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Stereoselective Total Synthesis of Aminoiminohexitols via Carbamate Annulation

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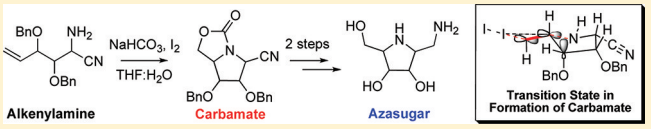
Supporting Information

ABSTRACT: New methodology for the preparation of a variety of aminoiminohextitols is described. Key in the synthesis is the application of a diastereoselective Strecker reaction and the extension of our carbamate annulation methodology to protected and functionalized alkenylamines. Insight into the effects that the substitution patterns of the alkenylamines have on the diastereoselectivity of the iodocyclization and carbamate annulation is discussed. An evaluation of the glycosidase inhibitory activity of the aminoiminohexitols and derivatives is also presented, with the previously undisclosed D-*talo* isomer showing good selective inhibition of β-D-glucosidase.



INTRODUCTION

The ability of azasugars to mimic the oxocarbenium transition state of carbohydrate-processing enzymes[1] has imparted on them much potential in the treatment of diseases such as diabetes, cancer, and lysosomal storage disorders.[2] Azasugars used as clinical drugs include the *N*-alkylated piperidine Glyset (**1a**, Figure 1), for noninsulin dependent diabetes, and Zavesca

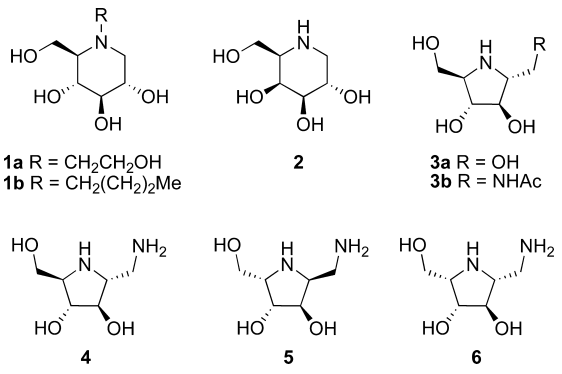


Figure 1. Representative azasugars.

(**1b**), for the control of Gaucher's disease. 1-Deoxygalactonojirimycin (DGJ, **2**), currently in clinical trials, has shown great promise in the treatment of Fabry's disease.[3] Five-membered azasugars, or pyrrolidines, also exhibit much promise as drug candidates. Notably, Wong et al. observed that derivatization of the naturally occurring 2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine (DMDP, **3a**) to the 1-amino-1-deoxy-DMDP analogue **3b** resulted in the generation of a compound with pronounced inhibitory activity against *N*-acetyl-β-D-glucosaminidase.[4] The subsequent synthesis of a library of *N*-functionalized DMDP analogues[5−8] then led to the identification of potential drug candidates for osteoarthritis[9,10] and bacterial infection.[11] Similarly, the groups of Stütz and Wrodnigg developed a series of glycosidase inhibitors via the one-step *N*-derivatization of 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol (**4**),[12−15] while more recently, Ramesh and coworkers prepared several selective glycosidase inhibitors based on modifications to the L-*ido* azasugar **5**.[16] An *N*-acyl derivative of imino-D-glucitol **6** was also found to exhibit potent and selective activity against β-glucosidase while the parent compound was inactive.[17]

Given the potential of pyrrolidines as glycosidase inhibitors,[18] we were interested in developing efficient methodology for the preparation of aminoiminohexitols. To this end, we demonstrated that the combination of a diastereoselective Strecker reaction and our recently developed I_2-promoted carbamate annulation methodology[19] allowed for the synthesis of the L-*ido*-derived aminoiminohexitol **5** in 39% overall yield from D-arabinose (Scheme 1).[20] Here, we illustrated that benzyl-protected aldehyde **7**, readily prepared from D-arabinose, underwent a highly diastereoselective Strecker[21] reaction to give the *syn*- and *anti*-alkenylamines **8** (dr = 9:1), which were readily separated by flash column chromatography. The major *syn*-isomer was subjected to I_2 and excess $NaHCO_3$ in THF/H_2O to give, by way of intermediate iodide **9**, the 4,5-*cis* carbamate **10** in excellent yield and diastereoselectivity (dr > 95:5). Treatment of carbamate **10** with $Pd(OH)_2/C$ in the presence of 2 M HCl then produced deprotected amine **11**,

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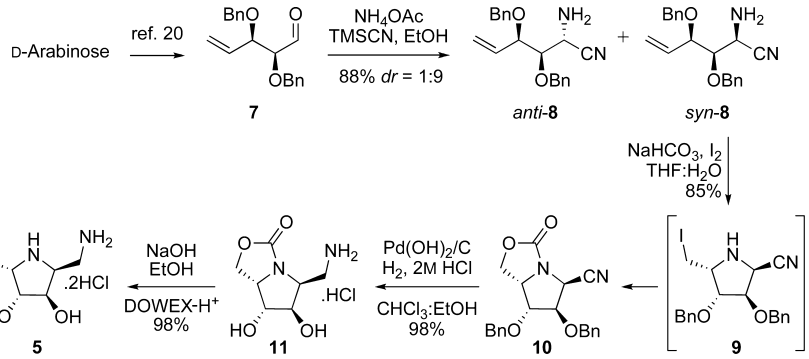
Scheme 1. Preparation of 5 from D-Arabinose



which upon hydrolysis gave the known L-*ido*-aminoiminohexitol **5**.[16]

To further explore this methodology, we herein report on the application of our carbamate annulation for the synthesis of other aminoiminohexitols including the D-*manno* **4** and D-*gluco* **6** derived azasugars (Figure 1) and the previously undisclosed stereoisomers with the D-*galacto* **12**, D-*talo* **13**, and L-*altro* **14** configurations (Figure 2). Factors influencing the diastereoselectivity of the iodocyclization and carbamate annulation will be presented, as well as an evaluation of the inhibitory activity of the aminoiminohexitols.

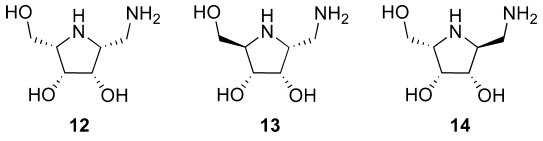
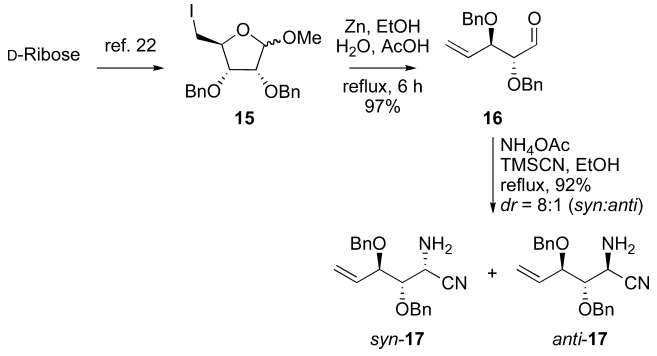


Figure 2. Novel aminoiminohexitols.

RESULTS AND DISCUSSION

To gain access to the 3,4-*cis*-series of hydroxylated azasugars, we required the 3,4-*anti*-substituted α-aminonitrile precursors and, consequently, D-ribose as the starting material (Scheme 2).

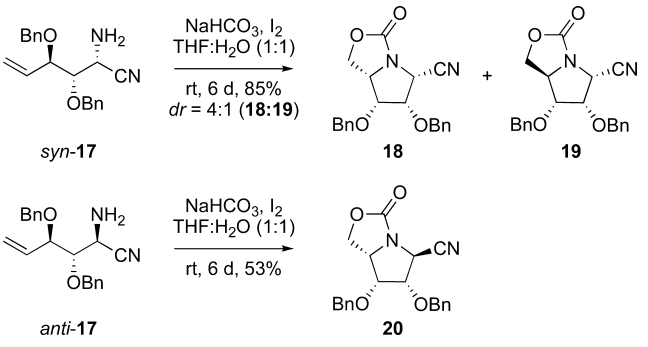
Scheme 2. Preparation of α-Aminonitriles Commencing with D-Ribose



Methyl iodoglycoside **15** was conveniently prepared according to literature precedent[22] and subjected to a Vasella reaction[23] to give aldehyde **16** in excellent (97%) yield. Aldehyde **16** was then treated with NH_4OAc and TMSCN to give α-aminonitrile *syn*-**17**, the chelation-controlled Cram product, as the major diastereomer (*syn*-**17**:*anti*-**17**, 8:1) and in excellent (92%) overall yield. It is interesting to note that the *syn*-stereoselectivity of the Strecker reaction does not appear to be affected by the relative configuration between C-2 and C-3 of the linear aldehyde, with similar diastereoselectivities being obtained for both the arabinose (cf. Scheme 1)[20] and ribose derived aldehydes. The diastereomers, *syn*-**17** and *anti*-**17**, were readily separated via flash column chromatography (hexanes/EtOAc, 2:1; R_f = 0.27 for α-aminonitrile *syn*-**17**, R_f = 0.16 for α-aminonitrile *anti*-**17**) and their relative configurations confirmed following subsequent cyclization (vide infra).

The major Strecker product *syn*-aminonitrile **17** was then subjected to a carbamate annulation via treatment with $NaHCO_3$ and I_2 (Scheme 3). Surprisingly, in contrast to the usual high selectivity of this reaction,[19,20] two diastereomeric carbamates **18** and **19** (dr = 4:1) were formed. Here, the major carbamate was the 4,5-*cis*-isomer **18**, as confirmed by X-ray analysis (Figure 3A). Cyclization of the minor Strecker product, *anti*-aminonitrile **17**, however, gave only one diastereomer **20**, in 53% yield. This was also crystallized and a crystal structure obtained (Figure 3B). Though the annulation yield for *anti*-aminonitrile **17** was modest, there was no evidence by ^1H NMR of the other carbamate diastereomer or the intermediate primary iodide. ^1H NMR of the crude reaction mixture, however, did indicate that retro-Strecker products (e.g., aldehydes) were formed in addition to the desired product. It is also interesting that both ribose-derived alkenylamines took longer to cyclize (6 days) when compared to the cyclization of arabinose-derived *syn*-**8** (20 h). This suggests that the activation energies for the formation of **18**−**20** are higher than for the formation of **10**, which could be due to steric constraints encountered by the benzyloxy groups at C-3 and C-4 when transforming from the linear to cyclized structures. In previous studies by Yoshida and co-workers,[24] it was also observed that

Scheme 3. Carbamate Annulations with D-Ribose-Derived α-Aminonitriles



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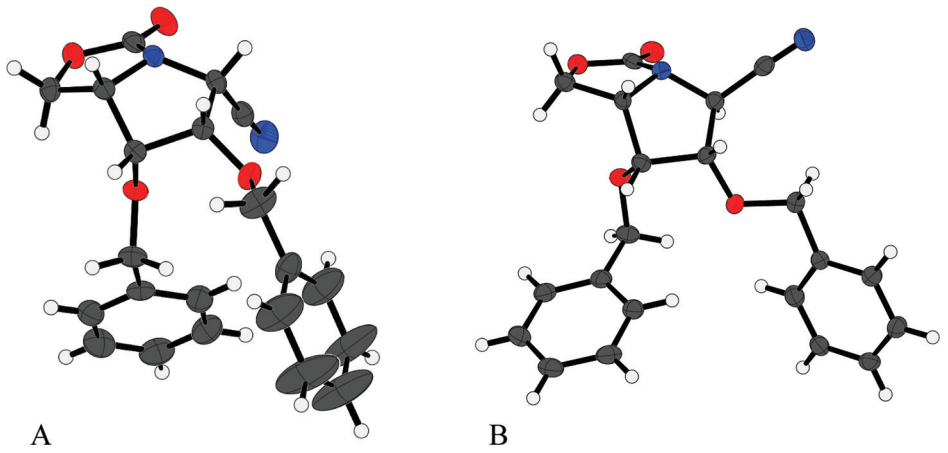
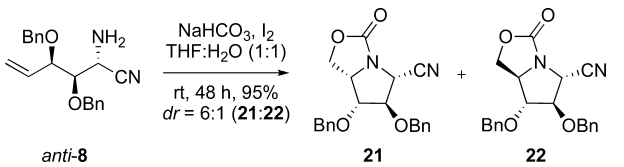


Figure 3. Crystal structures of carbamates **18** (A) and **20** (B).

cyclization of 1,2-alkoxy-substituted pentenylic alcohols proceeded much more slowly when forming the 2,5-*trans*, as compared to the 2,5-*cis*, products.

To further tease out the effects that the substituents have on the diastereoselectivity of the annulation, the minor arabinose-derived aminonitrile *anti*-**8** was also subjected to the carbamate annulation conditions (Scheme 4). Here, cyclization resulted in the generation of two carbamate products (**21**:**22**, dr = 6:1) following stirring at room temperature for 48 h, with the configuration of each diastereomer being determined at subsequent stages in the synthesis (vide infra).

Scheme 4. I_2-Mediated Carbamate Annulation Using D-Arabinose-Derived *anti*-8



To explain the diastereoselectivities observed in the carbamate annulation reaction, the transition states for the formation of the observed carbamates need to be considered. We previously established that the primary iodide (**9**, Scheme 1) is a key intermediate during the annulation[20] and as the formation of the iodide is irreversible, it is likely that this step determines the diastereoselectivity of the reaction. Building on seminal work by Chamberlin et al.[25−27] and the more recent theoretical studies presented by Gouverneur and co-workers,[28] we propose that the attack of the internal nucleophile on the I_2−alkene complex takes place via a 5-membered ring transition state in which the nitrogen approaches the double bond in an envelope conformation and follows a Bürgi−Dunitz-like trajectory. In the case of the cyclization of the D-ribose-derived Strecker product *syn*-**17** (Figure 4), the benzyloxy substituent on the ring (depicted in blue) can be positioned either in the plane of the double bond (**A**, OBn-in-plane) or almost perpendicular to that plane (**B**, H-in-plane). Of these two transition states, **A**, which ultimately leads to the major carbamate **18**, has minimal overlap between the electron-withdrawing σ^*_{C-O} and reacting $\pi_{C=C}$ orbitals, thereby resulting in a lower energy transition state. In contrast,

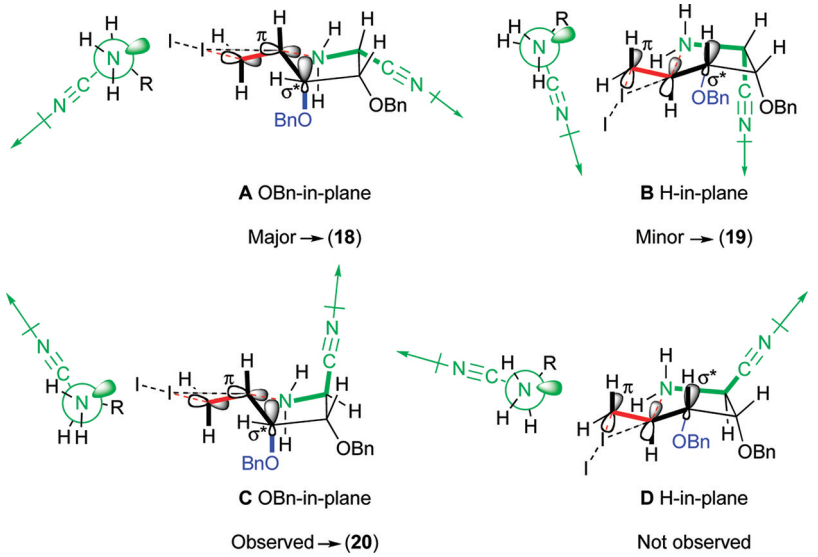


Figure 4. Transition states leading to the formation of carbamate **18** (**A**, major product) and **19** (**B**, minor product) from alkenylamine *syn*-**17** and the formation of carbamate **20** (**C**) from alkenylamine *anti*-**17**.

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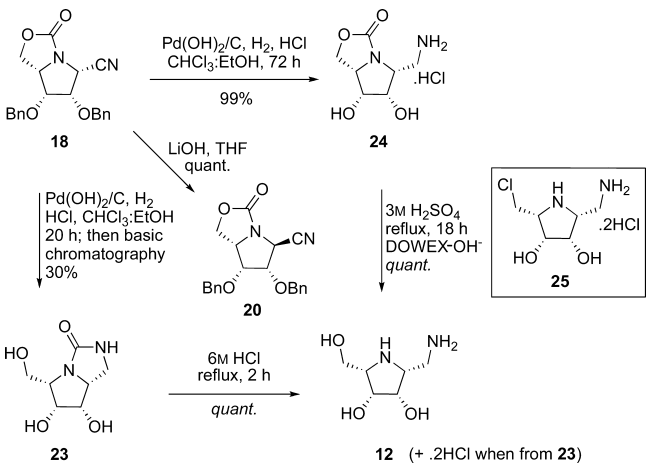
transition state **B** has overlapping benzyloxy σ^*_{C-O} and double bond $\pi_{C=C}$ orbitals, which results in the removal of electron density from the π-bond and a higher energy transition state. At this point, however, the influence of the nitrile substituent on the transition state also needs to be considered. In **A**, the dihedral angle between the plane of the nitrile dipole and the lone pair of electrons on the amine is approximately 180° (depicted in green). This results in electron density being withdrawn from the nitrogen nucleophile, thus raising the transition state energy of conformer **A**. In contrast, the dihedral angle between the nitrogen dipole and the lone pair of electrons of the amine in transition state **B** is approximately 90° and thus has less of an influence on the nucleophilicity of the amine. Accordingly, the transition states for **A** and **B** become closer in energy and some of the *trans*-carbamate product **19** is also formed in the cyclization.

When considering the formation of carbamate **20** from the *anti*-α-aminonitrile **17** (Figure 4), similar transition states can be drawn with the benzyloxy substituent in the plane of the double bond (**C**, OBn-in-plane, lower energy TS) or almost perpendicular to that plane (**D**, H-in-plane, higher energy TS). In addition, the nitrile group in transition state **C** does not reduce the nucleophilicity of the amine, while in transition state **D** the nitrile dipole leads to electron density being withdrawn from the amine through n–σ^*_{CCN} overlap. For this reason, there is a large energy difference between the two transition states, and carbamate **20** (from **C**) is the only product observed. Similar analyses can also be used when explaining the observed diastereoselectivity of the carbamate annulation for the D-arabinose-derived alkenylamines *syn*-**8** and *anti*-**8**.

Having determined the key influences on the diastereoselectivity of the carbamate annulation, we were then interested in using the said carbamates as intermediates for the synthesis of aminoiminohexitols. To this end, carbamate **18** was first hydrogenated using $Pd(OH)_2/C$ in the presence of 2 M HCl with the objective of simultaneously removing the benzyl groups and reducing the nitrile to the amine (Scheme 5). Via

Scheme 5. Deprotection of Carbamate 18



TLC analysis, this reaction appeared to proceed smoothly, and following silica gel chromatography (DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v) only one product was observed. HRMS also gave a molecular ion of 189.0869 $[M + H]^+$ corresponding to the expected $[C_7H_{12}N_2O_4 + H]^+$. Close analysis of the spectral data, however, revealed the presence of a carbonyl peak at δ 164.0 ppm in the ^{13}C NMR spectra, which correlated by HMBC to two protons at δ 3.59 and 3.49 ppm. Further analysis by 2D NMR (COSY, HMBC, HSQC) revealed that, rather than the desired amino sugar, urea derivative **23** was formed in 30% yield (unoptimized), presumably via the ring closure of the intermediate amine on the carbamate in **24**. An attempt was made to prevent urea formation by changing the deprotection order through the hydrolysis of carbamate **18** with LiOH; however, this led to epimerization of the proton α to the nitrile and carbamate **20** was isolated in quantitative yield. While not effecting the desired transformation, this epimerization to favor the thermodynamically more stable *trans* relationship between the carbamate and the nitrile provides a high-yielding route for the preparation of carbamate **20**. Previously, carbamate **20** could only be prepared from the minor ribose-derived Strecker product. The hydrogenation of carbamate **18** using $Pd(OH)_2/C$ was then repeated, and during workup it was observed that if the amine remained protonated, by keeping the conditions acidic throughout, the desired amine functionalized carbamate **24** could be obtained in excellent (99%) yield and without the need for further purification. Attempts to hydrolyze carbamate **24** then followed, but surprisingly, the use of 6 M HCl gave chloroaminoiminohexitol **25** as the major product and only minor amounts of the desired D-*galacto* aminoiminohexitol **12**. Though a useful synthetic intermediate, chloride **25** decomposed upon purification by silica gel chromatography and thus could not be isolated in sufficient purity for subsequent biological assessment. Subjecting carbamate **24** to 3 M H_2SO_4 at reflux, however, followed by neutralization with basic DOWEX allowed for aminoiminohexitol **12** to be obtained in quantitative yield as the free base. Urea derivative **23** could also be quantitatively converted to the desired aminoiminohexitol **12** as the hydrochloride salt following treatment with refluxing 6 M HCl. Using the optimized route (**18** → **24** → **12**), the target aminoiminohexitol **12** can now be prepared in 36% overall yield from D-ribose.

Armed with this knowledge, the remaining carbamates were then transformed into their corresponding aminoiminohexitols (Scheme 6). Treatment of carbamate **19** with $Pd(OH)_2/C$ in the presence of 2 M HCl led to the smooth conversion into amine **26** (98% yield). The carbamate in **26** was then hydrolyzed using a solution of NaOH in EtOH followed by neutralization with DOWEX-H^+ to complete the synthesis and generate novel D-*talo* aminoiminohexitol **13**. Here, it is important to note that when there is a 2,5-*trans* relationship between the aminomethyl and carbamate moieties, the corresponding urea derivative is not formed and base-mediated hydrolysis can be used. Carbamate **20** was then hydrogenated to give the corresponding amine **27** (99% yield), and subsequent hydrolysis proceeded uneventfully to yield the novel L-*altro* derived aminoiminohexitol **14** in 37% overall yield from D-ribose. Though we had already assigned the stereochemistry of **14** from the crystal structure of the precursor carbamate **20**, the ^1H NMR and ^{13}C NMR data were consistent with those of the known D-*altro* enantiomer and the optical rotation of similar magnitude but opposite sign.[29,30] Carbamate **21**, with the *cis*-relationship between the aminomethyl and carbamate functionalities, was then hydrogenated and the ammonium salt **28** obtained in excellent (99%) yield. The acid-catalyzed hydrolysis of **28** using 3 M H_2SO_4 then gave the D-glucitol-derived aminoiminohexitol **6**, again in excellent yield. Spectral data for **6** matched that previously reported.[12] Finally,

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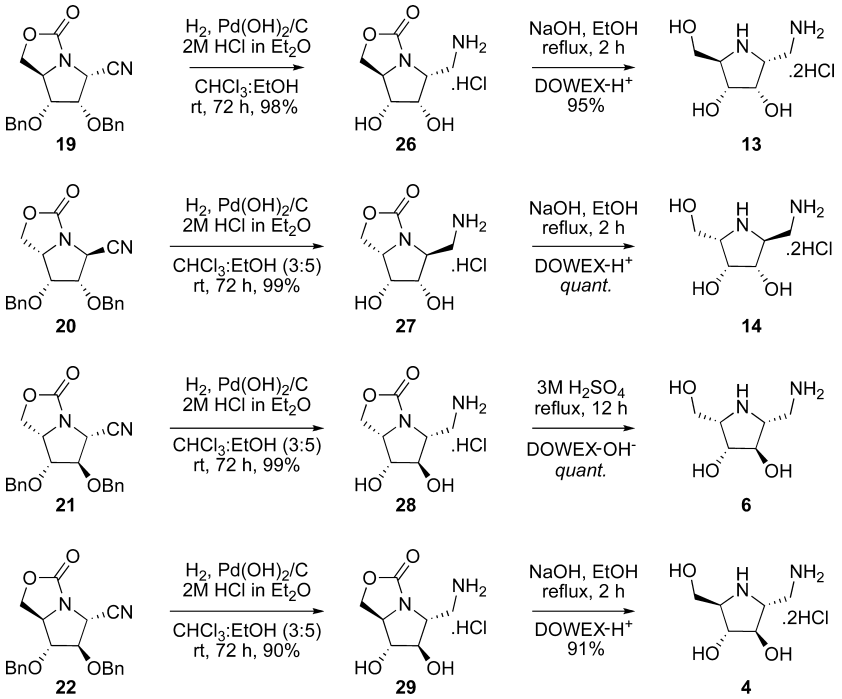
Scheme 6. Carbamate Deprotection and Hydrolysis



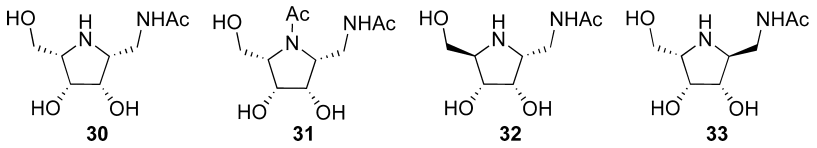


Figure 5. Structures of acetylated aminoiminohexitols **30**–**33**.

Table 1. Glycosidase Inhibition Studies[a]

	amines				carbamates				acetamides			
enzyme	**5**	**12**	**13**	**14**	**11**	**24**	**26**	**27**	**30**	**31**	**32**	**33**
GCase	9	n.i.*	n.i.	n.i.*	n.i.*	n.i.	n.i.	n.i.	n.i.*	n.i.*	n.i.*	n.i.*
*Sp*HEX	n.i.	n.i.	n.i.	n.i.§	n.i.	n.i.§	n.i.§	n.i.§	0.5	n.i.§	n.i.§	0.5
ABG	n.i.§	n.i.§	0.006	1.1	n.i.§	n.i.§	0.06	2.3	0.8	n.i.§	0.07	1.3

[a]Key: K_i values (mM) of compounds with GCase = β-D-glucocerebrosidase from human lysosome, *Sp*Hex = *N*-acetyl-β-D-hexosaminidase from *Streptomyces plicatus*, ABG = β-D-glucosidase from *Agrobacterium* sp., n.i. = no inhibition was observed up to 10 mM inhibitor concentration, n.i.* = no inhibition was observed up to 2 mM inhibitor concentration, and n.i.§ = no inhibition was observed up to 1 mM inhibitor concentration.

carbamate **22**, derived from D-arabinose, was hydrogenated in 90% yield to generate the deprotected amine **29**, which was subsequently hydrolyzed under basic conditions to give the known D-mannitol-derived aminoiminohexitol **4**.[12,31]

Acetylated derivatives of the novel stereoisomers D-*galacto* **12**, D-*talo* **13** and L-*altro* **14** were then prepared as literature precedence suggests that *N*-acylation improves glycosidase activity.[5−8,12−17] Subjection of D-*galacto*-hexitol **12** to acetic anhydride in MeOH[15] gave acetamide **30** along with the bis-acetamide **31** in 57% combined yield. Selective acetylation of D-*talo* **13** and L-*altro* **14**, however, proceeded smoothly to give the corresponding acetamides **32** and **33** in 77% and 65% yield, respectively (Figure 5).

The novel aminoiminohexitols (**12**−**14**), their carbamate precursors (**24**−**27**) and acetamides (**30**−**33**), and the previously reported L-*ido* derivative (**5**)[16] and carbamate precursor (**11**) were then tested for their ability to inhibit human lysosomal β-D-glucocerebrosidase (GCase), *N*-acetyl-β-D-hexosaminidase from *Streptomyces plicatus* (*Sp*HEX), and β-D-glucosidase from *Agrobacterium* sp. (ABG) (Table 1). Only weak inhibition of GCase, the enzyme involved in Gaucher's disease, was observed with a single compound (L-*ido* amine **5**) at levels lower than 10 mM, and this level of inhibition is likely to be ineffective for any therapeutic effect.[32] In the case of *Sp*HEX, two inhibitors were identified with activity in the submillimolar range. Both the D-*galacto* and L-*altro* isomers of the acylated aminoiminohexitols **30** and **33** had inhibitory activities of 0.5 and 0.5 mM, respectively. Given that the D-*manno* isomer of these compounds (**3b**, Figure 1) has been shown to inhibit Jack bean *N*-acetyl-β-D-glucosaminidase (K_i = 1.9 μm),[4] it appears as though the functional group pattern around the pyrrolidine scaffold is more important than stereochemistry for the inhibition of this enzyme.

Five compounds were found to be selective ABG inhibitors. The L-*altro* carbamate **27** and amine **14** had moderate K_i values of 2.3 and 1.1 mM, respectively, while the D-*talo* acetamide **32**

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and carbamate **26** had more potent inhibitory values of 0.07 and 0.06 mM. D-*Talo* amine **13** had the most potent inhibitory activity (K_i = 0.006 mM). This is surprising as generally *N*-acylated derivatives of iminohexitols are better inhibitors than their parent compounds.[5−8,12−17] Here, it should also be noted that more lipophilic *N*-substituted derivatives generally exhibit improved inhibitory activity. For example, D-*manno*-acetamide **3b** and amine **4** (Figure 1) both exhibited a K_i of 0.025 mM against ABG,[15] whereas *N*-functionalized lipophilic D-*manno* derivatives showed potent inhibition in the nanomolar scale.[13] In view of this, the preparation of lipophilic derivatives of the D-*talo* scaffold has the potential to produce noteworthy glycosidase inhibitors.

■ CONCLUSION

In summary, an efficient route for the preparation of a number of aminoiminohexitols has been presented. In particular, the two novel aminoiminohexitols **12** and **14** were efficiently prepared in 36% and 37% overall yield from D-ribose, respectively. During the course of this work, the power of a highly diastereoselective Strecker reaction without the need for chiral Lewis acids or catalysts has been demonstrated. The diastereoselectivity of the reaction can be explained by the Cram-chelation control model for both D-arabinose- and D-ribose-derived aldehydes. Moreover, the potential of our novel carbamate annulation for the cyclization of protected and functionalized alkenylamine precursors has been highlighted, and the effects that the substituent pattern of the α-aminonitrile has on the diastereoselectivity of the annulation reaction have been explained. The applicability of the carbamate annulation to a variety of alkenylamines and an understanding of the factors controlling the diastereoselectivity of the reaction should make this methodology a valuable addition to the synthetic chemists toolbox. Furthermore, several aminoiminohexitol derivatives have shown promising selective glycosidase activity (e.g., **13**, **14**, **26**, and **32**), with the D-*talo* configuration exhibiting good selective inhibition of β-D-glucosidase. Further derivatization of the D-*talo* scaffold has the potential to provide powerful glycosidase inhibitors, and we are currently exploring this avenue of research.

■ EXPERIMENTAL SECTION

Unless otherwise stated, all reactions were performed under atmospheric air. THF was distilled from $LiAlH_4$ prior to use. All chemicals obtained from commercial suppliers were used without further purification. Zn dust was activated by the careful addition of concd H_2SO_4, followed by decantation and washing with EtOH (3×) and hexanes (3×) and storage under dry hexanes. All solvents were removed by evaporation under reduced pressure. Reactions were monitored by TLC analysis on silica gel coated plastic sheets with detection by coating with 20% H_2SO_4 in EtOH followed by charring at ca. 150 °C, by coating with a solution of ninhydrin in EtOH followed by charring at ca. 150 °C, by coating with Hanessian's stain followed by charring at ca. 150 °C, or by coating with a solution of 5% $KMnO_4$ and 1% $NaIO_4$ in H_2O followed by heating. ^1H and ^{13}C chemical shifts (δ) were internally referenced to the residual solvent peak. NMR peak assignments are based on 2D NMR experiments (COSY, HSQC, and HMBC).

(2*R*,3*R*)-2,3-Dibenzyloxypent-4-enal (16). To a solution of methyl iodoriboside **15**[22] (1.63 g, 3.59 mmol) in EtOH/H_2O/AcOH (40/2/1, v/v/v, 54 mL) was added Zn (1.17 g, 18.0 mmol). The mixture was stirred at reflux for 3 h, cooled to room temperature, and filtered through a Celite plug with EtOAc. The resulting mixture was further diluted with EtOAc, washed twice with satd aq $NaHCO_3$ then H_2O and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to provide the aldehyde **16** as a colorless oil (1.03 g, 3.48 mmol, 97%): R_f = 0.57 (hexanes/EtOAc, 2/1, v/v); $[\alpha]^{17.6}_D$ = −29 (*c* = 1.0, $CHCl_3$); IR (film) 3064, 3031, 2925, 2868, 1729, 1455, 1207, 1069, 1027, 933, 735, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.64 (d, $J_{1,2}$ = 2.0 Hz, 1H, H-1), 7.38−7.27 (m, 10H, H−Ar), 5.88 (ddd, $J_{4,5b}$ = 17.7, $J_{4,5a}$ = 10.4, $J_{3,4}$ = 7.6 Hz, 1H, H-4), 5.38 (dt, $J_{4,5a}$ = 10.4, $^2J_{5a,5b}$ = $^4J_{3,5a}$ = 1.2 Hz, 1H, H-5a), 5.35 (dt, $J_{4,5b}$ = 17.7, $^2J_{5a,5b}$ = $^4J_{3,5b}$ = 1.2 Hz, 1H, H-5b), 4.71 (d, $^2J_{a,b}$ = 12.0 Hz, 1H, CHa 2-*O*-Bn), 4.66 (d, $^2J_{a,b}$ = 12.0 Hz, 1H, CHb 2-*O*-Bn), 4.65 (d, $^2J_{a,b}$ = 12.0 Hz, 1H, CHa 3-*O*-Bn), 4.42 (d, $^2J_{a,b}$ = 12.0 Hz, 1H, CHb 3-*O*-Bn), 4.17 (ddt, $J_{3,4}$ = 7.6, $J_{2,3}$ = 4.7 Hz, $^4J_{3,5}$ = 1.2 Hz, 1H, H-3), 3.90 (dd, $J_{2,3}$ = 4.7, $J_{1,2}$ = 2 Hz, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8 (C-1), 137.9 (C-*i* 3-*O*-Bn), 137.3 (C-*i* 2-*O*-Bn), 134.2 (C-4), 128.6 (C-Ar), 128.5 (C-Ar), 128.2 (C-Ar), 128.2 (C-Ar), 127.9 (C-Ar), 128.8 (C-Ar), 120.2 (C-5), 85.0 (C-2), 80.3 (C-3), 73.1 (CH_2 2-*O*-Bn), 70.6 (CH_2 3-*O*-Bn); HRMS(ESI) *m*/*z* calcd for $[C_{19}H_{20}O_3 + Na]^+$ 319.1305, obsd 319.1311.

(2*S*,3*S*,4*R*)-2-Amino-3,4-dibenzyloxyhex-5-enenitrile (*syn*-17) and (2*S*,3*S*,4*R*)-2-Amino-3,4-dibenzyloxyhex-5-enenitrile (*anti*-17). To a solution of aldehyde **16** (166 mg, 0.56 mmol) in EtOH (11.2 mL) was added NH_4OAc (471 mg, 5.60 mmol). The mixture was stirred at room temperature for 15 min, at which point TMSCN (147 μL, 1.12 mmol) was added dropwise. The clear colorless solution was stirred at room temperature for 48 h. The resulting solution was diluted with EtOAc, washed with satd aq $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the α-aminonitriles using gradient flash chromatography (hexanes/EtOAc, 10/1 → 1/1, v/v) gave first α-aminonitrile *syn*-**17** as a pale yellow oil (147 mg, 0.46 mmol, 82%) and then α-aminonitrile *anti*-**17** as a pale yellow oil (18.9 mg, 0.06 mmol, 10%) (dr = 8:1, *syn*-**17**:*anti*-**17**). *syn*-**17**: R_f = 0.27 (hexanes/EtOAc, 2/1, v/v); $[\alpha]^{19}_D$ = −22.4 (*c* = 1.0, $CHCl_3$); IR (film) 3397, 3327, 3088, 3064, 3032, 2871, 2372, 1710, 1497, 1455, 1392, 1214, 1088, 1072, 935, 741, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.30 (m, 10H, H−Ar), 5.84 (ddd, $J_{5,6a}$ = 17.2, $J_{5,6b}$ = 10.5, $J_{4,5}$ = 7.9 Hz, 1H, H-5), 5.46 (ddd, $J_{5,6a}$ = 17.2, $^2J_{6a,6b}$ = 1.7, $^4J_{4,6a}$ = 0.7 Hz, 1H, H-6a), 5.45 (ddd, $J_{5,6b}$ = 10.5, $^2J_{6a,6b}$ = 1.7, $^4J_{4,6a}$ = 0.7 Hz, 1H, H-6b) 4.76 (d, $^2J_{a,b}$ = 10.8 Hz, 1H, CHa 3-*O*-Bn), 4.68 (d, $^2J_{a,b}$ = 10.8 Hz, 1H, CHb 3-*O*-Bn), 4.62 (d, $^2J_{a,b}$ = 11.4 Hz, 1H, CHa 4-*O*-Bn), 4.36 (d, $^2J_{a,b}$ = 11.4 Hz, 1H, CHb 4-*O*-Bn), 4.08 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 4.06 (tt, $J_{4,5}$ = $J_{3,4}$ = 7.9, $^4J_{4,6}$ = 0.7 Hz, 1H, H-4), 3.66 (dd, $J_{3,4}$ = 7.9, $J_{2,3}$ = 2.0 Hz, 1H, H-3), 1.82 (br s, 2H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7 (C-*i* 4-*O*-Bn), 137.2 (C-*i* 3-*O*-Bn), 135.3 (C-5), 128.7 (C-Ar), 128.6 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 128.2 (C-Ar), 128.2 (C-Ar), 128.0 (C-Ar), 121.3 (C-1), 120.8 (C-6), 81.5 (C-3), 79.0 (C-4), 74.8 (CH_2 3-*O*-Bn), 70.8 (CH_2 4-*O*-Bn), 44.4 (C-2); HRMS (ESI) *m*/*z* calcd for $[C_{20}H_{22}N_2O_2 + H]^+$ 323.1754, obsd 323.1762. *anti*-**17**: R_f = 0.16 (hexanes/EtOAc, 2/1, v/v); $[\alpha]^{19}_D$ = −2.8 (*c* = 1.0, $CHCl_3$); IR (film) 3388, 3325, 3088, 3065, 3031, 2869, 2231, 1643, 1497, 1455, 1392, 1210, 1086, 1070, 1028, 936, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.30 (m, 10H, H−Ar), 5.90 (ddd, $J_{5,6a}$ = 17.3, $J_{5,6b}$ = 10.3, $J_{4,5}$ = 7.8 Hz, 1H, H-5), 5.51 (ddd, $J_{5,6a}$ = 17.3, $^2J_{6a,6b}$ = 1.7, $^4J_{4,6a}$ = 1.0 Hz, 1H, H-6a), 5.47 (ddd, $J_{5,6b}$ = 10.3, $^2J_{6a,6b}$ = 1.7, $^4J_{4,6a}$ = 1.0 Hz, 1H, H-6b) 4.81 (d, $^2J_{a,b}$ = 11.2 Hz, 1H, CHa 3-*O*-Bn), 4.64 (d, $^2J_{a,b}$ = 11.3 Hz, 1H, CHa 4-*O*-Bn), 4.62 (d, $^2J_{a,b}$ = 11.2 Hz, 1H, CHb 3-*O*-Bn), 4.39 (d, $^2J_{a,b}$ = 11.3 Hz, 1H, CHb 4-*O*-Bn), 4.08 (d, $J_{2,3}$ = 4.2 Hz, 1H, H-2), 4.05 (tt, $J_{4,5}$ = $J_{3,4}$ = 7.8, $^4J_{4,6}$ = 0.7 Hz, 1H, H-4), 3.64 (dd, $J_{3,4}$ = 7.8, $J_{2,3}$ = 4.2 Hz, 1H, H-3), 1.76 (br s, 2H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8 (C-*i* 4-*O*-Bn), 137.6 (C-*i* 3-*O*-Bn), 135.2 (C-5), 128.6 (C-Ar), 128.1 (C-Ar), 128.1 (C-Ar), 128.0 (C-Ar), 128.0 (C-Ar), 121.2 (C-1), 120.5 (C-6), 82.6 (C-3), 81.0 (C-4), 75.2 (CH_2 3-*O*-Bn), 70.9 (CH_2 4-*O*-Bn), 45.9 (C-2); HRMS(ESI) *m*/*z* calcd for $[C_{20}H_{22}N_2O_2 + H]^+$ 323.1754, obsd 323.1763.

General Procedure for the Carbamate Annulation. To a solution of α-aminonitrile (1 mmol) in THF (3.5 mL) were added I_2 (634 mg, 2.5 mmol), H_2O (3.5 mL), and $NaHCO_3$ (1.68 g, 20 mmol). The reaction mixture was stirred at room temperature for varying lengths of time (20 h−6 d), quenched with satd aq $Na_2S_2O_3$, and extracted with EtOAc. The organic layer was washed with H_2O and

brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification was achieved using gradient flash chromatography (hexanes/EtOAc, v/v) or (DCM/EtOAc, v/v).

(5*R*,6*S*,7*R*,7a*S*)-6,7-Dibenzyloxy-3-oxotetrahydropyrrolo[1,2-*c*]oxazole-5-carbonitrile (18). By subjecting α-aminonitrile *syn*-**17** (492 mg, 1.53 mmol) to the general procedure for the carbamate annulation for 6 d, carbamate **18** was obtained as a white solid (378 mg, 1.04 mmol, 68%, dr = 4:1, **18**:**19**). Crystallization (DCM) yielded fine white needles for which a single-crystal X-ray diffraction was obtained and then solved and refined using Olex2:[33] R_f = 0.19 (DCM/EtOAc, 50/1, v/v); mp = 198.9 − 199.9 °C; $[\alpha]^{20}_D$ = +34.5 (*c* = 1.0, $CHCl_3$); IR (film) 3066, 3028, 2953, 2921, 2887, 2251, 1737, 1395, 1269, 1256, 1150, 1101, 1046, 1002, 702, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43−7.30 (m, 10H, H−Ar), 5.18 (d, $^2J_{a,b}$ = 11.8 Hz, 1H, CHa 7-*O*-Bn), 4.78 (d, $^2J_{a,b}$ = 11.9 Hz, 1H, CHa 6-*O*-Bn), 4.71 (d, $^2J_{a,b}$ = 11.9 Hz, 1H, CHb 6-*O*-Bn) 4.68 (d, $^2J_{a,b}$ = 11.8 Hz, 1H, CHb 7-*O*-Bn), 4.51 (dd, $^2J_{1a,1b}$ = 8.8, $J_{1a,7a}$ = 6.8, Hz, 1H, H-1a), 4.42 (d, $J_{5,6}$ = 7.1 Hz, 1H, H-5), 4.35 (t, $J_{1a,1b}$ = $J_{1b,7a}$ = 8.8 Hz, 1H, H-1b), 4.37 (dd, $J_{5,6}$ = 7.1, $J_{6,7}$ = 2.7 Hz, 1H, H-6), 4.09 (ddd, $J_{7a,1b}$ = 8.8, $J_{1a,7a}$ = 6.8, $J_{7,7a}$ = 2.7 Hz, 1H, H-7a), 3.87 (t, $J_{7,7a}$ = $J_{6,7}$ = 2.7 Hz, 1H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4 (C-3), 137.4 (C-*i* 7-*O*-Bn), 136.1 (C-*i* 6-*O*-Bn), 129.0 (C-Ar), 128.9 (C-Ar), 128.7 (C-Ar), 128.3 (C-Ar), 128.3 (C-Ar), 128.2 (C-Ar), 112.9 (CN), 83.7 (C-6), 74.5 (C-7), 73.8 (CH_2 6-*O*-Bn), 73.6 (CH_2 7-*O*-Bn), 64.1 (C-1), 58.8 (C-7a), 47.2 (C-5); HRMS(ESI) *m*/*z* calcd for $[C_{21}H_{20}N_2O_4 + Na]^+$ 387.1315, obsd 387.1321.

(5*R*,6*S*,7*R*,7a*R*)-6,7-Dibenzyloxy-3-oxotetrahydropyrrolo-[1,2-*c*]oxazole-5-carbonitrile (19). By subjecting α-aminonitrile *syn*-**17** (492 mg, 1.53 mmol) to the general procedure for the carbamate annulation for 6 d, carbamate **19** was obtained as a colorless oil (94.5 mg, 0.26 mmol, 17%, dr = 4:1, **18**:**19**): R_f = 0.31 (DCM/EtOAc, 20/1, v/v); $[\alpha]^{20}_D$ = +45.2 (*c* = 1.0, $CHCl_3$); IR (film) 3064, 3032, 2919, 2872, 1761, 1455, 1393, 1306, 1214, 1136, 1027, 1010, 737, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45−7.27 (m, 10H, H-Ar), 4.96 (d, $^2J_{a,b}$ = 11.5 Hz, 1H, CHa 6-*O*-Bn), 4.77 (d, $J_{2,3}$ = 5.0 Hz, 1H, H-5), 4.73 (d, $^2J_{a,b}$ = 11.5 Hz, 1H, CHb 6-*O*-Bn), 4.64 (d, $^2J_{a,b}$ = 11.9 Hz, 1H, CHa 7-*O*-Bn), 4.46 (dd, $^2J_{1a,1b}$ = 9.6, $J_{1a,7a}$ = 8.3 Hz, 1H, H-1a), 4.36 (d, $^2J_{a,b}$ = 11.9 Hz, 1H, CHb 7-*O*-Bn), 4.29 (t, $J_{6,7}$ = $J_{5,6}$ = 5.0 Hz, 1H, H-3), 4.23 (td, $J_{1a,7a}$ = $J_{7,7a}$ = 8.3, $J_{1b,7a}$ = 2.7 Hz, H-7a), 4.08 (dd, $^2J_{1a,1b}$ = 9.6, $J_{1b,7a}$ = 2.7 Hz, 1H, H-1b), 3.56 (dd, $J_{7,7a}$ = 8.3, $J_{6,7}$ = 5.0 Hz, 1H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2 (C-3), 136.6 (C-*i* 7-*O*-Bn), 136.5 (C-*i* 6-*O*-Bn), 129.0 (C-Ar), 128.8 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.6 (C-Ar), 128.0 (C-Ar), 115.0 (CN), 80.7 (C-7), 77.1 (C-6), 74.5 (CH_2 6-*O*-Bn), 73.2 (CH_2 7-*O*-Bn), 66.3 (C-1), 60.0 (C-7a), 53.1 (C-5); HRMS(ESI) *m*/*z* calcd for $[C_{21}H_{20}N_2O_4 + Na]^+$ 387.1315, obsd 387.1328.

(5*S*,6*S*,7*R*,7a*S*)-6,7-Dibenzyloxy-3-oxotetrahydropyrrolo[1,2-*c*]oxazole-5-carbonitrile (20). By subjecting α-aminonitrile *anti*-**17** (25.0 mg, 0.08 mmol) to the general procedure for the carbamate annulation for 6 d, carbamate **20** was obtained as a white solid (14.9 mg, 0.04 mmol, 53%). Crystallization (DCM) yielded colorless plates for which a single-crystal X-ray diffraction was obtained then solved and refined using Olex2: R_f = 0.45 (DCM/EtOAc, 20/1, v/v); $[\alpha]^{20}_D$ = +13.6 (*c* = 0.5, $CHCl_3$); mp = 97.4 − 97.6°C; IR (film) 3034, 2953, 2923, 2852, 1757, 1456, 1395, 1207, 1141, 1075, 1005, 772, 735, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43−7.25 (m, 10H, H−Ar), 4.93 (d, $^2J_{a,b}$ = 11.9 Hz, 1H, CHa 7-*O*-Bn), 4.79 (d, $^2J_{a,b}$ = 11.9 Hz, 1H, CHa 6-*O*-Bn), 4.69 (d, $^2J_{a,b}$ = 11.9 Hz, 1H, CHb 6-*O*-Bn), 4.59 (d, $^2J_{a,b}$ = 11.9 Hz, 1H, CHb 7-*O*-Bn), 4.57 (d, $J_{5,6}$ = 6.8 Hz, 1H, H-5), 4.46 (dd, $J_{6,7}$ = 3.4, $J_{5,6}$ = 6.8 Hz, 1H, H-6), 4.40 (dd, $^2J_{1a,1b}$ = 8.6, $J_{7a,1a}$ = 3.7 Hz, 1H, H-1a), 4.34 (t, $^2J_{1a,1b}$ = $J_{1a,7a}$ = 8.6 Hz, 1H, H-1b), 4.03 (td, $J_{1a,7a}$ = $J_{1b,7a}$ = 8.6, $J_{7,7a}$ = 3.4 Hz, 1H, H-7a), 3.95 (t, $J_{7,7a}$ = $J_{6,7}$ = 3.4 Hz, 1H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8 (C-3), 137.2 (C-*i* 7-*O*-Bn), 136.1 (C-*i* 6-*O*-Bn), 129.0 (C-Ar), 128.8 (C-Ar), 128.8 (C-Ar), 128.4 (C-Ar), 128.1 (C-Ar), 128.0 (C-Ar), 117.9 (CN), 86.0 (C-6), 76.2 (C-7), 73.8 (CH_2 7-*O*-Bn), 73.8 (CH_2 6-*O*-Bn), 63.7 (C-1), 59.5 (C-7a), 50.9 (C-5); HRMS(ESI) *m*/*z* calcd for $[C_{21}H_{20}N_2O_4 + Na]^+$ 387.1315, obsd 387.1320.

Synthesis of 20 via Epimerization. To a solution of carbamate **18** (11.0 mg, 0.03 mmol) in THF (0.6 mL) was added LiOH aq (2 M, 0.3 mL). The reaction mixture was stirred at room temperature for 4 h, quenched with satd aq NH_4Cl, and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo to provide carbamate **20** as a colorless oil (11.0 mg, 0.03 mmol, quantitative). Spectral data as above.

(5*R*,6*R*,7*R*,7a*S*)-6,7-Dibenzyloxy-3-oxotetrahydropyrrolo-[1,2-*c*]oxazole-5-carbonitrile (21). By subjecting α-aminonitrile *anti*-**8**[20] (140 mg, 0.43 mmol) to the general procedure for the carbamate annulation for 48 h, carbamate **21** was obtained as a colorless oil (129 mg, 0.35 mmol, 81%, dr = 6:1, **21**:**22**): R_f = 0.29 (hexanes/EtOAc, 1/1, v/v); $[\alpha]^{24}_D$ = +25.7 (*c* = 1.0, $CHCl_3$); IR (film) 3064, 3032, 2919, 2872, 2247, 1752, 1471, 1395, 1246, 1096, 1077, 1007, 740, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42−7.27 (m, 10H, H−Ar), 4.73 (d, $^2J_{a,b}$ = 12 Hz, 1H, CHa 7-*O*-Bn), 4.60 (d, $^2J_{a,b}$ = 11.9 Hz, 1H, CHa 6-*O*-Bn), 4.55 (s, 1H, H-6), 4.53 (d, $^2J_{a,b}$ = 11.9 Hz, 1H, CHb 6-*O*-Bn), 4.46 (dd, $^2J_{1a,1b}$ = 8.6, $J_{1a,7a}$ = 5.6 Hz, 1H, H-1a), 4.44 (d, $^2J_{a,b}$ = 12 Hz, 1H, CHb 7-*O*-Bn), 4.42 (t, $J_{1a,1b}$ = $J_{1b,7a}$ = 8.6 Hz, 1H, H-1b), 4.36 (ddd, $J_{1b,7a}$ = 8.6, $J_{1a,7a}$ = 5.6, $J_{7,7a}$ = 3.2 Hz, 1H, H-7a), 4.22 (d, $J_{5,6}$ = 0.5 Hz, 1H, H-5), 3.79 (dd, $J_{7,7a}$ = 3.2, $J_{6,7}$ = 1.0 Hz, 1H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5 (C-3), 136.3 (C-*i* 7-*O*-Bn), 135.9 (C-*i* 6-*O*-Bn), 129.0 (C-Ar), 128.9 (C-Ar), 128.9 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 128.2 (C-Ar), 113.5 (CN), 87.0 (C-6), 78.2 (C-7), 73.2 (CH_2 6-*O*-Bn), 71.9 (CH_2 7-*O*-Bn), 62.6 (C-1), 62.0 (C-7a), 50.6 (C-5); HRMS(ESI) *m*/*z* calcd for $[C_{21}H_{20}N_2O_4 + Na]^+$ 387.1315, obsd 387.1324.

(5*R*,6*R*,7*R*,7a*R*)-6,7-Dibenzyloxy-3-oxotetrahydropyrrolo-[1,2-*c*]oxazole-5-carbonitrile (22). By subjecting α-aminonitrile *anti*-**8**[20] (140 mg, 0.43 mmol) to the general procedure for the carbamate annulation for 48 h, carbamate **22** was obtained as a colorless oil (21.4 mg, 0.06 mmol, 13.6%, dr = 6:1, **21**:**22**). R_f = 0.50 (hexanes/EtOAc, 1/1, v/v): $[\alpha]^{24}_D$ = +5.7 (*c* = 1.0, $CHCl_3$); IR (film) 3064, 3032, 2919, 2872, 2250, 1762, 1455, 1391, 1211, 1099, 1072, 740, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41−7.28 (m, 10H, H−Ar), 4.80 (d, $J_{5,6}$ = 2.1 Hz, 1H, H-5), 4.65 (d, $^2J_{a,b}$ = 12.0 Hz, 1H, CHa 7-*O*-Bn), 4.63 (d, $^2J_{a,b}$ = 11.5 Hz, 1H, CHa 6-*O*-Bn), 4.51 (ddd, $J_{1a,7a}$ = 8.7, $^2J_{1a,1b}$ = 7.5, $^4J_{1a,7}$ = 4.0 Hz, 1H, H-1a), 4.50 (d, $^2J_{a,b}$ = 12.0 Hz, 1H, CHb 7-*O*-Bn), 4.46 (d, $^2J_{a,b}$ = 11.5 Hz, 1H, CHb 6-*O*-Bn), 4.37 (dd, $J_{5,6}$ = 2.1, $J_{6,7}$ = 2.7 Hz, 1H, H-6), 4.12 (dd, $J_{1a,1b}$ = 7.5, $J_{1b,7a}$ = 4.4 Hz, 1H, H-1b), 4.09 (ddd, $J_{1a,7a}$ = 8.7, $J_{1b,7a}$ = 4.4, $J_{7,7a}$ = 0.5 Hz, 1H, H-7a), 3.87 (ddd, $^4J_{1a,7}$ = 4.0, $J_{6,7}$ = 2.7, $J_{7,7a}$ = 0.5 Hz, 1H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0 (C-3), 136.6 (C-*i* 7-*O*-Bn), 135.7 (C-*i* 6-*O*-Bn), 129.1 (C-Ar), 129.0 (C-Ar), 128.9 (C-Ar), 128.8 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 128.1 (C-Ar), 115.9 (CN), 86.8 (C-7), 86.4 (C-6), 73.0 (CH_2 7-*O*-Bn), 72.8 (CH_2 6-*O*-Bn), 67.4 (C-1), 62.7 (C-7a), 52.3 (C-5); HRMS(ESI) *m*/*z* calcd for $[C_{21}H_{20}N_2O_4 + Na]^+$ 387.1315, obsd 387.1321.

(5*S*,6*R*,7*S*,7a*R*)-6,7-Dihydroxy-5-(hydroxymethyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (23). Carbamate **18** (147 mg, 0.40 mmol) was dissolved in $CHCl_3$ (3.0 mL) and transferred into a Fischer−Porter bottle, EtOH (5.0 mL), HCl in ether (1.0 mL, 2 M), and $Pd(OH_2)/C$ (110 mg) were then added, and the vessel was charged with 7 bar of pressure of H_2. The reaction mixture was stirred vigorously at room temperature for 3 d. After H_2 pressure was released, the reaction mixture was filtered through a plug of Celite, washed with EtOH and DCM/MeOH/EtOH/30% aq NH_3 (5/2/2/1, v/v/v/v), and concentrated in vacuo. Purification was achieved by dry-loading using gradient flash chromatography (DCM/MeOH/EtOH/30% aq NH_3, 50/2/2/1 → 5/2/2/1, v/v/v/v) to provide the urea **23** as a colorless oil (23.0 mg, 0.12 mmol, 30%): R_f = 0.48 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); $[\alpha]^{21}_D$ = −22.0 (*c* = 1.0, H_2O); IR (film) 3288, 2927, 1658, 1492, 1451, 1372, 1130, 1025, 978, 757, 700 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.61 (dd, $J_{5,6}$ = 8.1, $J_{6,7}$ = 4.0 Hz, 1H, H-6), 4.13 (dd, $^2J_{a,b}$ = 12.0, $J_{5,CH2Oa}$ = 3.2, Hz, 1H, H-CH_2Oa) 4.12 (ddd, $J_{1b,7a}$ = 9.5, $J_{1a,7a}$ = 8.1, $J_{7,7a}$ = 4.0 Hz, 1H, H-7a), 3.99 (t, $J_{6,7}$ = $J_{7,7a}$ = 4.0 Hz, 1H, H-7), 3.76 (dt, $J_{5,6}$ = 8.1, $J_{5,CH2Oa}$ = $J_{5,CH2Ob}$ = 3.2 Hz, 1H, H-5), 3.72 (dd, $^2J_{a,b}$ = 12.0, $J_{5,CH2Ob}$ = 3.2 Hz, H−CH_2Ob) 3.59 (dd, $^2J_{1a,1b}$ = 9.5, $J_{1a,7a}$ = 8.1 Hz, 1H, H-1a), 3.49 (t, $^2J_{1a,1b}$ = $J_{1b,7a}$ = 9.5 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, D_2O) δ 164.0 (C-3), 74.2 (C-6), 69.1 (C-7), 60.1 (C-7a), 58.5 (C-5), 55.3 (CH_2O),

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38.7 (C-1); HRMS(ESI) m/z calcd for $[C_7H_{12}N_2O_4 + H]^+$ 189.0870, obsd 189.0869.

General Procedure for Hydrogenation of Carbamates. Protected carbamate (0.27 mmol) was dissolved in $CHCl_3$ (4.5 mL) and transferred into a Fischer–Porter bottle, EtOH (7.5 mL), HCl in ether (1.4 mL, 2 M), and $Pd(OH_2)/C$ (230 mg) were then added, and the vessel was charged with 7 bar of pressure of H_2. The reaction mixture was stirred vigorously at room temperature for 3 d. After H_2 pressure was released, the reaction mixture was filtered through a plug of Celite, washed with EtOH and H_2O, and concentrated in vacuo to provide the amino carbamate as the hydrochloride salt.

(5*R*,6*S*,7*R*,7a*S*)-5-(Aminomethyl)-6,7-dihydroxytetrahydropyrrolo[1,2-*c*]oxazole-3(1*H*)-one Hydrochloride (24). By subjecting carbamate **18** (60 mg, 0.16 mmol) to the general procedure for the hydrogenation of carbamates, ammonium salt **24** was obtained as a white solid (30.8 mg, 0.16 mmol, 99%) and further crystallized from MeOH: R_f = 0.29 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); $[\alpha]^{26.1}{}_D$ = +30.0 (c = 1.0, H_2O); mp = 230.0–230.5 °C; IR (film) 3362, 2960, 2930, 1724, 1633, 1433, 1261, 1127, 1075, 949, 897 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.66 (dd, $J_{5,6}$ = 7.6, $J_{6,7}$ = 3.4 Hz, 1H, H-6), 4.56 (t, $^2J_{1a,1b}$ = $J_{1a,7a}$ = 9.3 Hz, 1H, H-1a), 4.49 (dd, $^2J_{1a,1b}$ = 9.3, $J_{1a,7a}$ = 7.1 Hz, 1H, H-1b), 4.25 (ddd, $J_{1a,7a}$ = 9.3, $J_{1b,7a}$ = 7.1, $J_{7,7a}$ = 3.4 Hz, 1H, H-7a), 4.13 (t, $J_{7,7a}$ = $J_{6,7}$ = 3.4 Hz, 1H, H-7), 4.04 (td, $J_{5,6}$ = $J_{5,CH2Nb}$ = 7.6, $J_{5,CH2Na}$ = 3.4 Hz, 1H, H-5), 3.59 (dd, $^2J_{a,b}$ = 14.2, $J_{5,CH2Na}$ = 3.4 Hz, 1H, CH_2Na), 3.38 (dd, $^2J_{a,b}$ = 14.2, $J_{5,CH2Nb}$ = 7.6 Hz, 1H, CH_2Nb); ^{13}C NMR (125 MHz, D_2O) δ 159.7 (C-3), 74.3 (C-6), 69.1 (C-7), 64.5 (C-1), 60.3 (C-7a), 55.0 (C-5), 36.7 (CH_2N); HRMS(ESI) m/z calcd for $[C_7H_{12}N_2O_4 + H]^+$ 189.0870, obsd 189.0869.

(5*R*,6*S*,7*R*,7a*R*)-5-(Aminomethyl)-6,7-dihydroxytetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one Hydrochloride (26). By subjecting carbamate **19** (4 mg, 0.01 mmol) to the general procedure for the hydrogenation of carbamates, ammonium salt **26** was obtained as a colorless oil (2.0 mg, 0.01 mmol, 98%): R_f = 0.25 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); $[\alpha]^{25.7}{}_D$ = −10.0 (c = 0.7, H_2O); IR (film) 3382, 3284, 2927, 2855, 1735, 1630, 1402, 1243, 1221, 1114, 999, 768 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.59–4.56 (m, 1H, H-1a), 4.36–4.34 (m, 2H, H-6 and H-1b), 4.00–3.94 (m, 3H, H-5, H-7 and H-7a), 3.17 (dd, $^2J_{a,b}$ = 13.2, $J_{5,CH2Na}$ = 3.6 Hz, 1H, CH_2Na), 3.12 (dd, $^2J_{a,b}$ = 13.2, $J_{5,CH2Nb}$ = 7.8 Hz, 1H, CH_2Nb); ^{13}C NMR (125 MHz, D_2O) δ 163.7 (C-3), 74.3 (C-6), 73.3 (C-7), 67.9 (C-1), 60.2 (C-7a), 58.7 (C-5), 39.6 (CH_2N); HRMS(ESI) m/z calcd for $[C_7H_{12}N_2O_4 + H]^+$ 189.0870, obsd 189.0873.

(5*S*,6*S*,7*R*,7a*S*)-5-(Aminomethyl)-6,7-dihydroxytetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one Hydrochloride (27). By subjecting carbamate **20** (104 mg, 0.29 mmol) to the general procedure for the hydrogenation of carbamates, ammonium salt **27** was obtained as a colorless oil (53.0 mg, 0.28 mmol, 99%): R_f = 0.22 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); $[\alpha]^{25}{}_D$ = +14.8 (c = 1.0, H_2O); IR (film) 3233, 2978, 2903, 2837, 1736, 1622, 1506, 1403, 1236, 1089, 1013, 916, 823, 775 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.57 (t, $^2J_{1a,1b}$ = $J_{1a,7a}$ = 9.3 Hz, 1H, H-1a), 4.54 (dd, $^2J_{1a,1b}$ = 9.3, $J_{1b,7a}$ = 3.7 Hz, 1H, H-1b), 4.24 (dd, $J_{5,6}$ = 7.8, $J_{6,7}$ = Hz, 1H, H-6), 4.21–4.20 (m, 1H, H-7a) 4.06 (br s, 1H, H-7), 3.62 (td, $J_{5,6}$ = $J_{5,CH2Nb}$ = 7.8, $J_{5,CH2Na}$ = 3.4 Hz, 1H, H-5), 3.28 (dd, $^2J_{a,b}$ = 13.2, $J_{5,CH2Na}$ = 3.4 Hz, 1H, CH_2Na), 3.01 (dd, $^2J_{a,b}$ = 13.2, $J_{5,CH2Nb}$ = 7.8 Hz, 1H, CH_2Nb); ^{13}C NMR (125 MHz, D_2O) δ 164.4 (C-3), 76.6, (C-6), 71.4 (C-7), 64.6 (C-1), 60.7 (C-5), 60.4 (C-7a), 42.0 (CH_2N); HRMS(ESI) m/z calcd for $[C_7H_{12}N_2O_4 + H]^+$ 189.0870, obsd 189.0872.

(5*R*,6*R*,7*R*,7a*S*)-5-(Aminomethyl)-6,7-dihydroxytetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one Hydrochloride (28). By subjecting carbamate **21** (100 mg, 0.27 mmol) to the general procedure for the hydrogenation of carbamates, ammonium salt **28** was obtained as a white solid (51.4 mg, 0.27 mmol, 99%) and further crystallized from EtOH: R_f = 0.62 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); $[\alpha]^{25.8}{}_D$ = +60.2 (c = 0.83, H_2O); mp = 183.3–184.0 °C; IR (film) 3356, 2961, 2929, 1716, 1633, 1428, 1262, 1143, 1094, 1063, 1007, 949, 893 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.63–4.59 (m, 1H, H-1a), 4.52–4.47 (m, 2H, H-7a, and H-1b), 4.15 (t, $J_{6,7}$ = $J_{5,6}$ = 1.9 Hz, 1H, H-6), 4.01 (dd, $J_{7,7a}$ = 2.8, $J_{6,7}$ = 1.9 Hz, 1H, H-7), 3.72 (ddd, $J_{5,CH2Nb}$ = 10, $J_{5,CH2Na}$ = 3.2, $J_{5,6}$ = 1.9 Hz, 1H, H-5), 3.59 (dd, $^2J_{a,b}$ = 13.9, $J_{5,CH2Nb}$ = 3.2 Hz, 1H, CH_2Na), 3.53 (dd, $^2J_{a,b}$ = 13.9, $J_{5,CH2Nb}$ = 10 Hz, 1H, CH_2Nb); ^{13}C NMR (125 MHz, D_2O) δ 160.2 (C-3), 82.2 (C-6), 73.3 (C-7), 63.9 (C-1), 63.2 (C-7a), 62.5 (C-5), 39.3 (CH_2N); HRMS(ESI) m/z calcd for $[C_7H_{12}N_2O_4 + H]^+$ 189.0870, obsd 189.0871.

(5*R*,6*R*,7*R*,7a*R*)-5-(Aminomethyl)-6,7-dihydroxytetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one Hydrochloride (29). By subjecting carbamate **22** (16 mg, 0.04 mmol) to the general procedure for the hydrogenation of carbamates, ammonium salt **29** was obtained as a colorless oil (7.0 mg, 0.04 mmol, 90%): R_f = 0.41 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); $[\alpha]^{24.8}{}_D$ = +10.0 (c = 0.4, H_2O); IR (film) 3330, 3247, 2924, 1731, 1641, 1404, 1235, 1084, 1012, 918, 773 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ 4.70 (dd, $^2J_{1a,1b}$ = 9.6, $J_{1a,7a}$ = 8.1 Hz, 1H, H-1a), 4.48 (dd, $^2J_{1a,1b}$ = 9.6, $J_{1b,7a}$ = 4 Hz, 1H, H-1b), 4.07–4.02 (m, 3H, H-6, H-7 and H-7a), 3.84 (ddd, $J_{5,CH2Nb}$ = 11, $J_{5,6}$ = 4.9, $J_{5,CH2Na}$ = 3.3 Hz, 1H, H-5), 3.37 (dd, $^2J_{a,b}$ = 13.1, $J_{5,CH2Na}$ = 3.3 Hz, 1H, CH_2Na), 3.19 (dd, $^2J_{a,b}$ = 13.1, $J_{5,CH2Nb}$ = 11, 1H, CH_2Nb); ^{13}C NMR (125 MHz, D_2O) δ 163.6 (C-3), 79.2 (C-6), 78.4 (C-7), 68.4 (C-1), 61.6 (C-5), 60.9 (C-7a), 40.8 (CH_2N); HRMS(ESI) m/z calcd for $[C_7H_{12}N_2O_4 + H]^+$ 189.0870, obsd 189.0874.

1-Amino-6-chloro-1,2,5,6-tetradeoxy-2,5-imino-D-galactitol Hihydrochloride (25). Amino carbamate **24** (4 mg, 0.07 mmol) was dissolved in HCl (1.2 mL, concd). The solution was stirred at reflux for 3 h, cooled, and concentrated in vacuo. Purification was attempted using gradient flash chromatography (DCM/MeOH/EtOH/30% aq NH_3, 15/2/2/1 → 5/2/2/1, v/v/v/v) to provide chloroiminogalactitol **25** as a white solid with an inseparable decomposition product also observed: R_f = 0.37 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); ^1H NMR (500 MHz, 2% DCl in D_2O) δ 4.65 (dd, $J_{2,3}$ = 7.1, $J_{3,4}$ = 4.4 Hz, 1H, H-3), 4.47 (t, $J_{4,5}$ = $J_{3,4}$ = 4.4 Hz, 1H, H-4), 4.08 (td, $J_{2,3}$ = $J_{1a,2}$ = 7.1, $J_{1b,2}$ = 5.4 Hz, 1H, H-2), 4.02 (dd, $^2J_{6a,6b}$ = 13.2, $J_{5,6a}$ = 4.4 Hz, 1H, H-6a), 4.01 (td, $J_{5,6b}$ = 11.5, $J_{5,6a}$ = $J_{4,5}$ = 4.4, Hz, 1H, H-5), 3.90 (dd, $^2J_{6a,6b}$ = 13.2, $J_{5,6b}$ = 11.5 Hz, 1H, H-6b), 3.61 (dd, $^2J_{1a,1b}$ = 13.7, $J_{1a,2}$ = 7.1 Hz, 1H, H-1a), 3.44 (dd, $J_{1a,1b}$ = 13.7, $J_{1b,2}$ = 5.4 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, 2% DCl in D_2O) δ 70.2 (C-3), 70.2 (C-4), 62.4 (C-5), 55.8 (C-2), 39.5 (C-6), 36.9 (C-1); HRMS(ESI) m/z calcd for $[C_6H_{13}{}^{35}ClN_2O_2 + H]^+$ 181.0738, obsd 181.0741; m/z calcd for $[C_6H_{13}{}^{37}ClN_2O_2 + H]^+$ 183.0709, obsd 183.0713.

General Procedure for Acidic Hydrolysis of Carbamates. Amino carbamate (0.05 mmol) was dissolved in H_2SO_4 aq (1 mL, 3 M). The solution was refluxed for 12–18 h, cooled, and neutralized by the addition of Dowex-OH^- ion-exchange resin. The resin mixture was filtered with H_2O and the filtrate concentrated in vacuo to provide the pure aminoiminohexitols as the free base. Iminohexitols were also characterized as the dihydrochloride salt with the addition of deuterium chloride.

1-Amino-1,2,5-trideoxy-2,5-imino-D-galactitol (12). By subjecting amino carbamate **24** (9.7 mg, 0.05 mmol) to the general procedure for the acidic hydrolysis of carbamates for 18 h, imino-D-galactitol **12** was obtained as a white solid (8.4 mg, 0.05 mmol, quantitative): R_f = 0.01 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); (HCl salt) $[\alpha]^{19.6}{}_D$ = −2.0 (c = 0.47, H_2O); IR (film) 3316, 2965, 1644, 1364, 1315, 1081, 1019, 835 cm^{-1}; ^1H NMR (500 MHz, D_2O, 2HCl salt) δ 4.59 (dd, $J_{2,3}$ = 7.2, $J_{3,4}$ = 4.7 Hz, 1H, H-3), 4.42 (t, $J_{4,5}$ = $J_{3,4}$ = 4.7 Hz, 1H, H-4), 4.03 (td, $J_{2,3}$ = $J_{1a,2}$ = 7.2, $J_{1b,2}$ = 5.7 Hz, 1H, H-2), 3.97 (dd, $^2J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 4.7 Hz, 1H, H-6a), 3.88 (dd, $^2J_{6a,6b}$ = 12.5, $J_{5,6b}$ = 9.0 Hz, 1H, H-6b), 3.75 (dt, $J_{5,6b}$ = 9.0, $J_{5,6a}$ = $J_{4,5}$ = 4.7 Hz, 1H, H-5), 3.57 (dd, $^2J_{1a,1b}$ = 13.9, $J_{1a,2}$ = 7.2 Hz, 1H, H-1a), 3.42 (dd, $^2J_{1a,1b}$ = 13.9, $J_{1b,2}$ = 5.7 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, D_2O, 2HCl salt) δ 70.1 (C-3), 69.7 (C-4), 62.1 (C-5), 57.3 (C-6), 55.7 (C-2), 36.8 (C-1); HRMS(ESI) m/z calcd for $[C_6H_{14}N_2O_3 + H]^+$ 163.1077, obsd 163.1084; ^1H NMR (500 MHz, 2% NaOD in D_2O) δ 4.21 (dd, $J_{4,5}$ = 6.2, $J_{3,4}$ = 5.1 Hz, 1H, H-4), 4.03 (t, $J_{3,4}$ = $J_{2,3}$ = 5.1 Hz, 1H, H-3), 3.63 (dd, $^2J_{6a,6b}$ = 11.4, $J_{5,6a}$ = 5.1 Hz, 1H, H-6a), 3.58 (dd, $^2J_{6a,6b}$ = 11.4, $J_{5,6b}$ = 5.1 Hz, 1H, H-6b), 3.07 (dt, $J_{4,5}$ = 6.2, $J_{5,6a}$ = $J_{5,6b}$ = 5.1 Hz, 1H, H-5), 2.92 (td, $J_{1a,2}$ = $J_{1b,2}$ = 6.5, $J_{2,3}$ = 5.1 Hz,

1H, H-2), 2.76 (dd, $^2J_{1a,1b}$ = 13, $J_{1a,2}$ = 6.5 Hz, 1H, H-1a), 2.61 (dd, $^2J_{1a,1b}$ = 13, $J_{1b,2}$ = 6.5 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, 2% NaOD in D_2O) δ 73.0 (C-4), 71.6 (C-3), 61.3 (C-2), 60.4 (C-6), 60.3 (C-5), 40.2 (C-1).

1-Amino-1,2,5-trideoxy-2,5-imino-D-glucitol (6).[12] By subjecting amino carbamate **28** (4.2 mg, 0.02 mmol) to the general procedure for the acidic hydrolysis of carbamates for 12 h, imino-D-glucitol **6** was obtained as a white solid (3.6 mg, 0.02 mmol, *quantitative*): R_f = 0.01 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); (HCl salt) $[\alpha]^{20.1}_D$ = +8.0 (*c* = 0.38, H_2O); IR (film) 3121, 3050, 2930, 2799, 1633, 1401, 1082, 964, 879 cm^{-1}; ^{1}H NMR (500 MHz, D_2O, 2HCl salt) δ 4.38 (t, $J_{4,5}$ = $J_{3,4}$ = 3.0 Hz, 1H, H-4), 4.29 (t, $J_{3,4}$ = $J_{2,3}$ = 3.0 Hz, 1H, H-3), 4.03 (dd, $^2J_{6a,6b}$ = 9.8, $J_{5,6a}$ = 3.0 Hz, 1H, H-6a), 3.99 (dt, $J_{5,6b}$ = 7.3, $J_{5,6a}$ = $J_{4,5}$ = 3.0 Hz, 1H, H-5), 3.96 (dd, $^2J_{6a,6b}$ = 9.8, $J_{5,6b}$ = 7.3 Hz, 1H, H-6b), 3.84 (td, $J_{1,2}$ = 6.9, $J_{2,3}$ = 3 Hz, 1H, H-2), 3.57 (d, $J_{1,2}$ = 6.9 Hz, 2H, H-1); ^{13}C NMR (125 MHz, D_2O, 2HCl salt) δ 77.5 (C-3), 74.0 (C-4), 64.1 (C-5), 62.5 (C-2), 56.9 (C-6), 39.2 (C-1); HRMS(ESI) *m*/*z* calcd for $[C_6H_{14}N_2O_3 + H]^+$ 163.1077, obsd 163.1081; ^{1}H NMR (500 MHz, 2% NaOD in D_2O) δ 3.97 (dd, $J_{4,5}$ = 5.5, $J_{3,4}$ = 2.7 Hz, 1H, H-4), 3.67 (dd, $^2J_{6a,6b}$ = 11.5, $J_{5,6a}$ = 6.2 Hz, 1H, H-6a), 3.65 (t, $J_{3,4}$ = $J_{2,3}$ = 2.7 Hz, 1H, H-3), 3.55 (dd, $^2J_{6a,6b}$ = 11.5, $J_{5,6b}$ = 6.2 Hz, 1H, H-6b), 3.16 (td, $J_{5,6a}$ = $J_{5,6b}$ = 6.2, $J_{4,5}$ = 5.5 Hz, 1H, H-5), 2.78 (ddd, $J_{1b,2}$ = 7.0, $J_{1a,2}$ = 5.1, $J_{2,3}$ = 2.7 Hz, 1H, H-2), 2.74 (dd, $^2J_{1a,1b}$ = 12.8, $J_{1a,2}$ = 5.1 Hz, 1H, H-1a), 2.60 (dd, $^2J_{1a,1b}$ = 12.8, $J_{1b,2}$ = 7.0 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, 2% NaOD in D_2O) δ 80.7 (C-3), 77.6 (C-4), 65.5 (C-2), 60.7 (C-5), 60.3 (C-6), 43.5 (C-1).

General Procedure for Basic Hydrolysis of Carbamates. A solution of NaOH in EtOH (0.5 mL, 2 M) was added to the amino carbamate (0.08 mmol) and the mixture stirred under reflux for 2 h. The resulting reaction mixture was loaded directly on to a Dowex-H$^+$ ion-exchange resin column and washed with H_2O to remove excess salt. The amine product was then eluted with 30% aq NH_3 and concentrated in vacuo to provide the pure aminoiminohexitols as a mixture of protonation states, which were characterized as both the free base by adding sodium deuteroxide and the dihydrochloride salt with the addition of deuterium chloride

1-Amino-1,2,5-trideoxy-2,5-imino-D-talitol (13). By subjecting amino carbamate **26** (5 mg, 0.03 mmol) to the general procedure for the basic hydrolysis of carbamates, iminotalitol **13** was obtained as a colorless oil (4.1 mg, 0.03 mmol, 95%): R_f = 0.01 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); (HCl salt) $[\alpha]^{27.4}_D$ = +11.1 (*c* = 0.27 H_2O); IR (film) 3322, 2927, 1622, 1497, 1403, 1278, 1127, 1074, 1035, 981 cm^{-1}; ^{1}H NMR (500 MHz, 2% DCl in D_2O) δ 4.42 (t, $J_{3,4}$ = $J_{2,3}$ = 3.6 Hz, 1H, H-3), 4.31 (dd, $J_{4,5}$ = 8.6, $J_{3,4}$ = 3.6 Hz, 1H, H-4), 3.99–3.97 (m, 1H, H-2), 3.97 (dd, $^2J_{6a,6b}$ = 12.7, $J_{5,6a}$ = 3.4 Hz, 1H, H-6a), 3.83 (dd, $^2J_{6a,6b}$ = 12.7, $J_{5,6b}$ = 5.8 Hz, 1H, H-6b), 3.70 (ddd, $J_{4,5}$ = 8.6, $J_{5,6b}$ = 5.8, $J_{5,6a}$ = 3.4 Hz, 1H, H-5), 3.60 (dd, $^2J_{1a,1b}$ = 13.9, $J_{1a,2}$ = 7.1 Hz, 1H, H-1a), 3.43 (dd, $^2J_{1a,1b}$ = 13.9, $J_{1b,2}$ = 6.1 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, 2% DCl in D_2O) δ 71.2 (C-4), 70.0 (C-3), 62.4 (C-5), 57.9 (C-6), 57.6 (C-2), 35.9 (C-1); HRMS(ESI) *m*/*z* calcd for $[C_6H_{14}N_2O_3 + H]^+$ 163.1077, obsd 163.1084; ^{1}H NMR (500 MHz, 2% NaOD in D_2O) δ 4.03 (t, $J_{3,4}$ = $J_{2,3}$ = 4.1 Hz, 1H, H-3), 3.89 (dd, $J_{4,5}$ = 8.3, $J_{3,4}$ = 4.1 Hz, 1H, H-4), 3.68 (dd, $^2J_{6a,6b}$ = 11.7, $J_{5,6a}$ = 3.9 hz, 1H, H-6a), 3.56 (dd, $^2J_{6a,6b}$ = 11.7, $J_{5,6b}$ = 6.3 Hz, 1H, H-6b), 3.09 (td, $J_{1a,2}$ = $J_{1b,2}$ = 7.1, $J_{2,3}$ = 4.1 Hz, 1H, H-2), 2.99 (ddd, $J_{4,5}$ = 8.3, $J_{5,6b}$ = 6.3, $J_{5,6a}$ = 3.9 Hz, 1H, H-5), 2.77 (dd, $^2J_{1a,1b}$ = 13.0, $J_{1a,2}$ = 7.1 Hz, 1H, H-1a), 2.62 (dd, $^2J_{1a,1b}$ = 13.0, $J_{1b,2}$ = 7.1 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, 2% NaOD in D_2O) δ 74.1 (C-4), 72.4 (C-3), 62.4 (C-6), 62.0 (C-5), 60.6 (C-2), 40.4 (C-1).

1-Amino-1,2,5-trideoxy-2,5-imino-L-altritol (14). By subjecting amino carbamate **27** (12.3 mg, 0.06 mmol) to the general procedure for the hydrolysis of carbamates, iminohexitol **14** was obtained as a colorless oil (10.6 mg, 0.06 mmol, quantitative): R_f = 0.01 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); (HCl salt) $[\alpha]^{27.4}_D$ = −20.0 (*c* = 0.45 H_2O); IR (film) 3302, 2928, 1622, 1402, 1342, 1221, 1124, 1039, 1027 cm^{-1}; ^{1}H NMR (500 MHz, 2% DCl in D_2O) δ 4.18 (dd, $J_{3,4}$ = 3.7, $J_{4,5}$ = 2.9 Hz, 1H, H-4), 4.14 (dd, $J_{2,3}$ = 9.7, $J_{2,3}$ = 3.7 Hz, 1H, H-3), 3.84 (dd, $^2J_{6a,6b}$ = 16.1, $J_{5,6a}$ = 8.7 Hz, 1H, H-6a), 3.75 (dd, $^2J_{6a,6b}$ = 16.1, $J_{5,6b}$ = 8.7 Hz, 1H, H-6b), 3.74 (td, $J_{5,6a}$ = $J_{5,6b}$ = 8.7, $J_{4,5}$ = 2.9 Hz, 1H, H-5), 3.66 (ddd, $J_{2,3}$ = 9.7, $J_{1a,2}$ = 7.9, $J_{1b,2}$ = 5.9 Hz, 1H, H-2), 3.41 (dd, $^2J_{1a,1b}$ = 14.0, $J_{1a,2}$ = 7.9 Hz, 1H, H-1a), 3.36 (dd, $^2J_{1a,1b}$ = 14.0, $J_{1b,2}$ = 7.9 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, 2% DCl in D_2O) δ 74.0 (C-4), 69.3 (C-3), 62.8 (C-5), 57.3 (C-6), 56.9 (C-2), 39.0 (C-1); HRMS(ESI) *m*/*z* calcd for $[C_6H_{14}N_2O_3 + H]^+$ 163.1077, obsd 163.1079; ^{1}H NMR (500 MHz, 2% NaOD in D_2O) δ 4.05 (t, $J_{4,5}$ = $J_{3,4}$ = 4.1 Hz, 1H, H-4), 3.79 (dd, $J_{2,3}$ = 8.1, $J_{3,4}$ = 4.1 Hz, 1H, H-3), 3.70 (dd, $^2J_{6a,6b}$ = 11.2, $J_{5,6a}$ = 6.3 Hz, 1H, H-6a), 3.58 (dd, $^2J_{6a,6b}$ = 11.2, $J_{5,6b}$ = 6.3 Hz, 1H, H-6b), 3.17 (td, $J_{5,6a}$ = $J_{5,6b}$ = 6.3, $J_{4,5}$ = 4.1 Hz, 1H, H-5), 2.93 (td, $J_{2,3}$ = $J_{1b,2}$ = 8.1, $J_{1a,2}$ = 4.4 Hz, 1H, H-2), 2.76 (dd, $^2J_{1a,1b}$ = 13.2, $J_{1a,2}$ = 4.4 Hz, 1H, H-1a), 2.57 (dd, $^2J_{1a,1b}$ = 13.2, $J_{1b,2}$ = 8.1 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, 2% NaOD in D_2O) δ 75.6 (C-3), 72.6 (C-4), 62.7 (C-2), 60.6 (C-6), 59.6 (C-5), 43.8 (C-1).

1-Amino-1,2,5-trideoxy-2,5-imino-D-mannitol (4).[12,31] By subjecting amino carbamate **29** (4.0 mg, 0.02 mmol) to the general procedure for the basic hydrolysis of carbamates, iminomannitol **4** was obtained as a colorless oil (3.2 mg, 0.02 mmol, 91%): R_f = 0.01 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); (HCl salt) $[\alpha]^{27.4}_D$ = +40.0 (*c* = 0.10, H_2O); IR (film) 3209, 2925, 1603, 1503, 1406, 1123, 1065, 1034, 813 cm^{-1}. ^{1}H NMR (500 MHz, 2% DCl in D_2O) δ 4.08 (t, $J_{3,4}$ = $J_{2,3}$ = 7.0 Hz, 1H, H-3), 4.04 (t, $J_{4,5}$ = $J_{3,4}$ = 7.0 Hz, 1H, H-4), 3.89 (dd, $^2J_{6a,6b}$ = 12.7, $J_{5,6a}$ = 3.9 Hz, 1H, H-6a), 3.79 (dd, $^2J_{6a,6b}$ = 12.7, $J_{5,6b}$ = 7.0 Hz, 1H, H-6b), 3.73 (td, $J_{1,2}$ = 7.2, $J_{2,3}$ = 7.0 Hz, 1H, H-2), 3.61 (td, $J_{4,5}$ = $J_{5,6b}$ = 7.0, $J_{5,6a}$ = 3.9 Hz, 1H, H-5), 3.36 (d, $J_{1,2}$ = 7.2 Hz, 2H, H-1); ^{13}C NMR (125 MHz, 2% DCl in D_2O) δ 76.4 (C-3), 73.9 (C-4), 63.4 (C-5), 58.4 (C-6), 58.0 (C-2), 38.6 (C-1); HRMS(ESI) *m*/*z* calcd for $[C_6H_{14}N_2O_3 + H]^+$: 163.1077, obsd 163.1084; ^{1}H NMR (500 MHz, 2% NaOD in D_2O) δ 3.83 (t, $J_{4,5}$ = $J_{3,4}$ = 7.6 Hz, 1H, H-4), 3.75 (t, $J_{3,4}$ = $J_{2,3}$ = 7.6 Hz, 1H, H-3), 3.72 (dd, $^2J_{6a,6b}$ = 11.7, $J_{5,6a}$ = 4.4 Hz, 1H, H-6a), 3.64 (dd, $^2J_{6a,6b}$ = 11.7, $J_{5,6b}$ = 6.1 Hz, 1H, H-6b), 2.99 (ddd, $J_{4,5}$ = 7.6, $J_{5,6b}$ = 6.1, $J_{5,6a}$ = 4.4 Hz, 1H, H-5) 2.95 (td, $J_{2,3}$ = $J_{1b,2}$ = 7.6, $J_{1a,2}$ = 4.4 Hz, 1H, H-2), 2.83 (dd, $^2J_{1a,1b}$ = 13.2, $J_{1a,2}$ = 4.4 Hz, 1H, H-1a), 2.67 (dd, $^2J_{1a,1b}$ = 13.2, $J_{1b,2}$ = 7.6 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, 2% NaOD in D_2O) δ 79.4 (C-3), 77.7 (C-4), 62.0 (C-2), 61.9 (C-6), 61.5 (C-5), 43.5 (C-1).

General Procedure for the Acetylation of Aminoiminohexitols.[15] Aminoiminohexitol (0.05 mmol) was coevaporated with dry toluene (0.5 mL) three times, placed under argon, and dissolved in dry MeOH (500 μL). Acetic anhydride (0.05 mmol) was added to the solution at −15 °C. The solution was concentrated in vacuo when TLC analysis (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v) revealed the reaction was complete. Purification was achieved using flash chromatography to provide the pure acetamides (DCM/MeOH, 5/1, v/v containing 1% of 30% aq NH_3).

1-Acetamido-1,2,5-trideoxy-2,5-imino-D-galactitol (30). By subjecting imino-D-galactitol **12** (8.0 mg, 0.05 mmol) to the general procedure for the acetylation of aminoiminohexitols for 1 h at −15 °C, acetamide **30** was obtained as a colorless oil (4.0 mg, 0.02 mmol, 40%): R_f = 0.29 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); ^{1}H NMR (500 MHz, D_2O) δ 4.48 (dd, $J_{3,4}$= 4.7, $J_{2,3}$ = 6.3 Hz, 1H, H-3), 4.41 (t, $J_{3,4}$ = $J_{4,5}$ = 4.7 Hz, 1H, H-4), 3.94 (dd, $J_{6a,6b}$ = 12.2, $J_{5,6a}$ = 4.5 Hz, 1H, H-6a), 3.87 (dd, $J_{6a,6b}$ = 12.2, $J_{5,6b}$ = 8.6 Hz, 1H, H-6b), 3.77–3.74 (m, 2H, H-2, H-5), 3.64 (dd, $J_{1a,1b}$ = 14.5, $J_{1a,2}$ = 5.4 Hz, 1H, H-1a), 3.59 (dd, $J_{1a,1b}$ = 14.5, $J_{1b,2}$ = 7.8 Hz, 1H, H-1b), 2.00 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, D_2O) δ 175.2 (C=O), 69.9, 69.7 (C-3, C-4), 61.2, 59.4, 57.8 (C-2, C-5, C-6), 36.8 (C-1), 21.6 ($COCH_3$); HRMS(ESI) *m*/*z* calcd for $[C_8H_{17}N_2O_4 + H]^+$ 205.1183, obsd 205.1185.

1-Acetamido-1,2,5-trideoxy-2,5-acetimido-D-galactitol (31). By subjecting imino-D-galactitol **12** (8.0 mg, 0.05 mmol) to the general procedure for the acetylation of aminoiminohexitols for 1 h at −15 °C, bis-acetamide **31** was obtained as a colorless oil and appeared as a 1:1 mixture of rotamers in the NMR spectra (2.0 mg, 0.008 mmol, 17%): R_f = 0.50 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); ^{1}H NMR (500 MHz, D_2O) δ 4.38 (dd, $J_{4',5'}$ = 6.3, $J_{3',4'}$ = 5.6 Hz, 1H, H-4′), 4.34 (dd, $J_{4,5}$ = 7.6, $J_{3,4}$ = 5.4 Hz, 1H, H-4), 4.27 (dd, $J_{2',3'}$ = 7.0, $J_{3,4}$ = 5.4 Hz, 1H, H-3), 4.24 (dd, $J_{2',3'}$ = 3.0, $J_{3',4'}$ = 5.6 Hz, 1H, H-3′), 4.18–4.12 (m, 4H, H-2, H-2′, H-5, H-5′), 3.89 (dd, $J_{6a,6b}$ = 12.2, $J_{5,6a}$ = 5.0 Hz, 1H, H-6a), 3.87 (dd, $J_{6a',6b'}$ = 11.5, $J_{5',6a'}$ = 6.0 Hz, 1H, H-

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6a′), 3.81 (dd, $J_{6a',6b'}$ = 11.5, $J_{5',6b'}$ = 4.5 Hz, 1H, H-6b′), 3.79 (dd, $J_{6a,6b}$ = 12.2, $J_{5,6b}$ = 5.5, 1H, H-6b), 3.60 (dd, $J_{1a,1b}$ = 14.1, $J_{1a,2}$ = 6.3 Hz, 1H, H-1a), 3.57 (dd, $J_{1a',1b'}$ = 13.4, $J_{1a',2'}$ = 5.8 Hz, 1H, H-1a′), 3.50 (dd, $J_{1a,1b}$ = 14.1, $J_{1b,2}$ = 6.3 Hz, 1H, H-1b), 3.48 (dd, $J_{1a',1b'}$ = 13.4, $J_{1b',2'}$ = 7,7 Hz, 1H, H-1b), 2.12 (s, 3H, $NCOCH_3$), 2.11 (s, 3H, $NCOCH_3'$), 1.97 (s, 3H, $NHCOCH_3$), 1.94 (s, 3H, $NHCOCH_3'$); ^{13}C NMR (125 MHz, D_2O) δ 175.1 (NC═O), 175.0 (NC═O′), 174.3 (NHC═O), 174.1 (NHC═O′), 70.3 (C-3), 70.2 (C-4), 70.1 (C-4′), 69.6 (C-3′), 62.2 (C-5), 61.1 (C-5′), 60.0 (C-2′), 59.3 (C-6), 59.0 (C-6′), 58.7 (C-2), 38.9 (C-1), 38.1 (C-1′), 21.8 ($NHCOCH_3$), 21.8 ($NHCOCH_3'$), 21.7 ($NCOCH_3$), 21.2 ($NCOCH_3'$); HRMS(ESI) m/z calcd for $[C_{10}H_{18}N_2O_5 + Na]^+$ 269.1108, obsd 269.1115.

1-Acetamido-1,2,5-trideoxy-2,5-imino-D-talitol (32). By subjecting imino-D-talitol dihydrochloride **13** (4.0 mg, 0.017 mmol) to the general procedure for the acetylation of aminoiminohexitols for 3 h at −15 °C, then 1 h at room temperature, acetamide **32** was obtained as a colorless oil (2.0 mg, 0.009 mmol, 77%): R_f = 0.30 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); ^{1}H NMR (500 MHz, D_2O) δ 4.17 (t, $J_{2,3} = J_{3,4}$ = 3.8 Hz, 1H, H-3), 4.11 (dd, $J_{4,5}$ = 8.8, $J_{3,4}$ = 3.8 Hz, 1H, H-4), 3.83 (dd, $J_{6a,6b}$ = 12.2, $J_{5,6a}$ = 3.5 Hz, 1H, H-6a), 3.71 (dd, $J_{6a,6b}$ = 12.2, $J_{5,6b}$ = 5.8 Hz, 1H, H-6b), 3.55−3.49 (m, 1H, H-1a), 3.45−3.36 (m, 3H, H-1b, H-2, H-5), 1.97 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, D_2O) δ 174.7 (C═O), 72.2, 71.0 (C-3, C-4), 61.7, 59.9, 59.1 (C-2, C-5, C-6), 37.8 (C-1), 21.7 ($COCH_3$); HRMS(ESI) m/z calcd for $[C_8H_{17}N_2O_4 + H]^+$ 205.1183, obsd 205.1184.

1-Acetamido-1,2,5-trideoxy-2,5-imino-L-altritol (33). By subjecting imino-L-altritol dihydrochloride **13** (5.0 mg, 0.021 mmol) to the general procedure for the acetylation of aminoiminohexitols for 2 h at −15 °C, then 3 h at room temperature, acetamide **33** was obtained as a colorless oil (2.6 mg, 0.013 mmol, 65%): R_f = 0.31 (DCM/MeOH/EtOH/30% aq NH_3, 5/2/2/1, v/v/v/v); ^{1}H NMR (500 MHz, D_2O) δ 4.18 (t, $J_{4,5} = J_{3,4}$ = 3.9 Hz, 1H, H-4), 3.98 (dd, $J_{2,3}$ = 8.5, $J_{3,4}$ = 3.9 Hz, 1H, H-3), 3.80 (dd, $J_{6a,6b}$ = 11.4, $J_{5,6a}$ = 6.8 Hz, 1H, H-6a), 3.66 (dd, $J_{6a,6b}$ = 11.4, $J_{5,6b}$ = 6.8 Hz, 1H, H-6b), 3.47 (dd, $J_{1a,1b}$ = 14.1, $J_{1a,2}$ = 4.4 Hz, 1H, H-1a), 3.41 (td, $J_{5,6a} = J_{5,6b}$ = 6.8, $J_{4,5}$ = 3.9 Hz, 1H, H-5), 3.32 (dd, $J_{1a,1b}$ = 14.1, $J_{1b,2}$ = 7.4 Hz, 1H, H-1b), 3.22−3.25 (m, 1H, H-2), 2.00 (s, 3H, $COCH_3$), 174.9 (C═O), 74.5 (C-3), 71.3 (C-4), 60.0 (C-5), 59.7 (C-2), 59.6 (C-6), 41.1 (C-1), 21.7 ($COCH_3$); HRMS(ESI) m/z calcd for $[C_8H_{17}N_2O_4 + H]^+$ 205.1183, obsd 205.1185.

Kinetic Studies. *Agrobacterium* sp. β-D-Glucosidase/-Galactosidase (ABG). The enzyme was purified and assayed as previously described.[34] Kinetic studies were performed at 37 °C in pH 7.0 sodium phosphate buffer (50 mM) containing 0.1% bovine serum albumin with enzyme at 3×10^{-3} mg/mL for plate assays and 7.2×10^{-5} mg/mL for full K_i determination. Approximate values of K_i were determined by a screen of four inhibitor concentrations ranging from 0.01 to 1 mM at a fixed concentration of 4-nitrophenyl β-D-glucoside (0.11 mM; 1.5 × K_M) in a 96-well plate. Initial rates were monitored at 405 nm. The intersection of a linear fit to a plot of $1/V$ against [I] with a horizontal line through $1/V_{max}$ gave $-K_i$. V_{max} was determined by measuring initial rates with six substrate concentrations ranging from 0.2 to 5 × K_M on the same plate and fit to the Michaelis−Menten equation. Compounds giving apparent inhibition in this screen were further tested at a range of five inhibitor concentrations ranging from 0.2 to 5 times the apparent initial K_i to verify the results and further refine this value. Full K_i determination was carried out on the best inhibitor from the plate screens (**14**) by measuring rates at five inhibitor concentrations (0.2−5 × K_i determined in the plate assays; 0.6−15 μM) while also varying the substrate concentration from 0.2 to 5 × K_M (14 − 350 μM). Initial rates were determined by monitoring at 405 nm in matched quartz cuvettes. Data were fit directly to the Michaelis−Menten equation describing reaction in the presence of a competitive inhibitor, with competitive inhibition mode being confirmed by a Dixon plot. Initial rate fitting was performed in Microsoft Excel for the plate assays and proprietary software for the Cary 4000, while analyses of these initial rates were performed in GraFit 5.

***Streptomyces plicatus* N-acetyl-β-D-hexosaminidase (SpHex).** The enzyme was purified[35] and assayed[36] as previously described. Kinetic studies were performed at 37 °C in pH 5.0 sodium citrate/sodium phosphate buffer (25/50 mM) and NaCl (75 mM) with enzyme at 25 nM. Plate screening was as above for ABG, with 4-nitrophenyl *N*-acetyl-β-D-glucosaminide (0.33 mM; 1.5 × K_M) monitored at 340 nm. Following initial screening, the highest inhibitor concentrations able to be tested were limited to 8 mM for **11**, **14**, and **5** and to 14 mM for **12**, due to a limited amount of inhibitor. For **30**, a full K_i determination was carried out as described above for **14** with ABG, with substrate at 0.03−1 mM and inhibitor at 0.16−4 mM.

Recombinant Human β-D-Glucocerebrosidase (GCase) (Genzyme). The enzyme was assayed as previously described.[32] Kinetic studies were performed at 37 °C in pH 5.5 sodium citrate/sodium phosphate buffer (20/50 mM), EDTA (1 mM), Triton X-100 (0.25% v/v), and taurocholic acid (0.25% w/v) with enzyme at 4.0 nM. Plate screening was as above for ABG, with 2,4-dinitrophenyl β-D-glucoside (2.4 mM; 1.5 × K_M) monitored at 405 nm. No clear hits were detected in the initial screen, so all compounds were tested at four higher inhibitor concentrations (2−0.2 mM) to verify those compounds showing weak inhibition, with only compounds that gave repeatable concentration dependent inhibition with a determined K_i below 10 mM being reported.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra (^{1}H and ^{13}C) for all new compounds and X-ray structures and CIFs of **18** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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