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N-Alkyl-, 1-*C*-Alkyl-, and 5-*C*-Alkyl-1,5-dideoxy-1,5-imino-(L)-ribitols as Galactosidase Inhibitors

Sophie Front,[a] Estelle Gallienne,[a] Julie Charollais-Thoenig,[b] Stéphane Demotz,[b] and Olivier R. Martin*[a]

A series of 1,5-dideoxy-1,5-imino-(L)-ribitol (DIR) derivatives carrying alkyl or functionalized alkyl groups were prepared and investigated as glycosidase inhibitors. These compounds were designed as simplified 4-epi-isofagomine (4-epi-IFG) mimics and were expected to behave as selective inhibitors of β-galactosidases. All compounds were indeed found to be highly selective for β-galactosidases versus α-glycosidases, as they generally did not inhibit coffee bean α-galactosidase or other α-glycosidases. Some compounds were also found to be inhibitors of almond β-glucosidase. The *N*-alkyl DIR derivatives were only modest inhibitors of bovine β-galactosidase, with IC_{50} values in the 30–700 μM range. Likewise, imino-L-ribitol substituted at the C1 position was found to be a weak inhibitor of this enzyme. In contrast, alkyl substitution at C5 resulted in enhanced β-galactosidase inhibitory activity by a factor of up to 1000, with at least six carbon atoms in the alkyl substituent. Remarkably, the 'pseudo-anomeric' configuration in this series does not appear to play a role. Human lysosomal β-galactosidase from leukocyte lysate was, however, poorly inhibited by all iminoribitol derivatives tested (IC_{50} values in the 100 μM range), while 4-epi-IFG was a good inhibitor of this enzyme. Two compounds were evaluated as pharmacological chaperones for a GM1-gangliosidosis cell line (R301Q mutation) and were found to enhance the mutant enzyme activity by factors up to 2.7-fold.

Introduction

β-Galactosidase-linked lysosomal storage diseases (LSD) such as GM1-gangliosidosis, Morquio disease type B, and Krabbe disease remain major medical challenges, as there is no treatment available.[1] Significant advances have been achieved in the handling of certain LSDs using replacement enzymes (enzyme replacement therapy, ERT);[2] however, this approach is currently limited to non-neuronopathic forms of these diseases. The use of small organic molecules as a mode of treatment has shown some success in the form of substrate reduction therapy (SRT):[3] Miglustat (*N*-butyl-1-deoxynojirimycin, *N*-Bu-DNJ, an inhibitor of glucosylceramide synthase) was found to significantly improve patient conditions and to decrease symptoms when administered to type 1 Gaucher disease patients.[4] The use of organic compounds that act as molecular chaperones to stabilize mutant enzymes during their biosynthesis and transport to the lysosome (i.e., pharmacological chaperone therapy, PCT) is an approach in the treatment of LSD and mucopolysaccharidoses (MPS) which is gaining increasing importance and recognition.[5] Such chaperones, which are usually potent enzyme inhibitors, were shown to significantly increase the activity of certain mutant enzymes, provided the mutation does not completely abolish enzymatic activity. A significant advantage of small molecules over ERT or treatment with other biomolecular drugs is their potential capacity to cross the blood–brain barrier, as has been shown for certain iminosugar derivatives.[6] 1-Deoxygalactonojirimycin (DGJ), an inhibitor of lysosomal α-galactosidase, has successfully completed phase III clinical evaluations for Fabry disease,[7] establishing the adequacy of this approach for the therapeutic management of LSD. This situation has prompted various initiatives, and several other iminosugars are currently in preclinical development.

Following our initial work on pharmacological chaperones for Gaucher disease,[8] we became interested in the application of PCT toward β-galactosidase-linked LSDs.[9] As regards GM1-gangliosidosis, Suzuki et al. developed the carbasugar *N*-octyl-4-epi-β-valienamine (NOEV) as a potential treatment of this disease.[10] This compound was shown to enhance the activity of a number of mutated forms of lysosomal β-galactosidase.[11] Preclinical development of this compound was hampered by difficulties in its synthesis. More readily available, bicyclic DGJ derivatives were reported by Garcia-Fernandez and co-workers,[12] with interesting activities on a large number of GM1-gangliosidosis-linked mutations. DGJ derivatives exhibiting potent β-galactosidase chaperone activity were also reported by Paschke, Wrodnigg and colleagues, but these compounds have not been developed past the discovery phase.[13]

We have recently shown that 1-*C*-alkyl DGJ derivatives (Figure 1) are quite weak inhibitors of β-galactosidases, al-

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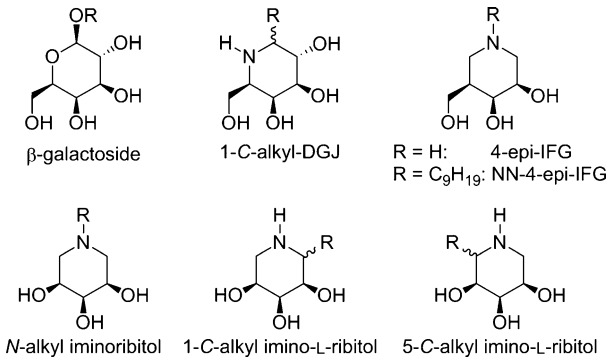


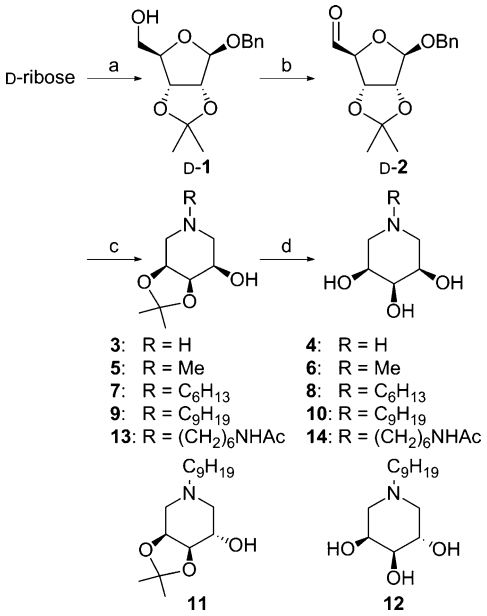
Figure 1. Iminosugars as galactoside mimics.

though they are potent inhibitors of α-galactosidases, including human lysosomal α-galactosidase.[9] In agreement with Heightman and Vasella's analysis of glycosidase inhibition by iminosugars,[14] we considered that selective inhibition of β-galactosidase might arise more effectively from structures in which the basic nitrogen atom occupies the anomeric position in the corresponding galactoside (isofagomine series): 4-epi-isofagomine (4-epi-IFG, Figure 1) is indeed a very potent galactosidase inhibitor.[15] We have shown that this compound is also a potent inhibitor of galactocerebrosidase (GALC), as subsequently confirmed by Deane and co-workers,[16] and of lysosomal β-galactosidase.[9] To reach a diversity of galactoside mimics more readily, we decided to investigate iminoribitol derivatives as simplified 4-epi-IFG mimics, and to prepare a series of *N*-alkyl as well as 1-*C*-alkyl and 5-*C*-alkyl imino-L-ribitols (=5-*C*-alkyl and 1-*C*-alkyl imino-D-ribitols). These compounds have the same configuration as a galactoside at the C3, C4, and C5 positions, but contain an OH group at C5 instead of CH_2OH. The new iminoribitol derivatives were evaluated for their efficiency and selectivity as β-galactosidase inhibitors, and compared with 4-epi-IFG and its *N*-nonyl derivative, NN-4-epi-IFG.

Results and Discussion

Synthesis of iminoribitol derivatives

Iminoribitol **4** is a known compound: it has been isolated from a plant used in folk medicine[17] and was subsequently prepared by several research groups semisynthetically, by starting from sugars (mostly D-ribose derivatives),[18] or by total synthesis.[19] We selected an approach based on a double reductive amination,[20] starting from *aldehydo*-D-ribodialdose derivative **2**, a known aldehyde.[21] The protocol we used is similar to that recently reported by Cardona and colleagues[22] from the D-*lyxo* epimer of D-**2**. The reaction of D-**2** in the presence of an amine under hydrogenation conditions followed by hydrolysis of the isopropylidene group gave 1,5-dideoxy-1,5-imino-ribitol (**4**, DIR, using benzylamine) and N-alkylated derivatives in good yields. The *N*-propyl[23] and *N*-butyl derivatives[18a] are the only N-alkylated DIRs that have been reported so far. The *N*-hexyl

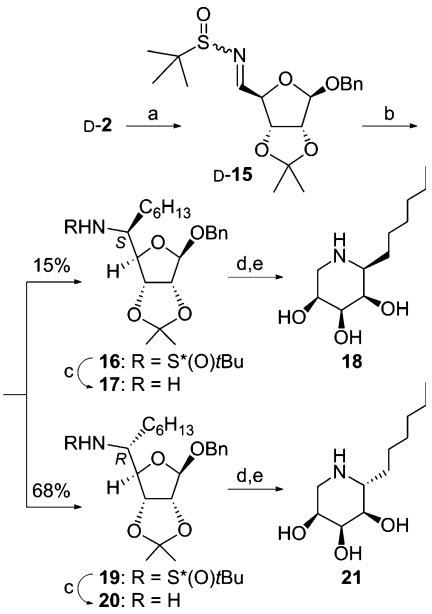


Scheme 1. Synthesis of *N*-alkyl imino-ribitol and -arabinitol derivatives. *Reagents and conditions*: a) For details, see Ref. [21a], 33%; b) Dess–Martin periodinane, CH_2Cl_2, quant.; c) R-NH_2 (R = Bn, C_6H_{13}, C_9H_{19}, $(CH_2)_6NHAc$), AcOH, 10% Pd/C, MeOH, 25–91%; d) Dowex 50WX8 (H^+), 1,4-dioxane/H_2O (9:1), 59–91%.

(**8**), *N*-nonyl (**10**), and *N*-(6-acetamidohexyl) (**14**) derivatives of DIR were prepared using the corresponding alkylamines. A very small amount of *N*-methyl DIR **6** was formed during the synthesis of **4** which involved hydrogenation in methanol.[24] We also isolated a small amount of the C4 epimer (L-*arabino* configuration) of **9**, compound **11**, probably resulting from the epimerization of the aldehyde D-**2** or the corresponding iminium salt during the reductive amination reaction. This intermediate was converted into *N*-nonyl imino-L-arabinitol **12** (Scheme 1).

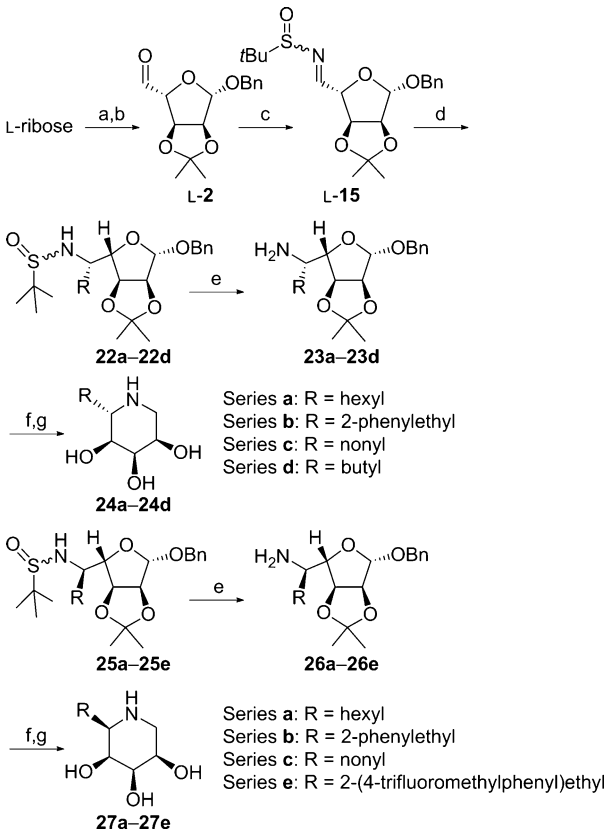
Very few 1/5-*C*-alkylated iminoribitols have been reported so far. Since the pioneering work of Nicotra and co-workers,[25] a few iminoribitol derivatives carrying a C-linked functionalized alkyl group have been described.[26] A significant investigation with medicinal chemistry implications was published recently by Siriwardena et al.[27] A number of imino-D-ribitol *C*-glycosides were prepared as galactoside mimics by way of cycloadditions between various alkenes and a D-ribose-derived cyclic nitrone. The resulting compounds were found to be modest glycosidase inhibitors with little selectivity between α- and β-galactosidases, as well as between different hexose configurations.

Our approach toward 1- and 5-C-alkylated iminoribitols followed the methodology we developed to reach similar compounds in the iminoxylitol and imino-L-arabinitol series.[28] Key intermediates were the *tert*-butanesulfinyl imines derived from *ribo*-pentodialdofuranoses D-**15** and L-**15**, and chain extension was performed by the addition of organomagnesium reagents (Schemes 2 and 3). The reactions were performed on the imine prepared from racemic *tert*-butanesulfinamide, thereby allowing the simultaneous preparation of both stereoisomers at C5 and



Scheme 2. Synthesis of 1-*C*-hexyl imino-L-ribitols. *Reagents and conditions*: a) (*rac*)-*t*BuS(O)NH_2, $CuSO_4$, CH_2Cl_2, 69%; b) $C_6H_{13}MgBr$, PhMe, −78 °C→RT, 83%; c) HCl, MeOH, RT, **17**: 61%, **20**: quant.; d) H_2, 10% Pd/C, 1,4-dioxane/H_2O/AcOH (8:1:1), (1*S*): 75%, (1*R*): 82%; e) Dowex 50WX8 (H^+), 1,4-dioxane/H_2O (2:1), **18**: 79%, **21**: 45%.

hence both pseudo-anomers of the glycoside mimics.[1] The configuration of the newly created stereocenters was determined after cyclization to piperidines **18**, **21**, **24**, and **27** through detailed NMR analysis. Final steps involved cleavage of the *tert*-butanesulfinyl group by methanolysis, intramolecular reductive amination upon hydrogenolysis of the benzyl glycoside, and hydrolysis of the protective group. A single example of 1-*C*-alkyl imino-L-ribitol was prepared from D-**15**, namely the *C*-hexyl derivatives in pseudo-β (**18**) and pseudo-α (**21**) configurations (Scheme 2). In the enantiomeric series, 5-*C*-alkylated imino-L-ribitols carrying a C4-, C6-, or C9-alkyl group as well as a 2-phenylethyl or 2-(4-trifluoromethylphenyl)ethyl group were prepared in most cases in both pseudo-anomeric configurations at position C5 (Scheme 3). The 5-*C*-hexyl derivatives **24a** and **27a** are thus enantiomers of **21** and **18**, respectively.



Scheme 3. Synthesis of 5-*C*-alkyl imino-L-ribitols. *Reagents and conditions*: a) For details, see Ref. [21a], 40%; b) Dess–Martin periodinane, CH_2Cl_2, quant.; c) (*rac*)-*t*BuS(O)NH_2, $CuSO_4$, CH_2Cl_2, 53%; d) RMgBr, PhMe, −78 °C→RT, 45–84%; e) HCl, MeOH, RT, 40–57%; f) H_2, 10% Pd/C, 1,4-dioxane/H_2O/AcOH (10:6:1); g) Dowex 50WX8 (H^+), 1,4-dioxane/H_2O (3:1), 30–84% (two steps).

Biological investigations

All new compounds were evaluated as inhibitors of bovine β-galactosidase, as well as inhibitors of other β-galactosidases including the human lysosomal enzyme. Assays were also performed on an α-galactosidase (coffee bean), a β-glucosidase (almond), and an α-glucosidase (*S. cerevisiae*) to determine selectivity. All results are listed in Table 1. 4-Epi-IFG and its *N*-nonyl derivative (NN-4-epi-IFG) were also included in the assays for comparison.

The following observations were made: 1) All compounds are highly selective for β-galactosidases over α-glycosidases, as they generally do not inhibit the coffee bean α-galactosidase (with the exception of NN-4-epi-IFG), although iminosugars in the DGJ series are very powerful inhibitors of this enzyme, and have little effect on α-glucosidase. 2) Some compounds are also inhibitors of almond β-glucosidase (down to the micromolar range for the most active ones), an enzyme that is known to have β-galactosidase activity as well. 3) The *N*-alkyl DIR derivatives are only modest inhibitors of bovine liver β-galactosidase, with IC_{50} values in the 30–700 μM range. Likewise, imino-L-ribitols substituted at C1 were found to be weak inhibitors of bovine liver β-galactosidase. In contrast, alkyl substitution at C5 results in enhancement of β-galactosidase inhibitory activity by a factor of up to 1000, when the chain contains at least six carbon atoms. Remarkably, the pseudo-anomeric configuration in this series does not seem to play a role, as very similar data were observed for both configurations at C5. Altogether, these results, summarized in Figure 2, indicate that the β-galactosidase inhibitory activity of hexyl-substituted iminoribitol derivatives is greatest when the chain is at C5, much weaker if the chain is at N or at C1. 4) Lysosomal β-galactosidase from human leukocyte lysate was poorly inhibited by all iminoribitol derivatives tested (IC_{50} values in the 100 μM range). In contrast,

[1] *In this series, stereocontrol appeared to be largely due to the chiral auxiliary. It follows that the reaction with one or the other of the stereoisomeric* tert-*butanesulfinylimines gives predominantly one or the other configuration of the addition product at C5.*

Table 1. IC_{50} values (μM) for 1,5-dideoxy-1,5-imino-L-ribitol (DIR) derivatives as inhibitors of glycosidases.[a]

Compd	Type	β-gal'ase bovine liver	β-gal'ase *E. coli*	β-gal'ase *A. oryzae*	β-gal'ase bovine testis	β-gal'ase human leukocyte lysate	α-gal'ase green coffee beans	β-glu'ase almonds	α-glu'ase *S. cerevisiae*
4-epi-IFG		8	0.3	2	0.8	0.4	500	2	>1000
NN-4-epi-IFG		20	40	0.1	50	10	20	200	–
4	DIR	300	10	–	–	300	>1000	100	500
8	N-C6-DIR	700	600	–	–	–	>1000	>1000	–
10	N-C9-DIR	40	>1000	–	>800	–	–	–	–
14	N-6 AcNHC6-DIR	400	1000	–	–	–	–	–	–
18	β-1C6-DIR	30	–	–	>800	–	–	–	–
21	α-1C6-DIR	400	–	–	–	–	–	–	–
24a	α-5C6-DIR	0.8	60	70	350	150	>1000	20	>1000
27a	β-5C6-DIR	1	60	–	–	70	>1000	6	>1000
24b	α-5PhEt-DIR	0.3	–	–	–	90	–	–	–
27b	β-5PhEt-DIR	0.3	–	–	–	100	>1000	20	>1000
24d	α-5C4-DIR	80	–	–	–	500	>1000	500	>1000
24c	α-5C9-DIR	0.3	–	–	–	40	>1000	100	>1000
27c	β-5C9-DIR	0.5	–	–	–	70	–	–	–
27e	β-5-CF_3PhEt-DIR	2	–	–	–	–	>1000	2	>1000

[a] Gal'ase = galactosidase; glu'ase = glucosidase; "–" denotes not determined; each value is the mean of at least two experiments that were run in duplicate. The variation of the absorbance and fluorescence values exploited for the determination of the IC_{50} is less than 20%.

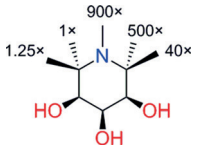


Figure 2. Structure–activity relationships of iminoribitol: the effect of the position of a hexyl chain on the IC_{50} value for inhibition of bovine liver β-galactosidase.

4-epi-IFG was found to be a potent inhibitor of human β-galactosidase.

We next evaluated whether the 5-*C*-hexyl iminoribitol derivative **24a**, despite its modest inhibitory activity toward human lysosomal β-galactosidase, is endowed with pharmacological chaperone activity in cells from patients of GM1-gangliosidosis. Remarkably, it was observed that residual β-galactosidase activity in GM02439 fibroblasts cultured for five days in the presence of **24a** (10 μM) was increased by twofold. Recovery of β-galactosidase activity was most readily achieved with 4-epi-IFG, likely reflecting that this compound has greater affinity than **24a** for the human enzyme. In contrast, no recovery of β-galactosidase activity was observed with GM03251 cells (W273L/W509C), establishing the likely β-galactosidase mutant specificity of the chaperone effect (Table 2). It was recently reported that GM02439 cells bear the R201C mutation, which is known for its chaperone sensitivity.[29] For comparison, a fourfold enhancement in the enzymatic activity of R201C β-galactosidase was obtained with NOEV at a concentration of 0.2 μM.

Table 2. Enhancement of residual β-galactosidase activity by **24a** in GM1-gangliosidosis.

Compd	Conc. [μM]	EE[a] GM03251	EE[a] GM02439
4-epi-IFG	0	1.0	1.0
4-epi-IFG	1	1.1	1.5
4-epi-IFG	10	1.1	2.7
24a	0	1.0	1.0
24a	1	1.0	1.1
24a	10	1.1	2.1

[a] EE = Enzyme activity fold enhancement.

Conclusions

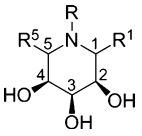
A series of new *N*-alkyl as well as 1- and 5-*C*-alkyl derivatives of 1,5-dideoxy-1,5-imino-L-ribitol (DIR) were prepared as simplified galactoside mimics in the 1*N* iminosugar series and evaluated as inhibitors of different glycosidases including five β-galactosidases, in comparison with 4-epi-IFG and its *N*-nonyl derivative. The results of these investigations show that all compounds are highly selective as β-glycosidase inhibitors, with little or no action on α-galactosidases and α-glucosidases. The addition of a lipophilic group in the DIR scaffold significantly increases the activity of the resulting iminoglycolipid on bovine liver β-galactosidase, provided that the chain is located at the C5 position, which indicates a highly organized recognition of the molecule by the enzyme. Such an effect is not observed if the alkyl group is at C1 or on the nitrogen atom, nor is it observed for the human lysosomal enzyme, for which the most active compound remains 4-epi-IFG. The 5-*C*-hexyl DIR derivative was found to have some pharmacological chaperone activity on cells from a GM1-gangliosidosis patient, an unexpected observation considering the modest inhibitory activity of this compound toward human lysosomal β-galactosidase. Substituents at the C5 position might therefore play a critical role in controlling the activity of β-galactosidase chaperones in the 1-*N*-iminosugar series, and further investigations are in progress in our laboratories to access such compounds.

Experimental Section

Chemical syntheses

Materials and methods: All reactions requiring anhydrous conditions were carried out with oven-dried glassware under an atmosphere of dry Ar. CH_2Cl_2 and Et_2O were distilled from P_2O_5 and CaH_2,

respectively. All reagent-grade chemicals, anhydrous MeOH, and toluene were obtained from commercial suppliers and were used as received. High-resolution mass spectra were recorded on a Bruker Q-TOF MaXis spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance II (250 MHz) or Bruker Avance III HD nanobay (400 MHz) spectrometers. Chemical shifts are given in ppm and are referenced to the residual solvent signal or to TMS as internal standard. Carbon multiplicities were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. ^{1}H and ^{13}C NMR signals were attributed on the basis of H–H and C–H correlations. Spectral splitting patterns are designated as follows: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad. Specific rotations were measured in a 1-dm cell with a PerkinElmer 341 polarimeter. Melting points were determined in capillary tubes with a Büchi apparatus and are uncorrected. Analytical thin-layer chromatography was performed using silica gel 60 F_{254} pre-coated plates (Merck) with visualization by UV light and ceric sulfate/ammonium molybdate solution (0.5 g/0.24 g in 500 mL 1 M aqueous H_2SO_4). Flash chromatography was performed with silica gel 60 (40–63 μm).



Numbering scheme for NMR data: Alkyl chain series labeled **a**, **b**, **c**…

Synthesis of *N*-alkyl iminoribitols

General procedure for reductive amination: To a solution of aldehyde D-**2**[21] in MeOH (0.1 M) was added the alkyl amine (1.2 equiv), AcOH (1 equiv) and 10% Pd/C (60 mg mmol^{-1}). The mixture was stirred for 48–72 h under an H_2 atmosphere at room temperature. The catalyst was removed by filtration through a membrane and washed with MeOH. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography.

***N*-Hexyl-2,3-*O*-isopropylidene-1,5-dideoxy-1,5-imino-D-ribitol (7)**: Compound **7** (90 mg, 25%) was obtained from D-**2** (395 mg, 1.42 mmol) and hexylamine (225 μL, 1.70 mmol, 1.2 equiv). Purification was performed using petroleum ether (PE)/EtOAc 3:2 to give **7** as a yellow syrup: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85–0.91 (m, 3H, CH_3), 1.24–1.35 (m, 6H, $3CH_2$), 1.38 (s, 3H, CH_3 *i*Pr), 1.41–1.52 (m, 2H, 2Hb), 1.56 (s, 3H, CH_3 *i*Pr), 2.33–2.46 (m, 4H, H1A, H5A, 2Ha), 2.60 (ddd, 1H, H1B, J = 0.8, 4.0, 11.2 Hz), 2.71 (ddd, 1H, H5B, J = 0.8, 5.4, 12.0 Hz), 3.88–3.92 (m, 1H, H2), 4.21 (t, 1H, H3, J = 4.6 Hz), 4.23–4.28 ppm (m, 1H, H4); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.15 (CH_3), 22.70 (CH_2), 26.39 (CH_3 *i*Pr), 26.85 (CH_2b), 27.16 (CH_2), 27.50 (CH_3 *i*Pr), 31.82 (CH_2), 54.93 (C5), 55.47 (C1), 57.47 (CH_2a), 66.63 (C2), 73.02 (C4), 74.75 (C3), 109.45 ppm (Cq); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{28}NO_3$: 258.206370, found: 258.206624.

General procedure for isopropylidene deprotection: To a solution of protected iminoribitol in 1,4-dioxane/H_2O (9:1, 0.03 M) was added Dowex 50W X8 ion-exchange resin (H^+ form, 6 mL mmol^{-1}), previously washed with 1,4-dioxane/H_2O (9:1). The mixture was stirred for 4–5 h at room temperature. The resin was then poured onto a column, washed with 1,4-dioxane/H_2O (9:1), then with H_2O. The product was eluted from the resin using aqueous 0.5 N NH_4OH. Fractions containing the iminoribitol derivatives were combined and concentrated under vacuum.

***N*-Hexyl-1,5-dideoxy-1,5-iminoribitol (8)**: Compound **8** (66 mg, 85%) was obtained from **7** (92 mg, 0.357 mmol) as a yellow solid: mp: 89–91 °C; ^{1}H NMR (250 MHz, CD_3OD): δ = 0.91 (t, 3H, CH_3, J = 6.5 Hz), 1.25–1.41 (m, 6H, $3CH_2$), 1.45–1.61 (m, 2H, 2Hb), 2.25–2.47 (m, 4H, H1A, H5A, 2Ha), 2.58 (dd, 2H, H1B, H5B, J = 4.1, 10.5 Hz), 3.67 (ddd, 2H, H2, H4, J = 3.1, 4.1, 9.8 Hz), 3.85 ppm (br s, 1H, H3); ^{13}C NMR (101 MHz, CD_3OD): δ = 14.36 (CH_3), 23.67 (CH_2), 27.59 (CH_2b), 28.32, 32.90 (CH_2), 54.60 (C1, C5), 59.22 (CH_2a), 69.41 (C2, C4), 71.99 ppm (C3); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{24}NO_3$: 218.175070, found: 218.175317.

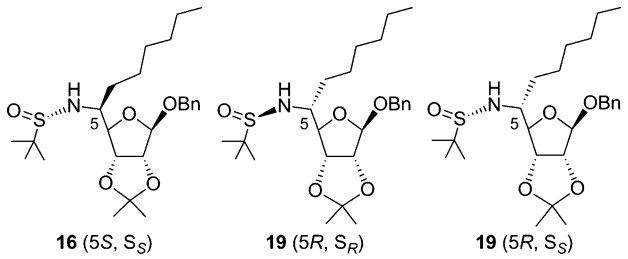
Synthesis of 1-*C*-alkyl imino-L-ribitols

***N*-*tert*-Butanesulfinylimine of benzyl 2,3-*O*-isopropylidene-*aldehydo*-β-D-*ribo*-pentodialdo-1,4-furanoside (D-15)**: To a solution of aldehyde D-**2** (347 mg, 1.25 mmol) in dry CH_2Cl_2 (13 mL) under Ar were added anhydrous $CuSO_4$ (995 mg, 6.23 mmol, 5 equiv) and racemic *tert*-butanesulfinamide (176 mg, 1.45 mmol, 1.2 equiv). The mixture was stirred for 18 h at room temperature, and then the copper salt was removed by filtration. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography (PE/EtOAc 4:1) to give D-**15** (328 mg, 69%) as a 1:1 mixture of two diastereomers and as a white solid; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.14 (s, 4.5H, CH_3 *t*Bu), 1.21 (s, 4.5H, CH_3 *t*Bu), 1.33 (s, 3H, CH_3 *i*Pr), 1.49 (s, 1.5H, CH_3 *i*Pr), 1.50 (s, 1.5H, CH_3 *i*Pr), 4.48 (d, 0.5H, CH_2Ph, J = 8.4 Hz), 4.53 (d, 0.5H, CH_2Ph, J = 8.6 Hz), 4.62 (dd, 0.5H, H3, J = 0.5, 5.8 Hz), 4.66 (dd, 0.5H, H3, J = 0.8, 6.0 Hz), 4.71 (d, 0.5H, CH_2Ph, J = 8.6 Hz), 4.76 (d, 0.5H, CH_2Ph, J = 8.4 Hz), 4.91–4.95 (m, 1H, H4), 5.16 (d, 0.5H, H2, J = 5.8 Hz), 5.21–5.24 (m, 0.5H, H2), 5.22 (s, 0.5H, H1), 5.25 (s, 0.5H, H1), 7.27–7.36 (m, 5H, Har), 8.10 (d, 0.5H, H5, J = 2.3 Hz), 8.12 ppm (d, 0.5H, H5, J = 2.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 22.48, 22.53, 25.06, 25.17, 26.40, 26.47 (CH_3), 57.22, 57.49 (C, *t*Bu), 69.61, 69.79 (CH_2Ph), 82.76, 82.78 (C2), 84.93, 84.97 (C3), 86.99, 87.01 (C4), 106.92, 107.20 (C1), 112.74, 112.85 (C, *i*Pr), 128.17–128.66 (CHar), 136.45, 136.54 (Car), 168.21, 168.26 ppm (C5); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{28}NO_5S$: 382.168270, found: 382.168682.

Compounds D-**15**-S_S and D-**15**-S_R were prepared according to the same conditions with each epimer of the chiral *tert*-butanesulfinamide.

Benzyl (5*S*,S_S)-5-*N*-*tert*-butanesulfinylamido-5-deoxy-5-*C*-hexyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (16) and benzyl (5*R*,S_{RS})-5-*N*-*tert*-butanesulfinylamido-5-deoxy-5-*C*-hexyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (19): To a solution of imine D-**15** (193 mg, 0.506 mmol) in toluene (5 mL) at −78 °C under Ar was added a commercial solution (2 M in Et_2O) of hexylmagnesium bromide (1.26 mL, 2.52 mmol, 5 equiv). The mixture was warmed to room temperature and stirred for 18 h. The reaction was quenched at 0 °C by the addition of a saturated NH_4Cl solution (5 mL), and the aqueous phase was extracted with Et_2O (3×15 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel column chromatography (PE/EtOAc 4:1) to give **16** (36 mg, 15%) as a single S*-stereoisomer and as a yellow syrup, and **19** (162 mg, 68%) as an inseparable 3:2 mixture of two S*-stereoisomers [**19** (5*R*,S_S)/**19** (5*R*,S_R)] and as a white solid.

Compound 16: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85–0.94 (m, 3H, CH_3 hex), 0.97 (s, 9H, CH_3 *t*Bu), 1.24–1.45 (m, 8H, $4CH_2$), 1.32 (s, 3H, CH_3 *i*Pr), 1.48 (s, 3H, CH_3 *i*Pr), 1.48–1.63 (m, 2H, 2Ha), 3.18–3.28 (m, 1H, H5), 4.46 (d, 1H, H4, J = 2.8 Hz), 4.56 (d, 1H, CH_2Ph, J = 11.2 Hz), 4.71 (d, 1H, CH_2Ph, J = 11.2 Hz), 4.74 (d, 1H, H3, J = 6.2 Hz), 4.90 (d, 1H, NH, J = 8.8 Hz), 5.12 (d, 1H, H2, J = 6.2 Hz), 5.18 (s, 1H, H1), 7.29–7.38 ppm (m, 5H, Har); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.22 (CH_3 hex), 22.72 (CH_2), 22.96 (CH_3 *t*Bu), 24.87 (CH_3 *i*Pr), 25.99 (CH_2), 26.50 (CH_3 *i*Pr), 29.22, 31.88 (CH_2), 35.00 (CH_2a), 56.16 (C, *t*Bu), 59.09 (C5), 70.86 (CH_2Ph), 83.36 (C2), 86.01 (C3), 90.14 (C4), 109.32 (C1), 112.10 (C, *i*Pr), 128.45, 128.71, 129.01 (CHar), 136.38 ppm (Car);



16 (5*S*, S_S) **19** (5*R*, S_R) **19** (5*R*, S_S)

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{42}NO_5S$: 468.277821, found: 468.277456.

Compound 19 (5*R*,S_S): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79–0.92 (m, 3H, CH_3 hex), 1.10–1.41 (m, 20H, CH_3 *t*Bu, CH_3 *i*Pr, $4CH_2$), 1.47 (s, 3H, CH_3 *i*Pr), 1.48–1.68 (m, 1H, HaA), 1.92–2.02 (m, 1H, HaB), 3.25–3.35 (m, 2H, H5, NH), 3.94 (d, 1H, H4, *J* = 8.8 Hz), 4.50 (d, 1H, CH_2Ph, *J* = 11.6 Hz), 4.67 (d, 1H, H2, *J* = 6.0 Hz), 4.72 (d, 1H, CH_2Ph, *J* = 11.6 Hz), 4.82 (dd, 1H, H3, *J* = 0.8, 6.0 Hz), 5.16 (s, 1H, H1), 7.27–7.37 ppm (m, 5H, Har); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.18 (CH_3 hex), 22.72 (CH_2), 22.89 (CH_3 *t*Bu), 24.70 (CH_2), 24.86 (CH_3 *i*Pr), 26.50 (CH_3 *i*Pr), 29.48 (CH_2), 31.81 (CH_2a), 56.55 (C, *t*Bu), 59.44 (C5), 70.14 (CH_2Ph), 82.08 (C3), 85.24 (C2), 89.94 (C4), 107.92 (C1), 112.31 (C, *i*Pr), 127.98–128.62 (CHar), 136.96 ppm (Car); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{42}NO_5S$: 468.277821, found: 468.277870.

Compound 19 (5*R*,S_R): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79–0.92 (m, 3H, CH_3 hex), 1.10–1.41 (m, 20H, CH_3 *t*Bu, CH_3 *i*Pr, $4CH_2$), 1.47 (s, 3H, CH_3 *i*Pr), 1.48–1.68 (m, 1H, HaA), 1.68–1.83 (m, 1H, HaB), 3.42–3.50 (m, 1H, H5), 4.07 (d, 1H, NH, *J* = 3.6 Hz), 4.30 (dd, 1H, H4, *J* = 1.2, 5.6 Hz), 4.55 (d, 1H, CH_2Ph, *J* = 12.2 Hz), 4.63 (d, 1H, H2, *J* = 6.0 Hz), 4.76 (d, 1H, CH_2Ph, *J* = 12.2 Hz), 4.97 (dd, 1H, H3, *J* = 1.2, 6.0 Hz), 5.16 (s, 1H, H1), 7.27–7.37 ppm (m, 5H, Har); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.15 (CH_3 hex), 22.66 (CH_2), 22.84 (CH_3 *t*Bu), 25.11 (CH_3 *i*Pr), 25.50 (CH_2), 26.66 (CH_3 *i*Pr), 31.79 (CH_2), 32.86 (CH_2a), 55.97 (C, *t*Bu), 56.64 (C5), 69.77 (CH_2Ph), 80.31 (C3), 85.87 (C2), 89.94 (C4), 107.57 (C1), 112.58 (C, *i*Pr), 127.98–128.62 (CHar), 136.70 ppm (Car).

Note: The configuration assignments were established according to the reactions with D-**15**-S_R and D-**15**-S_S, respectively. The diastereoselectivities are 100% from D-**15**-S_R (5*R* configuration) and 70% from D-**15**-S_S (5*S* configuration).

Benzyl (5*S*)-5-amino-5-deoxy-5-*C*-hexyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (17): Acetyl chloride (16 μL, 0.225 mmol, 3 equiv) was added to anhydrous MeOH (5 mL) under Ar. After 20 min of stirring, this solution was added to compound **16** (36 mg, 0.077 mmol) under Ar, and the reaction was stirred for 3 h 40 min at room temperature. The mixture was neutralized using a basic ion-exchange resin (IR400, OH^- form). The resin was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH 12:1) to give **17** (17 mg, 61%) as a yellow syrup and a significant amount of benzyl (5*S*)-5-amino-5-deoxy-5-*C*-hexyl-β-D-ribofuranoside (10 mg, 40%).

17: $[\alpha]_D^{20} = -66$ (*c* = 1.00, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.88–0.95 (m, 3H, CH_3 hex), 1.22–1.39 (m, 8H, $4CH_2$), 1.31 (s, 3H, CH_3 *i*Pr), 1.44 (s, 3H, CH_3 *i*Pr), 1.43–1.60 (m, 2H, 2Ha), 2.71 (dt, 1H, H5, *J* = 3.6, 8.6, 8.6 Hz), 3.91 (dd, H, H4, *J* = 1.2, 8.6 Hz), 4.58 (d, 1H, CH_2Ph, *J* = 11.8 Hz), 4.65 (d, 1H, H2, *J* = 6.0 Hz), 4.70 (dd, 1H, H3, *J* = 1.2, 6.0 Hz), 4.75 (d, 1H, CH_2Ph, *J* = 11.8 Hz), 5.15 (s, 1H, H1), 7.26–7.38 ppm (m, 5H, Har); ^{13}C NMR (101 MHz, CD_3OD): δ = 14.43 (CH_3 hex), 23.69 (CH_2), 25.16 (CH_3 *i*Pr), 26.88 (CH_3 *i*Pr), 26.90, 30.57, 32.92 (CH_2), 34.45 (CH_2a), 54.72 (C5), 71.19 (CH_2Ph), 83.26 (C3), 86.98 (C2), 92.68 (C4), 109.24 (C1), 113.59 (C, *i*Pr), 128.92, 129.03, 129.51 (CHar), 138.80 ppm (Car); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{34}NO_4$: 364.248235, found: 364.248379.

Benzyl (5*S*)-5-amino-5-deoxy-5-*C*-hexyl-β-D-ribofuranoside: ^{1}H NMR (250 MHz, CD_3OD): δ = 0.84–0.98 (m, 3H, CH_3), 1.25–1.44 (m, 8H, $4CH_2$), 1.44–1.57 (m, 1H, HaA), 1.57–1.74 (m, 1H, HaB), 2.75 (dt, 1H, H5, *J* = 4.2, 7.0, 7.0 Hz), 3.74 (t, 1H, H4, *J* = 7.0 Hz), 3.95 (d, 1H, H2, *J* = 4.8 Hz), 4.14 (dd, 1H, H3, *J* = 4.8, 7.0 Hz), 4.53 (d, 1H, CH_2Ph, *J* = 11.9 Hz), 4.73 (d, 1H, CH_2Ph, *J* = 11.9 Hz), 4.96 (s, 1H, H1), 7.23–7.39 ppm (m, 5H, Har); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{30}NO_4$: 324.216935, found: 324.217175.

(1*S*)-1-*C*-Hexyl-1,5-dideoxy-1,5-imino-L-ribitol (18): Compound **17** (17 mg, 0.047 mmol) was dissolved in 1,4-dioxane/H_2O/AcOH (4:0.5:0.5 mL) and 10% Pd/C was added (40 mg). The mixture was stirred for 12 h under an H_2 atmosphere at room temperature. The catalyst was removed by filtration through a membrane and washed with 1,4-dioxane/H_2O/AcOH. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography (CH_2Cl_2/acetone 2:1) to afford crude (1*S*)-1-*C*-hexyl-3,4-*O*-isopropylidene-1,5-dideoxy-1,5-imino-L-ribitol (9 mg, 75%). To a solution of this compound in 1,4-dioxane/H_2O (2:1; 3 mL) was added Dowex 50W X8 ion-exchange resin (H^+ form, 1 mL), previously washed with 1,4-dioxane/H_2O (2:1). The mixture was stirred for 18 h at room temperature. The resin was then poured onto a column, washed with 1,4-dioxane/H_2O (2:1, 20 mL) then with H_2O (20 mL). The product was eluted from the resin using aqueous 0.5 N NH_4OH (50 mL). Fractions containing the desired compound were combined and concentrated under vacuum to give **18** (6 mg, 79%) as a yellow syrup: $[\alpha]_D^{20} = +37.5$ (*c* = 1.00, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.86–0.94 (m, 3H, CH_3), 1.26–1.41 (m, 8H, $4CH_2$), 1.41–1.62 (m, 2H, $2H_a$), 2.45 (ddd, 1H, H1, *J* = 1.7, 6.1, 7.9 Hz), 2.69 (dd, 1H, H5A, *J* = 1.6, 14.0 Hz), 3.02 (dd, 1H, H5B, *J* = 2.6, 14.0 Hz), 3.46 (t, 1H, H3, *J* = 3.1 Hz), 3.71–3.74 (m, 1H, H2), 3.78–3.81 ppm (m, 1H, H4); ^{13}C NMR (63 MHz, CD_3OD + 1 drop of D_2O): δ = 14.43 (CH_3), 23.68, 26.96, 30.58 (CH_2), 32.67 (CH_2a), 32.96 (CH_2), 51.60 (C5), 59.99 (C1), 71.02 (C4), 71.34 (C3), 72.57 ppm (C2); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{24}NO_3$: 218.175070, found: 218.175636.

Benzyl (5*R*)-5-amino-5-deoxy-5-*C*-hexyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (20): Acetyl chloride (70 μL, 0.984 mmol, 2.9 equiv) was added to anhydrous MeOH (23 mL) under Ar. After 20 min of stirring, this solution was added to compound **19** (160 mg, 0.342 mmol) under Ar, and the reaction was stirred for 2 h 30 min at room temperature. The mixture was neutralized using a basic ion-exchange resin (IR400, OH^- form). The resin was removed by filtration, and the filtrate was concentrated under vacuum to give crude **20** (125 mg, quant.), which was used in the next step without purification. A sample of **20** was purified by silica gel column chromatography (CH_2Cl_2/MeOH 14:1) for analytical purposes to give a white amorphous solid: $[\alpha]_D^{20} = -57$ (*c* = 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81–0.90 (m, 3H, CH_3 hex), 1.23–1.35 (m, 8H, $4CH_2$), 1.32 (s, 3H, CH_3 *i*Pr), 1.42–1.56 (m, 1H, HaA), 1.47 (s, 3H, CH_3 *i*Pr), 1.67–1.82 (m, 1H, HaB), 3.00 (dt, 1H, H5, *J* = 4.5, 7.1, 7.1 Hz), 4.15 (dd, 1H, H4, *J* = 1.1, 7.1 Hz), 4.54 (d, 1H, CH_2Ph, *J* = 11.6 Hz), 4.68 (d, 1H, H2, *J* = 6.1 Hz), 4.74 (d, 1H, CH_2Ph, *J* = 11.6 Hz), 5.04 (dd, 1H, H3, *J* = 1.1, 6.1 Hz), 5.16 (s, 1H, H1), 7.26–7.38 ppm (m, 5H, Har); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.21 (CH_3 hex), 22.73 (CH_2), 25.04 (CH_3 *i*Pr), 25.75 (CH_2), 26.63 (CH_3 *i*Pr), 29.41, 31.84 (CH_2), 32.66 (CH_2a), 53.81 (C5), 70.18 (CH_2Ph), 80.99 (C3), 85.78 (C2), 90.07 (C4), 107.90 (C1), 112.69 (C, *i*Pr), 128.08,

128.15, 128.70 (CHar), 136.91 ppm (Car); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{34}NO_4$: 364.248235, found: 364.248401.

(1*R*)-1-*C*-Hexyl-1,5-dideoxy-1,5-imino-L-ribitol (21): Compound **20** (125 mg, 0.344 mmol) was dissolved in 1,4-dioxane/H_2O/AcOH (20:3:3 mL) and 10% Pd/C was added (80 mg). The mixture was stirred for 12 h under an H_2 atmosphere at room temperature. The catalyst was removed by filtration through a membrane and washed with 1,4-dioxane/H_2O/AcOH. The filtrate was concentrated under vacuum, and the procedure was repeated once under the same conditions to afford crude (1*R*)-1-*C*-hexyl-3,4-*O*-isopropylidene-1,5-dideoxy-1,5-imino-L-ribitol (73 mg, 82%). To a solution of this compound in 1,4-dioxane/H_2O (1:1; 6 mL) was added Dowex 50W X8 ion-exchange resin (H^+ form, 1.5 mL), previously washed with 1,4-dioxane/H_2O (1:1). The mixture was stirred for 36 h at room temperature. The resin was then poured onto a column and washed with H_2O (20 mL). The product was eluted from the resin using aqueous 0.5 N NH_4OH (70 mL). Fractions containing the desired compound were combined and concentrated under vacuum to give **21** (28 mg, 45%) as a white solid; mp: 123–131 °C (degradation); $[\alpha]_D^{20} = +30.3$ (*c* = 1.05, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.83–0.96 (m, 3H, CH_3), 1.18–1.41 (m, 8H, $4CH_2$), 1.41–1.56 (m, 1H, HaA), 1.73–1.85 (m, 1H, HaB), 2.66 (ddd, 1H, H1, *J* = 3.0, 8.4, 9.6 Hz), 2.70–2.78 (m, 2H, H5), 3.13 (dd, 1H, H2, *J* = 2.8, 9.6 Hz), 3.54–3.59 (m, 1H, H4), 3.95 ppm (t, 1H, H3, *J* = 2.8 Hz); ^{13}C NMR (101 MHz, CD_3OD): δ = 14.43 (CH_3), 23.71, 26.70, 30.79, 32.80 (CH_2), 32.96 (CH_2a), 46.43 (C5), 55.49 (C1), 70.24 (C4), 73.20 (C3), 74.09 ppm (C2); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{24}NO_3$: 218.175070, found: 218.175514.

Synthesis of 5-*C*-alkyl imino-L-ribitols

Benzyl 2,3-*O*-isopropylidene-*aldehydo*-β-L-*ribo*-pentodialdo-1,4-furanoside (L-2): Sulfuric acid (0.2 mL) was added to a suspension of L-ribose (5 g, 0.033 mol) in acetone (50 mL). The mixture was stirred for 2 h, then benzyl alcohol (10.4 mL) and toluene (17 mL) were added, and acetone was removed under vacuum. The residual mixture was stirred for 3 h and then neutralized with triethylamine. The mixture was diluted with CH_2Cl_2 (50 mL) and washed successively with aqueous 0.1 N HCl (20 mL), H_2O (20 mL), a saturated $NaHCO_3$ solution (20 mL) and H_2O (20 mL). The organic phase was dried over $MgSO_4$ and concentrated under high vacuum at 50 °C to remove most of the benzyl alcohol. The residue crystallized at room temperature. The crystals were washed with cold Et_2O and dried under vacuum to give an initial fraction of benzyl 2,3-*O*-isopropylidene-β-L-ribofuranoside L-**1** (1.54 g, 17%). A second crystallization gave another fraction of L-**1** (2.15 g, 23%) containing a small quantity of benzyl alcohol. Alcohol L-**1** (500 mg, 1.78 mmol) was then dissolved in anhydrous CH_2Cl_2 (18 mL) under Ar, and Dess–Martin periodinane (918 mg, 2.16 mmol, 1.2 equiv) was added. The reaction was stirred for 5 h at room temperature, and then concentrated under vacuum. Cold Et_2O was added at −20 °C and the precipitate was removed by filtration over Celite. The filtrate was concentrated under vacuum to give crude aldehyde L-**2** (512 mg, quant.), which was used in the next step without purification. ^{1}H NMR data are in accordance with published data for the enantiomer D-**2**.[21b]

***N*-*tert*-Butanesulfinylimine of benzyl 2,3-*O*-isopropylidene-*aldehydo*-β-L-*ribo*-pentodialdo-1,4-furanoside (L-15)**: To a solution of aldehyde L-**2** (496 mg, 1.78 mmol) in dry CH_2Cl_2 (18 mL) under Ar were added anhydrous $CuSO_4$ (1.42 g, 8.90 mmol, 5 equiv) and racemic *tert*-butanesulfinamide (238 mg, 1.96 mmol, 1.1 equiv). The mixture was stirred for 48 h at room temperature and then the copper salt was removed by filtration. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography (PE/EtOAc 6:1) to give pure L-**15** (363 mg, 53%) as a 1:1 mixture of two diastereomers and as a colorless syrup: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.14 (s, 4.5H, CH_3 *t*Bu), 1.21 (s, 4.5H, CH_3 *t*Bu), 1.33 (s, 3H, CH_3 *i*Pr), 1.49 (s, 1.5H, CH_3 *i*Pr), 1.50 (s, 1.5H, CH_3 *i*Pr), 4.48 (d, 0.5H, CH_2Ph, *J* = 8.4 Hz), 4.53 (d, 0.5H, CH_2Ph, *J* = 8.8 Hz), 4.62 (dd, 0.5H, H3, *J* = 0.6, 5.9 Hz), 4.66 (dd, 0.5H, H3, *J* = 0.6, 5.9 Hz), 4.71 (d, 0.5H, CH_2Ph, *J* = 8.8 Hz), 4.76 (d, 0.5H, CH_2Ph, *J* = 8.4 Hz), 4.91–4.95 (m, 1H, H4), 5.16 (d, 0.5H, H2, *J* = 5.8 Hz), 5.22–5.25 (m, 0.5H, H2), 5.22 (s, 0.5H, H1), 5.25 (s, 0.5H, H1), 7.27–7.39 (m, 5H, Har), 8.10 (d, 0.5H, H5, *J* = 2.3 Hz), 8.11 ppm (d, 0.5H, H5, *J* = 2.8 Hz); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{28}NO_5S$: 382.168270, found: 382.168463.

General procedure for the addition of Grignard reagents: To a solution of imine L-**15** in anhydrous toluene (0.1 M, v mL) at −78 °C under Ar was added a commercial solution of Grignard reagent (5 equiv). The mixture was warmed to room temperature and stirred for 18 h. The reaction was quenched at 0 °C by the addition of a saturated NH_4Cl solution, and the aqueous phase was extracted with Et_2O (3 × 2v mL). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel column chromatography (PE/EtOAc).

Benzyl (5*S*,S_{RS})-5-*tert*-butanesulfinamido-5-deoxy-5-*C*-hexyl-2,3-*O*-isopropylidene-β-L-ribofuranoside (22a) and benzyl (5*R*,S_R)-5-*tert*-butanesulfinamido-5-deoxy-5-*C*-hexyl-2,3-*O*-isopropylidene-β-L-ribofuranoside (25a): Compound **22a** (202 mg, 47%) as an inseparable 7:3 mixture of two S*-stereoisomers and as a white solid, and compound **25a** (102 mg, 23%) as a single S*-stereoisomer and as a colorless syrup were obtained from L-**15** (350 mg, 0.917 mmol) using hexylmagnesium bromide (2 M in Et_2O; 2.3 mL, 4.6 mmol, 5 equiv). Purification was performed with PE/EtOAc 4:1.

Compound 22a: R_f = 0.15 (PE/EtOAc 4:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83–0.93 (m, 3H, CH_3 hex), 1.16–1.40 (m, 20H, CH_3 *t*Bu, CH_3 *i*Pr, $4CH_2$), 1.47 (s, 3H, CH_3 *i*Pr), 1.53–1.67 (m, 1H, HaA), 1.68–1.82 (m, 0.7H, HaB), 1.91–2.02 (m, 0.3H, HaB), 3.21–3.32 (m, 0.6H, H5, NH), 3.41–3.50 (m, 0.7H, H5), 3.94 (d, 0.3H, H4, *J* = 9.3 Hz), 4.07 (d, 0.7H, NH, *J* = 4.0 Hz), 4.29 (dd, 0.7H, H4, *J* = 1.6, 5.6 Hz), 4.48–4.79 (m, 3H, H2, CH_2Ph), 4.82 (d, 0.3H, H3, *J* = 6.5 Hz), 4.97 (dd, 0.7H, H3, *J* = 1.6, 6.1 Hz), 5.16 (s, 1H, H1), 7.28–7.38 ppm (m, 5H, Har); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{42}NO_5S$: 468.277821, found: 468.277954. The ^{1}H NMR spectrum of **22a** is identical to that of compound **19** (enantiomers).

Compound 25a: R_f = 0.28 (PE/EtOAc 4:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85–0.95 (m, 3H, CH_3 hex), 0.98 (s, 9H, CH_3 *t*Bu), 1.25–1.41 (m, 8H, $4CH_2$), 1.32 (s, 3H, CH_3 *i*Pr), 1.48 (s, 3H, CH_3 *i*Pr), 1.50–1.63 (m, 2H, 2Ha), 3.17–3.30 (m, 1H, H5), 4.46 (d, 1H, H4, *J* = 3.3 Hz), 4.56 (d, 1H, CH_2Ph, *J* = 11.1 Hz), 4.72 (d, 1H, CH_2Ph, *J* = 11.1 Hz), 4.74 (d, 1H, H3, *J* = 6.1 Hz), 4.89 (d, 1H, NH, *J* = 8.8 Hz), 5.12 (d, 1H, H2, *J* = 6.1 Hz), 5.18 (s, 1H, H1), 7.29–7.39 ppm (m, 5H, Har); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{42}NO_5S$: 468.277821, found: 468.277971. The ^{1}H NMR spectrum of **25a** is identical to that of compound **16** (enantiomers).

General procedure for sulfinyl cleavage: Acetyl chloride (3 equiv) was added to anhydrous MeOH (0.03 M) under Ar. After 20 min, this solution was added to the sulfinylamine under Ar, and the mixture was stirred for the indicated time at room temperature. The solution was neutralized with Amberlite IR400 ion-exchange resin (OH^- form). The resin was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography.

Benzyl (5*S*)-5-amino-5-deoxy-5-*C*-hexyl-2,3-*O*-isopropylidene-β-L-ribofuranoside (23 a): Compound **23 a** (66 mg, 42%) as an amorphous white solid was obtained from **22 a** (202 mg, 0.432 mmol) after 3.5 h of reaction. Purification was performed using CH_2Cl_2/MeOH 30:1. R_f = 0.59 (CH_2Cl_2/MeOH 12:1); $[\alpha]_D^{20} = +63.5$ (c = 1.15, $CHCl_3$); ^{1}H NMR (250 MHz, CD_3OD): δ = 0.83–0.93 (m, 3H, CH_3 hex), 1.19–1.38 (m, 11H, 4CH_2, CH_3 *i*Pr), 1.44 (s, 3H, CH_3 *i*Pr), 1.44–1.55 (m, 1H, HaA), 1.62–1.77 (m, 1H, HaB), 2.77 (dt, 1H, H5, J = 3.6, 7.8, 7.8 Hz), 3.94 (dd, 1H, H4, J = 1.4, 7.8 Hz), 4.53 (d, 1H, CH_2Ph, J = 11.8 Hz), 4.64 (d, 1H, H2, J = 6.1 Hz), 4.73 (d, 1H, CH_2Ph, J = 11.8 Hz), 4.88 (dd, 1H, H3, J = 1.4, 6.1 Hz), 5.12 (s, 1H, H1), 7.26–7.38 ppm (m, 5H, Har); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{34}NO_4$: 364.248235, found: 364.248541.

Benzyl (5*R*)-5-amino-5-deoxy-5-*C*-hexyl-2,3-*O*-isopropylidene-β-L-ribofuranoside (26 a): Compound **26 a** (40 mg, 56%) as a colorless syrup was obtained from **25 a** (91 mg, 0.195 mmol) after 4.5 h of reaction. Purification was performed using CH_2Cl_2/MeOH 14:1. R_f = 0.44 (CH_2Cl_2/MeOH 14:1); $[\alpha]_D^{20} = +68.0$ (c = 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.87–0.95 (m, 3H, CH_3 hex), 1.21–1.40 (m, 11H, HaA, 3.5CH_2, CH_3 *i*Pr), 1.44 (s, 3H, CH_3 *i*Pr), 1.45–1.60 (m, 2H, HaB, 0.5CH_2), 2.71 (dt, 1H, H5, J = 3.6, 8.5, 8.5 Hz), 3.91 (dd, H, H4, J = 1.2, 8.5 Hz), 4.58 (d, 1H, CH_2Ph, J = 11.8 Hz), 4.65 (d, 1H, H2, J = 6.0 Hz), 4.70 (dd, 1H, H3, J = 1.2, 6.0 Hz), 4.74 (d, 1H, CH_2Ph, J = 11.8 Hz), 5.15 (s, 1H, H1), 7.26–7.38 ppm (m, 5H, Har); ^{13}C NMR (101 MHz, CD_3OD): δ = 14.42 (CH_3 hex), 23.69 (CH_2), 25.17 (CH_3 *i*Pr), 26.89 (CH_3 *i*Pr), 26.91, 30.58, 32.92 (CH_2), 34.52 (CH_2a), 54.71 (C5), 71.19 (CH_2Ph), 83.28 (C3), 87.0 (C2), 92.74 (C4), 109.25 (C1), 113.59 (C, *i*Pr), 128.91, 129.03, 129.50 (CHar), 138.81 ppm (Car); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{34}NO_4$: 364.248235, found: 364.248494.

General procedure for reductive amination and deprotection: The amine was dissolved in 1,4-dioxane/H_2O/AcOH (10:6:1, 0.01 M) and 10% Pd/C was added (300 mg mmol^{-1}). The mixture was stirred for 48 h under an H_2 atmosphere at room temperature. The catalyst was removed by filtration through a membrane and washed with 1,4-dioxane/H_2O/AcOH. The filtrate was concentrated under vacuum to give the protected iminoribitol. To a solution of this compound (0.02 M) in 1,4-dioxane/H_2O (3:1) was added Dowex 50W X8 ion-exchange resin (H^+ form, 8 mL mmol^{-1}), previously washed with 1,4-dioxane/H_2O (3:1). The mixture was stirred for 18 h at room temperature. The resin was then poured onto a column, washed with 1,4-dioxane/H_2O (1:1), then with H_2O. The product was eluted with aqueous 0.5 N NH_4OH. Fractions containing the iminoribitol derivatives were combined and concentrated under vacuum to afford the deprotected compound.

(5*S*)-5-*C*-Hexyl-1,5-dideoxy-1,5-imino-L-ribitol (24 a): Compound **24 a** (26 mg, 65%) was obtained as a white amorphous solid from **23 a** (67 mg, 0.184 mmol): $[\alpha]_D^{20} = -34.5$ (c = 1.01, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.87–0.94 (m, 3H, CH_3), 1.18–1.40 (m, 8H, 4CH_2), 1.43–1.54 (m, 1H, HaA), 1.75–1.85 (m, 1H, HaB), 2.61–2.68 (m, 1H, H5), 2.74 (d, 2H, H1, J = 8.0 Hz), 3.13 (dd, 1H, H4, J = 2.7, 9.6 Hz), 3.56 (dt, H2, J = 2.7, 8.0, 8.0 Hz), 3.94 ppm (t, H3, J = 2.7 Hz); ^{13}C NMR (101 MHz, CD_3OD): δ = 14.42 (CH_3), 23.70, 26.72, 30.80 (CH_2), 32.88 (CH_2a), 32.96 (CH_2), 46.52 (C1), 55.49 (C5), 70.37 (C2), 73.25 (C3), 74.20 ppm (C4); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{24}NO_3$: 218.175070, found: 218.175402.

(5*R*)-5-*C*-Hexyl-1,5-dideoxy-1,5-imino-L-ribitol (27 a): Compound **27 a** (17 mg, 71%) was obtained as a colorless syrup from **26 a** (40 mg, 0.110 mmol): $[\alpha]_D^{20} = -38.3$ (c = 1.00, MeOH); ^{1}H NMR (250 MHz, CD_3OD): δ = 0.85–0.96 (m, 3H, CH_3), 1.26–1.45 (m, 8H, 4CH_2), 1.45–1.66 (m, 2H, 2Ha), 2.42–2.48 (m, 1H, H5), 2.70 (dd, 1H, H1A, J = 1.8, 14.0 Hz), 3.03 (dd, 1H, H1B, J = 2.5, 14.0 Hz), 3.46 (t, 1H, H3, J = 3.1 Hz), 3.71–3.74 (m, 1H, H4), 3.77–3.82 ppm (m, 1H, H2); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{24}NO_3$: 218.175070, found: 218.175390.

Biological assays

Enzymatic assays: Unless otherwise indicated, all enzymes and reagents were obtained from Sigma (St. Louis, MO, USA). The enzymatic assays were run as follows, using one of the following substrates: β-*o*NPGal (2-nitrophenyl β-D-galactopyranoside), β-4MUGal (4-methylumbelliferyl β-D-galactopyranoside), α-*p*NPGal (4-nitrophenyl α-D-galactopyranoside), β- or α-*p*NPGlc (4-nitrophenyl β- or α-D-glucopyranoside). The β-galactosidase from bovine liver was used at a final concentration of 13 mU mL^{-1} in sodium phosphate (100 mM, pH 7.3) with β-*o*NPGal as substrate (2.25 mM). After 2 h incubation at 37 °C, the reaction was stopped by the addition of an equal volume of 0.2 M NaOH and absorbance was determined at λ 405 nm.

The β-galactosidase from *E. coli* was used at a final concentration of 1 U mL^{-1} in sodium phosphate (100 mM, pH 7.3), supplemented with $MgCl_2$ (1 mM) and 2-mercaptoethanol (112 mM), with β-*o*NPGal as substrate (2 mM). After 2 h incubation at 37 °C, the reaction was stopped by the addition of an equal volume of 0.2 M NaOH and absorbance was determined at λ 405 nm.

The β-galactosidase from *Aspergillus oryzae* was used at a final concentration of 0.2 U mL^{-1} in sodium phosphate (100 mM, pH 7.3) with β-*o*NPGal as substrate (2.25 mM). After 2 h incubation at 37 °C, the reaction was stopped by the addition of an equal volume of 0.2 M NaOH and absorbance was determined at λ 405 nm.

The β-galactosidase from bovine testis was used at a final concentration of 5 mU mL^{-1} in sodium phosphate (100 mM, pH 7.3) with β-4MUGal as substrate (0.8 mM). After 2 h incubation at 37 °C, the reaction was stopped by the addition of an equal volume of 0.15 M glycine (pH 10.2) and fluorescence emission was determined at λ 445 nm with excitation at λ 365 nm.

Human peripheral blood mononuclear cell lysate was used as a source of human β-galactosidase activity. The assay was conducted using lysate from 2×10^6 cells per reaction in sodium phosphate (50 mM, pH 7.3), supplemented with protease inhibitors (Complete Protease Inhibitor Cocktail Tablets, Roche) and 1% Triton X-100, with β-4MUGal as substrate (0.8 mM). After 1 h incubation at 37 °C, the reaction was stopped by the addition of an equal volume of 0.15 M glycine (pH 10.2) and fluorescence emission was determined at λ 445 nm with excitation at λ 365 nm.

The α-galactosidase from green coffee beans was used at a final concentration of 12.5 mU mL^{-1} in sodium citrate (100 mM, pH 6.5) with α-*p*NPGal as substrate (2 mM). After 1 h incubation at room temperature, the reaction was stopped by the addition of an equal volume of 0.2 M NaOH and absorbance was determined at λ 405 nm.

The β-glucosidase from almonds was used at a final concentration of 1.25 μg mL^{-1} in sodium acetate (100 mM, pH 5.0) with β-*p*NPGlc as substrate (2 mM). After 1 h incubation at room temperature, the reaction was stopped by the addition of an equal volume of 0.2 M NaOH and absorbance was determined at λ 405 nm.

The α-glucosidase from *Saccharomyces cerevisiae* was used at a final concentration of 12.5 mU mL^{-1} in sodium phosphate (100 mM, pH 6.8) with α-*p*NPGlc as substrate (2 mM). After 1 h in-

cubation at 37 °C, the reaction was stopped by the addition of an equal volume of 0.2 M NaOH and absorbance was determined at λ 405 nm.

Chaperone assays: The fibroblast cell lines derived from GM1-gangliosidosis patients GM02439 and GM03251 were obtained from Coriell Institute (Camden, NJ, USA). The chaperone assays were conducted by following the method described by Rigat et al.[30] Fibroblasts were cultured in 25 cm^2 flasks placed in a humidified incubator (37 °C and 5% CO_2) using DMEM complete (DMEM-c) made from DMEM supplemented with nonessential amino acids, penicillin, streptomycin and 10% fetal calf serum (Invitrogen ThermoFisher Scientific). For the chaperone assays, cells were harvested by trypsinization, seeded in triplicates at 2×10^4 cells per well of 24-well plates in 2 mL DMEM-c with the adequate compound concentrations. After 3 days in culture, 1 mL of medium was removed from each well and replaced by 1 mL of fresh DMEM-c medium containing the corresponding compound concentration. After two more days in culture, the medium of each well was discarded, and the cells were washed twice with phosphate-buffered saline. Lysis buffer (sodium citrate 100 mM, pH 4.3, supplemented with protease inhibitors from Roche and 1% Triton X-100; 125 µL) was added per well, and the plates were frozen at −80 °C. The lysates were then thawed and clarified by centrifugation (5 min at 15000 rpm in an Eppendorf microfuge). Lysate (80 µL) was distributed in wells of black-wall fluorimetric 96-well plates, and 20 µL substrate (β-4MUGal at 1.25 mM in lysis buffer) were added per well. The plates were then incubated for 17 h at 37 °C. The enzymatic reactions were stopped by the addition of an equal volume of 0.15 M glycine (pH 10.2) and fluorescence emission was determined at λ 445 nm with excitation at λ 365 nm.

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