Highly Diastereoselective Additions to Polyhydroxylated Pyrrolidine Cyclic Imines: Ready Elaboration of Aza-Sugar Scaffolds To Create Diverse Carbohydrate-Processing Enzyme Probes

Timothy M. Chapman,[a] Steve Courtney,[b] Phil Hay,[b] and Benjamin G. Davis*[a]

Abstract: Representative diastereomeric, erythritol and threitol polyhydroxylated pyrrolidine imine scaffolds have been rapidly elaborated to diversely functionalized aza-sugars through highly diastereoselective organometallic (RM) additions (R = Me, Et, allyl, hexenyl, Ph, Bn, *p*MeO-Bn). The yields for these additions have all been substantially enhanced from previously optimised levels (< 58 %) for normal additions using a reverse addition procedure (e.g. R = Ph; 44 % normal mode → 78 % reverse mode). The high diastereoselectivities (> 98 % de for all except R = Me) are consistent with additions that are controlled by the configuration of the C-2 centre adjacent to the azomethine imine carbon and the conformation of the pyrrolidine imine. The high potential of this method was demonstrated by concise syntheses of 1-epi- and 2-epi-desacetylanisomycins. In addition, the late stage addition of hydrophobic substituents, which this imine addition methodology allows, enabled the preparation of novel aza-sugars with enhanced inhibitory potential. This was highlighted by the screening of a representative selection of these "hydrophobically-modified" aza-sugars against a diverse panel of 12 non-mammalian and human carbohydrate-processing enzymes. This identified a novel nanomolar α-galactosidase inhibitor (IC_{50} = 250 nM) and a novel highly selective glucosylceramide synthase inhibitor (IC_{50} = 52 μM, no α-glucosidase inhibition at 1 mM). Furthermore, analysis of the structure – activity relationships of racemic series of inhibitors allowed some validation of Fleet's mirror-image enzyme active site postulate.

Keywords: asymmetric synthesis · azasugars · carbohydrates · enzyme catalysis · heterocycles

Introduction

The syntheses of aza-sugars, sugar mimics in which the ring oxygen has been substituted by a nitrogen atom, have been the subject of much continued interest over the last 25 years;[1] they have proved to be highly potent enzyme inhibitors, especially of carbohydrate-processing processing enzymes, and have been used as invaluable probes of the nature and mechanism of action of many enzymes.[2] For example, the aza-sugar *N*-butyldeoxynojirimycin (Zavesca), a potent glucosylceramide synthase inhibitor is now approved for use in Europe for the treatment of the glycolipid storage disease, type I Gaucher disease.[3][4] Most syntheses of aza-sugars have focused on logical designs based on the stereochemistry of the functional groups around the heterocyclic ring of the putative carbohydrate mimic, and this approach has yielded potent inhibitors. For example, deoxynojirimycin (DNJ), the direct configurational counterpart of 1-deoxy-D-glucopyranose is a potent α-glucosidase inhibitor.[5] Interestingly, however, this type of approach does not always result in high inhibition. Some striking exceptions exist: for example, deoxyrhamnojirimycin (LRJ)[6] is a poor inhibitor of α-L-rhamnosidase, and while deoxymannojirimycin (DMJ) is a potent inhibitor of class I α-D-mannosidases[7] it is a poor inhibitor of class II α-D-mannosidases.[7b] In addition, in certain cases, five-membered ring aza-sugars have been shown to give rise to higher inhibition than their six-membered ring counterparts[8] and subtle selectivities may be observed for five- versus six-membered ring systems. For example, the five-membered ring isomer of DMJ is a potent class II α-D-mannosidase inhibitor.[8] Therefore, it is not generally straightforward to predict by an entirely logical design based upon configurational analogy the structure of the best inhibitor for a given carbohydrate-processing enzyme.

The need for precise probes of carbohydrate-processing enzymes continues to build enormously. The burgeoning field of chemical genetics[9] demands broad-ranging probes and inhibitors of key enzymes to provide information on central biosynthetic glycosylation processes, often where little or no

[a] Dr. B. G. Davis, T. M. Chapman
Dyson Perrins Laboratory, Department of Chemistry
University of Oxford, South Parks Road, Oxford OX1 3QY (UK)
Fax: (+44) 1865 275674
E-mail: Ben.Davis@chem.ox.ac.uk

[b] Dr. S. Courtney, Dr. P. Hay
Oxford GlycoSciences Ltd, The Forum, 86 Milton Park
Abingdon, Oxfordshire OX14 4RY (UK)

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functional or structural information on putative protein targets exists.

As a solution to the need for more varied potential carbohydrate-processing probes, we have sought to design a general method that will allow the generation and screening of a broad range of potential inhibitors. This method retains three key structural features that have typically generated inhibitors: a five-membered ring nitrogen heterocycle core, polyhydroxylation and a hydrophobic group at or near putative aglycone binding sites. By varying hydroxyl stereochemistries and functional groups within this central aza-sugar scaffold design we sought to investigate their potential for inhibition of a number of carbohydrate-processing enzymes. This required a synthetic approach that would lend itself easily to the synthesis of diverse arrays of aza-sugars and allow the potential introduction of a wide range of substituents to an aza-sugar scaffold.

As part of our strategy, we have generated potential inhibitors in racemic series. This not only provides a greater potential for hits in enzyme inhibition from either aza-sugar enantiomer, but also allows the exploration of the concept of "mirror-image" enzyme active sites. There are several examples of mirror-image enzyme active sites in nature,[10] and Fleet has postulated that this may be a general structural theme for many carbohydrate-processing enzymes glycosidases;[11] thus, aza-sugars that are enantiomers of one another are able to inhibit the enzymes that process the natural sugars that are also enantiomers of one another. For example, L-rhamnose is the enantiomer of 6-deoxy-D-mannose; Fleet successfully predicted that L-swainsonine would be a powerful inhibitor of L-rhamnosidase by analogy with D-swainsonine a strong inhibitor of D-mannosidase,[11] despite the fact that no 3D structure of a rhamnosidase exists.

Previously, many syntheses of aza-sugars have relied on the introduction of substituents to the scaffold at an early stage, and therefore are limited in the range and number of substituents that may be readily introduced. Aza-sugars carrying hydrophobic substituents have shown, in some cases, increased enzyme inhibition and increased bioavailability.[12] Guided by these tantalizing indications we chose to investigate the introduction of such hydrophobic groups at a late stage to allow greater flexibility in the creation of a diverse array of potential enzyme probes.

The synthesis of functionalized aza-sugars by addition of organometallic nucleophiles to cyclic imines: Our strategy suggested the late convergent addition of substituents to an aza-sugar scaffold. Introduction of substituents through addition of a nucleophile to a cyclic imine is a potentially powerful but largely unexplored methodology that by virtue of an almost biomimetic convergence allows assembly of probes in a manner that divides nicely into component blocks of sugar mimic and aglycone mimic.

Due to the irreversible nature of their addition to imines, thereby allowing kinetic control of selectivity, we focused on the addition of organometallic reagents, and in particular Grignard reagents, as a source of nucleophile. Whilst there are many examples of additions of organometallic reagents to acyclic imines reported in the literature,[13] reports of additions to cyclic sugar imines are scarce, and such reactions of aza-sugar imines have been essentially limited to the iminoribitol **1** (Figure 1). Early studies with **1** outlined the synthetic potential of such an approach;[14] Furneaux et al. have since made very valuable progress in nucleophilic additions to **1** as a way of synthesising a wider range of potential nucleoside hydrolase inhibitors.[15] However, in this system yields have generally been only moderate to fair (35–64% for Grignard reagents,[14, 15d] 44–63% for organolithium reagents[15] from precursor amine). It has been previously suggested that such reactions prove challenging as a result of the low inherent electrophilicity of the azomethine carbon atom and the tendency for competing side reactions, such as deprotonation of tautomerisable imines.[13] Although a number of strategies for enhancing the reactivity of the C=N bond of imines for the subsequent addition of organometallics exist, for example N-alkylation,[16] N-oxidation,[17] N-acylation[18] or N-sulfonylation[19] to produce more reactive iminiums, nitrones, acylimines and sulfonimines, respectively, these require removal of these activating groups, which can be difficult, and the presence of the N-substituent may adversely affect diastereoselectivities.[20] Moreover, the installation of an activating N-substituent may not lend itself to iterative rounds of C=N formation and nucleophile addition.

We therefore chose to realize the potential of this powerful methodology by optimising the yields of such additions, in particular the additions of Grignard reagents, to parent imines bearing no N-substituent. Three model imines were chosen, based on a five-membered ring scaffold with 2,3-dihydroxy functionality, the threitol imine **2**, and those in the epimeric series, the erythritol imines **3** and **4** (Figure 1). These diastereomeric imines importantly allowed the effect of

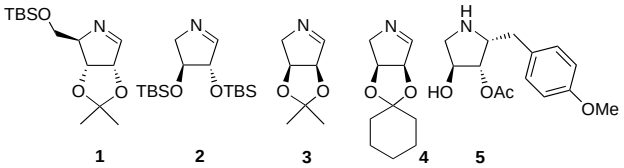
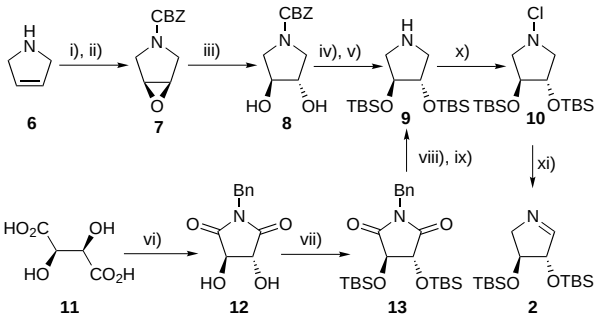


Figure 1.

structural factors, such as hydroxyl group stereochemistries and protecting group nature, on efficiency,[21] diastereoselectivity and resulting biological activity to be probed in a systematic way. Some initial aspects of this work have previously appeared in a brief communication.[22] Additionally, these imines allow access to scaffolds similar to those found in natural products of known activity, such as anisomycin **5**, a clinically proven peptidyl-transferase inhibitor, which exhibits strong and selective activity against pathogenic protozoa and fungi.[23] This paper demonstrates that this methodology may be applied to the addition of a variety of functional groups with excellent diastereoselectivities and in good to excellent yields beyond those previously observed for cyclic imines. In this way, structure–activity relationships for a wide variety of carbohydrate-processing enzymes can be readily derived from the resulting deprotected aza-sugar products, including the identification of novel strong inhibitors.

Results and Discussion

Preparation of the threitol imine: Threitol imine **2** was obtained from its iminothreitol precursor **9**. This was itself synthesized in two ways to illustrate two methods of construction (Scheme 1): firstly from the empty, unfunctionalized scaffold 3-pyrroline (**6**), and secondly via the manipulation of an existing dihydroxy scaffold from the chiral starting material, tartaric acid (**11**).

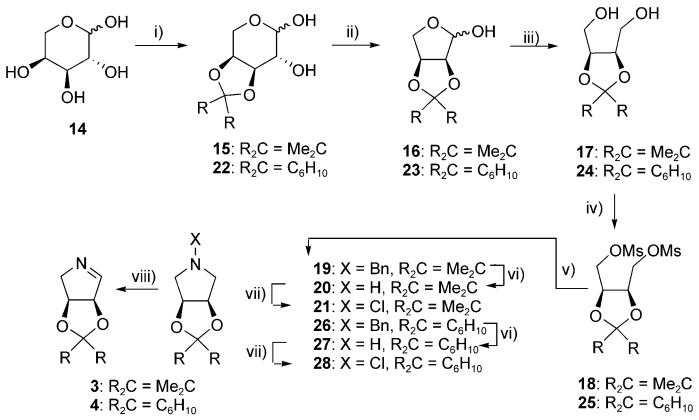


Scheme 1. i) $C_6H_5CH_2OCOCl$, NaOH, toluene, 93%; ii) *m*CPBA, CH_2Cl_2, 46%; iii) 2M H_2SO_4 (aq.), Et_2O, 87%; iv) TBDMSOTf, py, CH_2Cl_2, 92%; v) H_2, Pd/C, MeOH, 92%; vi) $BnNH_2$, xylene, reflux; vii) TBDMSCl, imidazole, DMF, 43% over two steps from tartaric acid; viii) $BH_3 \cdot Me_2S$, THF then MeOH, 40°C, 100%; ix) H_2, Pd/C, MeOH, 100%; x) NCS, Et_2O, 96%; xi) DBU, Et_2O.

Starting at 3-pyrroline **6**, the iminothreitol **9** was prepared through N-protection as its Z-carbamate then epoxidation, followed by ring opening of the epoxide **7** in aqueous sulfuric acid to yield the *trans* hydroxylated pyrrolidine **8**. Subsequent protecting group manipulation, di-O-protection using TBDMSOTf and N-deprotection through hydrogenolysis, afforded the iminothreitol **9**, obtained in 32% overall yield from 3-pyrroline (**6**) over five steps. A second route starting from cheap, readily available racemic tartaric acid was also used. Reaction of tartaric acid (**11**) with benzylamine in refluxing xylene led to cyclisation to yield the imide **12**, which without purification was reacted with *tert*-butyldimethylsilyl chloride according to the procedure of Ryu and Kim[24] to afford the di-*O*-silyl ether-protected imide **13** in 43% yield from tartaric acid (**11**). Reduction of imide **13** was achieved by reaction with borane/dimethylsulfide complex yielding the corresponding borazine as the sole product, which was cleaved to yield *N*-benzylpyrrolidine by heating overnight in methanol at 40°C (100% yield from **13**); this borazine-cleavage method provides a convenient alternative to other methods.[25] Removal of the *N*-benzyl group by catalytic hydrogenation over palladium-on-carbon yielded the iminothreitol **9** in 43% yield over four steps from tartaric acid, identical in all respects to that synthesized from **6**.

With two ready routes to **9** in hand, we focused on the elaboration of **9** to its corresponding aldimine **2**. Treatment of iminothreitol **9** with *N*-chlorosuccinimide (NCS) yielded the *N*-chloroamine **10** in excellent yield (96%). For the elimination of **10**, a number of bases were surveyed, which caused either decomposition, dechlorination (LDA, KHMDS) or no reaction (Et_3N, DABCO). However, treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) ensured smooth elimination to yield the desired threitol imine **2**. The presence of the imine C=N bond was confirmed by characteristic IR [$\tilde{\nu}_{max}$ 1645 cm^{-1}], ^1H NMR [δ_H ($CDCl_3$): 7.41 ppm (pt, 1H, J = 2.2 Hz)] and ^{13}C NMR [δ_C ($CDCl_3$): 169.0 ppm] resonances. Although the imine **2** was isolated for characterisation, better yields were obtained in subsequent reactions through in situ imine formation: the reaction mixture, upon imine formation as judged by TLC, ^1H NMR and IR, was immediately filtered to remove DBU·HCl, then reagents added to the resulting imine solution.

Preparation of erythritol imines: Starting with L-arabinose (**14**), the erythritol imines **3** and **4** were prepared as depicted in Scheme 2. L-Arabinose was selectively 3,4-*O* protected as its acetonide **15** using 2,2-dimethoxypropane according to the procedure of Kiso and Hasegawa[26] as adapted by Thompson et al.,[27] which was, without purification, reacted with sodium periodate. The resulting cleavage of the 1,2-diol unit followed by basic hydrolysis and subsequent ring closure afforded 2,3-*O*-isopropylidene-L-erythrose (**16**) in 57% yield (α:β 1:6) in two steps from **14**.[27] Subsequent reduction with sodium borohydride yielded the erythritol **17** in quantitative yield; this was followed by treatment with mesyl chloride and triethylamine in dichloromethane to afford the dimesylate **18**.[28] Reaction with benzylamine led to cyclisation giving the protected erythritol **19**. Hydrogenolytic removal of N-benzyl protection yielded the acetonide protected iminoerythritol **20**. This compound is unusually volatile, and care is required in its isolation. As for **9**, N-chlorination (86%) and subsequent elimination with DBU sucessfully provided the desired erythritol cyclic imine **3**.



Scheme 2. i) *p*-TsOH, dimethoxypropane, DMF; ii) $NaIO_4$, H_2O then Na_2CO_3, 57% for **16**, 57% for **23** over two steps from L-arabinose; iii) $NaBH_4$, MeOH, 100% for **17**, 89% for **24**; iv) MsCl, Et_3N, CH_2Cl_2, 72% for **18**, 85% for **25**; v) $BnNH_2$, 65°C, 76% for **19**, 87% for **26**; vi) H_2, $Pd(OH)_2$/C, MeOH, 98% for **20**, 97% for **27**; vii) NCS, Et_2O, 86% for **21**, 90% for **28**; viii) DBU, Et_2O.

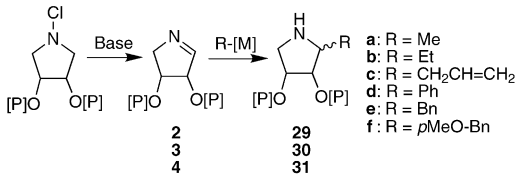
An essentially parallel route employing 3,4-*O*-cyclohexylidine protection gave protected iminoerythritol **27** in 36% yield over six steps from **14**. Compound **27** proved to be less volatile than **20**. Elaboration through N-chlorination (90%) and subsequent elimination with DBU proceeded smoothly

and yielded the alternatively protected erythritol cyclic imine **4**.

These routes using **14** as starting material were preferred to alternative routes employing moderate yielding *cis*-dihydroxylation of the Z-carbamate of 3-pyrroline (**6**).[29]

Screening of organometallics for addition to cyclic imines: Having obtained access to the cyclic imines **2**–**4**, we screened for the addition of Grignard reagents as representative, model nucleophiles (Table 1). Although imines **2**–**4** could be isolated, better yields were obtained if the Grignard reagents

Table 1. Organometallic additions to aza-sugar pyrrolidine imines **2**–**4**.[a]



	Imine	Base	Equiv	RM	Equiv	Order of Addition	Product	Yield[%][a]/ Conditions	*de*[b]
1	threitol **2**	DBU	3.0	MeMgBr	5.0	normal	**29a**	58	44
2	**2**	DBU	3.0	EtMgBr	5.0	normal	**29b**	45	96
3	**2**	DBU	3.0	AllylMgBr	5.0	normal	**29c**	26	85
4	**2**	DBU	1.0	PhMgBr	1.5	normal	**29d**	37	> 98
5	**2**	DBU	3.0	BnMgCl	5.0	normal	**29e**	48	> 98
6	**2**	DBU	3.0	*p*MeOBnMgCl	5.0	normal	**29f**	43[c]	> 98
7	**2**	DBU	3.0	PhMgBr	5.0	normal	**29d**	44	> 98
8	**2**	DBU	4.0	PhMgBr	5.5	normal	**29d**	44	> 98
9	**2**	DBU	3.0	PhMgBr	5.0	normal	**29d**	40[d]	> 98
10	**2**	DBU	3.0	PhMgBr	5.0	normal	**29d**	38[e]	> 98
11	**2**	DBU	3.0	PhMgBr	5.0	normal	**29d**	35[f]	> 98
12	**2**	DBU	3.0	PhMgBr	5.0	normal	**29d**	16[g]	–
13	**2**	Et_3N	12.0	–	–		–	–	–
14	**2**	DABCO	9.0	–	–		–	–	–
15	**2**	LDA	1.1	–	–		–	–	–
16	**2**	DBU	3.0	PhMgBr	5.0	normal	**29d**	5[h]	> 98
17	**2**	DBU	3.0	EtMgBr	5.0	normal	**29b**	10[h]	> 98
18	**2**	DBU	3.0	PhLi	5.0	normal	**29d**	39	> 98
19	**2**	DBU	3.0	Et_2Zn	5.0	normal	**29b**	26[d]	89
20	**2**	PhMgBr	2.2	–	–			0	
21	**2**	PhLi	2.2[g]	–	–			0	
22	erythritol **3**	DBU	1.1	PhMgBr	3.0	normal	**30d**	15	> 98
23	**3**	DBU	1.1	PhMgBr	2.0	normal	**30d**	12	> 98
24	**3**	DBU	1.1	PhMgBr	3.0	normal	**30d**	25[h]	> 98
25	**3**	DBU	1.1	PhMgBr	3.0	normal	**30d**	0[i]	–
26	**3**	DBU	1.1	PhMgBr	5.0	reverse	**30d**	56	> 98
27	**3**	DBU	1.1	PhMgBr	5.0	reverse	**30d**	23[j]	> 98
28	**3**	DBU	1.3	PhMgBr	5.0	reverse	**30d**	62[k, l]	> 98
29	**3**	DBU	1.3	PhMgBr	5.0	reverse	**30d**	70[k, m]	> 98
30	**3**	DBU	1.3	PhMgBr	5.0	reverse	**30d**	70[k, n]	> 98
31	**3**	DBU	1.3	PhMgBr	5.0	reverse	**30d**	68[k, o]	> 98
32	**3**	DBU	1.1	Ph_2Mg	5.0	reverse	**30d**	55[p]	> 98
33	**3**	DBU	1.3	EtMgBr	5.0	reverse	**30b**	76	> 98
34	**3**	DBU	1.3	BnMgCl	5.0	reverse	**30e**	73	> 98
35	**3**	DBU	1.3	*p*MeOBnMgCl	5.0	reverse	**30f**	76[c]	> 98
36	**2**	DBU	3.0	MeMgBr	5.0	reverse	**29a**	67	66
37	**2**	DBU	3.0	EtMgBr	5.0	reverse	**29b**	70	> 98
38	**2**	DBU	3.0	PhMgBr	5.0	reverse	**29d**	78	> 98
39	**2**	DBU	3.0	BnMgCl	5.0	reverse	**29e**	63	> 98
40	**2**	DBU	3.0	*p*MeOBnMgCl	5.0	reverse	**29f**	62[c]	> 98
41	**4**	DBU	1.3	EtMgBr	5.0	reverse	**31b**	76	> 98

[a] Yields quoted are determined over two-step elimination–addition sequence from corresponding chloramines. [b] As determined by ^{1}H NMR; configuration determined by NOESY or 1D NOE NMR spectroscopy. [c] Grignard formation and addition carried out in THF. [d] Pre-treatment of the imine solution with 0.95 equiv TMSOTf for 30 min prior to addition of the organometallic. [e] Addition of hexanes upon imine formation to encourage precipitation of DBU·HCl prior to filtration. [f] Imine formation and Grignard addition carried out in THF as solvent. [g] Addition of Grignard carried out at −78 °C, then reaction mixture allowed to warm to RT before quenching. [h] Aqueous work-up performed on imine, organic extract dried over $MgSO_4$, filtered and dissolved in fresh dry Et_2O prior to treatment with Grignard reagent. [i] Addition of Grignard and reaction quenched at −78 °C. [j] No filtration to remove DBU·HCl prior to Grignard addition. [k] Reaction of imine derived from 100 mg of chloramine starting material. [l] Addition of 0.14 M imine solution in of dry Et_2O to 0.96 M Grignard reagent in dry Et_2O. [m] Addition of 0.07 M imine solution in of dry Et_2O to 1.96 M Grignard reagent in dry Et_2O. [n] Addition of 0.047 M imine solution in of dry Et_2O to 3.0 M Grignard reagent in dry Et_2O. [o] Addition of 0.093 M imine solution in of dry Et_2O to 3.0 M Grignard reagent in dry Et_2O. [p] Addition of dioxane to Grignard reagent solution prior to addition of imine solution.

were added to imine generated in situ (see above). Pleasingly, addition of Grignard solution to a solution of threitol imine **2** (so-called "normal" mode, entries 1–6) successfully yielded the desired adducts **29a–f**, although the yields in all cases were low to moderate (26–58%). The observed diastereoselectivities ranged from fair to excellent (*de* 44–>98%); all nucleophiles showed a strong preference for the formation of *anti* diastereomers, the relative configurations of which were assigned by NOE NMR experiments. A marked dependence of this selectivity on nucleophile bulk was observed. Thus, for larger nucleophiles (R = Ph, Bn), including even the smaller ethyl, *de* values greater than 98% were observed, whereas for allylmagnesium bromide (85% *de*) and methylmagnesium bromide (44% *de*) poorer preferences were observed. These results are consistent with an addition selectivity that is governed by steric approach control (see below).

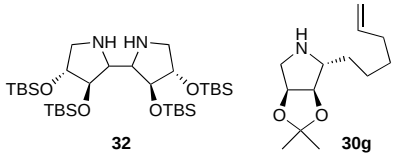
Optimisation of organometallic additions: In an attempt to improve yields of these promisingly diastereoselective reactions, optimisation of the additions of phenylmagnesium bromide to the imines **2** and **3** were investigated as model systems. It was found, via analysis of the formation of imine **2** by ^{1}H NMR spectroscopy, that 1.0 equivalent of DBU was not sufficient to provide complete imine formation. However, an increase in the amount of DBU to 3.0 equivalents while allowing more complete imine formation only led to a small increase in overall yield of resulting adduct (Table 1, entry 7). A further increase to 4.0 equivalents gave no further benefit (entry 8). Treatment of the N-chloramine with the bases triethylamine and diazabicyclooctane (DABCO) instead of DBU led to no imine formation, even after the adition of 12.0 and 9.0 equivalents respectively (entries 13 and 14). Similarly, treatment with 1.1 equivalents of lithium disopropylamine (LDA) led to no imine formation; instead the amine **20** was formed (entry 15) presumably through halogen-metal exchange and quench during work-up. It has been reported that pre-treatment of acyclic imines with the Lewis acid trimethylsilyltrifluoromethane sulfonate (TMSOTf), to activate the imine to addition by formation of the TMS-iminium salt has, in some cases, led to inceased yields of addition.[30] However, pre-treatment of **2** with 0.95 equivalents of TMSOTf led only to a reduced yield of adduct **29d** (40%). The addition of hexane upon imine formation, to encourage precipitation of DBU·hydrochloride, yielded **29d** in 38% (entry 10). The use of tetrahydrofuran in imine formation and subsequent addition similarly failed to enhance efficiency and resulted in a yield of only 35% of **29d** (entry 11). Temperature effects were also briefly investigated; addition of PhMgBr to a solution of imine cooled to −78 °C followed by warming to room temperature yielded the adduct **29d** in only 16% (entry 12). Purification of the imine by an aqueous work-up procedure to remove excess DBU,[31] followed by addition of Grignard led only to a much lower yield of adducts **29d**, **b** (5% for phenylmagnesium bromide, 10% for ethylmagnesium bromide, entries 16 and 17, respectively). It is possible that this may be attributed to the intermediate formation of a hydrated, hemiaminal form of imine **2** on exposure to water, which might be unreactive to subsequent Grignard addition.

Thus, despite these extensive variations in conditions adduct yields remained in the 40% region. It was considered that the high basicity of Grignard reagents might lead to unwanted side reactions such as elimination or tautomerisation, and therefore other potentially less basic and more azophilic organometallics, phenyllithium and diethylzinc were also investigated. Disappointingly, these yielded the respective adducts in only 39 and 26% yields, respectively (entries 18 and 19).

Corresponding variations in the addition of phenylmagnesium bromide to the erythritol imine **3** were similarly disappointing with the best yield of **30d** (25%), obtained by addition of Grignard reagent at −78 °C and allowing the mixture to warm to room temperature. It should be noted however that such moderate yields were consistent with those previously reported in the literature, which have been in the range 35–64%.[14, 15d]

Interestingly, the major side product of the addition reactions were the corresponding amines **9** and **20**; the formation of which is difficult to explain by a polar addition mechanism. Reductive β-hydride transfer reactions[32] by Grignard reagents are possible only for ethylmagnesium bromide and yet **9** and **20** were observed for all Grignards. Radical mechanisms have been reported in the literature for many Grignard reactions,[33] resulting in addition, reduction and dimerisation products, and radical mechanisms for the reduction of C=N bonds by other reagents have also been reported.[34] Such a radical mechanism might also account for the formation of amines **9** and **20** from imines **2** and **3**, respectively. Consistent with this possibility, a dimerisation product **32** was isolated as a consistent side product (8–10%), and suggested at least a partial radical character for additions. Indeed, the possibility of polar-radical mixed mechanisms in additions of Grignard reagents to acyclic imines has been noted previously.[35]

To test this possibility we used the Grignard reagent hexenylmagnesium bromide as a probe in additions to imine **3**, in which cyclisation of the hexenyl side chain during the addition process would be indicative of a radical process.[36] Uncyclized hexenyl adduct **30g** was the sole product in 46% yield; this inconclusive result does not preclude a radical process, which may have a rate greater than $\approx 10^5$ s^{-1}[37] or, alternatively, addition by any cyclized cyclopentylmethyl radical may compete unsuccessfully with addition by uncyclized hexenyl.



32 **30g**

Figure 2.

Investigations into a reverse addition procedure for the organometallic additions: Although the potential radical nature of the additions remained unconfirmed, the formation of dimer **32** nonetheless highlighted the propensity of imine substrates in such homo-coupling, perhaps through Mg-

chelated, pinacol reduction.[38] It was considered that addition of the imine *to* the Grignard, rather than Grignard to imine, might counter this problem. Such a reverse addition, by presenting a high Grignard concentration to a low imine concentration rather than vice versa, would likely curtail such dimerization side reactions that are more dramatically dependent on imine concentration.

Conditions for reverse addition were investigated using the erythritol imine **3** with PhMgBr as a nucleophile. Imine formation, with 1.1 equivalents of DBU, followed by the addition of imine solution to phenylmagnesium bromide led to a significant improvement in yield, and **30d** was obtained in 56% yield (entry 26) compared with 15% using the previous "normal" Grignard-to-imine order of addition. Reverse addition therefore appeared to be a key factor. Other potentially important yield determining factors were then studied: filtration to remove DBU·hydrochloride formed during imine synthesis was also shown to be an important factor, since the omission of filtration resulted in only a 23% yield of adduct **30d** (entry 27). As for "normal" mode additions (see above), the use of more DBU (here 1.3 equivalents) resulted in a concomitant increase in yield of **30d**, up to 62%. Finally, the absolute concentrations of imine and Grignard solutions were optimised. The use of a relatively dilute imine solution (≈0.05 M) added to a concentrated Grignard solution (≈3 M) gave the best yield of all achieved at 70% (entries 29 and 30), some six-fold improved over initial yields (12%, entry 23) in this system.

Addition of dioxane is known to affect the form of organomagnesium reagents in solution by altering the position of the Schlenk equilibrium, which favours the dialkylmagnesium species with concomitant precipitation of MgX_2.[39] The resulting R_2Mg species is less basic and might lead to decreased eliminative side reactions. However, addition of a solution of imine **3** to an unfiltered Ph_2Mg solution yielded **22d** in only 55% yield (entry 32); no improvement over the reaction conducted without added dioxane.

The application of the reverse addition methodology was extended to the other Grignard reagents ethylmagnesium bromide and benzylmagnesium chloride, in good yields of 76 and 73% for **30b** and **e** respectively. In view of the much improved yields obtained for the reverse addition of the erythritol imine **3**, this strategy was also investigated for the threitol imine **2** (entries 36–40). Gratifyingly, these yields were also much improved. For example, using the reverse rather than the normal mode of addition the yield of **29d** from the reaction of phenylmagnesium bromide with **2** improved from 44% (entry 7) to 78% (entry 38). To the best of our knowledge these represent some of the best yields of additions of organometallic nucleophiles to cyclic imines yet reported. It should be noted that the diastereoselectivities were also consistently good to excellent (>98% *de* for all except 66% *de* for **29a**), and indeed the *de* for the least selective addition, the addition of methylmagnesium bromide to **2** to give **29a**, was improved from 44% (entry 1) for the normal addition to 66% (entry 36) for the reverse addition procedure. The compatibility of the method with other protecting groups was also briefly explored through the addition reaction of EtMgBr with cyclohexylidene-protected erythritol imine **4**, which yielded adduct **31b** in similarly good yield (76%) and excellent *de* (>98%).

Diastereoselectivity in additions: Excellent diastereoselectivities were observed in almost all of the additions; for the larger nucleophiles (R ≠ Me, allyl) *de* values in excess of 98% were observed. The erythritol imines **3**,**4** generated adduct *de* values of greater than 98% for all nucleophiles regardless of the mode of addition. This is consistent with the expected[40] conformation of this imine, in which the acetonide group is likely to enforce a rigid butterfly conformation that favours nucleophile approach from the convex face (Figure 3). The similarly excellent *de* values (>98%), similar yields and rates for the addition of the ethyl nucleophile EtMgBr to both the acetonide and cyclohexylidene protected imines **3** and **4**, respectively, are therefore consistent with the model shown in Figure 3. In the case of TBDMS-protected threitol imine **2**, the bulk of the *O*-2-silyl group appears to be a key determining factor by limiting approach of the nucleophile to the *trans* α-face of the imine (Figure 3).

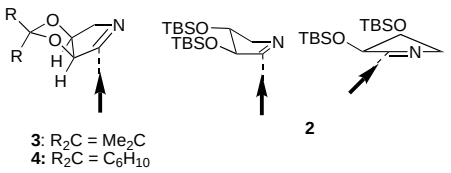
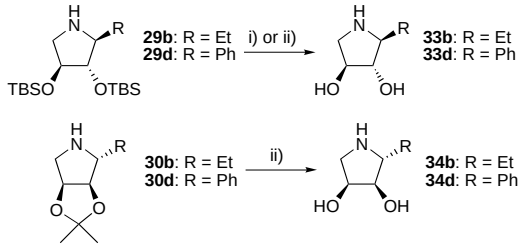


Figure 3.

Deprotection of adducts 29b,d and 30b,d: Ethyl and phenyl adducts **29b,d** and **30b,d** obtained from additions to both the threitol **2** and erythritol **3** imines were deprotected to yield their corresponding free aza-sugars **33b,d** and **34b,d**, respectively (Scheme 3). Treatment of **29b,d** with *tert*-butylammonium fluoride (TBAF) led to a successful cleavage of the silyl ether groups, but separation of the products from residual TBAF proved difficult. However, in all cases hydrolysis with aqueous trifluoroacetic acid followed by ion-exchange chromatography proved successful (Scheme 3).

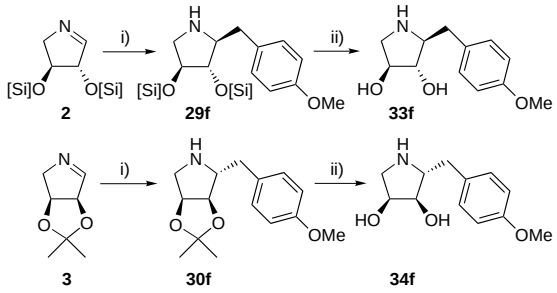


Scheme 3. i) 50% TFA (aq.), 76% for **33b**; ii) 25% TFA (aq.), THF then Dowex H^+ (NH_4OH (aq.)), 63% for **33d**, 96% for **34b**, 64% for **34d**.

Synthesis of anisomycin analogues: The methodology of addition of organometallics to cyclic imines offers potential access to interesting aza-sugar derivatives, such as analogues of the natural product anisomycin (**5**). Several syntheses of anisomycin have been reported in the literature,[20a],[41] but the

potential activity of anisomycin and its analogues towards glycosidases has been poorly explored.

To this end, we investigated the introduction of the 4-methoxybenzyl side chain of anisomycin through reaction of the threitol **2** and erythritol **3** imines with 4-methoxybenzylmagnesium chloride (Scheme 4). These yielded the TBDMS-protected threitol adduct, **29 f**, in 43% yield for the normal addition mode (Table 1, entry 6), and 62% for the reverse addition mode (entry 40); both with excellent diastereoselectivity (>98%). The erythritol adduct analogue **30 f** was obtained in similarly good yield (76%) and excellent diastereoselectivity (>98% *de*, entry 35). Interestingly, the use of THF solutions for the generation and use of *p*MeOBnMgCl proved critical, use of Et_2O at any stage failed to yield any adduct. Deprotection of **29 f** was conducted using essentially analogous conditions to those used for **29 b** and **d** to yield the unnatural analogue 1-epidesacetylanisomycin (**33 f**, 61%; 17% overall yield from tartaric acid). This methodology compares well in terms of the overall yields[42] reported for syntheses of desacetylanisomycin and highlights the high synthetic utility of the imine addition methodology. The 2-epidesacetylanisomycin diastereomer **34 f**, similarly an unnatural analogue, was synthesized in an essentially analogous way (Scheme 4).



Scheme 4. i) *p*-MeOBnMgCl, THF, 43–62% from **10** for **29 f**, 76% from **21** for **30 f**; ii) 25% TFA (aq.), 61% for **33 f**, 65% for **34 f**.

Carbohydrate-proccessing enzyme inhibition screening: The resulting deprotected compounds were screened for enzyme inhibition against a range of carbohydrate-processing enzymes (Tables 2–4), to allow a comparison of the effects of C-1 hydrophobic substituent and hydroxyl stereochemistry.

Table 2. Aza-sugar inhibition of non-mammalian glycosidases.[a]

Glycosidase	Inhibitor K_i [μM]					
	33 d	**33 b**	**33 f**	**34 d**	**34 b**	**34 f**
α-D-mannosidase (*Canavalia ensiformis*)	N.I.	15.1	16.7	N.I.	48.9	N.I.
β-D-mannosidase (snail)	N.I.	28.9	N.I.	N.I.	N.I.	N.I.
β-D-glucosidase (almond)	18.5	13.3	N.I.	N.I.	49.4	56.4
α-D-galactosidase (green coffee bean)	N.I.	N.I.	N.I.	N.I.	1.43	0.25
α-L-rhamnosidase (*Penicillium decumbens*)	13.0	5.9	3.0	N.I.	34.0	25.9
α-L-fucosidase (bovine kidney)	N.I.	7.6	33.5	5.0	9.0	2.4

[a] N.I. indicates no inhibition observed at 0.1 mM.

Table 3. Aza-sugar inhibition of human glycosidases.

Glycosidase	Inhibition [%]					
	33 d	**33 b**	**33 f**	**34 d**	**34 b**	**34 f**
α-D-glucosidsase[a]	N.I.	N.I.	9.3	3.0	11.3	13.0
β-D-glucosidase[a]	51.5	23.2	39.3	38.1	20.0	57.0
β-D-glucosidase[b] (non-lysosomal)	8.7	11.7	N.I.	–	–	–
α-D-galactosidase[a]	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
β-D-galactosidase[a]	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.

[a] At 1 mM. [b] At 1 μM.

Table 4. Inhibition of human glucosylceramide synthase (GCS).

Enzyme	Inhibition [%]					
	33 d	**33 b**	**33 f**	**34 d**	**34 b**	**34 f**
glycosylceramide synthase[a]	26.5	48.1	27.6	0	0	0

[a] At 50 μM.

Broad-ranging assessment of the inhibition of all of the deprotected "hydrophobically-modified" pyrrolidine aza-sugars **33 b, d, f** and **34 b, d, f** towards non-mammalian glycosidases revealed three broad trends: i) all the iminothreitol aza-sugars **33**, except for phenyl-substituted **33 d** which showed no inhibition towards α-D-mannosidase, showed relatively potent inhibition of α-L-rhamnosidase and α-D-mannosidase, with K_i values in the low micromolar range (3.0–16.7 μM); ii) all the erythritol sugars **34**, except for phenyl-substituted **33 d** which showed no inhibition towards α-D-galactosidase, showed relatively potent inhibition of α-L-fucosidase and α-D-galactosidase, with K_i values in the sub-micromolar to low micromolar range (0.25–9.0 μM); iii) several aza-sugars from both the threitol (Et- and Ph-substituted, **33 b, d**, respectively) and erythritol (Et- and *p*-MeO-Bn-substituted, **34 b, f**, respectively) families showed moderate inhibition of β-D-glucosidase. Additional individual moderate inhibitory activities (K_i 25.9–48.9 μM) with no broad trend were also observed: α-D-mannosidase by Et-erythritol **34 b**; β-D-mannosidase by Et-threitol **33 b**; α-L-rhamnosidase by Et- and *p*-MeO-Bn-erythritol **34 b, f**. All inhibitors displayed competitive inhibition, which indicates that their mode of binding and that of their corresponding substrate are similar.

The effective inhibition of α-L-rhamnosidase by the iminothreitol aza-sugars **33** can be dissected on the basis of structural similarities and differences. A stereochemical basis for the inhibition of L-rhamnosidase can be rationalized by the configurational similarity between OH-3,4 and C-5 of L-rhamnose (**36**) and OH-2,3 and C-4 of these threitol aza-sugars (Figure 4). The best inhibitor, the 4-methoxybenzyl derivative **33 f** ($K_i = 3.0$ μM), is a slightly better inhibitor (almost two-fold) than its ethyl counterpart **33 b** ($K_i = 5.9$ μM). The phenyl side chain in **33 d** results in >four-fold poorer inhibition ($K_i = 13.0$ μM). This may indicate that the CH_2 group present in the hydrophobic side chain, which ethyl- (**33 b**) and 4-methoxybenzyl- (**33 f**) derivatives both contain, is of some importance in the interactions with the active site of rhamnosidase. This raises the possibility, which is also consistent with the configurational mimicry outlined above, that the hydrophobic side chains, and in particular a CH_2 group within these side chains, may mimic the C-5 methyl

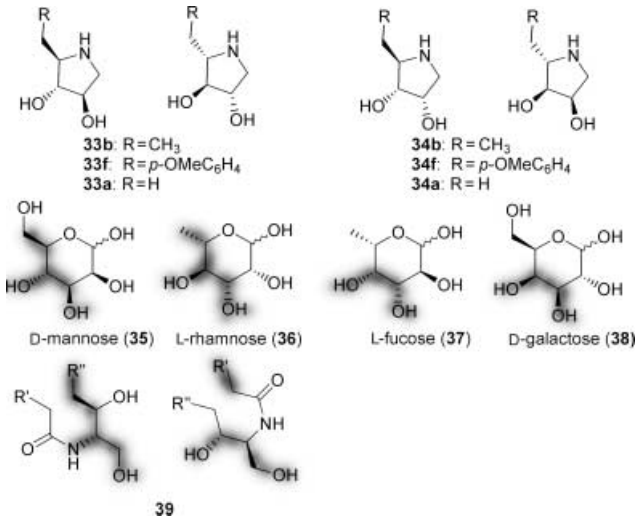


Figure 4.

group of L-rhamnose. In this regard, the phenyl derivative, which lacks a CH_2 in its hydrophobic side chain, is a poorer mimic of the C-5 methyl of L-rhamnose and this is consistent with the lower inhibitory potency observed for phenyl threitol **33d**, although the phenyl derivative is still a relatively good rhamnosidase inhibitor. Interestingly, the K_i values of ethyl threitol **33b** and *p*-methoxybenzyl threitol **33f** are similar. The extra aromatic functionality (replacement of the CH_3 terminus in **33b** by a *p*-methoxyphenyl terminus in **33f**) indicates that not only is the gain from additional remote hydrophobic or aromatic interactions in the active site small, but also that this region of the enzyme active site is able to accommodate the marked extra steric bulk of the 4-methoxybenzyl functionality.

Indeed, previous studies have established very similar inhibitory potency for the methyl threitol **33a** (K_i = 5.5 μM).[43] It should be noted that the results obtained here support previous findings that pyrrolidine aza-sugars are good inhibitors of α-L-rhamnosidase[11, 43] (for example, L-swainsonine and DRAM, two of the most powerful known pyrrolidine inhibitors display K_i = 0.45 and 1.0 μM, respectively)[11] and typically much better than piperidine analogues of L-rhamnose,[6, 44] possibly by virtue of the ability of envelope conformations of pyrrolidines to mimic boat,[45] envelope,[46] or half chair[47] transition state conformations in the rhamnosidase mechanism.

The ethyl- (**33b**) and 4-methoxybenzyl- (**33f**) threitols also showed significant α-D-mannosidase inhibition (K_i = 15.1 and 16.7 μM, respectively). These inhibition levels compare well with one of the most potent α-D-mannosidase inhibitors, L-swainsonine (K_i = 9.5 μM towards same enzyme[48]). This α-D-mannosidase inhibition may be readily rationalized since the 6-deoxy derivative of D-mannose **35** is the enantiomer of L-rhamnose (**36**). Thus, our strategy of constructing and testing racemic series of azasugars also provides the correct stereochemistry to mimic D-mannose (**35**). This similar inhibition of enzymes that process enantiomeric sugar substrates by a racemate therefore provides rapid confirmation in general terms of the applicability of Fleet's "mirror-image" enzyme active site postulate,[11] and highlights the potential of our approach: features that successfully generate inhibitory potency in one series do so in enantiomeric series also.

The benefit of this strategy is yet more clearly emphasized by near parallel and complementary results in the erythritol family of aza-sugars **34**. These also inhibited two "mirror-image" enzymes: α-L-fucosidase and α-D-galactosidase. Indeed, *p*-methoxybenzyl erythritol **34f** with a K_i = 250 nM towards α-D-galactosidase displays the most potent inhibition of non-mammalian carbohydrate processing enzymes determined in this study, although this is still an order magnitude lower than the piperidine DGJ, the D-*galacto* analogue of DNJ (K_i = 16 nM[49]). This inhibition of the D,L galactosidase/fucosidase enzyme pair by erythritol family **34** is, as for the threitol family **33**, partially consistent with configurational mimicry of the *cis*-diol OH-3,4 unit of galactosidase/fucosidase by the *cis*-diol OH-2,3 unit of **34** (Figure 4). Consistent with these results, methyl erythritol aza-sugar **34a** has previously been shown to be a good inhibitor of α-L-fucosidase (K_i 2.0 μM),[22] although this activity is modest compared with some of the most potent α-L-fucosidase aza-sugar inhibitors known (for example, the piperidine DFJ, the L-*fuco* analogue of DNJ, displays a K_i of 0.029 μM towards the same enzyme[50]). Thus, again the Fleet mirror-image postulate correctly predicts the observed additional inhibition of α-galactosidase by this family of racemates. Interestingly, however, the relative configuration of C-5 in galactose/fucose is opposite to that of C-4 in **34**. Such inhibition by aza-sugars with apparently the opposite configuration at the carbon that mimics C-5 has been observed previously.[6] It should also be noted that threitols **33b**,**f** also inhibit α-L-fucosidase perhaps through mimicry of the C-2,C-3 unit of **37**.

The inhibition pattern of threitol **33** and erythritol **34** aza-sugars towards human glycosidases largely followed that towards non-mammalian in that a moderate and broad inhibition of β-D-glucosidase, both lysosomal and non-lysosomal, was observed. The broad nature of this inhibition for both diastereomeric inhibitor families suggests an inhibitory mode that does not depend on functional or configurational mimicry. The complete lack of α- or β-D-galactosidase inhibition observed for **33** also mirrors that observed for non-mammalian glycosidase inhibition.

As Table 4 shows, some interesting inhibitory potency was observed towards glucosylceramide synthase (GCS). All three threitols **33b,d,f** showed fair levels of inhibition at 50 μM (26.5–48.1%). The most potent ethyl threitol **33b** in fact showed an IC_{50} (52 μM) that is within an order of magnitude of that for the Gaucher disease drug candidate *N*-butyl deoxynojirimycin (NB-DNJ or Zavesca), which has an in vitro IC_{50} = 20.4 μM.[3,51] This inhibitory activity may have its origin in a number of potential modes of mimicry (Figure 4): a) the *trans* OH-2,3 diol unit of **33** may mimic the trans diol units found at OH-2,3 or OH-3,4 in the D-glucoside unit that is transferred by GCS; or b) **33b** as a whole mimics the polar head (e.g. the 3-amino-3-deoxy-erythros-phingenine unit **39**) of the ceramide unit that is a glycosyl acceptor in the reaction catalyzed by GCS.[3, 52] These stereospecific, potential modes of action are strongly supported by the complete lack of inhibition shown by the diastereomeric erythritols **34b**, **d**, **f**.

It should be noted that in the quest[53, 54] for more selective, improved profile GCS inhibitors that display low α-glucosidase inhibition, **33b** with its complete lack of inhibition of human α-glucosidase at 1 mM and $IC_{50} = 52\,\mu M$ towards GCS makes for a good potential lead.

Conclusion

Highly diastereoselective additions of Grignard reagents to cyclic imines **2**–**4** has provided a ready route to novel aza-sugars with hydrophobic substituents. Optimization has accessed yields obtained for these additions that are some of the best reported for additions of organometallics to cyclic imines. This ready methodology lends itself to the easy and general introduction of substituents to an aza-sugar scaffold, and in this way a wide variety of substituents could be added to yield products that are potential enzyme inhibitors. As such, valuable information can be obtained on the mechanism of action of enzymes that process sugars as their substrates by investigating enzyme inhibition as a function of the substituents on an aza-sugar scaffold to create structure–activity relationships.

In this way we have generated aza-sugars as potential inhibitors based on a designed pyrrolidine scaffold with systematic variations in hydrophobic substituent and stereochemistry and screened them against a diverse panel of 12 carbohydrate-processing enzymes. This has revealed good inhibitors of α-L-rhamnosidase and α-D-mannosidase, with K_i values in the range 3.0–16.7 μM for the iminothreitol aza-sugars **33**, and relatively potent α-L-fucosidase and α-D-galactosidase inhibition, with K_i values in the range 250 nM–9.0 μM for the iminoerythritol aza-sugars **34**. It has also identified **33b** as a novel and selective inhibitor of the Gaucher disease therapeutic target enzyme GCS. The observation of parallel patterns of inhibition in enzymes that process enantiomeric sugar substrates also offers some confirmation of Fleet's mirror-image active site postulate[11] and highlights the value of this strategy, in the absence of other sources of 3D information for target active sites for generating nanomolar inhibitors such as **34f**.

Experimental Section

General: ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Varian Gemini 200, Bruker DPX200, Unity 300, VXR 400, Bruker DPX400 or Varian Inova 500 NMR spectrometers at the frequencies indicated. Where indicated, NMR peak assignments were made using COSY, DEPT, HETCOR or NOESY experiments; all others are subjective. All chemical shifts are quoted on the δ scale and were referenced to residual solvent as an internal standard. The following abbreviations are used to describe NMR multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; p, pseudo. IR spectra were recorded on a Perkin–Elmer Paragon 1000 Fourier Transform spectrophotometer. The following abbreviations are used to describe infrared absorption bands: br, broad; s, strong. Mass spectra were recorded by the Durham University and Dyson Perrins mass spectrometry services using electron impact (EI), chemical ionisation (CI), atmospheric pressure chemical ionisation (APCI), field ionization (FI) or electrospray ionisation (ES) techniques on Micromass LCT, Micromass GCT, Micromass AutoSpec-oaTof, Micromass Platform and VG Platform mass spectrometers; exact mass measurements were performed by the Dyson Perrins mass spectrometry service on a Walters 2790-Micromass LCT electrospray ionization mass spectrometer, and the EPSRC mass spectrometry service at Swansea, UK. Melting points were recorded using a Cambridge Instruments Gallen III Kofler Block melting apparatus and are uncorrected. Elemental analyses were performed by the Durham University microanalysis service and the Oxford University Inorganic Chemistry Laboratory microanalysis service. Thin-layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel $60F_{254}$ (Merck, 1.05554). Plates were developed using a phosphomolybdic acid or potassium permanganate dip. Flash column chromatography was performed using silica gel (Fluorochem, 60A, 40–63 micron). Solvents were dried immediately prior to use according to standard procedures: diethyl ether and tetrahydrofuran were distilled under N_2 over Na, dichloromethane was distilled under N_2 from CaH_2. All solvents were removed by evaporation under reduced pressure. All aqueous solutions were saturated unless otherwise stated. For convenience, aza-C-glycoside imine adduct products have been named based upon the threitol or erythritol scaffold from which they were derived; stereochemistry at the newly derived centre is indicated using the α/β carbohydrate convention.

1-Carboxybenzyl-3-pyrroline:[55] Benzyl chloroformate (1.33 mL, 9.4 mmol, 1.3 equiv) was added to a cooled (5 °C) stirred mixture of 3-pyrroline (**6**; 97%, 0.50 g, 7.24 mmol, 1.0 equiv) in toluene (13 mL) and 3 M NaOH (9 mL). After 1 h TLC (EtOAc/hexane 1:1) showed consumption of SM. The layers were separated and the organic layer was washed with distilled water (2×10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow oil (1.59 g). This crude product was purified by flash column chromatography on silica gel (EtOAc/hexane 3:7) to yield 1-carboxybenzyl-3-pyrroline as a pale yellow oil (1.37 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.20$ (m, 4H; $2 \times CH_2N$), 5.17 (s, 2H; PhCH_2), 5.79 (m, 2H; $2 \times$ C=CH), 7.36 (m, 5H; C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 52.8$, 53.3 (CH_2N), 66.7 (PhCH_2O), 112.4 (=CH), 128.3, 128.2, 127.8 (aromatic CH), 136.8 (quaternary aromatic C), 154.6 (C=O); IR (film): $\tilde{\nu} = 3064$, 3032 cm^{-1} (aromatic C-H), 2952, 2862 (aliphatic C-H), 1707 (C=O), 1623 (C=C); MS (ES): m/z (%): 240 (100), 226 (35) [M^++Na], 91 (48) [$C_6H_5CH_2^+$].

1-Carboxybenzyl-3,4-epoxy-pyrrolidine (7):[56] *m*CPBA (57–86%, 0.95 g) in CH_2Cl_2 (8 mL) was added a solution of to 1-carboxybenzyl-3-pyrroline (500 mg, 2.46 mmol) in dry CH_2Cl_2 (10 mL). The mixture was left to stir under N_2. After 19 h, TLC (Et_2O/hexane 1:1) showed that SM still remained. A second portion of *m*CPBA (0.95 g) in CH_2Cl_2 (6 mL) was then added. After a total of 23 h, TLC (Et_2O/hexane 1:1) showed consumption of SM and formation of a major product (R_f 0.5). The solvent was removed under reduced pressure, and the resultant white solid dissolved in Et_2O (30 mL) and washed with aqueous $NaHCO_3$ (6×20 mL) followed by brine (2×20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The resultant white solid (0.84 g) was purified by flash column chromatography (EtOAc/hexane 1:1) to give **7** as a colourless oil (249 mg, 46%). ^{1}H and ^{13}C NMR spectra show inequivalent CH_2N resonances that are consistent with a restricted rotation of the Cbz-N bond. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.38$ (dd, ^2J(H,H) = 12.7, ^3J(H,H) = 6.3 Hz, 1H; 1 of C*H*H′N), 3.39 (dd, ^2J(H,H) = 12.8, ^3J(H,H) = 6.4 Hz, 1H; 1 of C*H*H′N), 3.68 (m, 2H; $2 \times$ OCH), 3.84 (d, ^2J(H,H) = 12.7 Hz, 1H; 1 of CH*H*′N), 3.89 (d, ^2J(H,H) = 12.8 Hz, 1H; 1 of CH*H*′N), 5.11 (s, 2H; PhCH_2), 7.34 (m, 5H; C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 47.1$, 47.3 ($2 \times$ OCH), 54.9, 55.5 ($2 \times CH_2N$), 66.9 (PhCH_2O), 127.9, 128.0,128.4 ($3 \times$ aromatic CH), 136.5 (quaternary aromatic C), 155.2 (C=O); IR (film): $\tilde{\nu} =$ 3062, 3034 cm^{-1} (aromatic C-H), 2945, 2875 (aliphatic C-H), 1705 (C=O); MS (EI): m/z (%): 219 (91) [M^+], 91 (100) [$C_6H_5CH_2^+$]; HRMS (EI): m/z: calcd for $C_{12}H_{13}NO_3$: 219.0895; found: 219.0898 [M^+].

***N*-Carboxybenzyl-1,4-dideoxy-1,4-iminothreitol (8)**:[47] *N*-Carboxybenzyl-2,3-epoxy-1,4-dideoxy-1,4-imino-threitol (**7**; 52 mg, 0.24 mmol) was dissolved in 2 M aqueous H_2SO_4 (4 mL) and Et_2O (4 mL). This resulting solution was left to stir under argon at room temperature. After 21 h, TLC (EtOAc) showed consumption of SM (R_f 0.7) and formation of a major product (R_f 0.25). Et_2O (4 mL) was added and the layers separated. The organic layer was dried ($MgSO_4$) and concentrated under reduced to give a yellow oil (17 mg). The aqueous layer was extracted with EtOAc (6 mL), and the organic extract dried ($MgSO_4$) and concentrated under reduced pressure to give a colourless oil (33 mg). Both products were shown by ^{1}H NMR to be the diol **8** (50 mg in total, 88%). ^{1}H and ^{13}C NMR spectra

show inequivalent CH_2N resonances that are consistent with a restricted rotation of the Cbz-N bond. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.36$ (dd, $^2J(H,H) = 11.6$, $^3J(H,H) = 6.0$ Hz, 2H; 2 × CH*H*′N), 3.62 (br dd, $^2J(H,H) = 11.6$, $^3J(H,H) = 2.8$ Hz, 2H; 2 × C*H*H′N), 4.06 (m, 2H; 2 × C*H*OH), 4.24 (br s, 2H; 2 × OH), 5.05 (s, 2H; PhCH_2), 7.30 (m, 5H; C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 51.3$, 51.7 (2 × CH_2N), 67.2 (Ph*C*H_2O), 74.4, 75.0 (2 × CHOH), 127.7, 128.0,128.4 (3 × aromatic CH), 136.2 (quaternary aromatic C), 155.6 (C=O); IR (film): $\tilde{\nu} = 3402$ cm^{-1} (br, O-H), 3065, 3033 (aromatic C-H), 2945, 2887 (aliphatic C-H), 1677 (s, C=O); MS (EI): *m*/*z* (%): 237 (9) [M^+], 91 (100) [$C_6H_5CH_2^+$]; HRMS (EI): *m*/*z*: calcd for $C_{12}H_{15}NO_4$: 237.1001; found: 237.1006 [M^+].

***N*-Carboxybenzyl-2,3-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-threitol**: *tert*-Butyldimethylsilyl trifluoromethanesulphonate (4.35 mL, 5.01 g, 19.0 mmol, 3.0 equiv) was added at 0 °C to a solution of **8** (1.50 g, 6.32 mmol) in dry pyridine (3.70 mL, 3.00 g, 37.9 mmol, 6.0 equiv) and dry CH_2Cl_2 (90 mL). The reaction mixture was stirred under N_2. After 75 min TLC (EtOAc) showed consumption of SM and TLC (EtOAc/hexane 1:4) showed formation of a major product (R_f 0.6). The reaction mixture was washed with distilled water (30 mL) followed by 1M aqueous HCl (30 mL) and again by distilled water (30 mL). The aqueous extracts were back-extracted with CH_2Cl_2 (30 mL) and the combined organic layers dried ($MgSO_4$) and concentrated under reduced pressure to yield a yellow oil (3.50 g). The crude product was purified by flash column chromatography on silica gel (Et_2O/hexane 3:17) to yield *N*-carboxybenzyl-2,3-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-threitol as a pale yellow oil (2.70 g, 92%). ^{1}H and ^{13}C NMR spectra show inequivalent CH_2N resonances that are consistent with a restricted rotation of the Cbz-N bond. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.05$, 0.06 (2s, 2 × 6H; 2 × $Si(CH_3)_2$), 0.86, 0.86 (2s, 2 × 9H; 2 × $SiC(CH_3)_3$), 3.28 (d, $^2J(H,H) = 11.6$ Hz, 1H; C*H*H′N), 3.32 (d, $^2J(H,H) = 11.7$ Hz, 1H; CH*H*′N), 3.57 (dd, $^2J(H,H) = 11.2$, $^3J(H,H) = 3.4$ Hz, 1H; C*H*″H‴N), 3.62 (dd, $^2J(H,H) = 11.2$, $^3J(H,H) = 3.5$ Hz, 1H; CH″*H*‴N), 5.15 (s, 2H; PhCH_2), 3.98 (m, 2H; 2 × CHOSi), 7.36 (m, 5H; $C_6H_5CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.8$, −4.9 (2 × $OSi(CH_3)_2$), 17.8, 17.9 ($SiC(CH_3)_3$), 25.6, 25.7 (2 × $SiC(CH_3)_3$), 52.0, 52.3 (CH_2N), 66.6 (Ph*C*H_2O), 75.7, 76.4 (CHOSi), 127.6, 127.7, 128.3 (aromatic CH), 137.2 (quaternary aromatic C), 155.2 (C=O); IR (film): $\tilde{\nu} = 2929$, 2857 cm^{-1} (aliphatic C-H), 1712 (s, C=O); MS (ES): *m*/*z* (%): 488 (100) [M^++Na], 466 (10) [M^++H]; HRMS (ES): *m*/*z*: calcd for $C_{24}H_{44}NO_4Si_2$: 466.2809; found: 466.2803 [M^+].

2,3-*O*-*tert*-Butyldimethylsilyl-1,4-dideoxy-1,4-iminothreitol (9)[57]

Method i): Pd/C (10% wt Pd, 20 mg) was added to a solution of *N*-carboxybenzyl-2,3-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-threitol (149 mg, 0.32 mmol) in dry MeOH (5 mL). The reaction mixture was stirred under an atmosphere of H_2. After 3 h, TLC (EtOAc/hexane 1:4) showed consumption of SM. The mixture was filtered through a glass sinter and the solvent removed under reduced pressure to yield **9** as a colourless oil (98 mg, 92%).

Method ii): Pd/C (600 mg) was added to a solution of *N*-benzyl-2,3-*O*-di-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-threitol (4.95 g, 11.7 mmol) in MeOH (70 mL). The reaction mixture was stirred under an atmosphere of H_2. After 17 h the reaction was monitored by TLC (EtOAc/hexane 1:4). Some product formation was evident but SM (R_f 0.75) still remained. A further portion of palladium on activated carbon was added (1.00 g) and the H_2 atmosphere replenished. After a total of 20 h stirring TLC (EtOAc/hexane 1:4) showed consumption of SM. The reaction mixture was filtered through Celite and the solvent removed by evaporation to yield **9** as a colourless oil (3.85 g, 99%). Compound **9** was found to be a somewhat unstable to purification on silica gel as reported in the literature[57b] so was used without further purification in the following reactions. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.03$, 0.04 (2s, 2 × 6H; $OSi(CH_3)_2$), 0.85 (s, 18H; 2 × $SiC(CH_3)_3$), 2.77 (d, $^2J(H,H) = 12.0$ Hz, 2H; 2 × C*H*H′N), 3.16 (dd, $^2J(H,H) = 11.8$, $^3J(H,H) = 3.8$ Hz, 2H; 2 × CH*H*′N), 3.97 (m, 2H; 2 × CHOSi), 5.33 (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.8$ ($OSi(CH_3)_2$), 17.9 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 53.1 (CH_2N), 78.5 (CHOSi); IR (film): $\tilde{\nu} = 3304$ cm^{-1} (br, N-H), 2954, 2929, 2887, 2857 (aliphatic C-H); MS (ES): *m*/*z* (%): 332 (100) [M^++H]; HRMS (CI): *m*/*z*: calcd for $C_{24}H_{44}NO_4Si_2$: 332.2441; found: 332.2442 [M^++H].

***N*-Benzyl-2,3-*O*-di-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-iminothreitol-1,4-dione (13)**:[58b] A mixture of (±)-tartaric acid (9.0 g, 0.060 mol) and benzylamine (8.52 mL, 0.078 mmol, 1.3 equiv) in *p*-xylene (150 mL) was heated at reflux and passed through a dropping funnel packed with 4 Å molecular sieves in order to remove water formed for 19 h. The mixture was allowed to cool and then cooled to ice-bath temperature. The resulting orange precipitate was recrystallised from EtOAc, then filtered and washed with EtOAc to yield the crude hydroxyimide **12** as white crystals (10.1 g).

TBDMS-Cl (20.3 g, 0.135 mol, 3.0 equiv) was added as a solution in dry dimethylformamide (100 mL) under N_2 to a solution of **12** (10.0 g, 0.045 mol) and imidazole (15.3 g, 0.225 mol, 5.0 equiv) in dry dimethylformamide (100 mL). The reaction mixture was stirred for 21 h; dimethylformamide was then removed by evaporation under reduced pressure to yield a pale yellow oily solid. This residue was dissolved in $CHCl_3$ (200 mL) and washed with 1M HCl (3 × 50 mL) followed by water (3 × 50 mL). The aqueous layers were extracted with $CHCl_3$ (2 × 50 mL) and the combined organic layers dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield a yellow oil (20.5 g). The crude product was purified by flash column chromatography on silica gel (EtOAc/hexane 1:10) to yield pure **13** as a white solid (11.4 g, 43% from tartaric acid). M.p. 76.5–77.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.16$, 0.22 (2s, 2 × 6H; 2 × $Si(CH_3)_2$), 0.94 (s, 18H; 2 × $SiC(CH_3)_3$), 4.47 (s, 2H; 2 × CHOSi), 4.62 (s, 2H; PhCH_2), 7.30–7.40 (m, 5H; C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.5$, −5.1 (2 × $Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 42.3 (CH_2Ph), 76.9 (CHOSi), 128.0, 128.7, 129.0 (aromatic CH), 135.3 (quaternary aromatic C), 173.0 (C=O); IR (film): $\tilde{\nu} = 2956$, 2930, 2893, 2857 cm^{-1} (aliphatic C-H), 1716 (C=O); MS (ES): *m*/*z* (%): 472 (100) [M^++Na]; HRMS (CI): *m*/*z*: calcd for $C_{23}H_{43}N_2O_4Si_2$: 467.2761; found: 467.2768 [M^++NH_4]; elemental analysis calcd (%) for $C_{23}H_{39}NO_4Si_2$: C 61.42, H 8.74, N 3.11; found: C 61.26, H 8.86, N 3.05.

***N*-Benzyl-2,3-*O*-di-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-iminothreitol**:[57a] Borane dimethylsulfide (9.04 mL, 7.24 g, 95.3 mmol, 7.5 equiv) was added under N_2 to a solution of **13** (5.70 g, 12.7 mmol) in dry THF (90 mL). After 24 h stirring at RT the reaction was monitored by crude NMR. A little SM appeared to remain, so a further portion of borane dimethylsulfide (3.01 mL, 2.41 g, 31.8 mmol, 2.5 equiv) was added. After a further 6 h stirring, crude NMR and TLC (EtOAc/toluene 5:95) showed the conversion of SM (R_f 0.7) to product (R_f 0.75). The excess borane dimethylsulphide was carefully quenched with MeOH until no further effervescence was observed and the solvent removed to yield borazine product. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.01$, 0.03 (2s, 2 × 3H; 2 × $SiCH_3$), 0.12 (s, 6H; $Si(CH_3)_2$), 0.88, 0.93 (2s, 2 × 9H; 2 × $SiC(CH_3)_3$), 3.07 (dd, $^2J(H,H) = 12.6$, $^3J(H,H) = 7.0$ Hz, 1H; 1 of C*H*H′N), 3.09 (dd, $^2J(H,H) = 12.3$, $^3J(H,H) = 5.0$ Hz, 1H; 1 of C*H*H′N), 3.39 (dd, $^2J(H,H) = 12.3$, $^3J(H,H) = 6.7$ Hz, 1H; 1 of CH*H*′N), 3.48 (dd, $^2J(H,H) = 12.3$, $^3J(H,H) = 6.5$ Hz, 1H; 1 of CH*H*′N), 3.91 (ptd, $^3J(H,H) = 6.8$, $^3J(H,H) = 4.2$ Hz, 1H; 1 of CHOSi), 4.11 (s, 2H; CH_2Ph), 4.32 (ptd, $^3J(H,H) = 6.0$, $^3J(H,H) = 4.5$ Hz, 1H; 1 of CHOSi), 7.36–7.56 (m, 5H; C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.9$, −4.8 ($SiCH_3$), 17.8, 17.9 ($SiC(CH_3)$), 25.6, 25.8 ($SiC(CH_3)$), 64.3, 64.6, 67.3 (CH_2Ph, 2 × CH_2N), 78.0, 78.4 (2 × CHOSi), 128.1, 129.0, 132.7 (aromatic C). The solvent was removed under reduced pressure and the residue was repeatedly dissolved in MeOH followed by removal of the solvent under reduced pressure (3 × 50 mL). The residue was then dissolved in MeOH (90 mL), heated to 40 °C and left to stir for 20 h. The reaction mixture was concentrated under reduced pressure to yield a colourless oil (5.35 g, 100%). This product was concordant with pure *N*-benzyl-2,3-*O*-di-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-threitol and no further purification was required. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.05$, 0.07 (2s, 2 × 6H; 2 × $Si(CH_3)_2$), 0.90 (s, 18H; 2 × $SiC(CH_3)_3$), 2.47 (dd, $^2J(H,H) = 9.8$, $^3J(H,H) = 4.6$ Hz, 2H; 2 × C*H*H′N), 2.88 (dd, $^2J(H,H) = 9.8$, $^3J(H,H) = 6.0$ Hz, 2H; 2 × CH*H*′N), 3.52 (d, $^2J(H,H) = 13.2$ Hz, 1H; 1 of CHOSi), 3.74 (d, $^2J(H,H) = 13.2$ Hz, 1H; 1 of CHOSi), 4.13 (m, 2H; PhCH_2), 7.33–7.32 (m, 5H; C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.6$, −4.7 (2 × $OSi(CH_3)_2$), 18.0 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 60.7, 60.7 (CH_2N and PhCH_2), 79.8 (CHOSi), 126.8, 128.1, 128.6 (3 × aromatic CH), 135.3 (quaternary aromatic C); IR (film): $\tilde{\nu} =$ 3063, 3028 cm^{-1} (aromatic C-H), 2954, 2929, 2857 (aliphatic C-H); HRMS (CI): *m*/*z*: calcd for $C_{23}H_{44}NO_2Si_2$: 422.2910; found: 422.2911 [M^++H].

***N*-Chloro-2,3-*O*-di-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-iminothreitol (10)**:[57a] *N*-Chlorosuccinimide (266 mg, 1.99 mmol, 1.1 equiv) was added to a solution of **9** (600 mg, 1.81 mmol) in dry Et_2O (30 mL). The reaction mixture was stirred under N_2. After 4.5 h stirring TLC (EtOAc/hexane 1:4) showed the formation of a major product (R_f 0.8). The reaction mixture was diluted with Et_2O (30 mL) and washed with water (3 × 20 mL). The

aqueous extracts were extracted with Et_2O (2 × 20 mL) and the combined organic extracts dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield **10** as a pale yellow oil (640 mg, 96%). Compound **10** was unstable to purification on silica gel so it was used without further purification in the following reactions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05, 0.06 (2s, 2 × 6H; 2 × OSi(CH_3)$_2$), 0.87, 0.87 (2s, 2 × 9H; 2 × SiC(CH_3)$_3$), 3.06 (dd, ^2J(H,H) = 10.2, ^3J(H,H) = 5.9 Hz, 2H; 2 × C*H*H′N), 3.48 (dd, ^2J(H,H) = 10.2, ^3J(H,H) = 4.7 Hz, 2H; 2 × CH*H*′N), 4.11 (m, 2H; 2 × CHO[Si]); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.7, −4.9 (2 × O-Si(CH_3)$_2$), 17.9 (Si*C*(CH_3)$_3$), 25.7 (SiC(*C*H_3)$_3$), 69.1 (CH_2N), 79.0 (CHOSi); IR (film): $\tilde{\nu}$ = 2955, 2930, 2857 cm^{-1} (aliphatic C-H); HRMS (CI): *m*/*z*: calcd for $C_{16}H_{37}NO_2Si_2Cl$: 366.2051; found: 366.2067 [M^++H].

2,3-*O*-*tert*-Butyldimethylsilyl-1,4-dideoxy-1,4-imino-1,*N*-dehydrothreitol (2): DBU (0.027 mL, 27 mg, 0.18 mmol, 1.1 equiv) was added under N_2 to a solution of **10** (58 mg, 0.16 mmol) in dry Et_2O (5 mL). After 3 h the reaction mixture was filtered under Ar to remove DBU·HCl, then concentrated to yield as an orange oil (50 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = −0.02, −0.02 (2s, 2 × 3H; 2 × Si(CH_3)), 0.04 (s, 6H; Si(CH_3)$_2$), 0.80, 0.82 (2s, 2 × 9H; 2 × SiC(CH_3)$_3$), 3.47 (dddd, ^2J(H,H) = 15.8, ^3J(H,H) = 4.7, 2.4 Hz, 1.1 Hz, 1H; C*H*H′N), 3.97 (dddd, ^2J(H,H) = 16.0, ^3J(H,H) = 6.6, 2.2 Hz, 1.1 Hz, 1H; CH*H*′N), 4.10 (ddd, ^3J(H,H) = 6.5, 4.8 Hz, 3.9 Hz, 1H; NCH$_2$C*H*), 4.49 (br d, ^3J(H,H) = 4.0 Hz, 1H; N=CHC*H*), 7.41 (pt, ^3J(H,H) = 2.2 Hz, 1H; N=CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.9, −4.8, −4.7, −4.7 (4q, 4 × SiCH$_3$), 17.9, 18.0 (2s, 2 × Si*C*(CH_3)$_3$), 25.7, 25.7 (2q, 2 × SiC(*C*H_3)$_3$), 66.9 (t, NCH$_2$), 79.2 (d, NCH$_2$*C*H), 85.5 (d, N=CH*C*H), 168.4 (d, N=CH); IR (film): $\tilde{\nu}$ = 2928, 2856 cm^{-1} (aliphatic C-H), 1646 (C=N); HRMS (CI): *m*/*z*: calcd for $C_{16}H_{36}NO_2Si_2$: 330.2285; found: 330.2286 [M^++H].

2,3-*O*-Isopropylidene-L-erythrose (16):[27, 59] 2,2-Dimethoxypropane (27 mL, 22.9 g, 0.220 mmol, 3.3 equiv) was added to a solution of L-arabinose (**14**) (10.0 g, 0.067 mol, 1.0 equiv) and *p*-toluenesulphonic acid monohydrate (150 mg, 0.8 mmol, 0.01 equiv) in dimethylformamide (130 mL). The resulting solution was stirred for 2 h. and then neutralized by the addition of solid sodium carbonate and concentrated under reduced pressure. The residue was partitioned between water (120 mL) and 40–60 °C petroleum ether (60 mL). To the aqueous layer was then added sodium periodate (35.6 g, 0.166 mol, 2.5 equiv) portionwise, and the mixture stirred for 2 h. Solid sodium carbonate was added and the slurry was stirred for 1 h. Water was then added (80 mL) and the aqueous layer was extracted with EtOAc (3 × 80 mL), and the combined organic extracts concentrated under reduced pressure to yield a pale yellow oil (10.9 g). This residue was then dissolved in CH_2Cl_2 (80 mL) and washed with water (2 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield a pale yellow oil (7.2 g). The organic extracts from CH_2Cl_2 were not found to be purer by ^{1}H NMR than the original EtOAc extracts, although the mass was significantly reduced. Therefore the aqueous layers from the CH_2Cl_2 extraction were back-extracted with EtOAc and concentrated and all the organic extracts combined to give a yellow oil (8.2 g). This crude product was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 7:13) to yield pure **16** (6.05 g, 57% from L-arabinose) as a mixture of anomers (α:β 1:6). $[\alpha]^{25}_{D,\ eqlbm}$ = +75.0 (c = 0.1 in $CHCl_3$) {lit.:[27] $[\alpha]_D$ = +66.3 (c = 2.7 in $CHCl_3$); lit.:[59] $[\alpha]_D$ = +83.2 (c = 4.36 in EtOAc)}; α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36, 1.53 (2s, 2 × 3H; C(CH_3)$_2$), 2.09 (br s, 1H; OH), 3.53 (dd, ^2J(H,H) = 11.1, ^3J(H,H) = 3.7 Hz, 1H; C*H*H′), 3.96 (d, ^2J(H,H) = 11.6 Hz, 1H; CH*H*′), 4.47 (dd, ^3J(H,H) = 6.2, ^3J(H,H) = 3.6 Hz, 1H; CH$_2$C*H*), 4.74 (dd, ^3J(H,H) = 6.2, ^3J(H,H) = 3.7 Hz, 1H; CHOHC*H*), 4.98 (s, 1H; C*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ = 24.8, 25.9 (2q, C(*C*H_3)$_2$), 67.5 (t, *C*H$_2$), 78.2, 79.5 (2d, 2 × *C*HO-), 97.4 (d, *C*HOH), 113.4 (s, *C*(CH_3)$_2$); β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30, 1.45 (2s, 3H; C(CH_3)$_2$), 3.61 (br s, 1H; OH), 3.99 (d, ^2J(H,H) = 10.4 Hz, 1H; C*H*H′), 4.05 (dd, ^2J(H,H) = 10.4, ^3J(H,H) = 3.5 Hz, 1H; CH*H*′), 4.55 (d, ^3J(H,H) = 5.9 Hz, 1H; CHOHC*H*), 4.82 (dd, ^3J(H,H) = 5.9, ^3J(H,H) = 3.5 Hz, 1H; CH$_2$C*H*), 5.39 (s, 1H; C*H*OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.6, 26.1 (2q, 2 × C(*C*H_3)), 71.8 (t, CH$_2$), 79.9 (d, CH$_2$*C*H), 85.1 (d, CHOH*C*H), 101.6 (d, CHOH), 112.2 (s, *C*(CH_3)$_2$); IR (film): $\tilde{\nu}$ = 3426 cm^{-1} (br, O-H stretch), 2987, 2943, 2882 (aliphatic C-H stretch), 1460; HRMS (CI): *m*/*z*: calcd for $C_7H_{16}NO_4$: 178.1083; found: 178.1079 [M^++NH$_4$].

2,3-*O*-Isopropylidene-erythritol (17):[28] Sodium borohydride (47 mg, 1.24 mmol, 2.0 equiv) was added under Ar to a solution of **16** (100 mg, 0.62 mmol) in MeOH (4 mL). The reaction mixture was stirred for 1.5 h, whereupon TLC (EtOAc/cyclohexane 7:3) showed consumption of starting material (R_f 0.5). Solid ammonium chloride was added to quench excess borohydride and then the mixture was concentrated to yield a white solid. This crude product was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 13:7 increasing to 3:1 then 17:3) to yield pure **17** as an oily white solid (100 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36, 1.45 (2s, 2 × 3H; C(CH_3)$_2$), 3.28 (t, ^3J(H,H) = 5.9 Hz, 2H; 2 × OH), 3.77 (m, 4H; 2 × C*H*$_2$OH), 4.28 (m, 2H; 2 × CH$_2$C*H*); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ = 25.0, 27.5 (2q, C(*C*H_3)$_2$), 60.6 (t, *C*H$_2$OH), 76.9 (d, *C*H), 108.4 (s, *C*(CH_3)$_2$); IR (film): $\tilde{\nu}$ = 3398 cm^{-1} (br, O-H stretch), 2987, 2938 (aliphatic C-H stretch), 1457; HRMS (CI): *m*/*z*: calcd for $C_7H_{15}O_4$: 163.0970; found: 163.0970 [M^++H].

2,3-*O*-Isopropylidene-1,4-di-*O*-methanesulfonylerythritol (18):[28] Methanesulfonyl chloride (0.16 mL, 238 mg, 2.08 mmol, 4.0 equiv) was added under Ar at 0 °C to a solution of **17** (85 mg, 0.52 mmol, 1.0 equiv) and triethylamine (0.29 mL, 210 mg, 2.08 mmol, 4.0 equiv) in dry CH_2Cl_2 (3.5 mL). After 1 h TLC (Et_2O) showed consumption of starting material (R_f 0.2) and formation of a major product (R_f 0.25). The reaction mixture was poured into ice-water (20 mL) and diluted with CH_2Cl_2 (30 mL). The layers were separated and the organic phase washed with 1M HCl (10 mL) followed by $NaHCO_3$(aq) (10 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield a pale yellow oil (202 mg). This crude product was purified by flash column chromatography on silica gel (Et_2O) to yield pure **18** as a white solid (120 mg, 72%). M.p. 91–92 °C {lit.:[28] m.p. 92–93 °C}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38, 1.49 (2s, 2 × 3H; C(CH_3)$_2$), 3.09 (s, 6H; 2 × OSO$_2$CH$_3$), 4.33 (m, 4H; 2 × C*H*$_2$OMs), 4.48 (m, 2H; 2 × CH$_2$C*H*); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ = 25.4, 27.4 (2q, C(*C*H_3)$_2$), 37.7 (q, OSO$_2$CH$_3$), 66.5 (t, CH$_2$OMs), 74.1 (d, CH), 110.1 (s, *C*(CH_3)$_2$); IR (KBr disc): $\tilde{\nu}$ = 3023, 2979, 2942 cm^{-1} (aliphatic C-H stretch), 1352, 1172; MS (APCI): *m*/*z* (%): 319 (100) [M^++H]; HRMS (CI): *m*/*z*: calcd for $C_9H_{19}O_8S_2$: 319.0521; found: 319.0519 [M^++H]; elemental analysis calcd (%) for $C_9H_{18}O_8S_2$: C 33.95, H 5.70; found: C 33.87, H 5.73.

***N*-Benzyl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (19)**:[28] Benzylamine (3.0 mL) was added under Ar to **18** (200 mg, 0.63 mmol). The mixture was stirred at 65 °C for 24 h. The reaction was monitored by mass spectrometry (APCI), which showed consumption of SM and formation of the desired pyrrolidine (*m*/*z* 234 [M^++H]). The reaction mixture was diluted with EtOAc (30 mL) and washed with brine (10 mL) followed by water (10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated to yield a yellow oil. *p*-Xylene was then added and the mixture concentrated (3 × 20 mL) to remove excess benzylamine as its azeotrope with xylene. This crude product was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 1:4) to yield pure **19** as a colourless oil (112 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34, 1.59 (2s, 2 × 3H; C(CH_3)$_2$), 2.15 (ddd, ^2J(H,H) = 11.6, ^3J(H,H) = 3.0, ^3J(H,H) = 1.4 Hz, 2H; 2 × C*H*H′N), 3.05 (d, ^2J(H,H) = 11.5 Hz, 2H; 2 × CH*H*′N), 3.63 (s, 2H; C*H*$_2$Ph), 4.66 (m, 2H; 2 × OCH), 7.22–7.36 (m, 5H; C$_6$H$_5$); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ = 25.1, 26.5, (2q, C(*C*H_3)$_2$), 59.2, 59.7 (2t, PhCH$_2$ and *C*H$_2$N), 79.6 (d, OCH), 111.2 (s, *C*(CH_3)$_2$), 126.9, 128.2, 128.5 (3d, 3 × aromatic CH), 138.6 (s, quaternary aromatic C); IR (film): $\tilde{\nu}$ = 3028 cm^{-1} (aromatic C-H stretch), 2985, 2935, 2788 (aliphatic C-H stretch), 1454, 1379; HRMS (CI): *m*/*z*: calcd for $C_{14}H_{20}NO_2$: 234.1494; found: 234.1495 [M^++H].

2,3-*O*-Isopropylidene-1,4-dideoxy-1,4-iminoerythritol (20):[28] Pd(OH)$_2$/C (20% Pd, 80 mg) was added to a solution of **19** (283 mg, 1.21 mmol) in MeOH (5.0 mL) and the reaction mixture placed under an atmosphere of H_2. After 21 h TLC (EtOAc/cyclohexane 3:2) showed consumption of SM (R_f 0.6). The reaction mixture was filtered through celite to remove Pd(OH)$_2$ on C, then the filtrate concentrated under reduced pressure to yield **20** as a pale yellow oil (170 mg, 98%). (The product was found to be relatively volatile so when removing the solvent the pressure was not reduced below 60 mbar at 25 °C.) It was found to be unstable to purification on silica gel, but was sufficiently pure not to require further purification for the following reactions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29, 1.43 (2s, 2 × 3H; C(CH_3)$_2$), 2.47 (br s, 1H; NH), 2.51 (d, ^2J(H,H) = 13.6 Hz, 2H; 2 × C*H*H′N), 3.08 (d, ^2J(H,H) = 13.9 Hz, 2H; 2 × CH*H*′N), 4.65 (m, 2H, 2 × OCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7, 25.9 (2q, C(*C*H_3)$_2$), 54.1 (CH$_2$N), 81.4 (OCH), 110.2 (*C*(CH_3)$_2$); IR (film): $\tilde{\nu}$ = 3395 cm^{-1} (br, N-H stretch), 2935 (aliphatic C-H stretch), 1374; HRMS (CI): *m*/*z*: calcd for $C_7H_{14}NO_2$: 144.1025; found: 144.1026 [M^++H].

***N*-Chloro-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (21)**: *N*-Chlorosuccinimide, NCS (513 mg, 3.84 mmol, 1.1 equiv) was added under Ar to a solution of **20** (500 mg, 3.49 mmol) in dry Et_2O (50 mL). After 5 h TLC (EtOAc/cyclohexane 1:4) revealed consumption of SM and formation of a major product (R_f 0.3). The mixture was diluted with Et_2O (30 mL) and washed with water (3×20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford **21** as a pale yellow oil (532 mg, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.30$, 1.50 (2s, 2×3H; $C(CH_3)_2$), 2.84 (m, 2H; $2 \times CHH'N$), 3.62 (d, $^2J(H,H) = 11.2$ Hz, 2H; $2 \times CHH'N$), 4.71 (m, 2H; $2 \times OCH$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.5$, 26.0 ($C(CH_3)_2$), 67.2 (CH_2N), 78.3 (OCH), 111.6 ($C(CH_3)_2$); IR (KBr disc): $\tilde{\nu} = 2989$, 2840 cm^{-1} (aliphatic C-H stretch), 1464, 1382; HRMS (FI): *m*/*z*: calcd for $C_7H_{12}NO_2Cl$: 177.0557; found: 177.0558 [$M^{\cdot}$].

2,3-*O*-Isopropylidene-1,4-dideoxy-1,4-imino-1-*N*-dehydroerythritol (3): DBU (0.050 mL, 51 mg, 0.33 mmol, 1.1 equiv) was added under Ar to a solution of **21** (54 mg, 0.30 mmol) in dry Et_2O (3 mL). After 4 h TLC (EtOAc/cyclohexane 1:4) indicated conversion of SM (R_f 0.3) to a major product (R_f 0.1). The reaction mixture was filtered under Ar to remove DBU·HCl, and then concentrated to yield **3** as a yellow oily solid (43 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.22$, 1.22 (2s, 2×3H; $C(CH_3)_2$), 3.79 (dddd, $^2J(H,H) = 17.3$, $^3J(H,H) = 4.6$ Hz, 2.9 Hz, 0.9 Hz, 1H; $CHH'N$); 3.94 (ddpt, $^2J(H,H) = 17.3$, $^3J(H,H) = 2.0$ Hz, 1.0 Hz, 1H; $CHH'N$), 4.58 (ddd, $^3J(H,H) = 5.5$ Hz, 4.6 Hz, 1.0 Hz, 1H; NCH_2CH), 4.92 (br d, $^3J(H,H) = 5.5$ Hz, 1H; N=CHCH), 7.44 (dd, $^3J(H,H) = 3.0$ Hz, 2.0 Hz, 1H; N=CH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.4$, 26.7 (2q, $2 \times C(CH_3)$), 66.3 (t, CH_2N), 76.3 (d, NCH_2CH), 86.5 (d, N=CCH), 111.4 (s, $C(CH_3)_2$), 165.5 (d, N=CH); IR (film): $\tilde{\nu} = 2935$, 2860 cm^{-1} (aliphatic C-H), 1649 (C=N); HRMS (CI): *m*/*z*: calcd for $C_7H_{12}NO_2$: 142.0868; found: 142.0867 [M^++H]. Attempts to purify the imine by aqueous washing or by chromatography on a short column of silica gel (30:70 Et_2O/petroleum ether (40-60) eluting with 1% Et_3N) both led to extensive degradation.

3,4-*O*-Cyclohexylidene-L-arabinose (22): Cyclohexanone dimethyl ketal (0.61 mL, 575 mg, 3.99 mmol, 3.0 equiv) was added to a solution of L-arabinose (**14**) (200 mg, 1.33 mmol, 1.0 equiv) and *p*-toluenesulphonic acid monohydrate (2.5 mg, 0.0133 mmol, 0.01 equiv) in dimethylformamide (DMF) (4 mL). After 4 h stirring, TLC (MeOH/$CHCl_3$ 1:9) showed formation of a major product (R_f 0.3). Ion-exchange resin was added (Dowex OH^- form, 550A, Aldrich) to neutralize the acid. The mixture was filtered, the residue washed with dry DMF, and the filtrate concentrated under reduced pressure to yield a syrupy residue. This crude product was purified by flash column chromatography on silica gel (MeOH/$CHCl_3$ 7:93 to yield **22** as a white solid (203 mg, 66%) as a mixture of anomers (α:β 1:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO, COSY): $\delta = 1.34$–1.65 (m, 10H; cyclohexylidene), 3.16 (m, 0.5H; H-2 α), 3.33 (m, 0.5H; H-2 β), 3.65 (dd, 0.5H; $^2J(H,H) = 13.5$, $^3J(H,H) = 2.9$ Hz, H-4′ α), 3.70 (d, 0.5H; $^2J(H,H) = 13.5$ Hz, H-4′ β), 3.86 (dd, 0.5H; $^3J(H,H) = 6.9$, $^3J(H,H) = 6.0$ Hz, H-3 α), 3.94–4.01 (m, 1.5H; H-3 β, H-5 α, H-5 β), 4.08 (m, 0.5H; H-4 α), 4.14 (m, 0.5H; H-4 β), 4.19 (dd, 0.5H; $^3J(H,H) = 7.4$, $^3J(H,H) = 6.6$ Hz, H-1 α), 4.83 (dd, 0.5H; $^3J(H,H) = 4.6$, $^3J(H,H) = 4.4$ Hz, H-1 β), 4.89 (d, 0.5H; $^3J(H,H) = 6.8$ Hz, 2-OH β), 5.12 (d, 0.5H; $^3J(H,H) = 5.0$ Hz, 2-OH α), 6.32 (d, 0.5H; $^3J(H,H) = 4.7$ Hz, 1-OH β), 6.60 (d, 0.5H; $^3J(H,H) = 6.4$ Hz, 1-OH α); ^{13}C NMR (100 MHz, [D$_6$]DMSO, DEPT, HMQC, HMBC): $\delta = 23.4$, 23.5, 23.7, 23.8, 24.6, 24.7, 35.1, 37.6, 37.7 (cyclohexylidene), 58.0 (t, C-5 β), 62.2 (t, C-5 α), 70.4 (d, C-2 β), 72.4 (d, C-4 β), 72.8 (d, C-4 α), 74.1 (d, C-2 α), 75.4 (d, C-3 β), 78.6 (d, C-3 α), 92.2 (d, C-1 β), 96.5 (d, C-1 α), 108.8 (s, C-6 α), 113.0 (s, C-6 β). IR (KBr disc): $\tilde{\nu} = 3382$, 3272 (br, O-H stretch), 2951, 2856, (aliphatic C-H stretch), 1450 cm^{-1}; HRMS (ES): *m*/*z*: calcd for $C_{11}H_{19}O_5$: 231.1232; found: 231.1238 [M^++H].

2,3-*O*-Cyclohexylidene-L-erythrose (23): Sodium periodate (320 mg, 1.49 mmol, 2.25 equiv) was added to a solution of **22** (151 mg, 0.66 mmol) in water (6 mL). The reaction mixture was stirred under Ar. After 2.5 h, solid sodium carbonate was added and the slurry stirred for 1 h. The mixture was then diluted with water (30 mL) and extracted with EtOAc (3×20 mL) followed by $CHCl_3$ (2×20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a colourless oil (127 mg). This crude product was purified by flash column chromatography (EtOAc/cyclohexane 35:65) to yield pure **23** as a white solid (113 mg, 86%), as a mixture of anomers (α:β 1:5). ^{1}H NMR (400 MHz, $CDCl_3$, COSY): $\delta = 1.37$–1.69 (m, 10H; cyclohexylidene), 2.01 (s, 0.17H; OH α), 3.29 (d, 0.83H; $^3J(H,H) = 2.5$ Hz, OH β), 3.54 (dd, 0.17H; $^2J(H,H) = 11.2$, $^3J(H,H) = 3.8$ Hz, H-4′ α), 3.98 (dd, 0.17H; $^2J(H,H) = 11.3$, $^3J(H,H) = 4.7$ Hz, H-4 α), 4.02 (d, 0.83H; $^2J(H,H) = 10.0$ Hz, H-4′ β), 4.06 (dd, 0.83H; $^2J(H,H) = 10.0$, $^3J(H,H) = 3.5$ Hz, H-4 β), 4.48 (dd, 0.17H; $^3J(H,H) = 6.2$, $^3J(H,H) = 3.6$ Hz, H-3 α), 4.56 (d, 0.83H; $^3J(H,H) = 6.0$ Hz, H-2 β), 4.75 (dd, 0.17H; $^3J(H,H) = 5.4$, $^3J(H,H) = 3.8$ Hz, H-2 α), 4.82 (dd, 0.83H; $^3J(H,H) = 5.8$, $^3J(H,H) = 3.5$ Hz, H-3 β), 4.99 (dd, 0.17H; $^2J(H,H) = 10.5$, $^3J(H,H) = 3.6$ Hz, H-1 α), 5.42 (s, 0.83H; H-1 β); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, HMQC): $\delta = 23.6$, 23.7, 24.0, 24.9, 25.0, 34.2, 34.4, 35.6, 35.9, (cyclohexylidene), 67.7 (t, C-4 α), 72.0 (t, C-4 β), 77.8 (d, C-2 α), 79.1 (d, C-3 α), 79.4 (d, C-3 β), 84.7 (d, C-2 β), 97.4 (d, C-1 α), 101.8 (d, C-1 β), 113.0 (s, C-5 β), 114.2 (s, C-5 α); IR (KBr disc): $\tilde{\nu} = 3370$ (br, O-H stretch), 2934, 2860 (aliphatic C-H stretch), 1451, 1372 cm^{-1}; HRMS (ES): *m*/*z*: calcd for $C_{10}H_{15}O_4$: 199.0970; found: 199.0974 [M^- – H]; elemental anlysis calcd (%) for $C_{10}H_{16}O_4$: C 59.98, H, 8.05; found: C 60.01, H 8.05.

2,3-*O*-Cyclohexylideneerythritol (24): Sodium borohydride (39 mg, 1.02 mmol, 2.0 equiv) was added under Ar to a solution of **23** (102 mg, 0.51 mmol) in MeOH (4 mL). The reaction mixture was stirred for 30 min, whereupon TLC (EtOAc/cyclohexane 3:1) showed consumption of starting material (R_f 0.7) and formation of a major product (R_f 0.5). Solid ammonium chloride was added to quench excess borohydride, and the mixture was concentrated to yield a white solid. This crude product was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 3:2) to yield pure **24** as an oily white solid (91 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.39$–1.63 (m, 10H; cyclohexylidene), 3.09 (t, 2H; $^3J(H,H) = 6.1$ Hz, $2 \times$ OH), 3.78 (m, 4H; H-1, H-1′, H-4, H-4′), 4.28 (m, 2H; H-2, H-3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): $\delta = 23.6$, 24.0, 25.0, 34.5, 37.4 (5t, cyclohexylidene), 60.8 (t, C-1, C-4), 76.5 (d, C-2, C-3), 109.0 (s, C-5); IR (film): $\tilde{\nu} = 3389$ (br, O-H stretch), 2936, 2862 (aliphatic C-H stretch), 1449, 1368 cm^{-1}; HRMS (ES): *m*/*z*: calcd for $C_{10}H_{17}O_4$: 201.1127; found: 201.1120 [M^- – H].

1-Benzyl-3,4-*O*-cyclohexylidene-1,4-dideoxy-1,4-iminoerythritol (26): Methanesulfonyl chloride (0.11 mL, 170 mg, 1.48 mmol, 4.0 equiv) was added under Ar at 0 °C to a solution of **24** (75 mg, 0.37 mmol, 1.0 equiv) and triethylamine (0.21 mL, 150 mg, 1.48 mmol, 4.0 equiv) in dry CH_2Cl_2 (3.0 mL). After 45 min, TLC (Et_2O) showed consumption of starting material (R_f 0.7) and formation of a major product (R_f 0.4). The reaction mixture was poured onto ice-water (20 mL) and diluted with CH_2Cl_2 (30 mL). The layers were separated and the organic layer washed with 1M HCl (aq) (10 mL), $NaHCO_3$ (aq) (10 mL) followed by water (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to yield a pale yellow oil (164 mg). This crude product was purified by flash column chromatography on silica gel (Et_2O) to yield pure **25** as a white solid (113 mg, 85%). HRMS (CI): *m*/*z*: calcd for $C_{12}H_{23}O_8S_2$: 359.0834; found: 359.0827 [M^++H].

Benzylamine (3.0 mL) was added under Ar to **25** (113 mg, 0.32 mmol). The mixture was stirred at 65 °C for 48 h. The reaction mixture was then allowed to cool and diluted with EtOAc (30 mL) then washed with brine (10 mL) followed by water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated to yield a yellow oil. Xylene was then added and the mixture concentrated (3×20 mL) to remove excess benzylamine as its azeotrope with xylene. This crude product was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 3:17) to yield pure **26** as a colourless oil (75 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$, COSY): $\delta = 1.41$, 1.57, 1.67, 1.84 (4m, 2H, 2H, 4H, 2H; cyclohexylidene), 2.16 (m, 2H; $2 \times CHH'N$), 3.05 (d, 2H; $^2J(H,H) = 11.4$ Hz, $2 \times CHH'N$), 3.63 (s, 2H, CH_2Ph), 4.65 (m, 2H; $2 \times OCH$), 7.22–7.37 (m, 5H; C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, HMQC): $\delta = 23.8$, 24.2, 25.2, 34.5, 36.1 (5t, cyclohexylidene). 59.3 (t, $PhCH_2$), 59.8 (t, CH_2N), 79.1 (d, OCH), 111.9 (s, $C(CH_2)_2$), 126.9, 128.2, 128.5 (3d, $3 \times$ aromatic CH), 138.7 (s, quaternary aromatic C); HRMS (CI): *m*/*z*: calcd for $C_{17}H_{24}NO_2$: 274.1807; found: 274.1808 [M^++H].

2,3-*O*-Cyclohexylidene-1,4-dideoxy-1,4-iminoerythritol (27): Palladium hydroxide on carbon (20% $Pd(OH)_2$, 25 mg) was added to a solution of **26** (75 mg, 0.27 mmol) in MeOH (3.0 mL)and the reaction mixture placed under an atmosphere of H_2. After 4 h TLC (EtOAc/cyclohexane 1:4) showed consumption of SM (R_f 0.4). The reaction mixture was filtered through Celite to remove $Pd(OH)_2$ on C, then the filtrate concentrated under reduced pressure to yield **27** as a colourless oil (48 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.36$–1.67 (m, 10H; cyclohexylidene), 2.52 (m, 2H; $2 \times CHH'N$), 2.64 (br s, 1H; NH), 3.12 (m, 2H; $2 \times CHH'N$), 4.64 (m, 2H; $2 \times OCH$); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): $\delta = 23.6$,

24.0, 25.2, 33.2, 35.7 (5t, cyclohexylidene), 54.2 (t, CH_2N), 80.9 (d, OCH), 110.9 (s, $C(CH_2)_2$); HRMS (CI): *m/z*: calcd for $C_{10}H_{18}NO_2$: 184.1338; found: 184.1339 [M^++H].

1-Chloro-2,3-*O*-cyclohexylidene-1,4-dideoxy-1,4-iminoerythritol (28): NCS (39 mg, 0.29 mmol, 1.1 equiv) was added under Ar to a solution of **27** (48 mg, 0.26 mmol) in dry Et_2O (5 mL). After 2 h stirring TLC (EtOAc/cyclohexane 1:4) showed consumption of SM (R_f 0.0) and formation of a major product (R_f 0.6). The reaction mixture was diluted with Et_2O (30 mL) and washed with water (3 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to yield an oily solid (51 mg, 90%). This was consistent with pure *N*-chloramine and no further purification was required. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.19-1.75$ (m, 10H; 5 × CH_2 cyclohexylidene), 2.84 (m, 2H; 2 × C*H*H′N), 3.63 (d, ^2J(H,H) = 11.7 Hz, 2H; 2 × CH*H*′N), 4.71 (m, 2H; 2 × OCH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): $\delta = 23.7$, 24.0, 25.1, 33.9, 35.6 (5t, 5 × CH_2 cyclohexylidene), 67.3 (t, CH_2N), 77.8 (d, OCH), 112.4 ($C(CH_2)_2$); IR (KBr disc): $\tilde{\nu} = 2935$, 2853 (aliphatic C-H stretch), 1457, 1373 cm^{-1}; HRMS (FI): *m/z*: calcd for $C_{10}H_{16}NO_2Cl$: 217.0870; found: 217.0868 [$M^{\cdot}$].

2,3-*O*-Cyclohexylidene-1,4-dideoxy-1,4-imino-1,*N*-dehydroerythritol (4): DBU (0.045 mL, 45 mg, 0.30 mmol, 1.3 equiv) was added under Ar to a solution of **28** (50 mg, 0.23 mmol) in dry Et_2O (3 mL). After 3 h, the mixture was filtered under Ar to remove DBU·HCl, and then concentrated to yield **4** as an oil (42 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 1.46–1.58 (m, 10H; cyclohexylidene), 3.86 (dddd, ^2J(H,H) = 17.2, ^3J(H,H) = 4.5 Hz, 2.9 Hz, 0.8 Hz, 1H; C*H*H′N), 4.05 (ddpt, ^2J(H,H) = 17.2, ^3J(H,H) = 2.0 Hz, 1.0 Hz, 1H; CH*H*′N), 4.65 (ddd, 1H, ^3J(H,H) = 5.6 Hz, 4.5 Hz, 0.9 Hz, 1H; NCH_2CH), 5.00 (br d, ^3J(H,H) = 5.6 Hz, 1H; N=CHC*H*), 7.53 (dd, ^3J(H,H) = 2.8 Hz, 2.2 Hz, 1H; N=CH).

1α,β-Methyl-2,3-*O*-di-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-dideoxy-1,4-iminothreitol (29a)

i) General method for normal mode of addition: DBU (0.16 mL, 164 mg, 1.08 mmol, 4.0 equiv) was added under N_2 to a solution of **10** (100 mg, 0.27 mmol) in dry Et_2O (6 mL). The reaction mixture was stirred and DBU·HCl observed to precipitate as a white solid. After 2.5 h the reaction mixture was filtered through a glass sinter and the filtrate was concentrated under reduced pressure to yield an oil. Formation of imine **2** was confirmed by ^{1}H NMR. The oil was then redissolved in dry Et_2O (6 mL) and methyl magnesium bromide (3.0 M solution in Et_2O, 0.50 mL, 1.49 mmol, 5.5 equiv) was added. The reaction mixture was stirred for 3 h, diluted with Et_2O (20 mL) and washed with $NaHCO_3$ (3 × 10 mL). The aqueous layers were extracted with Et_2O (10 mL) and the combined organic layers dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield a pale yellow oil (131 mg). The crude product was purified by flash column chromatography on silica gel (EtOAc/hexane 3:7 then EtOAc) eluting initially as a single diastereomer (23 mg) and then as a mixture of diastereoisomers (32 mg) to give methyl adduct **29a** (total mass 55 mg, 58%, *dr* 5:2 as determined from ^{1}H NMR). The major diastereomer was shown by NMR experiments to be the *anti* or α diastereomer **α-29a**. ^{1}H NMR (500 MHz, $CDCl_3$, COSY, NOESY): $\delta = -0.02$ (s, 3H; $SiCH_3$), -0.01 (s, 3H; $SiCH_3$), 0.00 (s, 6H; $Si(CH_3)_2$), 0.81, 0.81 (2s, 2 × 9H; 2 × $SiC(CH_3)_3$), 1.14 (d, ^3J(H,H) = 7.0 Hz, 3H; NCH(C*H*$_3$)), 2.02 (br s, 1H; NH), 2.72 (d, ^2J(H,H) = 12.0 Hz, 1H; C*H*H′N), 2.82 (dq, ^3J(H,H) = 6.5, ^3J(H,H) = 3.0 Hz, 1H; NC*H*(CH_3)), 2.94 (dd, ^2J(H,H) = 12.0, ^3J(H,H) = 4.0 Hz,1H; CH*H*′N), 3.50 (m, 1H; NCH(Me)C*H*OSi), 3.85 (m, 1H; NCH_2CHOSi); ^{13}C NMR (125.7 MHz, $CDCl_3$, ^{1}H-^{13}C HETCOR): $\delta =$ -4.7, -4.7, -4.6, -4.5 (OSi(CH_3)$_2$), 17.9, 17.9 (Si*C*(CH_3)$_3$), 19.2 (NCH(*C*H$_3$)), 25.8 (SiC(*C*H$_3$)$_3$), 54.1 (NCH_2), 62.7 (N*C*H(CH_3)), 80.3 (NCH_2CHOSi), 85.4 (NCH(Me)*C*HOSi); IR (film): $\tilde{\nu} = 2956$, 2929, 2896, 2858 cm^{-1} (aliphatic C-H); MS (ES): *m/z* (%): 346 (100) [M^++H]; HRMS (ES): *m/z*: calcd for $C_{17}H_{40}NO_2Si_2$: 346.2597; found: 346.2602 [M^++H].

ii) Reverse mode of addition: DBU (0.074 mL, 75 mg, 0.49 mmol, 3.0 equiv) was added under Ar to a solution of **10** (60 mg, 0.16 mmol) in dry Et_2O (5 mL). The reaction mixture was stirred and DBU·HCl observed to precipitate as a white solid. After 4 h, the reaction mixture was filtered under Ar and the filtrate was concentrated under reduced pressure to yield imine **2** as an oil. This was dissolved in dry Et_2O (5 mL) under Ar. To a separate flask under Ar was added methylmagnesium bromide (3.0 M solution in Et_2O, 0.27 mL, 0.82 mmol, 5.0 equiv), then the imine solution was added dropwise by syringe to the Grignard reagent. The reaction mixture was stirred for 3 h, then quenched by the addition of NH_4Cl (aq.), diluted with Et_2O (30 mL) and washed with NH_4Cl (aq) (10 mL), water (10 mL) followed by $NaHCO_3$ (10 mL). The aqueous layers were basified with 3 M NaOH and back-extracted with Et_2O (2 × 10 mL) and the combined organic layers dried (Na_2SO_4) and concentrated under reduced pressure to yield a pale yellow oil (61 mg). The crude product was purified by flash column chromatography on silica gel (EtOAc/hexane 3:7 increasing to 1:1) to yield **29a** (38 mg, 67%) as a mixture of diastereomers (5:1 *anti*:*syn* as determined by ^{1}H NMR).

1α,β-Ethyl-2,3-*O*-di-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-iminothreitol (29b)

i) Normal mode of addition: According to method described for **29a** above using ethyl magnesium bromide (3.0 M solution in Et_2O, 0.50 mL, 1.49 mmol, 5.5 equiv) was added to yield a pale yellow oil (84 mg). The crude product was purified by flash column chromatography on silica gel (EtOAc/hexane 1:3) to yield ethyl adducts **α,β-29b** (44 mg, 45%, *dr* 98:2 as determined by ^{1}H NMR). The major diastereomer was purified and shown by NOESY NMR experiments to be the *anti* diastereomer **α-29b**. ^{1}H NMR (500 MHz, $CDCl_3$, COSY, NOESY): $\delta = 0.05$, 0.06, 0.06, 0.07 (4s, 4 × 3H; 4 × $Si(CH_3)$), 0.87, 0.87 (2s, 2 × 9H; 2 × $SiC(CH_3)_3$), 0.98 (t, ^3J(H,H) = 7.5 Hz, 3H; NCH(CH_2CH_3)), 1.48 (m; 1H, NCH(C*H*H′CH$_3$)), 1.64 (m, 1H; NCH(CH*H*′CH$_3$)), 2.27 (br s, 1H; NH), 2.73 (m, 1H; NC*H*(Et)), 2.78 (d, ^2J(H,H) = 12.5 Hz, 1H; C*H*H′N), 2.98 (dd, ^2J(H,H) = 12.5, ^3J(H,H) = 3.5 Hz, 1H; CH*H*′N), 3.63 (m, 1H; NCH(Et)C*H*OSi), 3.90 (m, 1H; NCH_2CHOSi); ^{13}C NMR (125.7 MHz, $CDCl_3$, ^{1}H-^{13}C HETCOR): $\delta = -4.7$, -4.6, -4.6, -4.4 (OSi(CH_3)$_2$), 11.7 (NCH(CH_2CH_3)), 17.9 (Si*C*(CH_3)$_3$), 25.7, 25.8 (SiC(*C*H$_3$)$_3$), 26.8 (NCH(CH_2CH_3)), 53.7 (NCH_2), 69.3 (N*C*H(CH_2CH_3)), 79.8 (NCH_2CHOSi), 83.4 (NCH(Et)*C*HOSi); IR (film): $\tilde{\nu} = 2956$, 2929, 2857 cm^{-1} (aliphatic C-H); MS (ES): *m/z* (%): 360 (100) [M^++H]; HRMS (ES): *m/z*: calcd for $C_{18}H_{42}NO_2Si_2$: 360.2754; found: 360.2752 [M^++H].

ii) Reverse mode of addition: According to method described for **29a** above using ethylmagnesium bromide (3.0 M solution in Et_2O, 0.27 mL, 0.82 mmol, 5.0 equiv) for adduct formation over 1.5 h to give a pale yellow oil (57 mg). The crude product was purified by flash column chromatography on silica gel (Et_2O/40–60 petroleum ether 3:7 increasing to 1:1) to yield **29b** (41 mg, 70%) as a single diastereomer.

1α,β-Allyl-2,3-di-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-iminothreitol (29c)

i) Normal mode of addition: According to method described for **29a** above using DBU (0.12 mL, 123 mg, 0.81 mmol, 3.0 equiv) for imine formation over 3.5 h and allylmagnesium bromide (1.0 M solution in Et_2O, 1.35 mL, 1.35 mmol, 5.0 equiv) over 2 h for adduct formation to yield an orange oil (90 mg). This crude product was purified by flash column chromatography on silica gel (EtOAc/hexane 3:17) to yield allyl adducts, major diastereomer **α-29c** (24 mg), and a minor diastereomer **β-29c** (2 mg) (total mass = 26 mg, 26%, *dr* 12:1). The major diastereomer was shown by NOESY NMR to be the *anti* diastereomer **α-29c**: ^{1}H NMR (500 MHz, $CDCl_3$, COSY, NOESY): $\delta = 0.06$ (s, 6H; $Si(CH_3)_2$), 0.07, 0.08 (2s, 2 × 3H; 2 × $Si(CH_3)$), 0.87, 0.89 (2s, 2 × 9H; 2 × $SiC(CH_3)_3$), 2.27 (m, 1H; C*H*H′CH=CH$_2$), 2.37 (m, 1H; CH*H*′CH=CH$_2$), 2.80 (d, ^2J(H,H) = 12.0 Hz, 1H; C*H*H′N), 2.90 (td, ^3J(H,H) = 7.0, ^3J(H,H) = 2.5 Hz, 1H; NC*H*(allyl)), 3.03 (dd, ^2J(H,H) = 12.0, ^3J(H,H) = 4.0 Hz, 1H; CH*H*′N), 3.70 (br s, 1H; NCH_2CHOSi), 3.91 (m, 1H; NCH(allyl)C*H*OSi), 5.07 (br d, $^3J(H,H)_{cis}$ = 10.0 Hz, 1H; CH=CH*H*′), 5.10 (br d, $^3J(H,H)_{trans}$ = 17.5 Hz, 1H; CH=CH*H*′), 5.83 (ddpt, $^3J(H,H)_{trans}$ = 17.5, $^3J(H,H)_{cis}$ = 10.0, ^3J(H,H) = 7.0 Hz, 1H; CH_2CH=CH$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$, DEPT, ^{1}H-^{13}C HSQC): $\delta = -4.7$, -4.7, -4.5, -4.4 (4q, 4 × $SiCH_3$), 17.9 (s, Si*C*(CH_3)$_3$), 25.8 (q, SiC(*C*H$_3$)$_3$), 38.1 (t, *C*H$_2$CH=CH$_2$), 53.9 (t, NCH_2), 66.7 (d, N*C*H(allyl)), 79.7 (d, NCH_2CHOSi), 82.7 (d, NCH(allyl)CHOSi), 116.9 (t, CH_2CH=*C*H$_2$), 135.7 (d, CH_2*C*H=CH$_2$); IR (film): $\tilde{\nu} = 2955$, 2929, 2897, 2857 cm^{-1} (aliphatic C-H), 1641 (C=C stretch); MS (ES): *m/z* (%): 372 (100) [M^++H]; HRMS (ES): *m/z*: calcd for $C_{19}H_{42}NO_2Si_2$: 372.2754; found: 372.2747 [M^++H].

1α-Phenyl-2,3-di-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-iminothreitol (29d)

i) Normal mode of addition: According to method described for **29a** above using DBU (0.040 mL, 41 mg, 0.27 mmol, 1.0 equiv) for imine formation over 90 min and phenylmagnesium bromide (3.0 M solution in Et_2O, 0.14 mL, 0.41 mmol, 1.5 equiv) for adduct formation over 90 min to yield a yellow oil (108 mg). The crude product was purified by flash column

chromatography on silica gel (EtOAc/hexane 1:3) to yield **29d** as a colourless oil (41 mg, 37%), as a single diastereomer. This was shown by NOESY NMR experiments to be the *anti* diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$, COSY, NOESY): $\delta = -0.19$, -0.06 (2s, 2×3H; $2\times$ PhCHCHOSi(CH_3)), 0.10 (s, 6H; $NCH_2CHOSi(CH_3)_2$), 0.83 (s, 9H; PhCHCHOSiC(CH_3)$_3$), 0.92 (s, 9H; $NCH_2CHOSiC(CH_3)_3$), 2.65 (brs, 1H; NH), 3.00 (d, ^2J(H,H) = 12.0 Hz, 1H; C*H*H′N,), 3.17 (dd, ^2J(H,H) = 12.0, ^3J(H,H) = 4.0 Hz, 1H; CH*H*′N), 3.85 (d, ^3J(H,H) = 3.0 Hz, 1H; C*H*Ph), 3.98 (brs, 1H; SiOC*H*CHPh), 4.09 (m, 1H; SiOC*H*CH_2N), 7.25–7.33 (m, 3H; 3 of C_6H_5), 7.41 (m, 2H; 2 of C_6H_5); ^{13}C NMR (125.7 MHz, $CDCl_3$, ^{1}H-^{13}C HETCOR): $\delta = -4.8$, -4.7, -4.7, -4.6 ($OSi(CH_3)_2$), 17.8, 18.0 (Si*C*(CH_3)$_3$), 25.6, 25.7, 25.8, 25.8 (SiC(CH_3)$_3$), 54.4 (CH_2N), 72.2 (*C*HPh), 80.1 (SiO*C*HCH_2N), 86.2 (SiO*C*HCHPh), 127.3, 127.7, 128.4 (3× aromatic CH), 141.8 (quaternary aromatic C); IR (film): $\tilde{\nu} = 3027$ cm^{-1} (aromatic C–H), 2954, 2929, 2857 (aliphatic C–H); MS (ES): *m*/*z* (%): 408 (100) [M^++H]; HRMS (CI): *m*/*z*: calcd for $C_{22}H_{42}NO_2Si_2$: 408.2754; found: 408.2747 [M^++H].

ii) Reverse mode of addition: According to method described for **29a** using phenylmagnesium bromide (3.0M solution in Et_2O, 0.27 mL, 0.82 mmol, 5.0 equiv) for adduct formation over 1.5 h to yield a pale yellow oil (75 mg). The crude product was purified by flash column chromatography on silica gel (Et_2O/40-60 petroleum ether 3:17 increasing to 3:7) to yield **29d** (52 mg, 78%) as a single diastereomer.

1α-Benzyl-2,3-*O*-di-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-iminothreitol (29e)

i) Normal mode of addition: According to method described for **29a** above using DBU (0.040 mL, 41 mg, 0.27 mmol, 1.0 equiv) for imine formation over 4 h and benzylmagnesium chloride (1.0M solution in Et_2O, 0.41 mL, 0.41 mmol, 1.5 equiv) for adduct formation over 3 h TLC to yield an orange oil (108 mg). The crude product was purified by flash column chromatography on silica gel (EtOAc/hexane 1:4) whereupon **29e** was obtained as an oil (55 mg, 48%), as a single diastereomer. This was shown by NOESY NMR experiments to be the *anti* diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$, COSY, NOESY): $\delta = -0.19$, -0.08 (2s, 2×3H; $2\times$ BnCHCHO-Si(CH_3)), 0.08, 0.11, (2s, 2×3H; $2\times NCH_2CHOSi(CH_3)$), 0.80 (s, 9H; BnCHCHOSiC(CH_3)$_3$), 0.93 (s, 9H; $NCH_2CHOSiC(CH_3)_3$), 2.32 (brs, 1H; NH), 2.84 (m, 3H; $C_6H_5CH_2$ and C*H*H′N), 3.08 (brd, ^2J(H,H) = 10.0 Hz, 1H; CH*H*′N), 3.14 (m, 1H; BnC*H*), 3.76 (s, 1H; BnCHC*H*OSi), 3.93 (s, 1H; NCH_2CHOSi), 7.31–7.19 (m, 5H; C_6H_5); ^{13}C NMR (125.7 MHz, $CDCl_3$, ^{1}H-^{13}C HETCOR): $\delta = -5.1$, -4.8, -4.7, -4.7 (Si(*C*H_3)$_2$), 17.9, 17.8 (Si*C*(CH_3)$_3$), 25.8, 25.7, 25.7 (SiC(*C*H_3)$_3$), 40.1 (Ph*C*H_2), 53.9 (NCH_2), 68.7 (Bn*C*H), 79.6 (NCH_2*C*HOSi), 82.0 (BnCH*C*HOSi), 126.2, 128.5, 129.2 (aromatic CH), 139.4 (quaternary aromatic C); IR (film): $\tilde{\nu} = 3027$ cm^{-1} (aromatic C-H), 2953, 2928, 2857 (aliphatic C-H); MS (CI): *m*/*z* (%): 422 (100) [M^++H]; HRMS (CI): *m*/*z*: calcd for $C_{23}H_{44}NO_2Si_2$: 422.2910; found: 422.2911 [M^++H].

ii) Reverse mode of addition: According to method described for **29a** using benzylmagnesium chloride (1.0M solution in Et_2O, 0.71 mL, 0.71 mmol, 5.0 equiv) for adduct formation over 1.5 h to give a pale yellow oil (68 mg). The crude product was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 1:4 increasing to 1:1) to yield **29e** (38 mg, 63%) as a single diastereomer.

1α-(4-Methoxybenzyl)-2,3-di-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-iminothreitol (29f)

i) Normal mode of addition: According to method described for **29a** above using DBU (0.12 mL, 123 mg, 0.81 mmol, 3.0 equiv) for imine formation over 3.5 h. Benzylmagnesium chloride was prepared as follows. To magnesium turnings (0.33g, 13.5 mmol, 50.0 equiv) in dry THF (5 mL) under Ar with two crystals of I_2 was added 4-methoxybenzyl chloride (0.92 mL, 1.06 g, 6.75 mmol, 25.0 equiv) as solution in THF (10 mL) over ≈30 min. The mixture turned a dark grey colour on this addition. After 1 h a small portion was removed and quenched with D_2O, then dissolved in [D_4]methanol for ^{1}H NMR. Grignard reagent formation was confirmed by the presence of the CH_2D resonance (triplet, ^{1}H NMR $\delta = 2.28$ ppm). 4-methoxybenzylmagnesium chloride solution in THF (6 mL, 2.7 mmol, 10 equiv) was added to a solution of imine in dry THF (5 mL) under Ar. The reaction course was followed by mass spectrometry (APCI) and after 2 h excess Grignard reagent was quenched by the dropwise addition of NH_4Cl (aq). The reaction mixture was concentrated to remove THF, the residue dissolved in $CHCl_3$ (30 mL) and washed with NH_4Cl (aq) (10 mL), water (10 mL) followed by $NaHCO_3$ (aq) (10 mL). The aqueous layers were extracted with $CHCl_3$ (2×10 mL) and the combined organic layers dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield a yellow oily solid (277 mg). This crude product was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 1:19 then EtOAc/cyclohexane 1:4 the EtOAc) to yield **29f** (53 mg, 43%) as a single diastereomer. This was shown by NOESY NMR experiments to be the *anti* diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, NOESY): $\delta = -0.16$, -0.07, 0.07, 0.10 (4s, 4×3H; $4\times SiCH_3$), 0.81, 0.92 (2s, 2×9H; $2\times SiC(CH_3)_3$), 2.14 (brs, 1H; NH), 2.78 (m, 2H; C$H_2C_6H_4$), 2.82 (d, ^2J(H,H) = 12.0 Hz, 1H; C*H*H′N), 3.06 (dd, ^2J(H,H) = 12.0, ^3J(H,H) = 4.0 Hz, 1H; CH*H*′N), 3.08 (td, ^3J(H,H) = 7.8, ^3J(H,H) = 2.2 Hz, 1H; NC*H*CH_2), 3.74 (brs, 1H; NCHC*H*OSi), 3.79 (s, 3H; OCH_3), 3.92 (m, 1H; NCH_2CHOSi), 6.84 (m, 2H; 2 of C_6H_4), 7.14 (m, 2H; 2 of C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$, HSQC, DEPT): $\delta = -5.0$, -4.7, -4.7, -4.6 (4q, $4\times SiCH_3$), 17.8, 17.9 (2s, $2\times$Si*C*(CH_3)$_3$), 25.7, 25.9 (2q, $2\times$ SiC(*C*H_3)$_3$), 39.1 (t, $C_6H_4CH_2$), 53.9 (t, NCH_2), 55.3 (q, OCH_3), 68.9 (d, NCH), 79.6 (d, NCH_2*C*HOSi), 82.1 (d, NCH*C*HOSi), 113.9, 130.0 (2d, 2× aromatic CH), 131.5 (s, quaternary aromatic C), 158.0 (s, quaternary aromatic C); IR (KBr disc): $\tilde{\nu} = 2951$, 2929, 2857 cm^{-1} (aliphatic C-H), 1613, 1514; MS (APCI): *m*/*z* (%): 452 (100) [M^++H]; HRMS (CI): *m*/*z*: calcd for $C_{24}H_{46}NO_3Si_2$: 452.3016; found: 452.3013 [M^++H].

ii) Reverse mode of addition: According to method described for **29a** using a THF solution of imine (6 mL) and 4-methoxybenzylmagnesium chloride (0.25M solution in Et_2O, 3.28 mL, 0.82 mmol, 5.0 equiv) for adduct formation over 2 h to give a pale yellow oil (97 mg). The crude product was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 1:4) to yield **29f** (46 mg, 62%) as a single diastereomer.

Dimer product 32: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.04$, 0.06, 0.08, 0.12, 0.14 (5s, 24H; $8\times Si(CH_3)$), 0.87, 0.89, 0.94 (m, 36H; $12\times SiC(CH_3)$), 2.59 (dd, ^2J(H,H) = 12.0, ^3J(H,H) = 9.4 Hz, 2H; $2\times$C*H*H′N), 2.71 (d, ^3J(H,H) = 3.0 Hz, 2H; $2\times$NCH), 3.48 (dd, ^2J(H,H) = 12.0, ^3J(H,H) = 8.3 Hz, 2H; $2\times$C*H*H′N), 3.97 (dd, ^3J(H,H) = 6.6, ^3J(H,H) = 3.0 Hz, 2H; NCHC*H*OSi), 4.45 (ptd, ^3J(H,H) = 8.8, ^3J(H,H) = 6.6 Hz, 2H; NCH_2CH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.0$, -4.8 ($SiCH_3$), 17.9, 18.1 (Si*C*(CH_3)), 25.7, 25.8 (SiC(*C*H_3)), 54.6, 56.5 (NCH_2, NCH), 78.1, 86.5 (NCH_2*C*H, NCH*C*H).

1β-Hex-5-enyl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (30g)

i) Imine formation: DBU (0.11 mL, 111 mg, 0.73 mmol, 1.3 equiv) was added under Ar to a solution of **21** (100 mg, 0.56 mmol) in dry THF (6 mL). The reaction mixture was stirred, whereupon the white salt DBU·HCl precipitated. After 3 h the reaction mixture was filtered under Ar to remove DBU·HCl and concentrated under reduced pressure to yield an orange oil. This was dissolved in dry THF (5 mL) under Ar.

ii) Preparation of Grignard reagent: To magnesium turnings (204 mg, 8.4 mmol, 15.0 equiv) in dry THF (2 mL) under Ar with two crystals of I_2 was added 6-bromo-1-hexene (0.75 mL, 913 mg, 5.6 mmol, 10.0 equiv) as a solution in THF (6 mL) over 20 min. The activity and identity of this Grignard stock solution was confirmed by reaction of a small portion with benzaldehyde which yielded only 1-phenyl-hept-6-en-1-ol.

iii) Normal mode addition: To the stirred imine **3** as a solution in dry THF (5 mL) under Ar was added a portion of the Grignard preparation (4 mL, 2.8 mmol, 5.0 equiv). After 3 h excess Grignard reagent was quenched by the dropwise addition of NH_4Cl (aq). The reaction mixture was concentrated and the residue dissolved in Et_2O (30 mL) and washed with NH_4Cl (aq., 10 mL), water (10 mL), $NaHCO_3$ (aq., 10 mL). The aqueous layers were basified with NaOH (aq., 1M) extracted with Et_2O (2×10 mL) and the combined organic layers dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield a yellow oily solid. This crude product was purified by flash column chromatography on silica gel (Et_2O/40-60 petroleum ether 3:7 then Et_2O then EtOAc) to give **30g** (58 mg, 46%) as a single diastereomer. This was shown by NOESY NMR experiments to be the *anti* β diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, NOESY): $\delta =$ 1.26 (m, 2H; 1 of $(CH_2)_3$), 1.31 (s, 3H; 1 of $C(CH_3)_2$), 1.40 (m, 4H; 2 of $(CH_2)_3$), 1.46 (s, 3H; 1 of $C(CH_3)_2$), 2.05 (m, 2H; CH_2CH=CH_2), 2.21 (brs, 1H; NH), 2.82 (dd, ^2J(H,H) = 13.5, ^3J(H,H) = 4.2 Hz, 1H; C*H*H′N), 2.99 (d, ^2J(H,H) = 13.5 Hz, 1H; CH*H*′N), 3.08 (pt, ^3J(H,H) = 7.7 Hz, 1H; NC*H*(hexenyl)), 4.37 (d, ^3J(H,H) = 5.5 Hz, 1H; NCH(hexenyl)C*H*), 4.67 (pt, ^{3}J(H,H) = 4.8 Hz, 1H; NCH_2CH), 4.93 (ddpt, $^3J(H,H)_{cis} = 10.2$, ^2J(H,H) = 2.0, ^3J(H,H) = 1.1 Hz, 1H; 1 of CH=CH_2), 4.99 (dpq, $^3J(H,H)_{trans}$

17.1 Hz, $^{2/3}J$(H,H) = 2.0 Hz, 1H; 1 of CH=CH_2), 5.79 (ddpt, ^3J(H,H)$_{trans}$ 17.1, ^3J(H,H)$_{cis}$ 10.2, ^3J(H,H), 6.7 Hz, 1H; CH_2CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, HMQC, DEPT): δ = 23.9, 26.2 (2q, 2 × (C(CH_3)$_2$)), 26.3, 28.7, 30.4, 33.6 (4t, 4 × CH_2 hexenyl), 51.7 (t, NCH_2), 64.8 (d, NCH(hexenyl)), 81.8 (d, CH_2CH), 86.0 (d, NCH(hexenyl)CH), 110.7 (s, C(CH_3)$_2$), 114.4 (t, CH=CH_2), 138.8 (d, CH=CH_2); IR (film): $\tilde{\nu}$ = 3315 (N-H), 2979, 2932, 2857 cm^{-1} (aliphatic C-H), 1641 (C=C); HRMS (ES): *m*/*z*: calcd for $C_{13}H_{24}NO_2$: 226.1807; found: 226.1807 [M^++H].

1β-Ethyl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (30b): DBU (0.16 mL, 167 mg, 1.10 mmol, 1.3 equiv) was added under Ar to a solution of **21** (150 mg, 0.84 mmol) in dry Et_2O (8 mL). The reaction mixture was stirred for 3 h, then the mixture was filtered under Ar to remove DBU hydrochloride. The filtrate was concentrated under reduced pressure to yield an oil. This was dissolved in dry Et_2O (8 mL) under Ar. To a separate flask under Ar was added ethylmagnesium bromide (3.0 M solution in Et_2O, 1.40 mL, 4.20 mmol, 5.0 equiv), and the imine solution was added to the Grignard reagent dropwise by syringe. After 1.5 h TLC and mass spectrometry (APCI) showed consumption of imine and formation of the desired adduct; excess Grignard reagent was quenched with NH_4Cl (aq), then the mixture was diluted with Et_2O (30 mL) and washed with NH_4Cl (aq) (10 mL), water (10 mL) and $NaHCO_3$ (aq., 10 mL). The aqueous layers were basified to pH 11 with 3 M NaOH (aq) then extracted with Et_2O (10 mL) and $CHCl_3$ (2 × 10 mL) and the combined organic layers dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield **30b** as a yellow oil as a single diastereomer (110 mg, 76%). (Careful control of pressure was required to avoid removing the product under vacuum, minimum p = 70 mbar.). ^{1}H NMR (400 MHz, $CDCl_3$, COSY, NOESY): δ = 0.97 (t, ^3J(H,H) = 7.4 Hz, 3H; CH_2CH_3), 1.30 (m, 2H; CH_2CH_3), 1.31, 1.47 (2s, 2 × 3H; 2 × C(CH_3)), 2.22 (brs, 1H; NH), 2.83 (dd, ^2J(H,H) = 13.8, ^3J(H,H) = 4.1 Hz, 1H; NCHH′), 2.99 (d, ^2J(H,H) = 13.5 Hz, 1H; NCHH′), 3.01 (d, ^3J(H,H) = 7.7 Hz, 1H; CHEt), 4.39 (d, ^3J(H,H) = 5.2 Hz, 1H; CH(Ph)CH), 4.68 (pt, ^3J(H,H) = 5.1 Hz, 1H, NCH_2CH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, HMQC): δ = 11.4 (q, CH_2CH_3), 23.6 (t, CH_2CH_3), 23.9, 26.3 (2q, 2 × C(CH_3)), 51.7 (t, NCH_2), 66.6 (d, CHEt), 81.8 (d, NCH_2CH), 85.6 (d, CH(Et)CH), 110.7 (s, C(CH_3)$_2$); IR (film): $\tilde{\nu}$ = 3337 cm^{-1} (br, N-H stretch), 2962, 2934, 2874 (aliphatic C-H stretch); HRMS (CI): *m*/*z*: calcd for $C_9H_{18}NO_2$: 172.1338; found: 172.1337 [M^++H].

1β-Phenyl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (30d)

i) Normal mode of addition: DBU (0.11 mL, 111 mg, 0.73 mmol, 1.3 equiv) was added under Ar to a solution of **21** (100 mg, 0.56 mmol) in dry Et_2O (6 mL). The reaction mixture was stirred for 4 h, then the mixture was filtered under Ar to remove DBU hydrochloride. The filtrate was concentrated under reduced pressure to yield an oil. This was dissolved in dry Et_2O (6 mL) under Ar, and phenylmagnesium bromide (3.0 M solution in Et_2O, 0.56 mL, 1.68 mmol, 3.0 equiv) was added. After 1.5 h TLC showed consumption of imine; excess Grignard reagent was quenched with NH_4Cl (aq) then the mixture was diluted with Et_2O (30 mL) and washed with NH_4Cl (aq) (10 mL), water (10 mL) followed by $NaHCO_3$ (aq) (10 mL). The aqueous layers basified and back-extracted with Et_2O (2 × 10 mL) and the combined organic layers dried (Na_2SO_4) and concentrated under reduced pressure to yield a yellow oil (198 mg). This crude product was purified by flash column chromatography on silica gel (Et_2O/40-60 petroleum ether 2:3) to yield **30d** as a pale yellow oil (19 mg, 15%), as a single diastereomer.

ii) Reverse mode of addition: According to method described for **30b** above using dry Et_2O (6 mL) for imine formation and phenylmagnesium bromide (3.0 M solution in Et_2O, 0.93 mL, 2.80 mmol, 5.0 equiv) over 2 h for adduct formation to yield a yellow oil (146 mg). This crude product was purified by flash column chromatography on gel (Et_2O/40-60 petroleum ether 2:3) to yield **30d** as a pale yellow oil (86 mg, 70%), as a single diastereomer. This was confirmed by NOESY NMR experiments to be the *anti* diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, NOESY): δ = 1.36, 1.55 (2s, 2 × 3H; 2 × C(CH_3)), 2.45 (brs, 1H; NH), 2.95 (dd, ^2J(H,H) = 13.4, ^3J(H,H) = 4.4 Hz, 1H; NCHH′), 3.13 (d, ^2J(H,H) = 13.4 Hz, 1H; NCHH′), 4.38 (brs, 1H; CHPh), 4.71 (m, 1H; NCH_2CH), 4.85 (dd, ^3J(H,H) = 5.7, ^3J(H,H) = 0.8 Hz, 1H; CH(Ph)CH), 7.23–7.44 (m, 5H; C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, HMQC): δ = 24.1, 26.4 (2q, 2 × C(CH_3)), 52.7 (t, NCH_2), 67.6 (d, CHPh), 82.2 (d, NCH_2CH), 88.1 (d, CH(Ph)CH), 111.1 (s, CMe$_2$), 126.7, 126.9, 128.5 (3d, aromatic CH), 139.5 (s, quaternary aromatic C); IR (film): $\tilde{\nu}$ = 3337 cm^{-1} (br, N-H stretch), 3061, 3027 (aromatic C-H stretch), 2986, 2935 (aliphatic C-H stretch), 1496, 1449; HRMS (CI): *m*/*z*: calcd for $C_{13}H_{18}NO_2$: 220.1338; found: 220.1333 ([M^++H].

1β-Benzyl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (30e): According to method described for **30b** above using dry Et_2O (6 mL) for imine formation and dry Et_2O (6 mL) with benzylmagnesium chloride (1.0 M solution in Et_2O, 2.80 mL, 2.80 mmol, 5.0 equiv) over 1.5 h for adduct formation to yield a yellow oil (168 mg). This crude product was purified by flash column chromatography on silica gel (Et_2O/40-60 petroleum ether 2:3 increasing up to Et_2O) to yield **30e** as a pale yellow oil (96 mg, 73%), as a single diastereomer. This was confirmed by NOESY NMR experiments to be the *anti* diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, NOESY): δ = 1.29, 1.46 (2s, 2 × 3H; 2 × C(CH_3)), 2.49 (brs, 1H, NH), 2.61 (dd, ^2J(H,H) = 14.0, ^3J(H,H) = 8.0 Hz, 1H; CHH′Ph), 2.67 (dd, ^2J(H,H) = 14.0, ^3J(H,H) = 8.0 Hz, 1H; CHH′Ph), 2.99 (dd, ^2J(H,H) = 13.3, ^3J(H,H) = 4.1 Hz, 1H; NCHH′), 3.07 (d, ^2J(H,H) = 13.3 Hz, 1H; NCHH′), 3.47 (t, ^3J(H,H) = 7.8 Hz, 1H; CHBn), 4.46 (d, ^3J(H,H) = 5.6 Hz, 1H; CH(Bn)CH), 4.74 (m, 1H; NCH_2CH), 7.20–7.33 (m, 5H; C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, HMQC): δ = 24.0, 26.3 (2q, 2 × C(CH_3)), 36.9 (t, CH_2Ph), 51.8 (t, NCH_2), 66.1 (d, CHBn), 81.7 (d, NCH_2CH), 84.9 (d, CH(Ph)CH), 110.9 (s, CMe$_2$), 126.3, 128.5, 129.0 (3d, aromatic CH), 138.9 (s, quaternary aromatic C); IR (film): $\tilde{\nu}$ = 3321 cm^{-1} (br, N-H stretch), 3062, 3027 (aromatic C-H stretch), 2985, 2934, 2865 (aliphatic C-H stretch), 1496, 1454; HRMS (CI): *m*/*z*: calcd for $C_{14}H_{20}NO_2$: 234.1494; found: 234.1504 [M^++H].

1β-(4-Methoxybenzyl)-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (30f): According to method described for **30b** above using dry Et_2O (6 mL) for imine formation and dry THF (6 mL) with 4-methoxybenzylmagnesium chloride (0.25 M solution in THF, 11.2 mL, 2.80 mmol, 5.0 equiv, prepared as described above) over 1.5 h for adduct formation to yield a yellow oil (421 mg). This crude product was purified by flash column chromatography on silica gel (Et_2O/40-60 petroleum ether 4:1, increasing to Et_2O then MeOH/Et_2O 1:9) to yield **30f** as a pale yellow oil (108 mg, 73%), as a single diastereomer. This was confirmed by NOESY NMR experiments to be the *anti* diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, NOESY): δ = 1.28, 1.45 (2s, 2 × 3H; 2 × C(CH_3)), 2.45 (brs, 1H; NH), 2.54 (dd, 1H, ^2J(H,H) = 14.1, ^3J(H,H) = 8.0 Hz, CHH′Ar), 2.60 (dd, ^2J(H,H) = 14.0, ^3J(H,H) = 7.8 Hz, 1H; CHH′Ar), 2.96 (dd, ^2J(H,H) = 13.4, ^3J(H,H) = 4.0 Hz, 1H; NCHH′), 3.05 (d, ^2J(H,H) = 13.3 Hz, 1H; NCHH′), 3.41 (t, ^3J(H,H) = 8.0 Hz, 1H; CH(CH_2Ar), 3.78 (s, 3H; OCH_3), 4.43 (d, ^3J(H,H) = 5.5 Hz, 1H; CH(CH_2Ar)CH), 4.72 (m, 1H; NCH_2CH), 6.83–6.87 (m, 2H; 2 of C_6H_4), 7.09–7.13 (m, 2H, 2 of C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, HMQC): δ = 24.0, 26.3 (2q, 2 × C(CH_3)), 36.0 (t, CH_2Ar), 51.8 (t, NCH_2), 55.2 (q, OCH_3), 66.3 (d, $CH$$CH_2$Ar), 81.7 (d, NCH_2CH), 84.9 (d, CH(Ph)CH)), 110.9 (s, CMe$_2$), 114.0, 129.9 (2d, 2 × aromatic CH), 138.9, 158.1 (2s, 2 × quaternary aromatic C); IR (film): $\tilde{\nu}$ = 3325 cm^{-1} (br, N-H stretch), 3028 (aromatic C-H stretch), 2987, 2934, 2836 (aliphatic C-H stretch), 1612; HRMS (CI): *m*/*z*: calcd for $C_{15}H_{22}NO_3$: 264.1600; found: 264.1595 [M^++H]$^+$

1β-Ethyl-2,3-*O*-Cyclohexylidene-1,4-dideoxy-1,4-iminoerythritol (31b): DBU (0.045 mL, 45 mg, 0.30 mmol, 1.3 equiv) was added under Ar to a solution of **28** (50 mg, 0.23 mmol) in dry Et_2O (3 mL). The reaction mixture was stirred for 3 h, then the mixture was filtered under Ar to remove DBU hydrochloride. The filtrate was concentrated under reduced pressure to yield an oil. ^{1}H NMR showed this to be consistent with imine formation (^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.54 (pt, J(H,H) = 2.4 Hz, 1H; N=CH)). This was dissolved in dry Et_2O (4 mL) under Ar. To a separate flask under Ar was added ethylmagnesium bromide (3.0 M solution in Et_2O, 0.38 mL, 1.15 mmol, 5.0 equiv), and the imine solution was added to the Grignard reagent dropwise by syringe. After 2 h, TLC and APCI mass spectrometry showed consumption of imine and formation of the desired adduct; excess Grignard reagent was quenched with NH_4Cl (aq), then the mixture was diluted with Et_2O (30 mL) and washed with NH_4Cl (aq) (10 mL), water (10 mL) followed by $NaHCO_3$ (aq) (10 mL). The aqueous layers were basified to pH 11 with 3 M NaOH (aq) then back-extracted with Et_2O (10 mL) followed by $CHCl_3$ (2 × 10 mL) and the combined organic layers dried (Na_2SO_4) and concentrated under reduced pressure to yield pure **31b** as a yellow oil (37 mg, 76%). No further purification was required, and ^{1}H NMR showed that the product was a single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, NOESY): δ = 0.97 (t, ^3J(H,H) = 7.4 Hz, 3H; CH_2CH_3), 1.25–1.68 (m, 10H, cyclohexylidene), 1.32 (m, 2H; CH_2CH_3), 2.85 (dd, ^2J(H,H) = 13.7, ^3J(H,H) = 4.2 Hz, 1H; NCHH′), 2.94 (brs, 1H;

NH), 3.03 (d, ^2J(H,H) = 13.7 Hz, 1H; NCHH'), 3.05 (app t, ^3J(H,H) = 7.8 Hz, 1H; CHEt), 4.39 (d, ^3J(H,H) = 5.5 Hz, 1H; NCH(Et)CH), 4.67 (app t, ^3J(H,H) = 7.8 Hz, 1H; NCH$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, HMQC): δ = 11.4 (q, CH$_2$CH_3), 23.6, 24.0, 25.2, 29.7, 33.5, 36.1 (6t, 5 × CH$_2$ cyclohexylidene, 1 × CH_2CH$_3$)), 51.8 (t, NCH$_2$), 66.7 (d, CHEt), 81.2 (d, NCH$_2$CH), 85.1 (d, CH(Et)CH), 111.5 (s, C(CH$_2$)$_2$); IR (film): $\tilde{\nu}$ = 3323 cm^{-1} (br, N-H stretch), 2934, 2854 (aliphatic C-H stretch), 1449, 1369; HRMS (CI): m/z: calcd for $C_{12}H_{22}NO_2$: 212.1651; found: 212.1655 [M^++H].

1α-Ethyl-1,4-dideoxy-1,4-imino-threitol (33b): A solution of TFA (aq., 50% v/v, 2 mL) and THF (2 mL) was added to **29b** (53 mg, 0.15 mmol). The reaction mixture was stirred under N_2. After 65 h TLC (EtOAc/hexane 1:1) showed consumption of SM (R_f 0.3). The reaction was then concentrated under reduced pressure, water was added to the residue and removed under reduced pressure (2 × 20 mL), toluene was added and removed under reduced pressure (2 × 20 mL) to yield a yellow oil (38 mg). This crude product was purified by ion-exchange chromatography (Dowex H$^+$ form, 50X2-200, Acros; water then 0.1M aqueous ammonia solution) to yield **33b** (15 mg, 76%). ^{1}H NMR (500 MHz, D_2O): δ = 0.83 (t, ^3J(H,H) = 7.5 Hz 3H; CH$_2$CH_3), 1.37 (m, 1H; CHH′CH$_3$), 1.56 (m, 1H; CHH'CH$_3$), 2.62 (m, 1H; NCH(Et)), 2.72 (dd, ^2J(H,H) = 12.5, ^3J(H,H) = 3.5 Hz, 1H; CHH′N), 2.94 (dd, ^2J(H,H) = 12.5, ^3J(H,H) = 5.5 Hz, 1H; CHH'N), 3.57 (dd, ^3J(H,H) = 5.5, ^3J(H,H) = 3.5 Hz, 1H; NCH$_2$CHOH), 3.98 (m, 1H; NCH(Et)CHOH); ^{13}C NMR (125.7 MHz, D_2O, DEPT): δ = 10.7 (q, NCH(CH$_2$CH_3), 25.9 (t, NCH(CH_2CH$_3$), 50.5 (t, CH$_2$N), 64.1 (d, NCH(Et)), 77.6 (d, NCH$_2$CHOH), 82.1 (d, CH(Et)CHOH); IR (KBr disc): $\tilde{\nu}$ = 3352 cm^{-1} (br, O-H stretch), 2966, 2932, 2880 (aliphatic C-H stretch); MS (ES): m/z (%): 132 (100) [M^++H]; HRMS (ES): m/z: calcd for $C_6H_{14}NO_2$: 132.1025; found: 132.1025 [M^++H].

1α-Phenyl-1,4-dideoxy-1,4-iminothreitol (33d): A 25% solution of TFA in water (4 mL) and THF (4 mL) to **29d** (74 mg, 0.18 mmol). The reaction mixture was stirred under N_2. After 48 h TLC (EtOAc/hexane 3:2) showed the consumption of SM (R_f 0.5). The reaction was concentrated under reduced pressure. Water was added to the residue and removed under reduced pressure (2 × 20 mL), then toluene was added and removed under reduced pressure (2 × 20 mL) to yield a yellow oil resulted (38 mg). This crude product was purified by flash column chromatography on silica gel (MeOH/$CHCl_3$ 3:17) to yield pure **33d**, as its trifluoroacetate salt, a pale yellow oil (33 mg, 63%). ^{1}H NMR (500 MHz, D_2O): δ = 3.18 (dd, ^2J(H,H) = 13.0, ^3J(H,H) = 3.0 Hz 1H; CHH′N), 3.45 (dd, ^2J(H,H) = 12.5, ^3J(H,H) = 5.5 Hz, 1H; CHH'N), 4.19 (d, ^3J(H,H) = 6.5 Hz, 1H; NCHPh), 4.25 (m, 2H; 2 × CHOH), 7.32–7.37 (m, 5H; C_6H_5); ^{13}C NMR (125.7 MHz, D_2O, DEPT): δ = 50.1 (CH$_2$N), 67.5 (NCH(Ph)), 74.9 (NCH$_2$CHOH), 80.6 (CH(Ph)CHOH), 116.5 (q, CF_3COO$^-$, ^1J(C,F) = 290 Hz), 128.1, 129.4, 129.7, 134.0 (4 × aromatic C), 163.2 (q, CF_3COO^-, ^2J(C,F) = 35 Hz); IR (KBr disc): $\tilde{\nu}$ = 3357 cm^{-1} (br, O-H), 2946 (aliphatic C-H), 1679 (CF_3C=O); MS (ES): m/z (%): 180 (100) [M^++H]; HRMS (ES): m/z: calcd for $C_{10}H_{14}NO_2$: 180.1025; found: 180.1020 [M^++H].

1α-(4-Methoxybenzyl)-1,4-dideoxy-1,4-iminothreitol (33f): A solution of TFA (aq., 25% v/v, 4 mL) and THF (2 mL) was added to **29f** (77 mg, 0.17 mmol). The reaction mixture was stirred under Ar. After 65 h TLC (EtOAc) revealed showed consumption of SM (R_f 0.2). The reaction was concentrated under reduced pressure, water was added to the residue and removed under reduced pressure (2 × 20 mL), then toluene was added and removed under reduced pressure (2 × 20 mL) to yield a yellow oil (60 mg). This crude product was purified by ion-exchange chromatography (Dowex, H$^+$ form, 50X2-200, Acros; water then 0.1M aqueous ammonia solution) to yield **33f** (23 mg, 61%) as a yellow oil. ^{1}H NMR (400 MHz, CD_3OD, COSY): δ = 2.74 (dd, ^2J(H,H) = 13.8, ^3J(H,H) = 8.2 Hz, 1H; CHH′C$_6$H$_4$), 2.88 (dd, ^2J(H,H) = 12.0, ^3J(H,H) = 2.6 Hz, 1H; CHH′N), 2.99 (dd, ^2J(H,H) = 13.8, ^3J(H,H) = 6.2 Hz, 1H; CHH'C$_6$H$_4$), 3.07 (dd, ^2J(H,H) = 12.0, ^3J(H,H) = 5.3 Hz, 1H; CHH'N), 3.08 (m, 1H, CH-pMeOBn), 3.75 (dd, ^3J(H,H) = 3.2, 5.2, 1H; NCHCHOH), 3.78 (s, 3H; OCH$_3$), 4.04 (pdt, ^3J(H,H) = 2.5, 2.5, 5.2, 1H; NCH$_2$CHOH), 6.88 (m, 2H; 2 of C$_6$H$_4$), 7.19 (m, 2H; 2 of C$_6$H$_4$); ^{13}C NMR (100 MHz, CD_3OD, DEPT): δ = 39.9 (t, CH_2C$_6$H$_4$), 53.3 (t, NCH$_2$), 56.1 (q, OCH$_3$), 68.7 (d, NCH), 79.4 (d, CHOH), 83.1 (d, CHOH), 115.4, 131.5 (2d, 2 × aromatic CH), 132.4 (s, quaternary aromatic C), 160.2 (s, quaternary aromatic C); IR (KBr disc): $\tilde{\nu}$ = 3273 cm^{-1} (brs, O-H stretch), 2928 (aliphatic C-H stretch), 1613, 1515; HRMS (CI): m/z: calcd for $C_{12}H_{18}NO_3$: 224.1287; found: 224.1285 [M^++H].

1β-Ethyl-1,4-dideoxy-1,4-iminoerythritol (34b): THF (1 mL) and a solution of TFA (aq., 25% v/v, 2 mL) was added to **30b** (110 mg, 0.64 mmol). The mixture was stirred vigorously under Ar. After 60 h stirring, TLC (EtOAc) showed consumption of SM (R_f 0.2). The mixture was concentrated under vacuum. Water was added and the solvent removed under high vacuum (3 × 20 mL), then toluene was added and the solvent evaporated (2 × 20 mL) to yield an oily solid. This was purified by ion-exchange chromatography (Dowex, 50X2-200, H$^+$ form, Acros, 10% v/v solution of "880" ammonia) the flash column chromatography on silica gel ($CHCl_3$/MeOH/"880" ammonia solution 30:15:4) to yield pure **34b** (81 mg, 96%). ^{1}H NMR (400 MHz, D_2O, COSY): δ = 0.94 (t, ^3J(H,H) = 7.5 Hz, 3H; CH$_2$CH_3), 1.61, 1.79 (2m, 2 × 1H; CH_2CH$_3$), 3.20 (dd, ^2J(H,H) = 13.1, ^3J(H,H) = 2.2 Hz, 1H; NCHH′), 3.31 (td, ^3J(H,H) = 5.4, ^3J(H,H) = 8.9 Hz, 1H; NCH(Et)), 3.41 (dd, ^2J(H,H) = 13.1, ^3J(H,H) = 4.5 Hz, 1H; NCHH'), 3.95 (dd, ^3J(H,H) = 8.6, ^3J(H,H) = 4.2 Hz, 1H; CH(Et)CH), 4.26 (m, 1H; NCH$_2$CH); ^{13}C NMR (100 MHz, D_2O, APT, HMQC): δ = 10.4 (q, CH(CH$_2$CH_3)), 23.4 (t, CH(CH_2CH$_3$), 49.2 (t, NCH$_2$), 62.6 (s, CH(Et)), 69.7 (d, NCH$_2$CH), 75.0 (d, CH(Et)CH); IR (film): $\tilde{\nu}$ = 3355 cm^{-1} (br, O-H, N-H stretches), 2969 (aliphatic C-H stretch); HRMS (CI): m/z: calcd for $C_{10}H_{14}NO_2$: 132.1025; found: 132.1018 [M^++H].

1β-Phenyl-3,4-dihydroxy-1,4-dideoxy-1,4-iminoerythritol (34d): THF (1 mL) and a solution of TFA (aq., 25% v/v solution, 2 mL) was added to **30d** (75 mg, 0.34 mmol). The mixture was vigorously stirred under Ar. After 48 h TLC (50:50 EtOAc/cyclohexane) showed consumption of SM (R_f 0.2). The solution was concentrated under vacuum, water was added and the solvent removed under vacuum (3 × 20 mL) then toluene was added and the solvent evaporated (2 × 20 mL) to yield an oily solid. This was purified by ion-exchange chromatography (Dowex, 50X2-200, H$^+$ form, Acros; 10% v/v solution of "880" ammonia) then flash column chromatography on silica gel ($CHCl_3$/MeOH/"880" ammonia solution 30:15:4) to yield **34d** (39 mg, 64%). ^{1}H NMR (400 MHz, D_2O, COSY): δ = 3.41 (d, ^2J(H,H) = 13.3 Hz, 1H; NCHH′), 3.73 (d, ^2J(H,H) = 13.3, ^3J(H,H) = 4.3 Hz, 1H; NCHH'), 4.48 (brt, ^3J(H,H) = 3.6 Hz, 1H; NCH$_2$CH), 4.55 (d, ^3J(H,H) = 10.1 Hz, 1H; NCH(Ph)), 4.62 (dd, ^3J(H,H) = 10.1, ^3J(H,H) = 3.9 Hz, 1H; NCH(Ph)CH), 7.46–7.50 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, D_2O, APT, HMQC): δ = 50.4 (t, NCH$_2$), 63.0 (d, CH(Ph)), 69.6 (d, NCH$_2$CH), 76.3 (d, CH(Ph)CH), 128.7, 130.0, 130.6 (3d, 3 × aromatic CH), 132.2 (s, quaternary aromatic C); IR (film): $\tilde{\nu}$ = 3336 cm^{-1} (br, O-H, N-H stretches), 3032 (aromatic C-H stretch), 2933 (aliphatic C-H stretch); HRMS (CI): m/z: calcd for $C_{10}H_{14}NO_2$: 180.1025; found: 180.1025 [M^++H].

1β-(4-Methoxybenzyl)-2,3-dihydroxy-1,4-dideoxy-1,4-iminoerythritol (34f): THF (1 mL) and trifluoroacetic acid (TFA) (25% aqueous solution, 2 mL) was added to **30f** (96 mg, 0.36 mmol). The mixture was vigorously stirred under Ar. After 50 h stirring, TLC (EtOAc) showed consumption of SM (R_f 0.2). The solution was concentrated under vacuum, water was added and the solvent removed under vacuum (3 × 20 mL), then toluene was added and the solvent evaporated (2 × 20 mL) to yield an oily solid. This was purified by ion-exchange chromatography (Dowex, 50X2-200, H$^+$ form, Acros; 10% solution of "880" ammonia) then flash column chromatography on silica gel ($CHCl_3$/MeOH/"880" ammonia solution, 30:15:4) to yield **34f** (52 mg, 65%) as a yellow oil. ^{1}H NMR (400 MHz, D_2O, COSY): δ = 2.63 (dd, ^2J(H,H) = 14.3, ^3J(H,H) = 9.3 Hz, 1H; CHH′C$_6$H$_4$), 2.81 (dd, ^2J(H,H) = 12.9, ^3J(H,H) = 3.0 Hz, 1H; CHH′N), 2.95 (dd, ^2J(H,H) = 14.3, ^3J(H,H) = 5.0 Hz, 1H; CHH'C$_6$H$_4$), 3.23 (dd, ^2J(H,H) = 12.8, ^3J(H,H) = 5.4 Hz, 1H; CHH'N), 3.27 (td, ^3J(H,H) = 9.0, ^3J(H,H) = 5.0 Hz 1H; NCH(CH$_2$Ar), 3.69 (s, 3H; OCH$_3$), 3.78 (dd, ^3J(H,H) = 8.3, ^3J(H,H) = 5.0 Hz, 1H; NCHCHOH), 4.13 (td, ^3J(H,H) = 5.0, ^3J(H,H) = 3.0 Hz, 1H; NCH$_2$CHOH), 6.86 (m, 2H; 2 of C$_6$H$_4$), 7.14 (m, 2H; 2 of C$_6$H$_4$); ^{13}C NMR (100 MHz, D_2O, APT, HMQC): δ = 36.3 (t, CH_2C$_6$H$_4$), 49.9 (t, NCH$_2$), 55.7 (q, OCH$_3$), 62.5 (d, NCH(CH$_2$Ar)), 70.2 (d, NCH$_2$CH), 75.4 (d, NCH(CH$_2$Ar)CH), 114.6 (d, aromatic CH), 130.4 (s, quaternary aromatic C), 130.5 (d, aromatic CH), 158.0 (s, quaternary aromatic C); IR (film): $\tilde{\nu}$ = 3328 cm^{-1} (br, O-H, N-H stretches), 3030 (aromatic C-H stretch), 2934 (aliphatic C-H stretch), 1612; HRMS (CI): m/z: calcd for $C_{12}H_{18}NO_3$: 224.1287; found: 224.1284 [M^++H].

Non-mammalian glycosidase inhibition assays: p-Nitrophenyl glycosides were purchased from Sigma-Aldrich Co. Ltd. Enzymes were purchased from Sigma-Aldrich: α-mannosidase (*Canavalia ensiformis*, jack beans, M7257), β-mannosidase (snail acetone powder, M9400), β-glucosidase (almonds, G0395), α-galactosidase (green coffee beans, G8507), α-rham-

nosidase (*Penicillium decumbens*, naringinase, N1385), α-L-fucosidase (bovine kidney, F5884). Recordings were made using a Molecular Devices SPECTRAmax Microplate Spectrophotometer.

3.5 mM stock solution of *p*-nitrophenyl α-L-rhamnopyranoside in 0.1M pH 7.0 orthophosphate buffer and 5.0 mM stock solutions of all other *p*-nitrophenyl glycosides in 0.1M pH 7.0 orthophosphate buffer were prepared and diluted to 3.0, 2.5, 2.0, 1.5, 1.0, 0.5, 0.25 mM and 4.0, 3.0, 2.0, 1.5, 1.0, 0.5, 0.25 mM, respectively. Enzyme solutions were prepared in 0.1M pH 7.0 orthophosphate buffer to a stock concentration of 2.0 U mL^{-1} and diluted to give a final assay concentration of 0.1 U mL^{-1}. Stock inhibitor solutions were prepared in deionised water to a concentration of 40 mM and diluted to give a final assay concentration range of 0.1, 0.05, 0.01, 0.005, 0.001 mM. Substrate solutions (185 μL of each) were pipetted into a multiwell plate and incubated for ten minutes at 37 °C prior to use. Enzyme solution (10 μL) was incubated for 5 minutes at 37 °C with appropriate inhibitor solution (5 μL) prior to use and pipetted into substrate solution. Release of *p*-nitrophenol from substrate was recorded at 405 nm for 5 minutes, reading every 10 s with agitation between each reading. Inhibition data was compiled and analysed using Excel2000 (Microsoft), and Grafit 4.0 (Erithacus Software Ltd.), using Dixon plot analysis.

Human lysosomal glycosidase inhibition assays: Enzymes were extracted from an MCF7 cell-line harvest: cells were harvested from ≈100 mL of standard culture, washed in phosphate buffered saline solution (PBS) and sonicated (3 × 10 s) in water (1 mL). Extract (5 μL) and inhibitor solution (0.04, 0.4 or 4 mM diluted using water from 100 mM stock in DMSO, 5 μL) were diluted with the appropriate enzyme assay solution (see below, 10 μL) and incubated for the appropriate length of time (see below). The course of the assay was stopped by addition of glycine-carbonate buffer solution (0.17M, pH 9.8, 150 μL) and absorbance (405 nm) or fluorescence (excitation 460 nm, emission 355 nm) recorded as appropriate. Assay solutions and incubation times: α-D-glucosidase [1.25 mM *p*-nitrophenyl α-D-glucopyranoside in 0.2M citrate/phosphate buffer, pH 4.4, 37 °C, 16 h]; β-D-glucosidase [5 mM 4-methylumbelliferyl β-D-glucopyranoside in 0.2M citrate/phosphate buffer, pH 5.8, 37 °C, 3 h]; α-D-galactosidase [20 mM *p*-nitrophenyl α-D-galactopyranoside, 180 mM *N*-acetyl-D-glucosamine in 0.2 mM citrate/phosphate buffer, pH 4.4, 37 °C, 4 h]; β-D-galactosidase [5 mM *p*-nitrophenyl β-D-galactopyranoside in 0.2M citrate/phosphate buffer, pH 4.3, 37 °C, 2 h]. IC_{50} values were determined from ×2 serial dilutions as appropriate of inhibitor concentrations from 40 mM. All assays were recorded in duplicate.

Non-lysosomal β-glucosidase inhibition assay: Conducted as for human lysosomal β-glucosidase inhibition assays except prior to assay, MCF7 extract (450 μL) was incubated for 30 min with the irreversible lysosomal β-glucosidase inhibitor conduritol β-epoxide (25 mM diluted from a 250 mM stock in DMSO, 4.5 μL).

Glucosylceramide synthase (GCS) assay: GCS [UDP-glucose *N*-acylsphingosine glucosyltransferase (EC 2.4.1.80)] assay was conducted using HL-60 cell microsomes as described in ref. [60].

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[21] Imines **3** and **4** contain the same core substructure as ribitol imine **1** (see ref. [14]), which prior to this work had been the substrate for one of the highest yielding examples of addition of an organometallic nucleophile to a cyclic imine reported in the literature. We therefore wondered if the increased rigidity of this bicyclic [3.3.0] geometry could be an important factor.

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