $C_{13}H_{28}N_2O_2$ (244.37): calcd. C 63.89, H 11.55, N 11.46; found C 64.15, H 11.78, N 11.63.

(3*R*,4*S*,5*S*)-5-Amino-3,4-dihydroxypiperidine (12d): Compound **22a** (35 mg, 0.10 mmol) was dissolved in MeOH (5 mL) and HCl (12 M; 3 drops), and Pd/C (18 mg) was added. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 6 d. The catalyst was filtered through Celite®, and the filtrate was concentrated under vacuum to give the hydrochloride salt of **12d** (quantitative). This was eluted through an ion-exchange resin (DOWEX® 50XW8–100) with MeOH, H_2O, and NH_4OH (6%) to give free amine **12d** (13 mg, 0.10 mmol, 100%). $[\alpha]_D^{25}$ = +3.84 (*c* = 0.25 in MeOH). ^{1}H NMR (400 MHz D_2O): δ = 3.84 (pseudo-t, $^3J_{H,H}$ = 2.5 Hz, 1 H, 4-H), 3.61 (m, 1 H, 3-H), 2.81 (m, 1 H, 5-H),

2.68 (dt, $^2J_{H,H}$ = 11.3, $^3J_{H,H}$ = 4.6 Hz, 2 H, 2a-H, 6a-H), 2.55 (t, $J_{H,H}$ = 11.1 Hz, 1 H, 2b-H), 2.45 (t, $J_{H,H}$ = 11.4 Hz, 1 H, 6b-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 70.3 (d, C-4), 68.4 (d, C-3), 50.0 (d, C-5), 44.7 (t, C-6), 44.2 (t, C-2) ppm. MS (ESI): *m*/*z* (%) = 155.11 (100) $[M + Na]^+$, 133.09 (32) $[M + H]^+$. $C_5H_{12}N_2O_2$ (132.16): calcd. C 45.44, H 9.15, N 21.20; found C 45.32, H 9.45, N 21.17.

1-*O*-Acetyl-2,3-*O*-isopropylidene-α-D-*lyxo*-pentofuranose-5-ulose (10): Compound **26** (7.22 g, 27.8 mmol) was dissolved in pyridine (12 mL) and Ac_2O (8 mL), and the mixture was stirred at room temperature for 3 h. The mixture was diluted with EtOAc (100 mL), and washed sequentially with a CH_3COOH (1 M; 2× 150 mL), saturated aqueous $NaHCO_3$ (2× 60 mL), and brine (60 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give **27** (8.21 g, 27.2 mmol, 98%).

A solution of **27** (8.21 g, 27.15 mmol), glacial AcOH (102 mL), and water (44 mL) was stirred for 18 h at room temperature, and then it was concentrated under reduced pressure. The residue was dissolved in EtOAc (200 mL), and this solution was washed sequentially with saturated aqueous $NaHCO_3$ (2× 70 mL), water (2× 40 mL), and brine (2× 50 mL), then it was dried (Na_2SO_4), and the solvent was removed in vacuo to give **28** (5.81 g, 22.2 mmol, 82%) as a colourless oil.

A solution of **28** (1.57, 5.99 mmol) in CH_2Cl_2 (25 mL) was added to a vigorously stirred suspension of silica-gel-supported $NaIO_4$ reagent[34] (12.1 g) in CH_2Cl_2 (25 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was then filtered, washing the residue with $CHCl_3$. The combined filtrates were concentrated under reduced pressure and the residue was purified by gradient flash chromatography (EtOAc/petroleum ether, from 1:1 to 7:1), to give **10** as a colourless oil (1.12 g, 4.87 mmol, 81%). R_f = 0.68 (EtOAc/petroleum ether, 7:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (d, $^3J_{H,H}$ = 1.6 Hz, 1 H, aldehyde), 6.29 (s, 1 H, 1-H), 5.11 (dd, $^3J_{H,H}$ = 5.8, 4.3 Hz, 1 H, 3-H), 4.73 (d, $^3J_{H,H}$ = 5.8 Hz, 1 H, 2-H), 4.42 (dd, $^3J_{H,H}$ = 4.3, 1.6 Hz, 1 H, 4-H), 2.05 (s, 3 H, OAc), 1.43 (s, 3 H, Me), 1.28 (s, 3 H, Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.7 (d, H*C*=O), 169.2 (s, O*C*=OCH$_3$), 114.0 (s, acetal), 100.1 (d, C-1), 85.3 (d, C-4), 84.5 (d, C-2), 80.9 (d, C-3), 25.8 (q, Me), 24.5 (q, Me), 20.9 (q, OC=O*C*H$_3$) ppm. MS (ESI): *m*/*z* (%) = 285.17 (100) [(M + MeOH) + Na]$^+$.

1-*O*-Acetyl-5-(benzylamino)-5-cyano-5-deoxy-2,3-*O*-(1-methylethylidene)-β-L-*erythro*-pentofuranose (29a): Aldehyde **10** (505 mg, 2.19 mmol) was dissolved in dry CH_3CN (11.0 mL) under a nitrogen atmosphere, and $BnNH_2$ (240 μL, 2.19 mmol) and molecular sieves (3 Å pellets) were added. The mixture was stirred at room temperature for 40 min, then TMSCN (274 μL, 2.19 mmol) was added dropwise. The solution was stirred at room temperature for 18 h, then it was diluted with EtOAc, washed with satd. aq. $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. The ^{1}H NMR spectrum of the crude mixture showed the formation of two diasteroisomers in an 86:14 ratio. Purification of the crude product using silica gel gradient flash chromatography (EtOAc/petroleum ether, from 1:2 to 1:1) gave the major diastereoisomer **29a** (516 mg, 1.49 mmol, 68%) as a white solid. R_f = 0.43 (EtOAc/petroleum ether, 1:2), m.p. 80–82 °C. $[\alpha]_D^{19}$ = +70.2 (*c* = 0.98 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.04 (m, 5 H, Ar), 6.00 (s, 1 H, 1-H), 4.68 (dd, $^3J_{H,H}$ = 5.8, 3.9 Hz, 1 H, 3-H), 4.50 (d, $^3J_{H,H}$ = 5.8 Hz, 1 H, 2-H), 4.03 (dd, $^3J_{H,H}$ = 7.8, 3.9 Hz, 1 H, 4-H), 3.89 (d, $^2J_{H,H}$ = 12.9 Hz, 1 H, Bn), 3.75 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 5-H), 3.64 (d, $^2J_{H,H}$ = 12.9 Hz, 1 H, Bn), 1.83 (s, 3 H, OAc), 1.32 (s, 3 H, Me), 1.11 (s, 3 H, Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.1 (s, O*C*=OCH$_3$), 138.0 (s, Ar), 128.6–127.7 (d, 5 C, Ar), 117.7, 114.2 (2 C, CN, acetal), 100.3 (d, C-1), 84.5 (d, C-2), 80.3 (d, C-4), 78.8 (d, C-3), 51.7 (t, Bn), 49.2 (d, C-5), 25.1 (q, Me), 24.5 (q, Me), 21.0 (q, OC=O*C*H$_3$) ppm. MS (ESI): *m*/*z* (%) = 369.08 (100) $[M + Na]^+$. IR (KBr): $\tilde{\nu}$ = 3483, 3350, 2988, 2943, 2920, 2359, 2231, 1747, 1605, 1460 cm^{-1}. $C_{18}H_{22}N_2O_5$ (346.38): calcd. C 62.42, H 6.40, N 8.09; found C 62.79, H 6.27, N 8.05.

(2*S*,3*R*,4*S*,5*R*)-2-(Aminocarbonyl)-1-benzyl-3-hydroxy-4,5-(isopropylidenedioxy)piperidine (30): Compound **29a** (376 mg, 1.09 mmol) was dissolved in MeOH (43 mL), Ambersep® 900-OH (8.5 g) was added, and the mixture was stirred at room temperature. After 2 h, the ion-exchange resin was removed by filtration, washing with MeOH, and $NaBH_3CN$ (75 mg, 1.20 mmol) and CH_3COOH (125 μL, 2.18 mmol) were added. The solution was stirred at room temperature for 18 h, until ^{1}H NMR spectroscopic analysis of the crude mixture showed the complete formation of a new product. The solvent was evaporated under vacuum, and the residue was purified using silica gel flash chromatography [CH_2Cl_2/MeOH/NH_4OH (6%), 10:1:0.1] to give compound **30** (262 mg, 0.86 mmol, 79%) as a waxy solid. R_f = 0.43 [CH_2Cl_2/MeOH/NH_4OH (6%), 10:1:0.1]. $[\alpha]_D^{29}$ = –5.6 (*c* = 0.76 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H, Ar), 5.99 (br. s, 2 H, NH_2), 4.29 (dt, $^3J_{H,H}$ = 6.9, 3.4 Hz, 1 H, 5-H), 4.24 (t, $^3J_{H,H}$ = 6.4 Hz, 1 H, 4-H), 4.17 (m, 1 H, 3-H), 4.02 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H, Bn), 3.86 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H, Bn), 3.51 (d, $^3J_{H,H}$ = 4.4 Hz, 1 H, 2-H), 3.15 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 3.0 Hz, 1 H, 6a-H), 2.94 (dd, $^3J_{H,H}$ = 14.2, $^3J_{H,H}$ = 3.7 Hz, 1 H, 6b-H), 1.56 (s, 3 H, Me), 1.34 (s, 3 H, Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.4 (s, C=O), 138.2 (s, Ar), 128.9–127.5 (d, 5 C, Ar), 109.2 (s, acetal), 76.0 (d, C-4), 73.6 (d, C-5), 68.8 (d, C-3), 62.3 (d, C-2), 61.0 (t, Bn), 45.9 (t, C-6), 27.4 (q, Me), 24.6 (q, Me) ppm. MS (ESI): *m*/*z* (%) = 329.33 (100) $[M + Na]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3687, 3608, 3498, 3364, 3031, 2991, 2935, 1676, 1384, 1210, 1049 cm^{-1}. $C_{16}H_{22}N_2O_4$ (306.36): calcd. C 62.73, H 7.24, N 9.14; found C 62.76, H 7.24, N 9.19.

(2*R*,3*R*,4*R*,5*R*)-2-(Aminocarbonyl)-1-benzyl-3,4,5-trihydroxypiperidine (13a): A solution of **30** (17 mg, 0.05 mmol) in MeOH (4.0 mL) and HCl (1 M; 4 drops) was stirred at room temperature overnight. The crude mixture was concentrated to give the hydrochloride salt of **13a**, which was eluted through ion-exchange resin (DOWEX® 50XW8-100) with MeOH, H_2O, and NH_4OH (6%) to give free amine **13a** (11 mg, 0.04 mmol, 80%). $[\alpha]_D^{26}$ = +17.0 (*c* = 0.56 in H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 7.30–7.21 (5 H, Ar), 3.90–3.85 (m, 3 H, 3-H, 4-H, 5-H), 3.71 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H, Bn), 3.45 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H, Bn), 3.26 (br. s, 1 H, 2-H), 2.86 (dd, $^2J_{H,H}$ = 12.2, $^3J_{H,H}$ = 3.4 Hz, 1 H, 6a-H), 2.36 (pseudo-t, $J_{H,H}$ = 9.0 Hz, 1 H, 6b-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 175.7 (s, C=O), 136.4 (s, Ar), 129.8–127.9 (d, 5 C, Ar), 69.7, 69.4, 66.1 (d, 3 C, C-3, C-4, C-5), 64.6 (d, C-2), 59.2 (t, Bn), 50.5 (t, C-6) ppm. MS (ESI): *m*/*z* (%) = 289.13 (100) $[M + Na]^+$, 267.33 (48) $[M + H]^+$. $C_{13}H_{18}N_2O_4$ (266.29): calcd. C 58.63, H 6.81, N 10.52; found C 58.15, H 7.26, N 10.32.

(2*R*,3*R*,4*R*,5*R*)-2-(Aminocarbonyl)-3,4,5-trihydroxypiperidine (13b): Compound **30** (50 mg, 0.16 mmol) was dissolved in MeOH (4 mL) and HCl (1 M; 30 drops), and Pd/C (25 mg) was added. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 48 h. The catalyst was removed by filtration through Celite®, and the filtrate was concentrated under vacuum, to give the hydrochloride salt of **13b** (quantitative). This was eluted through ion-exchange resin (DOWEX® 50XW8–100) with MeOH, H_2O, and NH_4OH (6%) to give free amine **13b** (23 mg, 0.13 mmol, 82%). $[\alpha]_D^{21}$ = +27.2(*c* = 0.38 in H_2O). ^{1}H NMR (400 MHz, D_2O):

δ = 4.02 (dd, $^3J_{H,H}$ = 4.3, 2.4 Hz, 1 H, 3-H), 3.90 (pseudo-t, $^3J_{H,H}$ = 3.7 Hz, 1 H, 4-H), 3.83 (ddd, $^3J_{H,H}$ = 11.0, 5.1, 3.1 Hz, 1 H, 5-H), 3.55 (d, $^3J_{H,H}$ = 2.4 Hz, 1 H, 2-H), 2.84 (dd, $^2J_{H,H}$ = 12.7, $^3J_{H,H}$ = 5.1 Hz, 1 H, 6a-H), 2.62 (dd, $^2J_{H,H}$ = 12.7, $^3J_{H,H}$ = 11.0 Hz, 1 H, 6b-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 174.6 (s, C=O), 69.7 (d, C-3), 69.1 (d, C-4), 63.9 (d, C-5), 55.7 (d, C-2), 42.7 (t, C-6) ppm. MS (ESI): *m*/*z* (%) = 199.08 (100) $[M + Na]^+$. $C_6H_{12}N_2O_4$ (176.17): calcd. C 40.91, H 6.87, N 15.90; found C 40.35, H 6.85, N . 16.05.

(2*R*,3*R*,4*R*,5*R*)-1-Benzyl-2-carboxy-3,4,5-trihydroxypiperidinium Chloride [(2*R*,3*R*,4*R*,5*R*)-1-Benzyl-3,4,5-trihydroxypipecolid Acid Hydrochloride Salt] (14a·HCl): A solution of **30** (50 mg, 0.17 mmol) in HCl (6 M; 1 mL) was heated to gentle reflux. After 16 h, TLC revealed that the reaction was complete. The solution was cooled to room temperature and then extracted with Et_2O (3 × 4 mL) to remove ether-soluble material. The hydrochloric acid was evaporated to dryness under reduced pressure, then the residue was dissolved in MeOH (5 mL), and NaOH (13 mg, 0.32 mmol) was added. The reaction mixture was stirred for 1 h to obtain the corresponding sodium salt, which was passed over Ambersep® 900-OH, eluting with MeOH, water, and HCl (6 M). This procedure allowed us to obtain pure **14**·HCl (35 mg, 0.12 mmol, 71%) as a waxy solid. $[\alpha]_D^{23}$ = +26.6 (*c* = 0.32 in MeOH). ^{1}H NMR (400 MHz, D_2O): δ = 7.44–7.35 (5 H, Ar), 4.54 (d, $^2J_{H,H}$ = 12.7 Hz, 1 H, Bn), 4.27 (d, $^2J_{H,H}$ = 11.7 Hz, 2 H, Bn, 3-H), 4.10–4.07 (m, 1 H, 5-H), 3.91 (pseudo-t, $^3J_{H,H}$ = 3.9 Hz, 1 H, 4-H), 3.90 (d, $^3J_{H,H}$ = 11.7 Hz, 1 H, 2-H), 3.16 (dd, $^2J_{H,H}$ = 11.2, $^3J_{H,H}$ = 4.4 Hz, 1 H, 6a-H), 3.02 (t, *J* = 11.2 Hz, 1 H, 6b-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 169.0 (s, *C*OOH), 130.9 (s, Ar), 129.6–126.7 (d, 5 C, Ar), 68.7 (d, C-3), 67.0 (d, C-4), 62.2 (d, C-2), 61.0 (d, C-5), 59.7 (t, Bn), 47.1 (t, C-6) ppm. MS (ESI): *m*/*z* (%) = 266.33 (100) $[M - H]^+$. $C_{13}H_{18}ClNO_5$ (303.74): calcd. C 51.41, H 5.97, N 4.61; found C 51.57, H 5.83, N 4.50.

(2*R*,3*R*,4*R*,5*R*)-2-Carboxy-3,4,5-trihydroxypiperidinium Chloride [(2*R*,3*R*,4*R*,5*R*)-3,4,5-Trihydroxypipecolid Acid Hydrochloride Salt] (14b·HCl): Compound **30** (49 mg, 0.16 mmol) was dissolved in MeOH (4 mL) and HCl (1 M; 15 drops), and Pd/C (25 mg) was added. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 16 h. The catalyst was removed by filtration through Celite®, and the filtrate was concentrated under vacuum. Then HCl (6 M; 1 mL) was added, and the mixture was heated to gentle reflux. After 16 h at reflux, TLC showed that the reaction was complete. The solution was cooled to room temperature, and then extracted with Et_2O (4 mL) to remove ether-soluble material. The aqueous layer was evaporated and dried under vacuum to give **14b**·HCl (34 mg, 0.16 mmol, 100%). A small portion of the product was dissolved in MeOH and treated with excess NaOH. The reaction mixture was stirred for 1 h to obtain the corresponding sodium salt, which was passed over Ambersep® 900-OH, eluting with MeOH, water, and a HCl (6 M). This procedure allowed us to obtain pure **14b**·HCl. $[\alpha]_D^{25}$ = –79.1 (*c* = 0.32, H_2O). ^{1}H NMR (400 MHz, CD_3OD): δ = 4.33 (br. m, 1 H, 3-H), 4.15 (br. m, 2 H, 5-H, 2-H), 3.93 (br. m, 1 H, 4-H), 3.04 (br. m, 2 H, 6a-H, 6b-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 168.6 (s, *C*OOH), 69.0 (d, C-3), 68.7 (d, C-4), 61.9 (d, C-5), 55.9 (d, C-2), 42.0 (t, C-6) ppm. MS (ESI): *m*/*z* (%) = 212.00 (100) $[M - H]^+$.

(2*S*,3*R*,4*S*,5*R*)-2-(Aminomethyl)-1-benzyl-3-hydroxy-4,5-(isopropylidenedioxy)piperidine (31): A solution of **30** (103 mg, 0.33 mmol) in dry THF (15 mL) was cooled to 0 °C, and $LiAlH_4$ (1 M, THF; 0.99 mL) was added. The reaction mixture was heated to reflux and stirred for 1.5 h, under a nitrogen atmosphere, after which time TLC showed the complete disappearance of the starting material. The reaction solution was cooled to room temperature, then an aqueous saturated solution of Na_2SO_4 was added, and the mixture was stirred for 15 min. The mixture was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried with Na_2SO_4 and concentrated. The crude product was purified by flash chromatography [CH_2Cl_2/MeOH/NH_4OH (6%), 10:2:0.2] to give **31** (76 mg, 0.26 mmol, 79%). R_f = 0.23 [CH_2Cl_2/MeOH/NH_4OH (6%), 10:2:0.2]. $[\alpha]_D^{25}$ = +24.3 (*c* = 1.01 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 5 H, Ar), 4.31 (dt, $^3J_{H,H}$ = 6.8, 3.4 Hz, 1 H, 5-H), 4.16–4.12 (m, 2 H, 4-H, 3-H), 3.89 (s, 2 H, Bn), 3.26–3.20 (m, 2 H, 6a-H, CH_2NH$_2$), 2.88 (dt, $^3J_{H,H}$ = 3.9, 2.0 Hz, 1 H, 2-H), 2.84–2.80 (m, 2 H, 6b-H, CH_2NH$_2$), 1.54 (s, 3 H, Me), 1.34 (s, 3 H, Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.4 (s, Ar), 128.4–126.9 (d, 5 C, Ar), 108.4 (s, acetal), 74.9 (d, C-4), 73.3 (d, 2 C, C-5, C-3), 60.4 (t, Bn), 56.5 (d, C-2), 47.9 (t, C-6), 43.3 (t, CH_2NH_2), 27.2 (q, Me), 24.2 (q, Me) ppm. MS (ESI): *m*/*z* (%) = 293.25 (100) $[M + H]^+$. IR ($CDCl_3$): $\tilde{\nu}$ = 3689, 3604, 3399, 3086, 3065, 3029, 2991, 2922, 2868, 2247, 1601, 1561, 1383, 1209, 1027 cm^{-1}. $C_{16}H_{24}N_2O_3$ (292.37): calcd. C 65.73, H 8.27, N 9.58; found C 66.12, H 8.12, N 9.22.

(2*S*,3*R*,4*R*,5*R*)-2-(Aminomethyl)-1-benzyl-3,4,5-trihydroxypiperidine (15a): A solution of **31** (25 mg, 0.09 mmol) in MeOH (2.3 mL) was stirred with HCl (12 M; 75 μL, 0.9 mmol) at room temperature for 48 h. The crude mixture was concentrated to give the hydrochloride salt of **15a**. The corresponding free amine was obtained by passing the hydrochloride salt through DOWEX® 50XW8–100 ion-exchange resin. Elution with ammonia (33%) gave free base **15a** (20 mg, 0.08 mmol, 89%). $[\alpha]_D^{24}$ = +21.2 (*c* = 1.29 in MeOH). ^{1}H NMR (400 MHz, D_2O): δ = 7.33–7.24 (m, 5 H, Ar), 4.00 (dd, $^3J_{H,H}$ = 6.9, 3.9 Hz, 1 H, 3-H), 3.89 (dt, $^3J_{H,H}$ = 7.2, 3.6 Hz, 1 H, 5-H), 3.85 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, Bn), 3.70 (dd, $^3J_{H,H}$ = 6.9, 3.6 Hz, 1 H, 4-H), 3.62 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, Bn), 2.99 (d, $^3J_{H,H}$ = 6.4 Hz, 2 H, CH_2NH$_2$), 2.76–2.73 (m, 1 H, 2-H), 2.64 (dd, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 3.4 Hz, 1 H, 6a-H), 2.46 (dd, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 7.2 Hz, 1 H, 6b-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 137.6 (s, Ar), 129.7–127.6 (d, 5 C, Ar), 70.1 (d, C-4), 69.0 (d, C-3), 67.1 (d, C-5), 59.1 (d, C-2), 57.7 (t, Bn), 49.9 (t, C-6), 36.7 (t, CH_2NH_2) ppm. MS (ESI): *m*/*z* (%) = 253.28 (100) $[M + H]^+$, 275.29 (27) $[M + Na]^+$. $C_{13}H_{20}N_2O_3$ (252.31): calcd. C 61.88, H 7.99, N 11.10; found C 61.38, H 8.04, N 10.72.

(2*S*,3*R*,4*R*,5*R*)-2-(Aminomethyl)-3,4,5-trihydroxypiperidine (15b):[39] Compound **31** (19 mg, 0.07 mmol) was dissolved in MeOH (4 mL) and HCl (12 M; 7 drops), and Pd/C (15 mg) was added. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 3 d. The catalyst was filtered through Celite®, and the filtrate was concentrated under vacuum to give the hydrochloride salt of **15b**. This was eluted through ion-exchange resin (DOWEX® 50XW8–100) with MeOH, H_2O, and NH_4OH (15%) to give free amine **15b** (10 mg, 0.06 mmol, 95%). The NMR spectra showed that a mixture of the free amine and the corresponding protonated form was recovered. $[\alpha]_D^{23}$ = +4.30 (*c* = 0.58 in H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 3.89–3.72 (m, 3 H, 3-H, 4-H, 5-H), 3.01–2.57 (m, 5 H, 6-H, 2-H, CH_2NH$_2$) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 69.4, 69.0, 68.8, 68.2 (d, 2 C, C-3, C-4), 64.9, 64.6 (d, 1 C, C-5), 52.4, 52.0 (d, 1 C, C-2), 43.3, 43.2 (t, 1 C, C-6), 40.2, 39.6 (t, 1 C, CH_2NH_2) ppm. MS (ESI): *m*/*z* (%) = 185.10 (100) $[M + Na]^+$.

Biological Evaluation: The percentage inhibition of the corresponding glycosidase was determined in the presence of 1 mM of the inhibitor in the well. Each enzymatic assay (final volume 0.12 mL) contained 0.01 to 0.5 units mL^{-1} of the enzyme, and 10 mM aqueous solution of the appropriate *p*-nitrophenyl glycoside substrate buff-

ered to the optimal pH of the enzyme. The enzyme and the inhibitor were preincubated for 5 min at room temp., and the reaction was started by addition of the substrate. After 20 min of incubation at 37 °C, the reaction was stopped by the addition of sodium borate buffer (0.1 mL; pH 9.8). The *p*-nitrophenolate formed was measured by visible absorption spectroscopy at 405 nm. Under these conditions, the *p*-nitrophenolate released led to optical densities that varied linearly with both reaction time and concentration of the enzyme. For the best inhibitors (% inhibition ≥ 80), the IC_{50} values (concentration of inhibitor required for 50% inhibition of enzyme activity) were calculated from plots of percentage of inhibition vs. inhibitor concentration. Each experiment (%, IC_{50}) was performed in duplicate, and the average values are given.

Supporting Information (see footnote on the first page of this article): ^1H NMR and ^{13}C NMR spectra of all new compounds.

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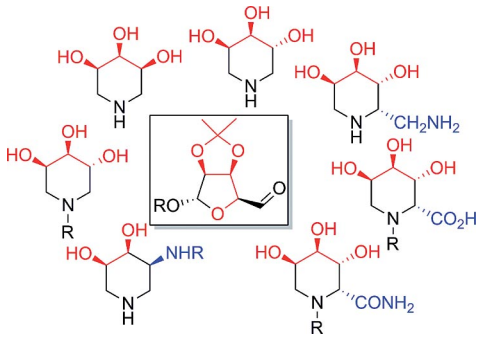

The synthesis of diversely substituted polyhydroxypiperidines, polyhydroxyaminopiperidines, and trihydroxypipecolic acid derivatives is reported, using Strecker reactions and double reductive aminations, starting from a D-mannose-derived aldehyde.

Keywords: Nitrogen heterocycles / Alkaloids / Carbohydrates / Amination / Glycomimetics / Biological activity

