Synthesis of polyhydroxy piperidines and their analogues: a novel approach towards selective inhibitors of α-glucosidase†‡

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Various polyhydroxy piperidine azasugars have been synthesized from precursors **18a** and **18b**, obtained in both enantiomeric forms from D-ribose. Out of these polyhydroxy piperidine azasugars, **22**, **39** and **20** were found to be potent as well as selective inhibitors of α-glucosidase with K_i values ranging as low as 1.07 μM, 16.4 μM, and 88.2 μM, respectively. Replacement of the hydroxy methylene moiety of **19** (K_i 33% at 1 mM) by an amino methylene moiety (**32**, K_i 36.8 μM) showed a remarkable increase in the activity (almost 30 times). Furthermore, increasing the lipophilicity of **33** by *N*-alkylation with a dodecyl group (**36**) showed a three-fold enhancement in the activity (K_i 217 μM to K_i 72.3 μM).

Introduction

Since the time glycosidases/glycosyl transferases[1] were identified as key carbohydrate processing enzymes, interest in developing carbohydrate mimics as inhibitors has intensified, because many of them show promising chemotherapeutic potential in the treatment of various diseases such as viral infection,[2] cancer,[3] AIDS,[4] and diabetes.[5] In this context, iminosugars[6] and carbasugars[7] have emerged as important compound classes of specific and competitive inhibitors.

A large number of sugar analogues having a nitrogen atom in place of the oxygen atom in the ring, such as nojirimycin (**1**), deoxynojirimycin (**2**) and fagomine (**3**), (Fig. 1) are reported[6] to be glycosidase inhibitors. Similarly, another class of sugar analogues in which the nitrogen atom is placed at the anomeric carbon, such as isofagomine[8] (**4**), isogalactofagomine[9a] (**5**), isofucofagomine[9b,c] (**6**), 5-hydroxy isofagomine[9d] (**7**) and their derivatives,[9] have also emerged as potent glycosidase inhibitors as they are believed to mimic the oxocarbenium ion transition state.[10] Polyhydroxy piperidines (**8–10**), isolated by Kusano[11] *et al.* as an active component of the extract of the plant *Eupatorium fortunei* used in folk medicine for various diseases and synthesized by Ganem[12] *et al.* (**8–11**), have been shown to be potent glycosidase inhibitors.[13]

Although there are a few good strategies[9,13] known for the synthesis of these inhibitors, they lack generality for diversity oriented syntheses. Since previously[14] we had developed scaffold **12** in both enantiomeric forms starting from the corresponding tartaric acids, utilizing a photoinduced electron transfer (PET) cyclization as the strategy[15] (Fig. 2), in order to synthesize isofagomine (a mimic of D-glucose) and other piperidinols (**8**, **10** and **11**), we envisaged extending the scope of this strategy to discover more potent and specific enzyme inhibitors.[16]

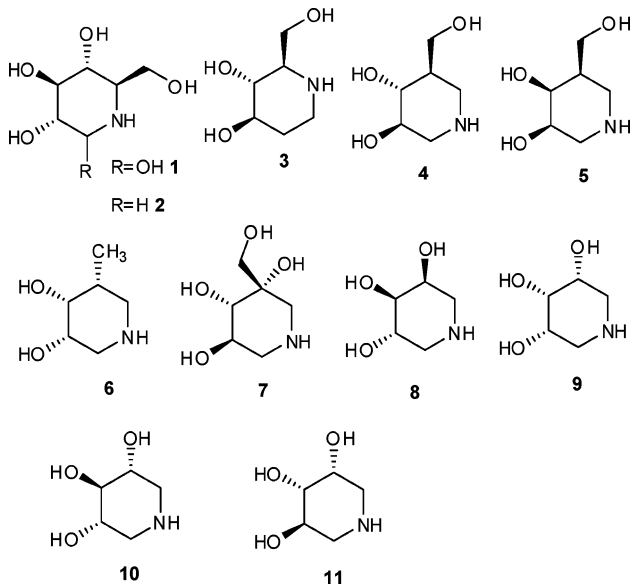

Fig. 1 Various potent glycosidase inhibitors.

Towards this endeavor, we envisioned that starting with D-ribose (Scheme 1) and through selective protection and installation of the acetylenic moiety, it might be possible to obtain two enantiomeric synthons (**A** and **B**) that would allow the synthesis of other azasugars such as **5** (galacto type), **6** and **9** (fuco type) and other structural analogues of them. We have explored this aspect in detail and would like to discuss the findings in this article, along with enzyme inhibition studies.

Results and Discussion

Initially, we directed our efforts towards synthesizing synthon **A** as a proposed precursor for compounds **6** and **9**. Towards this

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† Electronic supplementary information (ESI) available: X-ray crystal structure analysis for compounds **18a** and **18b**, general procedure for the enzyme inhibition assay, general experimental methods, general procedures for *N*-debenzylation, acetonide cleavage and the conversion of the hydroxyl moiety to the amine, and experimental procedures for compounds **16a**, **17**, **18a**, **21**, **38**. See DOI: 10.1039/b804278k

‡ CCDC reference numbers 673352 and 673353. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b804278k

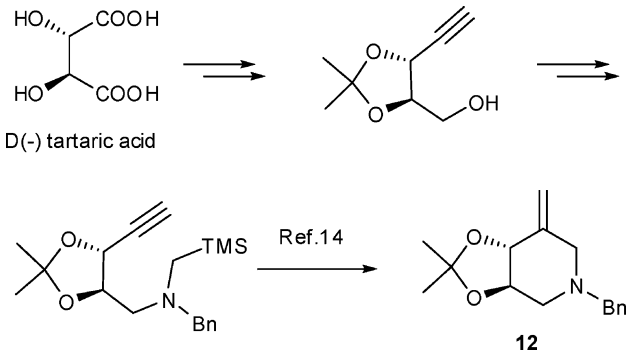
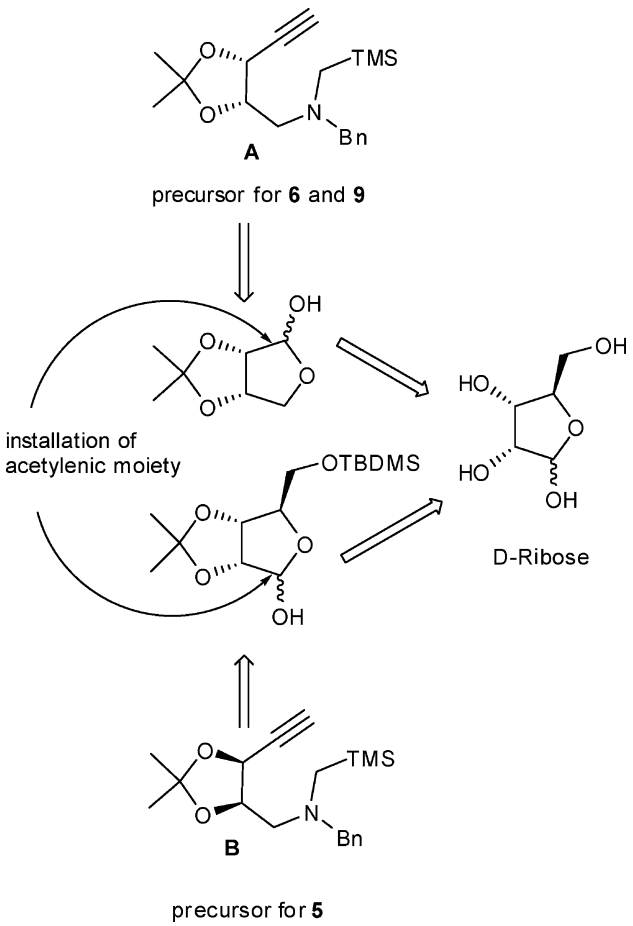
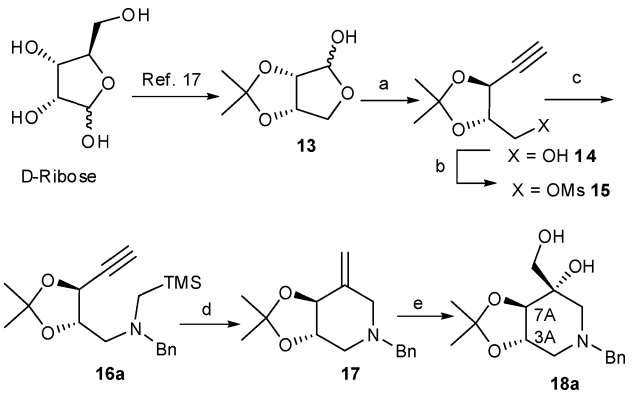


Fig. 2 Synthesis of **12**.



Scheme 1 Proposed route for enantiomeric synthons **A** and **B**.

end, the acetonide protected D-ribose (obtained by refluxing D-ribose with acetone in the presence of a few drops of conc. H_2SO_4) (Scheme 2), upon $NaBH_4$ reduction followed by sodium periodate cleavage of the resultant diol produced lactol **13** in 70% yield.[17] The masked carbonyl group of **13** was converted to the corresponding acetylenic moiety by the gradual addition of Bestmann–Ohira reagent[18] to obtain **14** in 70% yield.[19] The free hydroxyl moiety of **14** was subsequently transformed into mesylate **15** in quantitative yield, which upon refluxing (96 h) with trimethylsilylmethyl benzylamine ($BnNHCH_2TMS$) in the presence of anhydrous K_2CO_3 gave **16a** in 80% yield. Compound **16a**, upon photoinduced electron transfer (PET) mediated cyclization,[15] carried out



Scheme 2 **Reagents and conditions:** (a) $(MeO)_2P(O)C(N_2)COMe$, K_2CO_3, MeOH, 65 °C, 6 h, 70%; (b) $MeSO_2Cl$, Et_3N, DCM, 0 °C to rt, 5 h, 100%; (c) $BnNHCH_2TMS$, TBAI (cat.), K_2CO_3, CH_3CN, reflux, 96 h, 80%; (d) *hv*, DCN, 2-PrOH, 1 h, 60%; (e) OsO_4, NMO (50% aq. solution), *t*-BuOH, rt, 24 h, 90%.

by irradiating a dilute solution of **16a** (2.9 mmol) and 1,4-dicyanonaphthalene (0.9 mmol) in *iso*-propanol (200 mL) in a pyrex vessel, using a 450 W Hanovia medium pressure lamp as the light source, produced cyclized product **17** in 60% yield. In the ^1H NMR of **17**, the coupling constant between protons H_{3A} and H_{7A} was noticed to be unexpectedly higher in magnitude (J = 9.22 Hz) than expected for the original *cis*- relationship, indicating a possible inversion. As it was difficult to prove, beyond doubt, the stereochemistry of **17** at this stage, we dihydroxylated the olefinic double bond by using OsO_4 in *t*-BuOH, producing **18a** as a single diastereomer in 90% yield (crystalline solid, m.p.152–154 °C).

X-Ray[20] (Fig. 3) analysis of **18a** established the *trans*-stereochemistry between H_{3A} and H_{7A}. The spectral data and optical rotation ($[a]_D^{29}$ +24.2 (*c* 0.6, MeOH)) of **18a** also matched those of the compound previously prepared by us starting from L-tartaric acid.[14d,e]

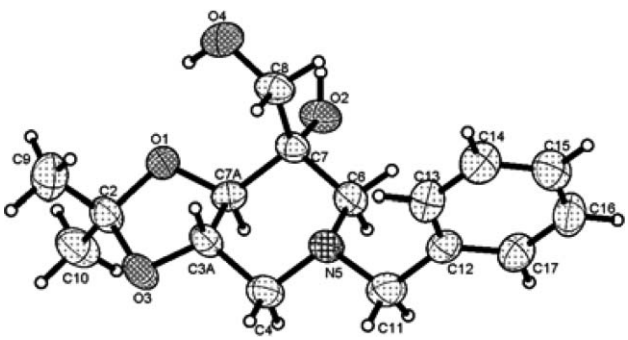
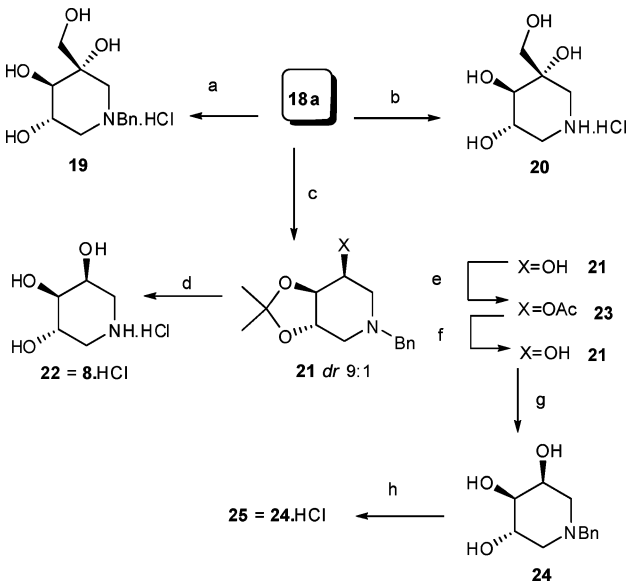


Fig. 3 ORTEP diagram of **18a**.[20] Ellipsoids are drawn at 50% probability.

These observations led us to speculate that the possible step for inversion could be the reaction of lactol **13** with the Bestmann–Ohira reagent. Careful literature[21] scrutiny revealed a precedence for such an epimerization. This observed inversion could be attributed to the greater thermodynamic stability of the *trans*- over the *cis*- structure.

Although this unexpected result was disappointing, nevertheless the current protocol appeared to be more attractive for the synthesis of **18a** (6 steps) than the earlier one, reported[14e] by us

starting with tartaric acid (11 steps). As the synthesis of other analogues from **18a** and the exploration of their enzyme inhibitory activity against various other enzymes was forthcoming from our group, we decided to continue with the existing protocol and synthesized azasugars such as **22**, **20** by following simple synthetic steps[14e] as shown in Scheme 3. The major diastereomers of **21**, formed by the sodium borohydride reduction of the corresponding ketone, were separated after the *N*-debenzylation during the synthesis of **22**, whereas the corresponding acetate **23** was used to obtain pure diastereomer for the preparation of **25**.



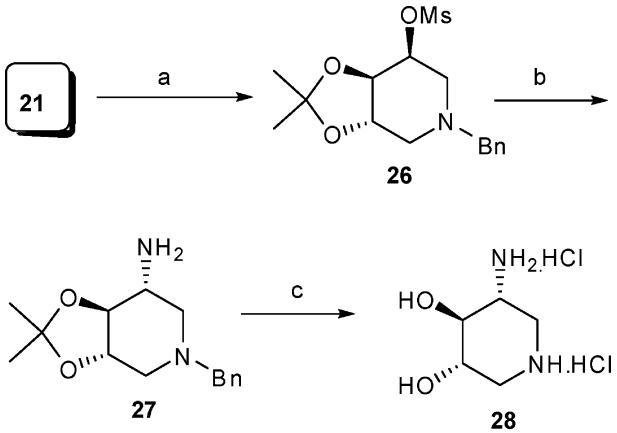
Scheme 3 **Reagents and conditions:** (a) HCl, MeOH, rt, 4 h, 100%; (b) (i) $Pd(OH)_2$ on C, H_2 (1 atm.), EtOH, rt, 10 h; (ii) HCl, MeOH, rt, 4 h, 100% over 2 steps; (c) (i) $NaIO_4$, EtOH : H_2O (4 : 1), rt, 0.5 h; (ii) $NaBH_4$, MeOH, 0 °C to rt, 24 h, 85% over 2 steps, dr 9 : 1; (d) (i) $Pd(OH)_2$ on C, H_2 (1 atm.), EtOH, rt, 10 h; (ii) HCl, MeOH, rt, 4 h, 85% over 2 steps; (e) AcCl, Py, DCM, 30 h, rt; 80%; (f) K_2CO_3, MeOH, rt, 12 h, 90%; (g) HCl, MeOH, rt, 4 h, 90%; (h) HCl, MeOH, rt, 15 min, 100%.

C-3 amine analogue azasugars

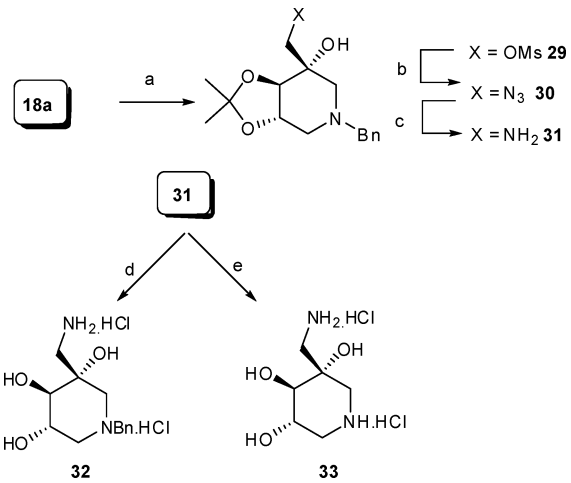
In order to create a different class of azasugars having another basic site[6f,22] for binding to the enzyme, we thought of transforming the hydroxy moiety at C_3 of **8** as well as the hydroxy methylene group at C_3 of **19** and **20** into the corresponding amine functionality (Schemes 4 and 5). Mesylate **26**, obtained from **21** (Scheme 4), was purified by column chromatography to obtain the major diastereomer. Replacement of the mesylate with azide by using LiN_3, followed by reduction of the crude azide with LAH, furnished **27** as the free amine in 60% yield. Reductive *N*-debenzylation followed by acetonide deprotection of **27** gave **28** in quantitative yield.

A similar sequence of reactions was also carried out to prepare amine analogues **32** and **33** from the corresponding diol **18a**, through the synthetic intermediates **29**, **30** and **31** (Scheme 5).

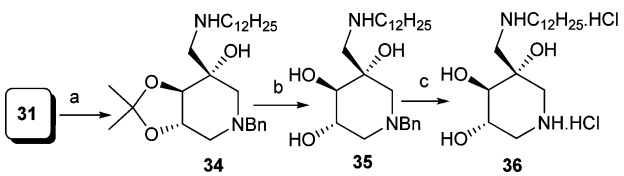
Furthermore, in order to increase the lipophilicity of **33** and also to evaluate the role it plays in the enzyme inhibition, we attached a long hydrocarbon chain to its primary amine functionality (Scheme 6).



Scheme 4 **Reagents and conditions:** (a) $MeSO_2Cl$, Py, 0 °C to rt, 6 h, 85%; (b) (i) LiN_3, DMF, 110 °C, 20 h; (ii) LAH, THF, 12 h, 60% over 2 steps; (c) (i) $Pd(OH)_2$ on C, H_2 (1 atm.), EtOH, rt, 10 h; (ii) HCl, MeOH, rt, 4 h, 100% over 2 steps.



Scheme 5 **Reagents and conditions:** (a) $MeSO_2Cl$, Et_3N, DCM, 0 °C to rt, 6 h, 90%; (b) LiN_3, DMF, 110 °C, 20 h, 90%; (c) LAH, THF, 12 h, 90%; (d) HCl, MeOH, rt, 4 h, 100%; (e) (i) $Pd(OH)_2$ on C, H_2 (1 atm.), EtOH, rt, 10 h; (ii) HCl, MeOH, rt, 4 h, 100% over 2 steps.

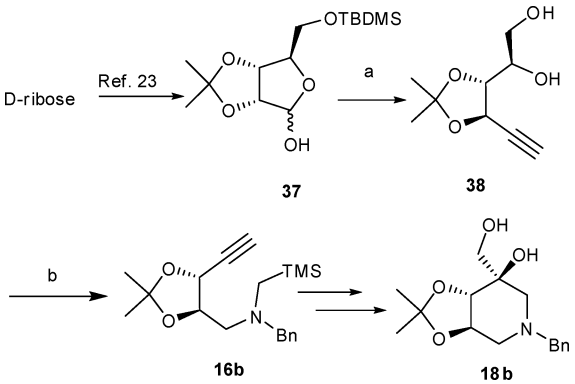


Scheme 6 **Reagents and conditions:** (a) $C_{12}H_{25}Br$, K_2CO_3, CH_3CN : THF (3 : 1), rt to reflux, 6 h, 70%; (b) HCl, MeOH, rt, 4 h, 70%; (c) (i) $Pd(OH)_2$ on C, H_2 (1 atm.), EtOH, rt, 10 h; (ii) HCl, MeOH, rt, 15 min, 100% over 2 steps.

The alkylation was carried out by refluxing **31** with dodecyl bromide in the presence of K_2CO_3 in CH_3CN : THF (3 : 1) to obtain **34** in 70% yield. Acetonide deprotection of **34** yielded **35** in 70% yield, which upon *N*-debenzylation and salt formation gave **36** in quantitative yield.

Synthesis of enantiomers 39, 40 and 41

As discussed in Scheme 1, the same reaction sequence (as shown in Schemes 7 and 8) was repeated to obtain the enantiomers of the above azasugars. Starting from synthon **37** (prepared from D-ribose itself),[23] the corresponding diol **38** was obtained by using Bestmann–Ohira reagent[18] in 55% yield. As usual in this case, epimerization was observed at C_{3A} during the course of the reaction. The diastereomeric ratio was found to be 16 : 1 (determined from the ^{1}H NMR); the major one being the epimerized product.[24] Sodium periodate cleavage of the diol moiety of **38** gave the corresponding aldehyde, which was converted directly to **16b** by reductive amination[25] with $BnNHCH_2TMS$ in 50% yield. Following similar steps as described above, the enantiomeric compound **18b** was obtained (Scheme 7).



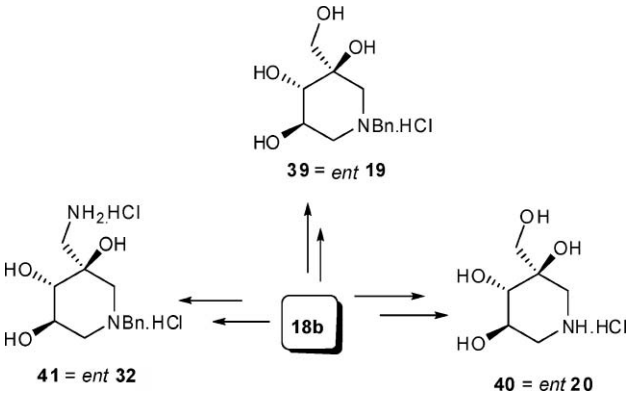
Scheme 7 **Reagents and conditions:** (a) $(MeO)_2P(O)C(N_2)COMe$, K_2CO_3, MeOH, 65 °C, 6 h, 55%; (b) (i) $NaIO_4$, EtOH : H_2O (4 : 1), rt, 0.5 h; (ii) $Na(OAc)_3BH$, EDC, $BnNHCH_2TMS$, rt, 24 h, 50% over 2 steps.

The X-ray[26] analysis of **18b** further confirmed the epimerization during the acetylenylation step (Fig. 4).

Identical reaction sequences as described earlier led us to synthesize **39**, **40** and **41** from **18b** (Scheme 8).

Enzyme inhibition studies

The inhibitory activities of all the final molecules **19**, **20**, **39**, **40**, **25**, **22**, **28**, **32**, **33**, **41**, **36** were tested against various



Scheme 8 Synthesis of **39**, **40** and **41**.

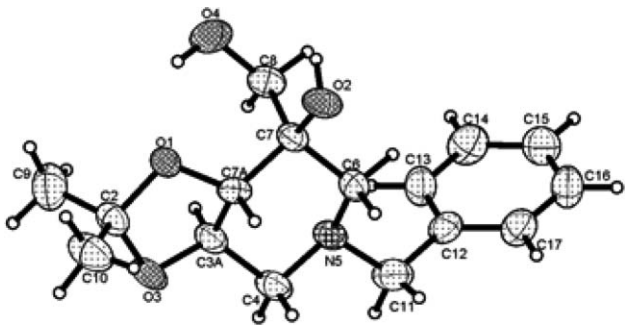


Fig. 4 ORTEP diagram of **18b**.[26] Ellipsoids are drawn at 50% probability.

enzymes and the results are summarized in Table 1. None of the compounds (except **22**) showed any significant activity against both α- and β-galactosidase as well as mannosidases (from jack beans). However, all the compounds showed inhibitory activity against α-glucosidase. Compounds **20**, **39**, **22**, **32**, **36** were found to be anomer specific and inhibited α-glucosidase strongly, with K_i values (in μM) of 88.2, 16.4, 1.07, 36.8, 72.3, respectively, whereas there wasn't any significant inhibition of the corresponding β-glucosidase. Compounds **25**, **28**, **33** and **36** proved to be selective inhibitors of α-glucosidase. This reflects the fact that the current framework has the potential to inhibit this class of enzyme, and the results can be explored further and analyzed for further increases in inhibition and to gain an understanding of the

Table 1 Inhibition[a] (K_i in μM) of glycosidases by inhibitors

	Enzymes (source)						
Inhibitor	β-Gal. (*Aspergillus oryzaie*)	α-Gal. (green coffee beans)	β-Man. (snail)	α-Man. (jack beans)	β-Glu. (almond)	α-Glu. (yeast)	α-Man. (*Aspergillus fischeri*)
19	967	NI	20%[b]	NI	NI	*33%*[b]	NI
20	NI	NI	27%[b]	NI	NI	*88.2*	217
39	NI	NI	NI	NI	NI	*16.4*	41.4
40	NI	NI	NI	NI	1066	*42%*[b]	NI
25	6%[b]	890	NI	23%[b]	NI	*210*	50%[b]
22	*504*	*85*	*578*	*991*	*456*	*1.07*	*325*
28	NI	NI	NI	NI	NI	*153*	35%[b]
32	NI	NI	NI	10%[b]	20%[b]	*36.8*	37.3
33	NI	NI	NI	14%[b]	NI	*217*	930
41	NI	NI	NI	17%[b]	34%[b]	*471.3*	NI
36	NI	NI	NI	NI	NI	*72.3*	35%[b]

[a] NI, no inhibition up to 1 mM. [b] Percent inhibition at 1 mM level.

mechanistic pathway. The introduction of a second basic site in the form of amine functionality proved to be fruitful since the amine analogue **32** (K_i 36.8 μM and 37.3 μM) proved to be approximately 30 times more potent against both α-glucosidase and α-mannosidase (*A. fischeri*) than its hydroxy analogue **19** (K_i 33%, and no inhibition at 1 mM). However, there was a slight reduction in the activity of the *N*-debenzylated analogue (**20** *vs* **33**) against both the enzymes and also a decrease in the activity against α-mannosidase (*A. fischeri*) when comparing **36** with **20**. Increasing the lipophilicity, was also fruitful as the alkylated product **36** was not only selective for α-glucosidase but also showed more activity (3 times) than its non alkylated form **33** (K_i 217 μM to K_i 72.3 μM). Compound **22** proved to be a very potent inhibitor, in particular, for α-glucosidases (K_i 1.07 μM) but also exhibited some inhibition properties for all the other enzymes tested. In addition, compounds **39** and **32** also displayed good activities (K_i 41.4 μM and 37.3 μM) against the α-mannosidase that was indigenously isolated from *Aspergillus fischeri*.

Conclusion

In conclusion we have developed a versatile strategy for the synthesis of polyhydroxy azasugars, which we have shown to be selective inhibitors of α-glucosidase. The utility of this protocol lies in being diversity oriented yet simple in nature. The reaction sequence for the various azasugars remains almost similar and thus doesn't require a variety of reactions to be tried. The triol **22** showed moderate to good activities against the various enzymes tested. The new amine analogue azasugars showed promising activity, introducing another area of research to be explored.

Experimental

General experimental methods

Unless mentioned, all reactions were performed under an argon atmosphere. All commercially available reagents were used without further purification unless otherwise noted. Enzymes were purchased from commercial sources. Tetrahydrofuran was freshly distilled from benzophenone ketyl radical under argon prior to use. Column chromatography was performed with silica gel (100–200 and 230–400 mesh). The combined organic layers were dried over $NaSO_4$. Solvents were evaporated under reduced pressure. All yields given refer to isolated yields. Melting points are reported uncorrected. Optical rotations were measured on a precision automated polarimeter. NMR spectra were recorded on 200, 400, and 500 MHz spectrometers. Chemical shifts are reported in ppm. Coupling constants (*J* values) are reported in Hertz. ^{13}C peak multiplicity assignments were made based on DEPT data. IR spectra were recorded on a FT-IR spectrometer. MS experiments were performed on a low resolution magnetic sector mass spectrometer. GC analysis was performed on a Varian CP 3800 GC using a CP-Sil 5CB column. The optical density measurements were carried out on a Varian CARY-50 BIO UV-vis spectrophotometer.

General procedure for the enzyme inhibition assays

Inhibition assays to determine the inhibitory potencies of the azasugars were carried out by spectrophotometrically measuring the residual hydrolytic activities of the glycosidases on the corresponding *p*-nitrophenyl glycosides in the presence of the azasugars. The absorbance of the resulting solution was read at 405 nm.

((4*S*,5*S*)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (14)

To a stirring mixture of **13** (10.0 g, 62.5 mmol) and anhydrous K_2CO_3 (11.37 g, 81.25 mmol) in dry MeOH (240 mL) at 65 °C was added a solution of Bestmann–Ohira reagent (15.6 g, 81.25 mmol) in dry MeOH (80 mL) dropwise over a period of 6 h under an argon atmosphere. After neutralization with acetic acid, the solvent was removed *in vacuo*, water was added and the mixture extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (pet. ether–ethyl acetate, 4 : 1) to obtain **14** (6.82 g, 70%) as a colorless liquid. $[\alpha]_D^{27}$ −8.6 (*c* 1.0, MeOH); lit.[14b] $[\alpha]_D^{20}$ −7.3 (*c* 2.0, MeOH); anal. calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74; found: C, 61.79; H, 7.84; IR (neat) υ_{max}/cm^{-1}, 3452, 3284, 2121, 848, 665; ^1H NMR (200 MHz, $CDCl_3$, D_2O exchange), δ 1.42 (s, 3H), 1.48 (s, 3H), 2.53 (d, 1H, J = 2.15 Hz), 3.64 (dd, 1H, J = 12.25, 3.67 Hz), 3.87 (dd, 1H, J = 12.25, 3.03 Hz), 4.16 (ddd, 1H, J = 7.58, 3.67, 3.03 Hz), 4.56 (dd, 1H, J = 7.57, 2.15 Hz); ^{13}C NMR (50 MHz, $CDCl_3$), δ 25.7 (CH_3), 26.4 (CH_3), 60.4 (CH_2), 66 (CH), 74.7 (CH), 80.5 (C), 81.7 (CH), 110.4 (C); mass: *m*/*z* (%), 179 (M^+ + Na, 100), 157 (M^+ + H, 32), 139 (57).

((4*S*,5*S*)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)methyl methanesulfonate (15)

To a stirring solution of **14** (7.0 g, 44.87 mmol) and triethylamine (6.87 mL, 49.35 mmol) in dry DCM (100 mL) under an argon atmosphere was added methanesulfonyl chloride (3.82 mL, 49.35 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm to room temp. and stirred for 5 hours. Water was added and the mixture extracted with DCM (2 × 100 mL). The organic layer was given a brine wash, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and chromatographed (pet. ether–EtOAc, 4 : 1), to give **15** (10.49 g) as a yellow liquid in quantitative yield. $[\alpha]_D^{29}$ −29.36 (*c* 0.6, $CHCl_3$); anal. calcd for $C_9H_{14}O_5S$; C, 46.14; H, 6.02; S, 13.69; found: C, 46.24; H, 5.90; S, 13.66; IR υ_{max}/cm^{-1} in $CHCl_3$, 3282, 2123, 1359, 1219; ^1H NMR (200 MHz, $CDCl_3$), δ 1.42 (s, 3H), 1.49 (s, 3H), 2.58 (d, 1H, J = 2.02 Hz), 3.06 (s, 3H), 4.25–4.44 (m, 3H), 4.54 (dd, 1H, J = 6.82, 2.02 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 26.0 (CH_3), 26.6 (CH_3), 37.6 (CH_3), 66.5 (CH), 67.1 (CH_2), 75.5 (CH), 79.1(CH), 79.7(C), 111.5 (C); mass: *m*/*z* (%), 234 (M^+, 8), 217 (71), 186 (64), 123 (100).

(3*S*,4*R*,5*S*)-1-Benzyl-3-(hydroxymethyl)piperidine-3,4,5-triol hydrochloride (19)

Diol **18a** (0.025 g, 0.085 mmol), upon acetonide cleavage, afforded pure **19** (0.024 g) quantitatively as a white solid. $[\alpha]_D^{22}$ −2.90 (*c* 1.05, MeOH), *ent* $[\alpha]_D^{27}$ +3.73 (*c* 0.75, MeOH); anal. calcd for $C_{13}H_{20}ClNO_4$: C, 53.89; H, 6.96; N, 4.83; found: C, 53.69; H, 6.86 N, 4.97; ^1H NMR (400 MHz, D_2O), δ 3.19 (d, 1H, J = 12.80 Hz), 3.30 (d, 1H, J = 12.80 Hz), 3.44 (d, 1H, J = 13.05 Hz), 3.52–3.56 (m, 2H), 3.69 (d, 1H, J = 12.04 Hz), 3.88 (s, 1H), 4.16 (d, 1H, J = 3.26 Hz), 4.45 (d, 1H, J = 13.05 Hz), 4.51 (d, 1H, J = 13.05 Hz),

7.57–7.60 (m, 5H); ^{13}C NMR (100 MHz, D_2O), δ 53.06 (CH_2), 53.13 (CH_2), 60.8 (CH_2), 64.1 (CH_2), 65.4 (CH), 67.8 (CH), 72.8 (C), 127.6 (C), 129.3 (CH), 130.4 (CH), 131.7 (CH); mass: *m/z* (%), 255 (33), 254 (100), 236 (13).

(3*S*,4*R*,5*S*)-3-(Hydroxymethyl)piperidine-3,4,5-triol hydrochloride (20)

Diol **18a** (0.02 g, 0.068 mmol), upon *N*-debenzylation and acetonide cleavage, afforded pure **20** (0.013 g) quantitatively as a white solid. $[\alpha]_D^{28}$ −16.98 (*c* 0.5, MeOH), *ent* $[\alpha]_D^{28}$ +15.47 (*c* 0.65, MeOH); lit.[14d,e] $[\alpha]_D^{25}$ −12.1 (*c* 0.15, EtOH), *ent* $[\alpha]_D^{25}$ +11.0 (*c* 0.2, EtOH); anal. calcd for $C_6H_{14}ClNO_4$: C, 36.10; H, 7.07; N, 7.02; found: C, 36.23; H, 7.27; N, 7.21; ^{1}H NMR (400 MHz, D_2O), δ 3.15 (d, 1H, J = 13.14 Hz), 3.25 (d, 1H, J = 5.56 Hz), 3.32 (d, 1H, J = 5.18 Hz), 3.43 (dd, 1H, J = 13.39, 2.91 Hz), 3.62 (d, 1H, J = 11.87 Hz), 3.71 (d, 1H, J = 11.88 Hz), 3.85 (d, 1H, J = 4.68 Hz), 4.11 (dd, 1H, J = 7.39, 4.11 Hz). ^{13}C NMR (100 MHz, D_2O), δ 45.3 (CH_2), 46.2 (CH_2), 63.7 (CH_2), 66.7 (CH), 68.0 (CH), 71.7 (C); mass: *m/z* (%), 164 (100), 146 (26), 128 (16).

(3*S*,5*S*)-Piperidine-3,4,5-triol hydrochloride (22)

Alcohol **21** (0.05 g, 0.19 mmol), upon *N*-debenzylation, column purification of the diastereomer (230 : 400 mesh, DCM–MeOH, 95 : 5) and acetonide cleavage, gave **22** (0.027 g, 85% yield) as a white viscous liquid. $[\alpha]_D^{27}$ +15 (*c* 0.3, MeOH); lit.[12] $[\alpha]_D^{25}$ +16 (*c* 0.5, MeOH); anal. calcd for $C_5H_{12}ClNO_3$: C, 35.41; H, 7.13; N, 8.26; found: C, 35.23; H, 7.27; N, 8.21; ^{1}H NMR (400 MHz, D_2O), δ 3.04 (dd, 1H, J = 12.80, 8.28 Hz), 3.28 (dd, 1H, J = 13.05, 2.76 Hz), 3.37 (dd, 1H, J = 13.05, 6.02 Hz), 3.49 (dd, 1H, J = 12.80, 4.01 Hz), 3.86 (dd, 1H, J = 7.78, 3.01 Hz), 4.18 (dt, 1H, J = 8.03, 4.01 Hz), 4.30–4.33 (m, 1H); ^{13}C NMR (100 MHz, D_2O), δ 45.5 (CH_2), 46.0 (CH_2), 64.7 (CH), 65.0 (CH), 70.8 (CH); mass: *m/z* (%), 132 (100), 107 (45).

(3a*S*,7*S*,7a*R*)-5-Benzyl-2,2-dimethyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridin-7-yl acetate (23)

To a solution of alcohol **21** (0.1 g, 0.38 mmol) and pyridine (0.036 ml, 0.45 mmol) in dry DCM (2 mL) under an argon atmosphere, was added acetyl chloride (0.027 ml, 0.38 mmol) and the reaction mixture was allowed to stir at room temperature for 30 h. After adding a few drops of water, it was extracted with DCM (2 × 5mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography (silica 230–400, pet. ether–ethyl acetate, 7 : 3), to give **23** (0.092 g, 80%) as a colorless liquid. $[\alpha]_D^{31}$ +60.54 (*c* 1.85, $CHCl_3$); anal. calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59; found: C, 66.53; H, 7.89 N, 4.23; IR (neat) υ_{max}/cm^{-1}, 1741, 1217, 756; ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.42 (s, 6H), 2.13 (s, 3H), 2.27 (t, 1H, J = 9.85 Hz), 2.38 (dd, 1H, J = 13.13, 1.90 Hz), 3.08 (d, 1H, J = 13.39 Hz), 3.26–3.38 (m, 2H), 3.70 (s, 2H), 4.05 (dt, 1H, J = 9.72, 3.91 Hz), 5.34 (dd, 1H, J = 4.74, 2.46 Hz) 7.21–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 21.0 (CH_3), 26.4 (CH_3), 26.8 (CH_3), 53.9 (CH_2), 54.6 (CH_2), 61.5 (CH_2), 67.4 (CH), 71.4 (CH), 79.6 (CH), 110.5 (C), 127.3 (CH), 128.3 (CH), 128.9 (CH), 137.2 (C), 170.5 (C); mass: *m/z* (%), 328 (M^+ + Na, 75), 306 (M^+ + H, 100), 266 (64), 229 (95).

(3*S*,5*S*)-1-Benzylpiperidine-3,4,5-triol (24)

Diastereomerically pure **21** (0.022 g, 0.083 mmol), upon acetonide cleavage, basic work up and column purification (DCM–MeOH, 92.5 : 7.5), gave **24** as a white solid (0.016 g, 90%). $[\alpha]_D^{23}$ +26.66 (*c* 0.3, MeOH); anal. calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27; found: C, 64.44; H, 7.87; N, 6.37; ^{1}H NMR (400 MHz, $CDCl_3$, D_2O exchange), δ 2.04–2.08 (m, 1H), 2.35 (d, 1H, J = 11.80 Hz), 2.91 (d, 1H, J = 9.03 Hz), 2.99 (d, 1H, J = 8.03 Hz), 3.36 (d, 1H, J = 5.02 Hz), 3.61 (s, 2H), 3.79 (dt, 1H, J = 8.78, 4.77 Hz), 3.91 (s, 1H), 7.28–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 56.5 (CH_2), 56.8 (CH_2), 61.9 (CH_2), 68.3 (CH), 69.5 (CH), 127.5 (CH), 128.5 (CH), 129.1 (CH), 137.3 (C); mass: *m/z* (%), 246 (M^+ + Na, 42), 224 (M^+ + H, 100).

(3a*S*,7*S*,7a*R*)-5-Benzyl-2,2-dimethyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridin-7-yl methanesulfonate (26)

Alcohol **21** (0.1 g, 0.38 mmol), upon mesylation and column purification of the diastereomers (pet. ether–ethyl acetate, 4 : 1) gave **26** (0.11 g, 85%) as a colorless liquid. $[\alpha]_D^{20}$ +46.66 (*c* 0.45, $CHCl_3$); IR (neat) υ_{max}/cm^{-1}, 1361, 738; anal. calcd for $C_{16}H_{23}NO_5S$: C, 56.29; H, 6.79; N, 4.10; S, 9.39; found: C, 56.18; H, 6.75; N, 4.58; S, 9.36; ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.41 (s, 3H), 1.43 (s, 3H), 2.32 (t, 1H, J = 10.11 Hz), 2.52 (d, 1H, J = 13.64 Hz), 3.09, (s, 3H), 3.19–3.38 (m, 3H), 3.76 (s, 2H), 4.04 (dt, 1H, J = 9.86, 3.92 Hz), 5.13 (dd, 1H, J = 4.36, 2.34 Hz), 7.26–7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 26.3 (CH_3), 26.8 (CH_3), 38.9 (CH_3), 54.2 (CH_2), 55.0 (CH_2), 61.2 (CH_2), 71.1 (CH), 75.1 (CH), 79.2 (CH), 110.9 (C), 127.4 (CH), 128.4 (CH), 128.8 (CH), 137 (C); mass: *m/z* (%), 342 (M^+ + H, 93), 224 (100).

(3a*S*,7*R*,7a*S*)-5-Benzyl-2,2-dimethyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridin-7-amine (27)

Mesylate **26** (0.05 g, 0.14 mmol) was converted to azide, which upon LAH reduction afforded amine **27** as a yellow liquid (0.023 g, 60%). $[\alpha]_D^{22}$ +14.29 (*c* 1.4, $CHCl_3$); IR (neat) υ_{max}/cm^{-1}, 3390, 2343, 736; anal. calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68; found: C, 68.52; H, 8.35; N, 10.77; ^{1}H NMR (400 MHz, $CDCl_3$, D_2O exchange), δ 1.44 (s, 3H), 1.45 (s, 3H), 1.89 (dd, 1H, J = 11.29, 9.28 Hz), 2.22 (t, 1H, J = 10.04 Hz), 2.97 (dd, 1H, J = 11.34, 3.66 Hz), 3.04–3.14 (m, 2H), 3.21 (dd, 1H, J = 9.66, 3.89 Hz), 3.56–3.63 (m, 1H), 3.66 (s, 2H), 7.25–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 26.7 (CH_3), 26.8 (CH_3), 50.2 (CH), 54.3 (CH_2), 59.4 (CH_2), 61.7 (CH_2), 75.4 (CH), 85.8 (CH), 110.6 (C), 127.3 (CH), 128.3 (CH), 128.9 (CH), 137.8 (C); mass: *m/z* (%), 285 (M^+ + Na, 5), 263 (M^+ + H, 100), 205 (44).

(3*S*,4*S*,5*R*)-5-Aminopiperidine-3,4-diol dihydrochloride (28)

Amine **27** (0.02 g, 0.075 mmol), upon *N*-debenzylation and acetonide cleavage, afforded pure diamine hydrochloride salt **28** (0.015 g) quantitatively as a white viscous liquid. $[\alpha]_D^{25}$ −1.05 (*c* 0.95, MeOH); anal. calcd for $C_5H_{14}Cl_2N_2O_2$: C, 29.28; H, 6.88; N, 13.66; found: C, 29.38; H, 6.56; N, 13.56; ^{1}H NMR (400 MHz, D_2O), δ 3.11 (dd, 1H, J = 12.80, 10.29 Hz), 3.35 (dd, 1H, J = 10.67, 12.93 Hz), 3.58–3.67 (m, 2H), 3.80–3.85 (m, 2H), 3.93–3.99

(m, 1H); ^{13}C NMR (100 MHz, D_2O), δ 42.8 (CH_2), 46.1 (CH_2), 48.7 (CH), 66.8 (CH), 70.9 (CH); mass: *m/z* (%), 133 (100), 116 (81), 102 (20).

((3a*S*,7*S*,7a*S*)-5-Benzyl-7-hydroxy-2,2-dimethyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridin-7-yl)methyl methanesulfonate (29)

Diol **18a** (0.2 g, 0.68 mmol) was converted to mesylate **29** (0.23 g, 90%) as a white solid. Mp 100–102 °C. $[\alpha]_D^{30}$ +46.52 (*c* 0.35, $CHCl_3$), *ent* $[\alpha]_D^{32}$ −43.47 (*c* 1.40, $CHCl_3$); IR (in $CHCl_3$) υ_{max}/cm^{-1}, 2933, 1359, 1228; ^{1}H NMR (200 MHz, $CDCl_3$, D_2O exchange), δ 1.41 (s, 3H), 1.42 (s, 3H), 2.03 (d, 1H, J = 11.87 Hz), 2.25 (dd, 1H, J = 9.72, 9.61 Hz), 2.95 (s, 3H), 3.00 (dd, 1H, J = 11.88, 1.01 Hz), 3.22 (ddd, 1H, J = 9.60, 3.92, 1.14 Hz), 3.49 (d, 1H, J = 9.60 Hz), 3.59 (dd, 1H, J = 9.6, 3.91 Hz), 3.65 (s, 1H), 3.67 (s, 1H), 4.49 (d, 1H, J = 10.49 Hz), 4.57 (d, 1H, J = 10.23 Hz), 7.21–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 26.45 (CH_3), 26.5 (CH_3), 37.2 (CH_3), 54.6 (CH_2), 57.9 (CH_2), 61.3 (CH_2), 69.2 (CH_2), 71.1 (C), 73.1 (CH), 84.5 (CH), 111.1 (C), 127.4 (CH), 128.4 (CH), 128.8 (CH), 137.5 (C); mass: *m/z* (%), 394 (M^+ + Na, 75), 372 (M^+ + H, 42), 236 (59%), 229 (100).

(3a*S*,7*S*,7a*S*)-7-(Azidomethyl)-5-benzyl-2,2-dimethyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridin-7-ol (30)

Mesylate **29** (0.1 g, 0.27 mmol) was converted to azide **30** (0.077 g, 90%) as a colorless liquid. $[\alpha]_D^{29}$ +41.86 (*c* 0.35, $CHCl_3$), *ent* $[\alpha]_D^{30}$ −38.41 (*c* 1.55, $CHCl_3$); anal. calcd for $C_{16}H_{22}N_4O_3$: C, 60.36; H, 6.97; N, 17.60; found: C, 60.56; H, 7.04; N, 17.83; IR (neat) υ_{max}/cm^{-1}, 2925, 2360, 2102; ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.35 (s, 3H), 1.36 (s, 3H), 1.94 (d, 1H, J = 11.75 Hz), 2.15 (dd, 1H, J = 9.85, 9.60 Hz), 2.42 (s, 1H), 2.85 (dd, 1H, J = 11.75, 1.06 Hz), 3.13 (ddd, 1H, J = 9.73, 4.04, 1.27 Hz), 3.39 (d, 1H, J = 9.60 Hz), 3.50 (dd, 1H, J = 9.60, 3.92 Hz), 3.59 (s, 2H), 3.66 (s, 1H), 3.72 (d, 1H, J = 12.26 Hz), 7.13–7.31 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 26.45 (CH_3), 26.5 (CH_3), 52.9 (CH_2), 54.5 (CH_2), 59.0 (CH_2), 61.3 (CH_2), 71.8 (C), 73.2 (CH), 84.6 (CH), 110.9 (C), 127.4 (CH), 128.3 (CH), 128.6 (CH), 137.5 (C); mass: *m/z* (%), 341 (M^+ + Na, 56), 319 (M^+ + H, 61), 301 (33), 279 (100), 229 (63).

(3a*S*,7*R*,7a*S*)-7-(Aminomethyl)-5-benzyl-2,2-dimethyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridin-7-ol (31)

LAH reduction of **30** (0.1 g, 0.31 mmol) gave the corresponding amine compound as a white crystalline solid **31** (0.08 g, 90%). Mp 165–168 °C (from EtOAc–pet. ether); $[\alpha]_D^{28}$ +46.67 (*c* 0.3, $CHCl_3$), *ent* $[\alpha]_D^{28}$ −44.33 (*c* 0.55, $CHCl_3$); anal. calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58; found: C, 65.63; H, 8.15; N, 9.70; ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.44 (s, 3H), 1.45 (s, 3H), 2.16–2.21 (m, 2H), 2.90 (d, 1H, J = 12.05 Hz), 3.16–3.21 (m, 2H), 3.40 (d, 1H, J = 13.05 Hz), 3.52 (d, 1H, J = 9.53 Hz), 3.60–3.70 (m, 3H), 3.72–3.93 (bs, 3H), 7.26–7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 26.6 (CH_3), 42.4 (CH_2), 54.5 (CH_2), 60.1 (CH_2), 61.3 (CH_2), 70.0 (C), 73.3 (CH), 85.4 (CH), 110.5 (C), 127.2 (CH), 128.3 (CH), 128.6 (CH), 138 (C); mass: *m/z* (%), 315 (M^+ + Na, 6), 293 (M^+ + H, 86), 235 (100), 179 (13).

(3*R*,4*R*,5*S*)-3-(Aminomethyl)-1-benzylpiperidine-3,4,5-triol dihydrochloride (32)

Amino alcohol **31** (0.025 g, 0.085 mmol), upon acetonide cleavage, afforded pure **32** (0.024 g) quantitatively as a white solid. $[\alpha]_D^{22}$ −3.00 (*c* 1.00, MeOH), *ent* $[\alpha]_D^{28}$ +4.00 (*c* 1.00, MeOH); anal. calcd for $C_{13}H_{22}Cl_2N_2O_3$: C, 48.01; H, 6.82; N, 8.61; found: C, 48.11; H, 6.52; N, 8.41; ^{1}H NMR (400 MHz, D_2O), δ 3.07 (d, 1H, J = 13.30 Hz), 3.31–3.41 (m, 3H), 3.49–3.59 (m, 2H), 3.90 (s, 1H), 4.25 (s, 1H), 4.50 (d, 1H, J = 13.30 Hz), 4.55 (d, 1H, J = 13.30 Hz), 7.60 (s, 5H); ^{13}C NMR (100 MHz, D_2O), δ 43.4 (CH_2), 52.5 (CH_2), 53.5 (CH_2), 61.0 (CH_2), 65.3 (CH), 67.1 (CH), 70.4 (C), 127.4 (C), 129.4 (CH), 130.6 (CH), 131.8 (CH); mass: *m/z* (%), 254 (28), 253 (100), 206 (12).

(3*R*,4*R*,5*S*)-3-(Aminomethyl)piperidine-3,4,5-triol dihydrochloride (33)

31 (0.02 g, 0.068 mmol), upon *N*-debenzylation and acetonide cleavage, afforded pure **33** (0.016 g) quantitatively as a white solid. $[\alpha]_D^{31}$ −8.27 (*c* 1.45, MeOH); anal. calcd for $C_6H_{16}Cl_2N_2O_3$: C, 30.65; H, 6.86; N, 11.92; found: C, 30.66; H, 6.52; N, 11.72; ^{1}H NMR (400 MHz, D_2O), δ 3.14 (d, 1H, J = 13.55 Hz), 3.33 (d, 1H, J = 13.05 Hz), 3.37 (s, 1H), 3.41 (d, 1H, J = 2.51 Hz), 3.43 (d, 1H, J = 3.01 Hz) 3.52 (dd, 1H, J = 13.55, 2.51 Hz), 3.94 (d, 1H, J = 4.01 Hz), 4.22–4.25 (m, 1H); ^{13}C NMR (100 MHz, D_2O), δ 43.4 (CH_2), 44.6 (CH_2), 46.3 (CH_2), 66.3 (CH), 66.7 (CH), 69.3 (C); mass: *m/z* (%), 229 (98), 213 (59), 163 (100).

(3a*S*,7*R*,7a*R*)-5-Benzyl-7-((dodecylamino)methyl)-2,2-dimethyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridin-7-ol (34)

To a stirring solution of **31** (0.05 g, 0.17 mmol) in dry CH_3CN and THF (3 : 1), (2 mL), was added dodecyl bromide and stirring continued for 3 h at rt. K_2CO_3 (0.047 g, 0.34 mmol) was added and the mixture refluxed for 3 h. Water was added and the mixture was extracted with ethyl acetate (2 × 5 mL), dried over Na_2SO_4, concentrated and purified by column chromatography (pet. ether–ethyl acetate, 8 : 2), to give **34** (0.055 g, 70%) as a yellow liquid. $[\alpha]_D^{30}$ +26.66 (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, D_2O exchange), δ 0.89 (t, 3H, J = 6.78 Hz), 1.26 (bs, 20H), 1.42–1.43 (m, 8H), 2.10 (d, 1H, J = 11.80 Hz), 2.21 (t, 1H, J = 9.79 Hz), 2.61 (t, 1H, J = 7.03 Hz), 2.69 (d, 1H, J = 11.80 Hz), 2.88 (d, 1H, J = 12.23 Hz), 3.06 (d, 1H, J = 12.30 Hz), 3.19 (dd, 1H, J = 9.29, 3.89 Hz), 3.49 (d, 1H, J = 9.29 Hz), 3.57 (d, 1H, J = 13.05 Hz), 3.65 (s, 1H), 7.25–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 14.1 (CH_3), 22.7 (CH_2), 26.6 (CH_3), 26.7 (CH_3), 27.0 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.6 (CH_2),29.7 (CH_2), 31.9 (CH_2), 50.2 (CH_2), 50.3 (CH_2), 54.9 (CH_2), 61.0 (CH_2), 61.5 (CH_2), 69.4 (C), 73.4 (CH), 85.4 (CH), 110.5 (C), 127.3 (CH), 128.3 (CH), 128.7 (CH), 138.1 (C); mass: *m/z* (%), 461 (M^+ + H, 100), 403 (34), 229 (12).

(3*R*,4*R*,5*S*)-1-Benzyl-3-((dodecylamino)methyl)piperidine-3,4,5-triol (35)

Acetonide deprotection of **34** (0.05 g, 0.108 mmol), basification and column purification (silica gel, DCM–MeOH, 9 : 1) gave **35** as a yellow liquid (0.032 g, 70%). $[\alpha]_D^{29}$ +15.10 (*c* 0.55, $CHCl_3$); anal. calcd for $C_{25}H_{44}N_2O_3$: C, 71.39; H, 10.54; N, 6.66; found:

C, 71.55; H, 10.65; N, 6.75; ^{1}H NMR (400 MHz, $CDCl_3$, D_2O exchange), δ 0.88 (t, 3H, $J = 6.78$ Hz), 1.25 (bs, 20H), 1.69 (s, 2H), 2.23 (d, 1H, $J = 11.54$ Hz), 2.65 (d, 1H, $J = 11.04$ Hz), 2.84 (d, 1H, $J = 12.80$ Hz), 2.91–2.95 (m, 2H), 3.45–3.55 (m, 3H), 3.65 (d, 1H, $J = 7.78$ Hz), 3.72–3.80 (m, 1H), 7.23–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 14.1 (CH_3), 22.7 (CH_2), 25.6 (CH_2), 26.7 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 49.1 (CH_2), 52.4 (CH_2), 61.7 (CH_2), 69.4 (CH), 70.9 (C), 127.4 (CH), 128.4 (CH), 129 (CH), 137.6 (C).

(3*R*,4*R*,5*S*)-3-((Dodecylamino)methyl)piperidine-3,4,5-triol dihydrochloride (36)

N-Debenzylation of **35** (0.025 g, 0.059 mmol) followed by diamine hydrochloride salt formation gave **36** (0.023 g, quantitative) as a white solid. $[\alpha]_D^{26}$ +7.27 (*c* 0.55, MeOH); anal. calcd for $C_{18}H_{40}Cl_2N_2O_3$: C, 53.59; H, 9.99; N, 6.94; found: C, 53.79; H, 10.09; N, 6.84; ^{1}H NMR (400 MHz, D_2O), δ 0.90 (s, 3H), 1.32 (bs, 20H), 1.78 (s, 2H), 3.15 (s, 2H), 3.36–3.52 (m, 4H), 3.96 (s, 1H), 4.23 (s, 1H); ^{13}C NMR (100 MHz, D_2O), δ 13.6 (CH_3), 22.2 (CH_2), 25.1 (CH_2), 26.0 (CH_2), 28.5 (CH_2), 28.8 (CH_2), 29.1 (CH_2), 31.5 (CH_2), 44.6 (CH_2), 46.4 (CH_2), 49 (CH_2), 51.1 (CH_2), 66.3 (CH), 66.8 (CH), 69.5 (C); mass: *m*/*z* (%), 345 (39), 331 (100).

N-Benzyl-((4*R*,5*R*)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)-*N*-((trimethylsilyl)methyl)methanamine (16b)

To a solution of **38** (5.0 g, 26.89 mmol) in ethanol–water (100 mL, 4 : 1), was added sodium periodate (6.9 g, 32.25 mmol) gradually. The white suspension was stirred for 0.5 h at room temperature and filtered. The filtrate was concentrated and the white pasty mass was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. To a solution of this aldehyde in EDC (ethylene dichloride, 90 mL), was added $BnNHCH_2TMS$ (6.25 g, 32.25 mmol) and $Na(OAc)_3BH$ (7.98 g, 37.63 mmol) under an argon atmosphere and stirred for 24 h. The reaction mixture was quenched with aq. saturated $NaHCO_3$ solution while stirring for 0.5 h then extracted with DCM. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (pet. ether–ethyl acetate, 95 : 5) to furnish **16b** (4.45 g, 50% over two steps). $[\alpha]_D^{28}$ +0.72 (*c* 1.35, $CHCl_3$); lit.[14b] $[\alpha]_D^{20}$ +1.2 (*c* 21.2, $CHCl_3$), *ent* $[\alpha]_D^{27}$ −0.73 (*c* 0.5, $CHCl_3$); lit[14b] $[\alpha]_D^{20}$ −0.7 (*c* 11.0, $CHCl_3$); anal. calcd for $C_{19}H_{29}NO_2Si$: C, 68.83; H, 8.82; N, 4.22; found: C, 68.63; H, 8.60; N, 4.38; IR υ_{max}/cm^{-1}, in $CHCl_3$ 3307, 1674, 757; ^{1}H NMR (200 MHz, $CDCl_3$), δ 0.00 (s, 9H), 1.29 (s, 3H), 1.39 (s, 3H), 1.95 (d, 1H, $J = 14.66$ Hz), 2.08 (d, 1H, $J = 14.65$ Hz), 2.43 (d, 1H, $J = 2.02$ Hz), 2.51–2.56 (m, 2H), 3.42 (d, 1H, $J = 13.64$ Hz), 3.64 (d, 1H, $J = 13.51$ Hz), 4.14–4.23 (m, 1H), 4.30 (dd, 1H, $J = 7.33$, 2.03 Hz), 7.12–7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$), δ −1.4 (CH_3), 25.8 (CH_3), 26.8 (CH_3), 46.9 (CH_2), 58.1 (CH_2), 62.7 (CH_2), 68.6 (CH), 74.3 (CH), 80.4 (CH), 81.3 (C), 110.0 (C), 126.7 (CH), 127.9 (CH), 128.7 (CH), 139.3 (C); mass: *m*/*z* (%), 332 (M^+ + H, 100), 284 (22), 246 (19), 238 (33).

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Notes and references

1 L. L. Lairson and S. G. Withers, *Chem. Commun.*, 2004, 2243–2248.
2 C. U. Kim, W. Lew, M. A. Williams, H. Liu, L. Zhang, S. Swaminathan, N. Bischofberge, M. S. Chen, D. B. Mendel, C. Y. Tai, W. G. Laver and R. C. Stevens, *J. Am. Chem. Soc.*, 1997, **119**, 681–690.
3 P. E. Gross, M. A. Baker, J. P. Carver and J. W. Dennis, *Clin. Cancer Res.*, 1995, **1**, 935–944.
4 L. Ratner, N. V. Heyden and D. Dedera, *Virology*, 1991, **181**, 180–192.
5 (*a*) P. B. Anzeveno, L. J. Creemer, J. K. Daniel, C.-H. R. King and P. S. Liu, *J. Org. Chem.*, 1989, **54**, 2539–2542; (*b*) J. A. Balfour and D. McTavish, *Drugs*, 1993, **46**, 1025.
6 (*a*) B. Ganem, *Acc. Chem. Res.*, 1996, **29**, 340–347; (*b*) A. de Raadt, C. W. Ekhart, M. Ebner and A. E. Stütz, *Top. Curr. Chem.*, 1997, **187**, 157–186; (*c*) Y. Ichikawa, Y. Igarashi, M. Ichikawa and Y. Suhara, *J. Am. Chem. Soc.*, 1998, **120**, 3007–3018; (*d*) A. E. Stütz, *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*, Wiley-VCH, Weinheim, Germany, 1999; (*e*) N. Asano, R. J. Nash, R. J. Molyneux and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 2000, **11**, 1645–1680; (*f*) V. H. Lillelund, H. H. Jensen, X. Laing and M. Bols, *Chem. Rev.*, 2002, **102**, 515–553; (*g*) M. S. M. Pearson, M. Mathé-Allainmat, V. Fargeas and J. Lebreton, *Eur. J. Org. Chem.*, 2005, 2159–2191; (*h*) K. Afarinkia and A. Bahar, *Tetrahedron: Asymmetry*, 2005, **16**, 1239–1287; (*i*) L. J. Whalem and C.-H. Wong, *Aldrichimica Acta*, 2006, **39**, 63–71; (*j*) C. Gravier-Pelletier and Y. Le Merrer, *Curr. Org. Synth.*, 2007, **4**, 1–13; (*k*) T. M. Wrodnigg, A. J. Steiner and B. J. Bernhard, *Anti-Cancer Agents Med. Chem.*, 2008, **8**, 77–85; (*l*) X. Song and R. I. Hollingsworth, *Tetrahedron Lett.*, 2007, **48**, 3115–3118; (*m*) P. Maier, S. M. Andersen and I. Lundt, *Synthesis*, 2006, 827–830.
7 (*a*) E. Borges de Melo, A. da Silveira Gomes and I. Carvalho, *Tetrahedron*, 2006, **62**, 10277–10302; (*b*) O. Arjona, A. M. Gómez, J. C. López and J. Plumet, *Chem. Rev.*, 2007, **107**, 1919–2036.
8 (*a*) T. M. Jespersen, W. Dong, M. R. Sierks, T. Skrydstrup, I. Lundt and M. Bols, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1778–1779; (*b*) I. Panfil, J. Solecka and M. Chmielewski, *J. Carbohydr. Chem.*, 2006, **25**, 673–684.
9 (*a*) Y. Ichikawa and Y. Igarashi, *Tetrahedron Lett.*, 1995, **36**, 4585–4586; (*b*) Y. Igarashi, M. Ichikawa and Y. Ichikawa, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 553–558; (*c*) A. Hansen, T. M. Tagmose and M. Bols, *Chem. Commun.*, 1996, 2649–2650; (*d*) M. Ichikawa, Y. Igarashi and Y. Ichikawa, *Tetrahedron Lett.*, 1995, **36**, 1767–1770; (*e*) M. Bols, M. P. Persson, W. M. Butt, M. Jørgensen, P. Christensen and L. T. Hansen, *Tetrahedron Lett.*, 1996, **37**, 2097–2100; (*f*) G. Zhao, U. C. Deo and B. Ganem, *Org. Lett.*, 2001, **3**, 201–203; (*g*) M. M. Matin, T. Sharma, S. G. Sabharwal and D. D. Dhavale, *Org. Biomol. Chem.*, 2005, **3**, 1702–1707; (*h*) S. D. Markad, N. S. Karanjule, T. Sharma, S. G. Sabharwal and D. D. Dhavale, *Bioorg. Med. Chem.*, 2006, **14**, 5535–5539.
10 Ref. 6*a* and (*a*) P. Sears and C.-H. Wong, *Angew. Chem., Int. Ed.*, 1999, **38**, 2300–2324; (*b*) T. D. Heightman and A. T. Vasella, *Angew. Chem., Int. Ed.*, 1999, **38**, 750–770.
11 T. Sekioka, M. Shibano and G. Kusano, *Nat. Med. (N. Y.)*, 1995, **49**, 332.
12 R. C. Bernotas, G. Papandreou, J. Urbach and B. Ganem, *Tetrahedron Lett.*, 1990, **31**, 3393–3396.
13 Ref. 9*c* and (*a*) T. Tschamber, F. Backenstrass, M. Neuberger, M. Zhender and J. Streith, *Tetrahedron*, 1994, **50**, 1135–1152; (*b*) G. Legler, A. E. Stütz and H. Immich, *Carbohydr. Res.*, 1995, **272**, 17–30; (*c*) M. Godskesen, I. Lundt, R. Madsen and B. Winchester, *Bioorg. Med. Chem.*, 1996, **4**, 1857–1865; (*d*) K. C. Jang, I.-Y. Jeong, M. S. Yang, S. U. Choi and K. H. Park, *Heterocycles*, 2000, **53**, 887; (*e*) M. Amat, N. Llor, M. Huguet, E. Molins, E. Espinosa and J. Bosch, *Org. Lett.*, 2001, **3**, 3257–3260; (*f*) N. T. Patil, S. John, S. G. Sabharwal and D. D. Dhawale, *Bioorg. Med. Chem.*, 2002, **10**, 2155–2160; (*g*) H. Han, *Tetrahedron Lett.*, 2003, **44**, 1567–1569; (*h*) M. G. Szczepina, B. D. Johnston, Y. Yuan, B. Svensson and B. M. Pinto, *J. Am. Chem. Soc.*, 2004, **126**, 12458–12469; (*i*) H. Ouchi, Y. Mihara and H. Takahata, *J. Org. Chem.*, 2005, **70**, 5207–5214; (*j*) M. S. Reddy, M. Narender and K. R. Rao, *Tetrahedron*, 2007, **63**, 331–336.

14 (*a*) G. Pandey and M. Kapur, *Tetrahedron Lett.*, 2000, **41**, 8821–8824; (*b*) G. Pandey and M. Kapur, *Synthesis*, 2001, 1263–1267; (*c*) G. Pandey and M. Kapur, *Org. Lett.*, 2002, **4**, 3883–3886; (*d*) M. Kapur, Ph.D. thesis, University of Pune, 2002; (*e*) G. Pandey, M. Kapur, M. I. Khan and S. M. Gaikwad, *Org. Biomol. Chem.*, 2003, **1**, 3321–3326.
15 (*a*) G. Pandey, G. Kumaraswamy and U. T. Bhalerao, *Tetrahedron Lett.*, 1989, **30**, 6059–6062; (*b*) G. Pandey, G. D. Reddy and G. Kumaraswamy, *Tetrahedron*, 1994, **50**, 8185–8194.
16 (*a*) G. Pandey, S. G. Dumbre, M. I. Khan, M. Shabab and V. G. Puranik, *Tetrahedron Lett.*, 2006, **47**, 7923–7926; (*b*) G. Pandey, S. G. Dumbre, M. I. Khan and M. Shabab, *J. Org. Chem.*, 2006, **71**, 8481–8488; (*c*) G. Pandey, S. G. Dumbre, S. Pal, M. I. Khan and M. Shabab, *Tetrahedron*, 2007, **63**, 4756–4761.
17 H. Kotsuki, T. Araki, A. Miyazaki, M. Iwasaki and P. K. Datta, *Org. Lett.*, 1999, **1**, 499–502.
18 (*a*) S. Müller, B. Liepold, G. J. Roth and H. Bestmann, *Synlett*, 1996, 521–522; (*b*) G. J. Roth, B. Liepold, S. Müller and H. Bestmann, *Synthesis*, 2004, 59–62; (*c*) J. Pietruszka and A. Witt, *Synthesis*, 2006, 4266–4268.
19 (*a*) J.-C. Thiéry, C. Fréchou and G. Demailly, *Tetrahedron Lett.*, 2000, **41**, 6337–6339; (*b*) E. Alcázar, J. M. Pletcher and F. E. McDonald, *Org. Lett.*, 2004, **6**, 3877–3880.
20 CCDC number 673352.
21 F. Dolhem, C. Liévre and G. Demailly, *Tetrahedron*, 2003, **59**, 155–164.
22 (*a*) D.-K. Kim, G. Kim and Y.-W. Kim, *J. Chem. Soc., Perkin Trans. 1*, 1996, 803–808; (*b*) A. Kilonda, F. Compernolle, K. Peeters, G. J. Joly, S. Toppet and G. J. Hoornaert, *Tetrahedron*, 2000, **56**, 1005–1012; (*c*) E. Poupon, B.-X. Luong, A. Chiaroni, N. Kunesch and H.-P. Husson, *J. Org. Chem.*, 2000, **65**, 7208–7210; (*d*) I. McCort, S. Fort, A. Duréault and J.-C. Depezay, *Bioorg. Med. Chem.*, 2000, **8**, 135–143; (*e*) T. Tite, M.-C. Lallemand, E. Poupon, N. Kunesch, F. Tillequin, C. Gravier-Pelletie, Y. L. Merrer and H.-P. Hussonc, *Bioorg. Med. Chem.*, 2004, **12**, 5091–5097.
23 D. N. Kumar, B. V. Rao and G. S. Ramanjaneyulu, *Tetrahedron: Asymmetry*, 2005, **16**, 1611–1614.
24 The authors in reference 19*b* did not observe any epimerization.
25 F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff and R. D. Shah, *J. Org. Chem.*, 1996, **61**, 3849–3862.
26 CCDC number 673353.