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Synthesis of Azasugars as Potent Inhibitors of Glycosidases

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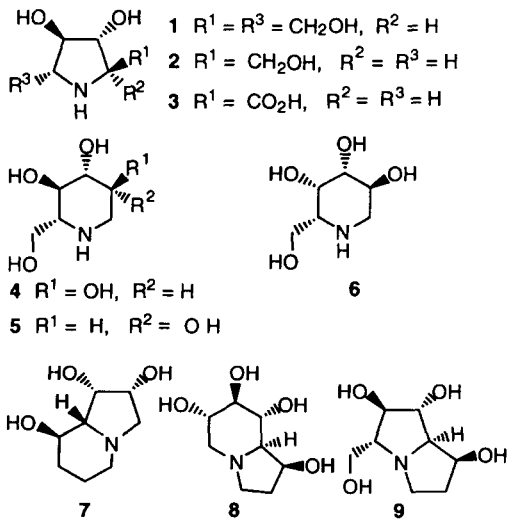
Abstract—A series of enantiomerically pure azasugars (2,5-dideoxy-2,5-imino-D-mannitol, 1-deoxynojirimycin, 1-deoxymannojirimycin, and related compounds) was synthesized from D-mannitol via aminoheterocyclization of C_2-symmetric bis-epoxides and subsequently followed by ring isomerization in few cases. These compounds have been evaluated as inhibitors of several glycosidases (α- and β-D-glucosidases, α-D-mannosidase and α-L-fucosidase). Inhibition studies indicate notably that the polyhydroxylated azepanes are inhibitors of glycosidases, with K_i in the micromolar range. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

Many polyhydroxylated pyrrolidines or piperidines are compounds that have been shown to selectively inhibit the oligosaccharide processing enzymes (i.e. glycosidases or glycosyltransferases).[1] Azasugars that inhibit these enzymes are potentially useful for treating metabolic disorders such as diabetes,[2] cancer[3] and AIDS.[4] Among them are (a) polyhydroxylated pyrrolidines such as **1** (DMDP),[5] **2**,[6] and **3**,[7] (b) polyhydroxylated piperidines like 1-deoxynojirimycin **4** (DNJ),[8] 1-deoxymannojirimycin **5** (DMJ)[9] and the galactose analogue **6**,[10] (c) the indolizidine alkaloids swainsonine **7**[11] and castanospermine **8**,[12] and (d) the pyrrolizidine alkaloid australine **9**[13] (Scheme 1).



Scheme 1.

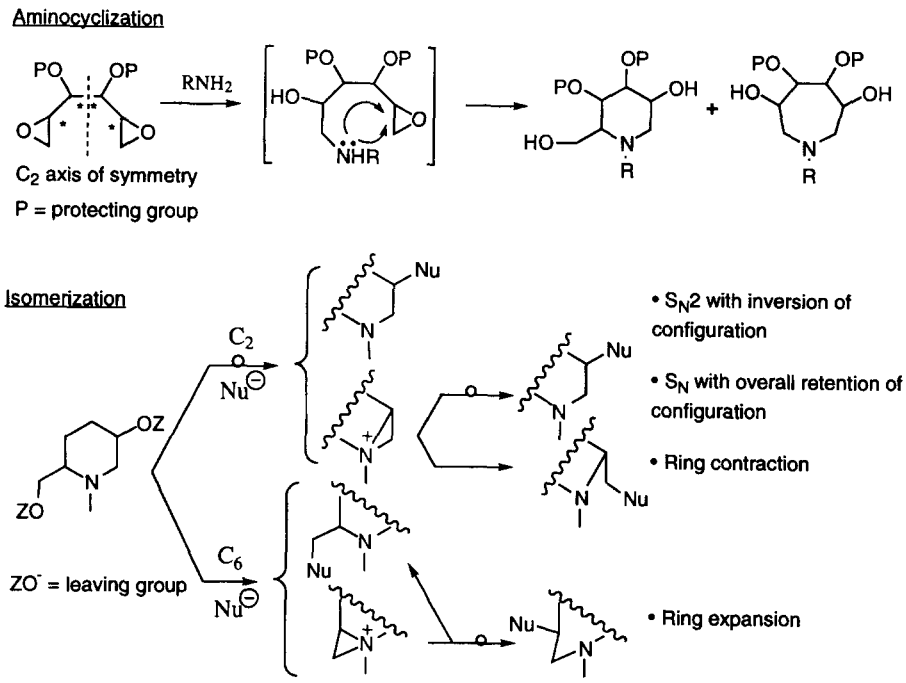
Because of the potential chemotherapeutic applications of such compounds, there is continuing interest in the synthesis of both mono- and bicyclic analogues. In an effort to develop new syntheses of enantiomerically pure azasugars we have examined (Scheme 2) the opening of homochiral C_2-symmetric bis-epoxides by amines. This approach, which involves a regiospecific opening of one epoxy function followed by the expected aminocyclization, would lead to the polyhydroxy-piperidine (6-*exo-tet* process)[14]/azepane (7-*endo-tet* process). Isomerization of these structures, after activation of the free hydroxyl groups, via an S_N process either by direct nucleophilic substitution or by neighbouring nitrogen participation would lead to other isomers.

This is in fact a viable approach, since by these two key steps we have obtained DMDP, DNJ, DMDP and various other analogues from D-mannitol, as a single starting material.[15] Our synthetic results have already been disclosed in a preliminary form.[16] We detail here our synthetic routes, the structure of the related compounds and the results of the inhibition analysis.

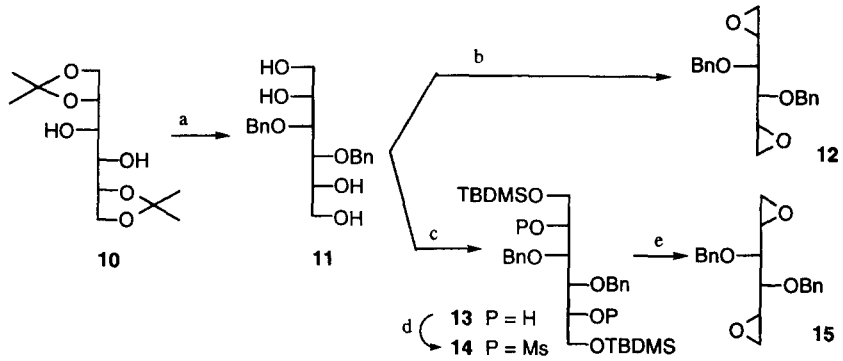
Results and Discussion

C_2-symmetric bis-epoxides and aminocyclization

Flexible optically pure C_2-symmetric bis-epoxides **12** and **15** were easily obtained, on multigram scales, from the commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol **10** (Scheme 3), via the previously described 3,4-di-*O*-benzyl-D-mannitol **11**.[17] Using Mitsunobu conditions,[18] the tetrol **11** was directly transformed in high yield (86%) to the 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-D-mannitol **12** with retention of configuration at C_2 and



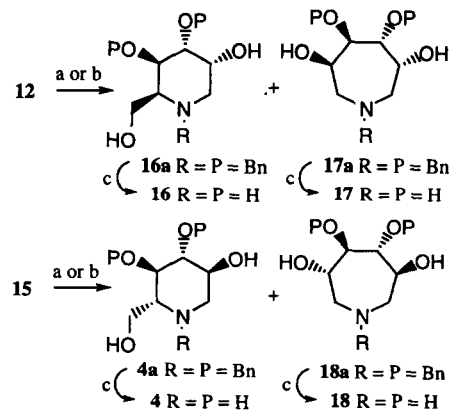
Scheme 2.



Scheme 3. (a) NaH, BnBr, *n*-Bu_4NI, THF, then AcOH, H_2O, 87%. (b) Ph_3P, DIAD, 130 °C, 86%. (c) TBDMSCl, imidazole, DMF, 0 °C, 80%. (d) MsCl, NEt_3, CH_2Cl_2, 98%. (e) HCl, MeOH, then NaOH, H_2O, 75%.

C_5. On the other hand, the tetrol **11** afforded the bis-epoxide **15** with inversion of configuration at C_2 and C_5 in 59% overall yield by the following reactions: selective silylation at the primary 1,6-hydroxyl functions, mesylation at the secondary 2,5-hydroxyl functions, then acidic removal of silyl groups followed by a base promoted intramolecular S_N2.

The opening of bis-epoxide **12** (Scheme 4) with benzylamine has been examined under different experimental conditions,[16] and among them reaction with excess benzylamine (five equivalents) in refluxing $CHCl_3$ during 48 h, afforded a mixture of two compounds that could be easily separated by flash chromatography. The piperidine **16a** and the azepane **17a** were isolated in 50 and 45% yield, respectively. Under the same experimental conditions, the diastereomeric bis-epoxide **15** gave the corresponding piperidine **4a** (45%) and azepane **18a** (33%).[19] In contrast, we found that in presence of perchloric acid which should serve as Lewis



Scheme 4. (a) $BnNH_2$ (5 equivalents), Δ, $CHCl_3$, 48 h, 50, 45, 45, and 33% yield for **16a**, **17a**, **4a**, and **18a**, respectively. (b) $BnNH_2$ (10 equivalents), $HClO_4$ (5 equivalents), H_2O, 28, 67, 9, and 66% yield for **16a**, **17a**, **4a**, and **18a**, respectively. (c) H_2, Pd black, CH_3CO_2H, 100%.

acid to enhance the epoxide opening, fast reaction occurs at 25 °C (4 h), and affords mainly the azepane structure. So, from **12** (or **15**), azepane **17a** (or **18a**) was isolated in 67% (66%) yield, whereas the piperidine **16a** (or **4a**) was isolated in only 28% (9%). The aminocyclization of 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol or L-iditol gave only the seven-membered azasugars.[15,20] Comparison of these results indicates that with a flexible bis-epoxide, with acyclic hydroxyl protecting groups at C_3–C_4, the heterocyclization can be directed towards the six- or the seven-membered ring depending on the experimental conditions, whereas, with a more rigid bis-epoxide, for which the protecting group of hydroxyl functions at C_3–C_4 is a *trans*-acetonide, heterocyclization furnishes exclusively seven-membered ring.

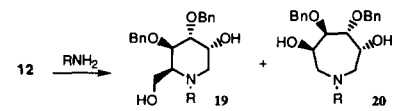
This aminocyclization can be performed with other primary amines (Table 1), such as 2-phenylethylamine, *N*-acetyl-1,4-butyldiamine, *O*-benzylhydroxylamine, *N*,*N*-dibenzylhydrazine, or more interestingly with glycine *tert*-butyl ester, tryptamine.[21] In the particular case of *N*-benzyl piperidines **4a**, **16a** or azepanes **17a**, **18a** hydrogenolytic removal of both *N*,*O*-benzyl protecting groups using palladium black in acetic acid gave, after purification by ion exchange chromatography, the corresponding azasugars **4** (DNJ), **16**, **17** or **18** in quantitative yield.

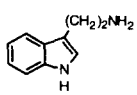
With these *N*-benzyl-polyhydroxylated-piperidines **4a** and **16a**, and C_2-symmetric azepanes **17a** and **18a**, in hand, we focused then on their isomerization.

Isomerization of piperidines

Skeletal rearrangement of pyrrolidines, piperidines or azepanes, via an aziridinium or azetidinium salt has already been reported,[22] but this method has found little application in polysubstituted heterocycles. Only few cases have been described in synthesis,[23] and more interestingly in bicyclic alkaloids such as swainsonine or castanospermine.[23c–e]

Table 1



RNH_2	Conditions[a,b,c]	Yield[d] piperidine	azepane
$PhCH_2CH_2NH_2$	a	**19a**: 31%	**20a**: 66%
$AcHN(CH_2)_4NH_2$	b	**19b**: 48%	**20b**: 32%
$BnONH_2$·HCl	c	**19c**: 22%	**20c**: 51%
$(Bn)_2NNH_2$	b	**19d**: 30%	**20d**: 23%
$^tBuO_2CCH_2NH_2$·HCl	b+Et_3N (4 equiv)	**19e**: 40%	**20e**: 33%
	a	**19f**: 26%	**20f**: 64%
	b	**19f**: 50%	**20f**: 45%

[a] RNH_2 (10 equiv), $HClO_4$ (5 equiv), H_2O, 25 °C, 4 h.
[b] RNH_2 (5 equiv), $CHCl_3$, Δ, 48 h.
[c] RNH_2 (4 equiv), NEt_3 (5 equiv), H_2O, 80 °C, 15 h.
[d] Unoptimized yield for each isolated compound.

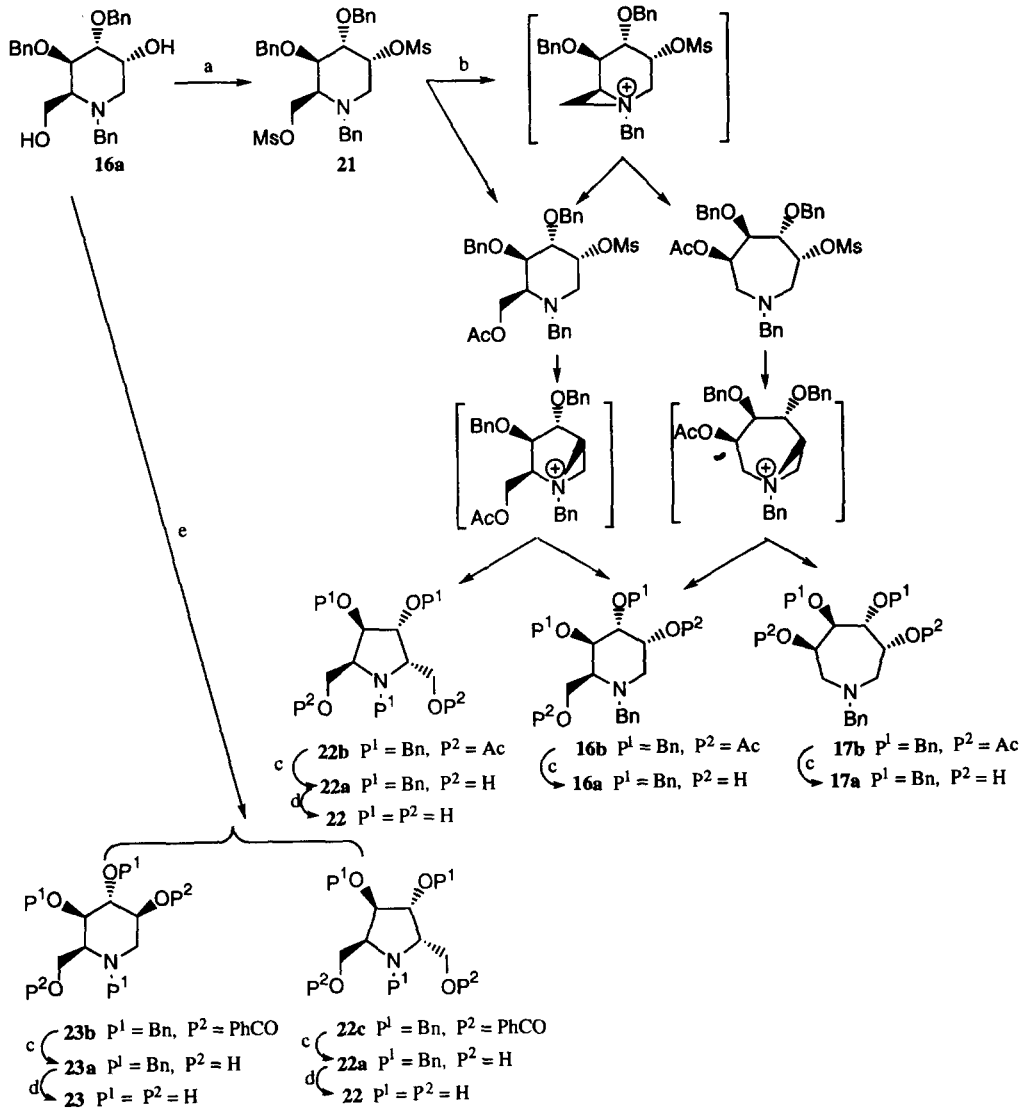
The L-*gulo*-piperidine **16a** was readily transformed (Scheme 5) to the dimesylate **21** (100% yield). The latter treated by caesium acetate in dimethylformamide, followed by methanolysis in presence of potassium carbonate gave three compounds **16a**, **17a** and **22a** in 18, 8 and 45% yield, respectively. The first has been identified to the starting L-*gulo*-piperidine, and the second to the D-*manno*-azepane. The third product (**22a**) has been correlated, after hydrogenolytic removal of both *N*,*O*-protecting groups to the 2,5-dideoxy-2,5-imino-L-iditol **22**.[24] This diastereomer of DMDP has been obtained in 45% overall yield from **16a** (55% based on recuperation of **16a**). On the other hand, treatment of **16a** with four equivalents of triphenylphosphine-diethyl azodicarboxylate-benzoic acid[18] in THF at 0 °C gave a mixture of only two products (**23b** and **22c**), which after methanolysis and flash chromatography separation, led to **23a** and **22a** in 70 and 18% yield, respectively. Compound **23a** that is the result of an S_N2 reaction at C_2 has been converted by hydrogenolysis to the new compound **23** (5-epi-DNJ).

Thus, from the L-*gulo*-piperidine **16a** these two procedures appear to be different and show that the normal S_N2 reaction competes with the aziridinium pathway. With the mesylate, substitution is more difficult and requires more drastic conditions (heating, long reaction time) that allows the aziridinium formation, followed mainly by ring contraction. In the case of Mitsunobu conditions (fast reaction at 0 °C), the intermolecular S_N2 is easier than the intramolecular participation of the nitrogen, which requires an inversion of the chair conformation (Scheme 6).

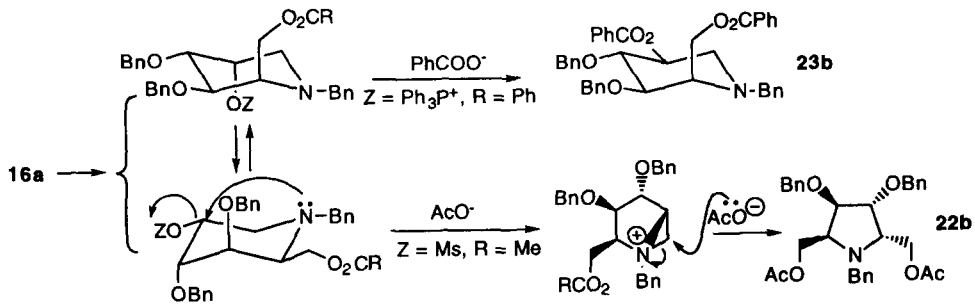
Similar reactions were performed (Scheme 7) on the D-*gluco*-piperidine **4a** by treatment with mesyl-chloride (100% yield of dimesylate **24**) and then caesium acetate, or Mitsunobu conditions (four equivalents of Ph_3P-DEAD-$PhCO_2H$, THF, 0 °C). In all cases, a mixture of two products has been obtained, and its methanolysis (MeOH, K_2CO_3) has furnished, after flash chromatography separation, the initial D-*gluco*-piperidine **4a** (31 and 29% overall yield from **4a**, respectively) and the pyrrolidine **1a** (51 and 64% overall yield from **4a**, respectively). The latter gave **1** (DMDP),[25] after hydrogenolysis of both *N*,*O*-benzyl protecting groups and purification by ion exchange chromatography.

In this case, these two procedures give mainly the ring contraction to the pyrrolidine, due to an easy neighbouring nitrogen participation, since the leaving group is in equatorial position, and subsequent ring opening of the aziridinium at the less substituted side.

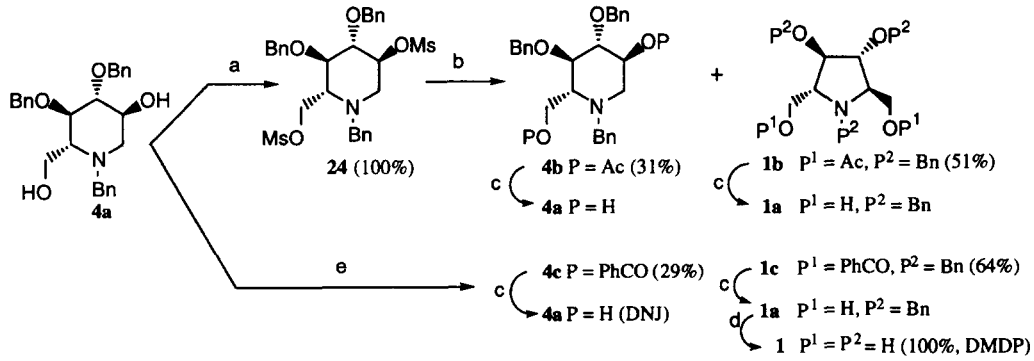
To avoid the neighbouring nitrogen participation, we have converted **4a** into the carbamate **4e** (Scheme 8) by



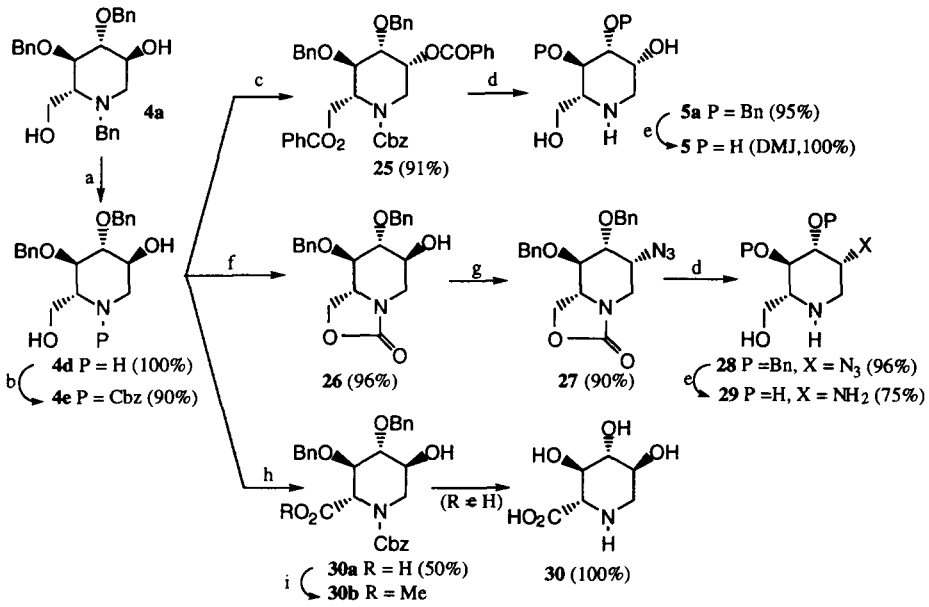
Scheme 5. (a) MsCl (2.3 equivalents), Et_3N, CH_2Cl_2, 100%. (b) AcOCs, DMF. (c) MeOH, K_2CO_3. (d) H_2, Pd black, CH_3CO_2H, 100%. (e) Ph_3P-DEAD-$PhCO_2H$ (4 equiv), THF.



Scheme 6.



Scheme 7. For reaction conditions of a, b, c, d and e see Scheme 5.



Scheme 8. (a) H_2, $Pd(OH)_2/C$, EtOH. (b) BnOCOCl, K_2CO_3, DMF. (c) Ph_3P-DEAD-$PhCO_2H$ (4 equivalents), THF. (d) MeOH, K_2CO_3 in vacuo. (e) H_2, Pd black, AcOH. (f) MeOH, K_2CO_3. (g) Ph_3P-DEAD-HN_3 (3 equivalents), THF. (h) $Na_2Cr_2O_7$, H_2SO_4, Et_2O, H_2O. (i) CH_2N_2.

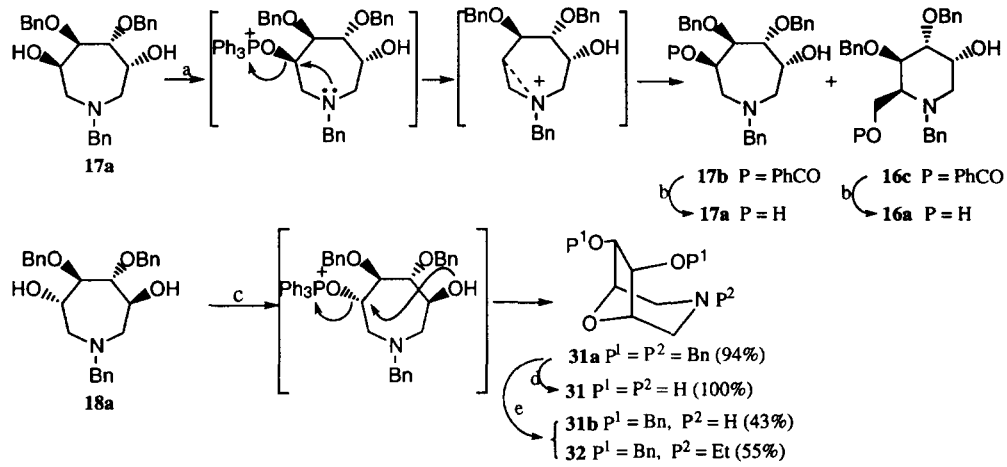
selective hydrogenolysis of the benzyl–nitrogen bond using Pearlman's catalyst,[26] followed by action of benzylchloroformate (90% overall yield). The carbamate **4e** underwent substitution under Mitsunobu conditions in presence of benzoic acid to yield only **25** (91%). To confirm the inversion of configuration at C_2, **25** was fully deprotected by methanolysis in very mild conditions (MeOH, K_2CO_3, in vacuo, 40 °C) and hydrogenolysis to give **5** (DMJ).[27]

Furthermore, methanolysis of the carbamate **4e** led to the oxazolidinone **26** (96%), and the Mitsunobu reaction in presence of hydrazoic acid[28] in benzene yielded the azido-oxazolidinone **27** (90%). Inversion of configuration at C_2 was confirmed by the modification of the coupling constants in ^1H NMR: $^3J_{3,4} = {}^3J_{4,5} = {}^3J_{2,3} = 9$ Hz to $^3J_{3,4} = {}^3J_{4,5} = 9$ Hz and $^3J_{2,3} = 2.5$ Hz for **26** and **27**, respectively. The oxazolidinone **27** was subjected to methanolysis, and then hydrogenolysis to give the 2-amino-2-deoxy-DMJ **29**.[29]

Interestingly, selective oxidation of the primary hydroxyl group of the *N*-Cbz protected piperidine **4e** can be efficiently performed by $Na_2Cr_2O_7$ under biphasic conditions[30] to give **30a**, which was fully characterized as its methyl ester **30b**. The moderate yield (50%) for **30a** was due to the difficulty in product extraction. Subsequent hydrogenolysis of **30a** afforded the (2*S*,3*R*,4*R*,5*S*)-3,4,5-trihydroxypipecolic acid **30** in quantitative yield.[31] By comparison, oxidation of the *N*-Cbz analogue derived from the L-*gulo*-piperidine **16a** gave the corresponding acid in poor yield (15%), and a hemiketal (10%) which results of both oxidation at the primary and the secondary alcohol functions.

Isomerization of azepanes (Scheme 9)

Reaction of the azepane **17a** with 1.2 equivalents of triphenylphosphine-diethyl azodicarboxylate-benzoic acid at 0 °C yielded a mixture of two monobenzoyl



Scheme 9. (a) Ph_3P-DEAD-$PhCO_2H$ (1.2 equiv), THF. (b) MeOH, K_2CO_3. (c) Ph_3P-DEAD (1.2 equiv), THF. (d) H_2, Pd black, AcOH. (e) H_2, $Pd(OH)_2/C$, EtOH.

Table 2

Enzyme	Inhibitor[a,b]										
	1	**4**	**5**	**16**	**17**	**18**	**22**	**23**	**29**	**30**	**31**
α-Glucosidase	97% **0.03** (c)	100% **0.44** (c)	100% **18** (c)	30% –	55% **70** (c)	97% **4.8** (c)	55% –	74% **65** (c)	88% **53** (c)	66% **83** (c)	6% –
β-Glucosidase	91% **160** (c)	64% **1700**	39% **1400** (c)	13% –	1% –	86% **17** (c)	42% –	11% –	4% –	8% –	0% –
α-Mannosidase	38% –	44% **1000**	49% **600** (c)	15% –	1% –	25% –	40% –	17% –	98% **20** (c)	31% –	3% –
α-Fucosidase	35% –	27% **500**	100% **0.13** (c)	94% **22** (c)	94% **28** (c)	4% –	84% **170** (c)	50% **260** (c)	63% **190** (c)	2% –	29% –

[a]% Inhibition determined at 1 mM concentration of inhibitor.
[b]Inhibition constants (K_i (μM)) in bold, and mode of inhibition (c for competitive) in parentheses were determined by the Lineweaver–Burk plot.

derivatives **17b** and **16c** (65%). By methanolysis, **17b** gave back alcohol **17a** (36%), and **16c** afforded the piperidine **16a** (24%). This result shows that the reaction undergoes via an aziridinium intermediate, the nucleophilic opening of which giving rise to the formation of the two regioisomers **17b** and **16c**.[32]

Similar treatment of the L-*ido*-azepane **18a** gave only one product **31a** (80%). In absence of benzoic acid, the yield of **31a** could be improved up to 94%. The chiral bridged morpholine **31** was then obtained after full deprotection by hydrogenolysis.[33] The formation of the bridged compound **31** can be interpreted as an intramolecular displacement of the alkoxyphosphonium intermediate by the other free hydroxyl group of the azepane, concurrently to the evolution towards the aziridinium. This bridged morpholine **31** is an interesting structure because the *N*-substituted derivatives possess various biological activities.[34]

Inhibition studies[35]

The obtained azasugars (Table 2) were evaluated as inhibitors of different glycosidases (α-D-glucosidase, β-D-glucosidase, α-D-mannosidase and α-L-fucosidase). Results obtained for DMDP **1**, DNJ **4**, and DMJ **5** are comparable with those reported. For the other compounds, never described or for which glycosidase inhibitor properties have never been reported, interesting results have been obtained. For example, **16**, a diastereomer of DNJ, is a competitive inhibitor of α-L-fucosidase ($K_i = 22$ μM), while **23** (5-epi-DNJ) inhibits α-D-glucosidase ($K_i = 65$ μM). Furthermore, the C_2-amino derivative of DMJ **29** shows analogous properties to this latter, but with weaker inhibition for α-L-fucosidase ($K_i = 190$ μM against 0.13 for DMJ). The glucuronic acid **30**, known as α-D-glucuronidase and iduronidase inhibitors,[36] is also an α-D-glucosidase inhibitor ($K_i = 83$ μM). Finally, the polyhydroxylated azepanes **17** and **18** are inhibitors of glycosidases. In particular **18** inhibits α-D-glucosidase ($K_i = 4.8$ μM) and β-D-glucosidase ($K_i = 17$μM), while its diastereomer **17** inhibits α-D-glucosidase ($K_i = 70$ μM) and α-L-fucosidase ($K_i = 28$ μM).[37] These K_i values, in the low micromolar range, show that the greater flexibility of the seven-membered ring makes these compounds capable of mimicking the putative oxonium ion transition state that it generated during the carbohydrate hydrolysis by glycosidases. By comparison, the rigid bridged morpholine **31** abolishes the inhibition.

Conclusion

The present work outlined an efficient synthetic pathway to construct various azasugars with a pyrrolidine, piperidine, or an azepane framework. Biological studies indicate, notably, that the polyhydroxylated azepanes are inhibitors of glycosidases with the K_i values in the low micromolar range. Further utilization of this methodology in the synthesis of other azasugars and related systems will be reported in due course.

Experimental

Prior to use, THF and Et_2O were distilled from sodium benzophenone and CH_2Cl_2 from P_2O_5. CH_2Cl_2 and AcOEt were filtered on K_2CO_3 prior to use. ^1H and ^{13}C NMR (250 and 63 MHz, respectively) were recorded in $CDCl_3$ (unless indicated) on a Bruker instrument. Chemical shifts are reported in δ (ppm) and coupling constants are given in Hz. Mass spectra, chemical ionization (CI), and high resolution (HRMS), were recorded in Service de Spectrométrie de Masse, Université Pierre et Marie Curie. Specific rotations were measured on a Perkin Elmer 241C polarimeter with sodium (589 nm) lamp. All reactions were run under an argon atmosphere, unless otherwise stated, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 μm) on glass. Chromatography was performed with Merck Kielselgel 60 (200–500 μm) or 60 H (5–40 μm). Spectroscopic (^1H and ^{13}C NMR, MS)/analytical data were obtained using chromatographically homogeneous samples.

Synthesis of bis-epoxides 12 and 15

1,2:5,6-Dianhydro-3,4-di-*O*-benzyl-D-mannitol (12). A suspension of the tetrol **11**[17] (12 g, 33 mmol) in toluene (150 mL) was concentrated twice in vacuo to avoid any trace of water. Then toluene (150 mL) and triphenylphosphine (20.2 g, 77 mmol) were added, and the resulting mixture was concentrated again in vacuo until it remained a volume of ca. 60 mL. The mixture was then cooled to 0 °C, and diisopropyl diazodicarboxylate (DIAD) (15.4 mL, 78 mmol) was slowly added. After 30 min stirring at 0 °C, the pale-orange resulting mixture was concentrated in vacuo and heated for 2.5 h under $P = 0.01$ mmHg to 130 °C. Flash chromatography of the crude (cyclohexane:AcOEt, 8:2) afforded 9.2 g (86%) of **12** (R_f 0.35). $[\alpha]_D$+5(*c* 1.0, CH_2Cl_2); ^1H NMR 7.26 (s, 10 H, Ph), 4.66, 4.55 (AB, 4 H, OCH_2Ph), 3.38 (m, 2 H, H_3), 3.11 (m, 2 H, H_2), 2.73 (dd, 2 H, H_1), 2.61(dd, 2H, $H_{1'}$), $^2J_{AB} = 12$, $^2J_{1,1'} = 5.5$, $^3J_{1,2} = 4$, $^3J_{1',2} = 2.5$; ^{13}C NMR 138.0, 130.8, 128.7, 127.9, 127.8 (Ph), 78.5 (C_3), 73.5 (OCH_2Ph), 50.6 (C_2), 46.0 (C_1); Anal. calcd for $C_{20}H_{22}O_4$: C, 73.60, H, 6.79; found: C, 73.50, H, 6.94.

3,4-Di-*O*-benzyl-1,6-di-*O*-*tert*-butyl dimethylsilyl-D-mannitol (13). To a stirred solution of **11**[17] (12 g, 33 mmol) in DMF (32 mL) was successively added at 0 °C imidazole (9 g, 132 mmol), and *tert*-butyldimethylsilyl chloride (10.2 g, 69.3 mmol). After 2 h stirring at 0 °C, aq saturated solution of NH_4Cl (60 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (cyclohexane:AcOEt, 85:15) afforded 15.6 g (80%) of **13** (R_f 0.30). $[\alpha]_D$ +30 (*c* 1.0, CH_2Cl_2); ^1H NMR 7.35 (m, 10 H, Ph), 4.72, 4.60 (AB, 4H, OCH_2Ph), 3.90–3.80 (m, 4 H, $H_{2,3}$), 3.76 (dd, 2 H, H_1), 3.62 (dd, 2 H, $H_{1'}$), 0.90 (s, 18H, *t*-BuSi), 0.07 (s, 12 H, Me_2Si), $^2J_{AB} = 12$, $^2J_{1,1'} = 10$, $^3J_{1,2} = 3$, $^3J_{1',2} = 5$; Anal. calcd for $C_{32}H_{54}O_6Si_2$: C, 65.09, H, 9.22; found: C, 65.06, H, 9.36.

3,4-Di-*O*-benzyl-1,6-di-*O*-*tert*-butyl dimethyl silyl-2,5-di-*O*-mesyl-D-mannitol (14). To a cooled solution of **13** (14.45 g, 24.4 mmol) in CH_2Cl_2 (30 mL) at 0 °C was successively added NEt_3 (13.8 mL, 100 mmol), and methanesulfonyl chloride (5.7 mL, 73.5 mmol). After 15 min stirring at 0 °C, the reaction was quenched by addition of water (30 mL) and diluted with CH_2Cl_2 (40 mL). After decantation and extraction with CH_2Cl_2 (3 × 60 mL), the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude **14** was used in the next step without further purification. $[\alpha]_D$ +20 (*c* 1.3, CH_2Cl_2); ^1H NMR 7.30 (m, 10 H, Ph), 4.80 (m, 2 H, H_2), 4.76, 4.66 (AB, 4 H, OCH_2Ph), 4.12 (dd, 2 H, H_1), 3.99 (s, 2 H, H_3), 3.24 (dd, 2 H, $H_{1'}$), 0.90 (s, 18 H, *t*-BuSi), 0.07 (s, 12 H, Me_2Si), $^2J_{AB} = 12$, $^2J_{1,1'} = 12$, $^3J_{1,2} = 3.5$, $^3J_{1',2} = 5.5$.

1,2:5,6-Dianhydro-3,4-di-*O*-benzyl-L-iditol (15). To a cooled solution of **14** (18.2 g, 24.2 mmol) in MeOH (41 mL) at 0 °C was slowly added concentrated aqueous hydrochloric acid (5.2 mL, 58.8 mmol). After 2 h stirring at 20 °C, the mixture was cooled to 0 °C and an aq solution of KOH (20%, 42 mL, 147 mmol) was added. The resulting mixture was stirred for 3 h at 20 °C, then concentrated in vacuo. After addition of water (25 mL) and CH_2Cl_2 (50 mL), decantation, extraction with CH_2Cl_2 (3 × 60 mL), the combined organic layers were washed with a saturated aqueous solution of NH_4Cl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (cyclohexane:AcOEt, 7:3) afforded 6.19 g (78%) of **15** (R_f 0.30). Mp 28 °C; $[\alpha]_D$ −43 (*c* 1.1, CH_2Cl_2); ^1H NMR 7.35 (s, 10 H, Ph), 4.85, 4.61 (AB, 4 H, OCH_2Ph), 3.29 (m, 2 H, H_3), 3.21 (m, 2 H, H_2), 2.74 (dd, 2 H, H_1), 2.53 (dd, 2 H, $H_{1'}$), $^2J_{AB} = 12$, $^2J_{1,1'} = 5$, $^3J_{1,2} = 4.5$, $^3J_{1',2} = 2.5$; ^{13}C NMR 137.9, 128.3, 127.9, 127.7 (Ph), 80.7 (C_3), 72.3 (OCH_2Ph), 52.4 (C_2), 43.1 (C_1); Anal. calcd for $C_{20}H_{22}O_4$: C, 73.60, H, 6.79; found: C, 73.46, H, 6.91.

Aminocyclization of bis-epoxide 12 or 15 with benzylamine

In aprotic solvent, method (a) in Scheme 4: a mixture of **12** (3.5 g, 10.74 mmol) and benzylamine (5.9 mL, 53.7 mmol) in $CHCl_3$ (50 mL) was refluxed for 48 h. Concentration in vacuo and flash chromatography (CH_2Cl_2:acetone, 9:1) afforded 2.3 g (50%) of **16a** (R_f

0.35) and 2.1 g (45%) of **17a** (R_f 0.30). From **15** (2.0 g, 6.13 mmol), 1.2 g (45%) of **4a** (R_f 0.30) and 0.88 g (33%) of **18a** (R_f 0.35) have been obtained.

In protic solvent, method (b) in Scheme 4: to **12** (2 g, 6.13 mmol) in water (40 mL) was added benzylamine (6.7 mL, 61.3 mmol) followed by $HClO_4$ in aqueous solution 70% (2.6 mL, 30.6 mmol). After 4 h stirring at 20 °C, CH_2Cl_2 (30 mL) was added. After decantation and extraction (4 × 50 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography of the crude (CH_2Cl_2:acetone, 9:1) afforded 0.74 g (28%) of **16a** (R_f 0.35) and 1.78 g (67%) of **17a** (R_f 0.30). From **15** (1.5 g, 4.6 mmol), 0.18 g (9%) of **4a** (R_f 0.30) and 1.31 g (66%) of **18a** (R_f 0.35) have been obtained.

***N*-Benzyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (4a)**. Mp 109 °C; $[\alpha]_D$ +4 (*c* 1.1, $CHCl_3$); ^1H NMR 7.30 (m, 15 H, Ph), 4.90 (dd, 2 H, OCH_2Ph), 4.71 (m, 2 H, OCH_2Ph), 4.50, 3.86 (AB, 2 H, NCH_2Ph), 4.01 (dd, 1 H, H_6), 3.69 (t, 1 H, H_4), 3.61 (ddd, 1 H, H_2), 3.39 (t, 1 H, H_3), 3.36 (d, 1 H, $H_{6'}$), 3.05 (dd, 1 H, H_{1a}), 2.44 (m, 1 H, H_5), 2.15 (dd, 1 H, H_{1e}), $^3J_{3,4} = {}^3J_{4,5} = {}^3J_{2,3} = 8.5$, $^3J_{2,1e} = 4$, $^3J_{2,1a} = 9.5$, $^3J_{6,5} = 3$, $^2J_{1,1'} = 11$, $^2J_{6,6'} = 12$, $^2J_{A,B} = 13$; ^{13}C NMR 138.6, 138.3, 138.0, 128.8, 128.5, 128.4, 127.8, 127.4 (Ph), 85.8, 78.3 ($C_{3,4}$), 74.8, 74.6 (OCH_2Ph), 69.3 (C_2), 65.6 (C_5), 58.2 (C_6), 57.3 (NCH_2Ph), 55.2 (C_1); Anal. calcd for $C_{27}H_{31}NO_4$, 0.4 H_2O: C, 73.64, H, 7.22, N, 3.18; found: C, 73.68, H, 7.14, N, 3.24.

***N*-Benzyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-L-gulitol (16a)**. Mp 75 °C; $[\alpha]_D$ −9 (*c* 1.0, $CHCl_3$); ^1H NMR 7.30 (m, 15H, Ph), 4.70–4.57 (m, 4 H, OCH_2Ph), 4.06 (dd, 1 H, H_4), 4.02 (m, 1 H, H_2), 3.92 (d, 2 H, NCH_2Ph), 3.84 (dd, 1 H, H_6), 3.69 (m, 2 H, $H_{3,6'}$), 3.11 (m, 1 H, H_5), 2.76 (m, 2 H, $H_{1,1'}$), $^3J_{4,5} = 5$, $^3J_{3,4} = 8$, $^3J_{5,6} = 6$, $^3J_{5,6'} = 7$, $^2J_{6,6'} = 11$, $^3J_{2,3} = 3$, $^2J_{NCH2Ph} = 2$; ^{13}C NMR 138.9, 138.1, 137.9, 128.9, 128.5, 127.9, 127.7, 127.2 (Ph), 78.1, 75.4 ($C_{3,4}$), 73.3, 72.5 (OCH_2Ph), 67.9 (C_2), 59.8 (C_5), 59.3 (C_6), 57.9 (NCH_2Ph), 49.3 (C_1); MS (CI, NH_3) 434 ($M^+ + 1$).

***N*-Benzyl-3,4-di-*O*-benzyl-1,6-dideoxy-1,6-imino-D-mannitol (17a)**. $[\alpha]_D$ −6 (*c* 1.0, $CHCl_3$); ^1H NMR 7.30 (m, 15 H, Ph), 4.75, 4.60 (AB, 4 H, OCH_2Ph), 4.08 (m, 2 H, H_2), 3.84 (s, 2H, H_3), 3.68 (s, 2 H, NCH_2Ph), 2.83 (dd, 2 H, H_1), 2.71 (dd, 2 H, $H_{1'}$), $^2J_{A,B} = 12$, $^3J_{1,2} = 4$, $^3J_{1',2} = 6.5$, $^2J_{1,1'} = 13$; ^{13}C NMR 138.3, 128.7, 128.3, 127.8, 127.6, 127.2 (Ph), 80.9 (C_3), 73.1 (OCH_2Ph), 68.6 (C_2), 63.4 (NCH_2Ph), 57.0 (C_1); Anal. calcd for $C_{27}H_{31}NO_4$, 0.5 H_2O: C, 73.30, H, 7.24, N, 3.16; found: C, 73.45, H, 7.26, N, 3.16.

***N*-Benzyl-3,4-di-*O*-benzyl-1,6-dideoxy-1,6-imino-L-iditol (18a)**. Mp 77 °C; $[\alpha]_D$ +15 (*c* 1.6, $CHCl_3$); ^1H NMR 7.30 (m, 15 H, Ph), 4.76, 4.62 (AB, 4 H, OCH_2Ph), 3.81 (m, 2 H, H_2), 3.71 (d, 2 H, NCH_2Ph), 3.63 (dd, 2 H, H_3), 2.92 (d, 2H, H_1), 2.63 (dd, 2H, $H_{1'}$), $^2J_{A,B} = 11.5$, $^3J_{1,1'} = 12.5$, $^3J_{1',2} = 8$, $^3J_{2,3} = 4$, $^3J_{3,4} = 1.5$; ^{13}C NMR 138.1, 137.8, 129.1, 128.5, 127.8, 127.6 (Ph), 86.7 (C_3), 73.7 (OCH_2Ph), 68.3 (C_2), 63.6 (NCH_2Ph), 57.6 (C_1); HMRS calcd for $C_{20}H_{24}NO_4$ ($M^+ - PhCH_2$) 342.1705; found 342.1706.

Aminocyclization of 12 with other amines

Aminocyclization of **12** (2 g, 6.13 mmol) with 2-phenylethylamine (7.7 mL, 6.13 mmol) was carried out under identical conditions described above in protic solvent, to give after flash chromatography (CH_2Cl_2:acetone, 85:15) 850 mg (31%) of **19a** (R_f 0.35) and 1.81 g (66%) of **20a** (R_f 0.24).

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-imino-*N*-(2′-phenylethyl)-L-gulitol (19a): $[\alpha]_D$ +1 (*c* 1.0, $CHCl_3$); ^1H NMR 7.40–7.10 (m, 15 H, Ph), 4.75–4.52 (m, 4 H, OCH_2Ph), 4.02 (m, 1 H, H_2), 3.95 (dd, 1 H, H_4), 3.80 (dd, 1 H, H_6), 3.64 (dd, 1 H, H_3), 3.59 (dd, 1 H, $H_{6'}$), 3.20–2.68 (m, 7 H, $H_{5,1,1'}$, $(CH_2)_2$), $^3J_{3,4} = 8$, $^3J_{4,5} = 5$, $^3J_{2,3} = 3.5$, $^3J_{6,5} = 6$, $^3J_{6',5} = 6.5$, $^2J_{6,6'} = 11.5$; ^{13}C NMR 140.0, 137.9, 128.6, 128.4, 128.3, 128.0, 127.9, 127.6, 126.0 (Ph), 77.9, 75.7 ($C_{3,4}$), 73.2, 72.4 (OCH_2Ph), 67.7 (C_2), 59.9 (C_5), 58.0 (C_6), 56.4 (CH_2), 50.1 (C_1), 33.9 (CH_2); MS (CI, NH_3) 448 ($M^+ + 1$).

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-imino-*N*-(2′-phenylethyl)-D-mannitol (20a). $[\alpha]_D$+5 (*c* 1.0, $CHCl_3$); ^1H NMR 7.40–7.13 (m, 15 H, Ph), 4.76–4.52 (AB, 4 H, OCH_2Ph), 4.07 (m, 2 H, H_2), 3.77 (s, 2H, H_3), 2.91 (dd, 2 H, H_1), 2.85–2.70 (m, 6 H, $H_{1'}$, $(CH_2)_2$), $^2J_{A,B} = 12$, $^3J_{1,2} = 4$, $^2J_{1,1'} = 13$.

Aminocyclization of **12** (90 mg, 0.276 mmol) with *N*-acetyl-1,4-butyl-diamine (143 mg, 1.1 mmol) was carried out under identical conditions described above in aprotic solvent (refluxing for 6 h), to give after flash chromatography (CH_2Cl_2:MeOH, 9:1) 60 mg (48%) of **19b** (R_f 0.35) and 40 mg (32%) of **20b** (R_f 0.25).

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-*N*-(1-*N*′-acetyl-1-aminobut-4-yl)-imino-L-gulitol (19b). $[\alpha]_D$ +5 (*c* 0.9, $CHCl_3$); ^1H NMR 7.30 (m, 10 H, Ph), 6.0 (m, 1 H, NH), 4.75–4.53 (m, 4 H, OCH_2Ph), 4.0 (m, 1 H, H_2), 3.92 (dd, 1 H, H_4), 3.81 (dd, 1 H, H6), 3.68–3.57 (m, 2 H, $H_{3,6'}$), 3.30–2.90 (m, 2 H, CH_2NH), 3.0 (m, 1 H, H_5), 2.83–2.57 (m, 4 H, $H_{1,1'}$, CH_2N), 1.92 (s, 3 H, CH_3), 1.45 (m, 4 H, $(CH_2)_2$), $^3J_{3,4} = 7.5$, $^3J_{4,5} = 4.5$, $^3J_{6,5} = 6$, $^2J_{6,6'} = 11.5$; ^{13}C NMR 170.2 (CO), 138.0, 137.8, 128.5, 128.0, 127.7 (Ph), 77.5, 76.2 ($C_{3,4}$), 73.4, 72.6 (OCH_2Ph), 67.2 (C_2), 60.4 (C_5), 58.1 (C_6), 54.1, 50.3, 39.1, 27.1, 24.4 (C1, CH_2)$_4$), 23.2 (CH_3); HMRS calcd for $C_{25}H_{33}N_2O_4$ ($M^+ - CH_2OH$) 425.2440, found 425.2438.

3,4-Di-*O*-benzyl-1,6-dideoxy-*N*-(1-*N*′-acetyl-1-aminobut-4-yl)-imino-D-mannitol (20b). $[\alpha]_D$+2.5 (*c* 1.5, $CHCl_3$); ^1H NMR 7.30 (m, 10 H, Ph), 6.10 (m, 1 H, NH), 4.72–4.61 (AB, 4 H, OCH_2Ph), 4.10 (m, 2 H, H_2), 3.78 (s, 2 H, H_3), 3.30–3.05 (m, 2 H, CH_2NH), 2.80 (m, 4 H, $H_{1,1'}$), 2.58 (m, 2 H, CH_2N), 1.92 (s, 3 H, CH_3), 1.50 (m, 4 H, $(CH_2)_2$), $^2J_{A,B} = 12$; ^{13}C NMR 170.4 (CO), 138.2,

128.4, 127.9, 127.8 (Ph), 80.4 (C_3), 73.4 (OCH_2Ph), 68.2 (C_2), 58.4, 56.6, 39.1, 26.9, 24.0 (C_1, $(CH_2)_4$), 23.2 (CH_3); MS (CI, NH_3) 457 ($M^+ + 1$).

Aminocyclization of **12** (100 mg, 0.306 mmol) in water (3 mL) with *O*-benzyl-hydroxylamine hydrochloride (196 mg, 1.22 mmol) was carried out at 80 °C for 15 h in presence of NEt_3 (212 μL, 1.53 mmol), to give after flash chromatography (CH_2Cl_2:Et_2O, 92:8) 26 mg (22%) of **19c** (R_f 0.28) and 61 mg (51%) of **20c** (R_f 0.19).

***N*-Benzyloxy-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-L-gulitol (19c)**. $[\alpha]_D$ +58 (*c* 0.7, $CHCl_3$); ^1H NMR 7.30 (m, 15 H, Ph), 4.77 (AB, 2 H, $NOCH_2Ph$), 4.64–4.40 (m, 4 H, OCH_2Ph), 4.07 (m, 1 H, H_2), 3.92 (m, 1 H, H_6), 3.80 (m, 1 H, H_4), 3.72 (dd, 1 H, $H_{6'}$), 3.63 (m, 1 H, H_3), 3.43 (dd, 1 H, H_1), 2.95 (m, 1 H, H_5), 2.79 (t, 1 H, $H_{1'}$), $^2J_{A,B} = 2$, $^3J_{1,2} = 4.2$, $^2J_{1,1'} = {}^3J_{1',2} = 10$, $^2J_{6,6'} = 10.5$, $^3J_{6',5} = 8$; ^{13}C NMR 137.5, 137.1, 136.5, 128.9, 128.6, 128.4, 128.1, 127.7 (Ph), 76.5 ($NOCH_2Ph$), 75.3, 74.9 ($C_{3,4}$), 73.0, 72.7 (OCH_2Ph), 66.0 (C_2), 64.8 (C_5), 62.5 (C_6), 56.1 (C_1); HMRS calcd for $C_{26}H_{28}NO_4$ ($M^+ - CH_2OH$) 418.2018; found 418.2015.

***N*-Benzyloxy-3,4-di-*O*-benzyl-1,6-dideoxy-1,6-imino-D-mannitol (20c)**. Mp 45 °C; $[\alpha]_D$ −4 (*c* 0.9, $CHCl_3$); ^1H NMR 7.30 (m, 15 H, Ph), 4.73–4.59 (AB, 4 H, OCH_2Ph), 4.65 (s, 2 H, $NOCH_2Ph$), 4.11 (m, 2 H, H_2), 3.77 (s, 2 H, H_3), 3.18 (m, 4 H, $H_{1,1'}$), $^2J_{A,B} = 11$; ^{13}C NMR 138.1, 137.2, 128.8, 128.4, 128.3, 127.8 (Ph), 79.9 (C_3), 74.3 ($NOCH_2Ph$), 73.5 (OCH_2Ph), 67.3 (C_2), 60.9 (C_1); HMRS calcd for $C_{26}H_{28}NO_4$ ($M^+ - C_7H_7$) 358.1654; found 358.1655.

Aminocyclization of **12** (100 mg, 0.306 mmol) with *N*,*N*-dibenzylhydrazine (259 mg, 1.224 mmol) in $CHCl_3$ (2 mL) was carried out at reflux for 10 days, to give after flash chromatography (CH_2Cl_2:Et_2O, 92:8, then 97:3) 49 mg (30%) of **19d** (R_f 0.35) and 38 mg (23%) of **20d** (R_f 0.28).

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-*N*,*N*-dibenzylhydrazino-L-gulitol (19d). $[\alpha]_D$ +40 (*c* 1.1, $CHCl_3$); ^1H NMR 7.40-7.05 (m, 20 H, Ph), 4.70–4.18 (m, 4 H, OCH_2Ph), 4.03 (m, 1 H, H_2), 3.85 (m, 2 H, NCH_2Ph), 3.65 (m, 1 H, H_3), 3.54 (d, 2 H, NCH_2Ph), 3.45 (m, 1 H, H_4), 3.23–3.19 (m, 3 H, $H_{6,6',1}$), 3.08 (m, 1 H, H_5), 2.76 (t, 1 H, $H_{1'}$), $^2J_{NCH_2Ph} = 12$, $^2J_{1,1'} = {}^3J_{1',2} = 10$; ^{13}C NMR 137.9, 137.8, 137.6, 129.9, 128.6, 128.2, 127.9, 127.5, 127.3, 127.1 (Ph), 76.3, 75.6 ($C_{3,4}$), 72.7 (OCH_2Ph), 66.7 (C_2), 65.0 (C_6), 58.5 (C_5), 53.9 (NCH_2Ph), 45.1 (C_1); HMRS calcd for $C_{27}H_{31}N_2O_4$ ($M^+ - C_7H_7$) 447.2884; found 447.2884.

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-*N*,*N*-dibenzylhydrazino-D-mannitol (20d). $[\alpha]_D$ +6 (*c* 0.7, $CHCl_3$); ^1H NMR 7.40-7.20 (m, 20 H, Ph), 4.64-4.50 (AB, 4 H, OCH_2Ph), 3.95 (m, 2 H, H_2), 3.64 (s, 4 H, NCH_2Ph), 3.50 (s, 2 H, H_3), 3.10 (dd, 2 H, H_1), 2.99 (dd, 1 H, $H_{1'}$), $^2J_{AB} = 11$, $^3J_{1,2} = 4$, $^3J_{1',2} = 6$, $^2J_{1,1'} = 13$; ^{13}C NMR 138.8, 138.4, 128.6, 128.3, 127.9, 127.6, 127.2 (Ph), 80.5 (C_3), 73.3 (OCH_2Ph), 68.4 (C_2), 54.9, 54.3 (NCH_2Ph, C_1); HMRS calcd for $C_{27}H_{31}N_2O_4$ ($M^+ - C_7H_7$) 447.2884; found 447.2880.

Aminocyclization of **12** (100 mg, 0.306 mmol) with glycine *tert*-butyl ester hydrochloride (103 mg, 0.612 mmol) was carried out under identical conditions described above, in aprotic solvent (refluxing for 48 h) in presence of Et_3N (171 μL, 1.22 mmol), to give after flash chromatography (AcOEt:cyclohexane:CH_2Cl_2, 5:3:2.5) 56 mg (40%) of **19e** (R_f 0.31) and 46 mg (33%) of **20e** (R_f 0.35).

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-[*tert*-butyloxycarbonyl-methyl]-imino-L-gulitol (19e). $[\alpha]_D$ −2 (*c* 1.1, $CHCl_3$); ^1H NMR 7.30 (m, 10 H, Ph), 4.70–4.50 (m, 4 H, OCH_2Ph), 3.99 (m, 1 H, H_2), 3.87 (dd, 1 H, H_4), 3.78-3.58 (m, 4 H, $H_{6,6',3}$, CH_2CO_2), 3.40 (d, 1 H, CH_2CO_2), 3.20 (m, 1 H, H_5), 2.91 (d, 2 H, $H_{1',1}$), 1.43 (s, 9 H, Me_3), $^3J_{4,5} = 4.5$, $^3J_{3,4} = 7$, $^3J_{1,2} = {}^3J_{1',2} = 4$; ^{13}C NMR 171.5 (CO), 138.0, 137.8, 128.5, 128.0, 127.9, 127.8 (Ph), 81.3 (CMe_3), 77.3, 75.6 ($C_{3,4}$), 73.0, 72.6 (OCH_2Ph), 67.4 (C_2), 59.9 (C_5), 59.1 (C_6), 57.0 (C_1), 51.3 (CH_2CO_2), 28.1 (Me_3); HMRS calcd for $C_{21}H_{26}NO_4$ ($M^+ - CO_2t$-Bu) 356.1861; found 356.1861.

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-[*tert*-butyloxycarbonyl-methyl]-imino-D-mannitol (20e). $[\alpha]_D$ −1 (*c* 1.2, $CHCl_3$); ^1H NMR 7.30 (m, 10 H, Ph), 4.77–4.62 (m, 4 H, OCH_2Ph), 4.07 (m, 2 H, H_3), 3.82 (s, 2 H, H_2), 3.29 (s, 2 H, CH_2CO_2), 3.01 (dd, 2 H, H_1), 2.81 (dd, 2 H, $H_{1'}$), 1.43 (s, 9 H, Me_3), $^2J_{A,B} = 12$, $^3J_{1,2} = 3$, $^3J_{1',2} = 6$, $^2J_{1,1'} = 13$; ^{13}C NMR 170.7 (CO), 138.5, 128.3, 127.9, 127.6 (Ph), 81.5 (CMe_3), 80.6 (C_3), 73.5 (OCH_2Ph), 69.0 (C_2), 60.9 (CH_2CO_2), 57.1 (C_1), 28.1 (Me_3); HMRS calcd for $C_{21}H_{26}NO_4$ ($M^+ - CO_2t$-Bu) 356.1861; found 356.1865.

Aminocyclization of **12** (2.4 g, 7.36 mmol) with tryptamine (4.71 g, 29.44 mmol) was carried out under identical conditions described above, in aprotic solvent (refluxing for 24 h), to give after flash chromatography (CH_2Cl_2:acetone, 7:3) 1.79 g (50%) of **19f** (R_f 0.35) and 1.81 g (45%) of **20f** (R_f 0.30).

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-[2′-(1H-indol-3-yl)-ethyl]-imino-L-gulitol (19f). $[\alpha]_D$ −9 (*c* 1.0, $CHCl_3$); ^1H NMR 7.94 (s, 1 H, NH), 7.57 (d, 1 H indol), 7.2–6.96 (m, 14 H, Ar), 4.71-4.52 (m, 4 H, OCH_2Ph), 4.02 (m, 1 H, H_2), 3.96 (dd, 1 H, H_4), 3.80 (dd, 1 H, H_6), 3.64 (dd, 1 H, H_3), 3.60 (dd, 1 H, $H_{6'}$), 3.23-2.80 (m, 7 H, $H_{1',1,5}$, $(CH_2)_2$), $^3J_{2,3} = 3.5$, $^3J_{3,4} = 8$, $^3J_{4,5} = 5$, $^3J_{5,6} = 6$, $^3J_{5,6'} = 7$, $^2J_{6,6'} = 11$; ^{13}C NMR 138.0, 137.9, 136.2, 128.4, 128.0, 127.9, 127.7, 127.3, 121.7, 119.1, 118.7, 113.7, 111.1 (Ar), 77.8, 75.7 ($C_{3,4}$), 73.2, 72.4 (OCH_2Ph), 67.6 (C_2), 59.9 (C_5), 58.0 (C_6), 55.2, 23.6 ($(CH_2)_2$), 50.2 (C_1); HMRS calcd for $C_{21}H_{26}NO_4$ ($M^+ - C_9H_8N$) 356.1861; found 356.1865; Anal. calcd for $C_{30}H_{34}N_2O_4$, H_2O: C, 71.42, H, 7.14, N, 5.55; found: C, 71.68, H, 6.96, N, 5.63.

3,4-Di-*O*-benzyl-1,6-dideoxy-1,6-[2′-(1H-indol-3-yl)-ethyl]-imino-D-mannitol (20f). $[\alpha]_D$ −4 (*c* 0.9, $CHCl_3$); ^1H

NMR 8.06 (s, 1 H, NH), 7.54 (d, 1 H, H indol), 7.30–6.96 (m, 14 H, Ar), 4.72–4.60 (AB, 4 H, OCH_2Ph), 4.08 (m, 2 H, H_2), 3.77 (s, 2 H, H_3), 2.93 (dd, 2 H, H_1), 2.92–2.85 (m, 4 H, $(CH_2)_2$), 2.80 (dd, 2 H, $H_{1'}$), $^2J_{A,B} = 12$, $^2J_{1,1'} = 13$, $^3J_{1,2} = 3$, $^3J_{1',2} = 6$; ^{13}C NMR 138.3, 136.2, 128.4, 128.3, 127.8, 127.6, 127.2, 121.9, 121.6, 118.9, 118.4, 113.2, 111.3 (Ar), 80.8 (C_3), 73.1 (OCH_2Ph), 68.5 (C_2), 59.4, 23.0 ($(CH_2)_2$), 56.6 (C_1); HMRS calcd for $C_{21}H_{26}NO_4$ (M^+-C_9H_8N) 356.1861; found 356.1861.

1-Deoxynojirimycin (4). Palladium black (120 mg) in acetic acid (3 mL) was completely hydrogenated prior to the addition of **4a** (300 mg, 0.69 mmol) in AcOH (2 mL). After 18 h stirring, the catalyst was removed by filtration through a celite pad and rinsed with AcOH. Concentration in vacuo and purification of the residue by ion-exchange chromatography (DOWEX 50 × 8, 50–100 mesh, elute with aqueous ammonia (1%)) afforded 113 mg (100%) of **4**. Mp 194–196 °C, $[\alpha]_D$ +46 (*c* 0.9, H_2O); lit[8] mp 196 °C, $[\alpha]_D$ +47 (H_2O); ^1H NMR (D_2O) 3.82 (dd, 1 H, H_6), 3.62 (dd, 1 H, $H_{6'}$), 3.48 (ddd, 1'H, H_2), 3.31 (t, 1'H, H_3), 3.22 (t, 1'H, H_4), 3.12 (dd, 1'H, H_{1e}), 2.56 (m, 1'H, H_5), 2.46 (dd, 1'H, H_{1a}) $^2J_{1a,1e} = 13$, $^3J_{1e,2} = 5$, $^3J_{1a,2} = 11$, $^3J_{3,4} = {}^3J_{4,5} = {}^3J_{3,2} = 9$, $^3J_{6,5} = 2.5$, $^3J_{6',5} = 6$, $^2J_{6,6'} = 11.5$; ^{13}C NMR (D_2O) 80.7, 73.8, 73.2 ($C_{2\text{-}4}$), 63.7 (C_6), 62.9 (C_5), 51.0 (C_1); HMRS calcd for $C_5H_{10}NO_3$ ($M^+ - CH_2OH$) 132.0660; found 132.0660.

1,5-Dideoxy-1,5-imino-L-gulitol (16). Hydrogenolysis of **16a** was carried out under identical conditions as for **4a** described above (100%). $[\alpha]_D$ +9 (*c* 0.6, H_2O); ^1H NMR (D_2O) 4.05 (ddd, 1 H, H_2), 3.96 (br s, 2 H, $H_{3,4}$), 3.70 (m, 2 H, $H_{6,6'}$), 3.20 (t, 1 H, H_5), 3.05 (dd, 1 H, H_{1e}), 2.87 (dd, 1 H, H_{1a}), $^3J_{1e,2} = 4.5$, $^3J_{2,1a} = 11$, $^3J_{2,3} = 2$, $^3J_{5,6} = {}^3J_{5,6'} = 6$, $^2J_{1e,1a} = 12.5$; ^{13}C NMR (D_2O) 71.8, 70.7, 66.6 ($C_{2\text{-}4}$), 62.4 (C_6), 57.1 (C_5), 45.7 (C_1); HMRS calcd for $C_5H_{10}NO_3$ ($M^+ - CH_2OH$) 132.0660; found 132.0660.

1,6-Dideoxy-1,6-imino-D-mannitol (17). Hydrogenolysis of **17a** was carried out under identical conditions as for **4a** described above (100%). Mp 183–185 °C; $[\alpha]_D$ −38 (*c* 0.5, H_2O); ^1H NMR (D_2O) 4.05 (m, 2 H, H_2), 3.90 (s, 2 H, H_3), 2.93 (dd, 2 H, H_1), 2.84 (dd, 2H, $H_{1'}$), $^3J_{1,2} = 3.5$, $^3J_{1',2} = 6$, $^2J_{1,1'} = 14$; ^{13}C NMR (D_2O) 75.7, 73.1 ($C_{2,3}$), 51.1 (C_1); MS (CI, NH_3) 164 (M^++1).

1,6-Dideoxy-1,6-imino-L-iditol (18). Hydrogenolysis of **18a** was carried out under identical conditions as for **4a** described above (100%). $[\alpha]_D$ +20 (*c* 0.8, H_2O), lit[38] +19.9 (*c* 2, H_2O); ^1H NMR (D_2O) 3.70 (m, 2 H, H_2), 3.49 (dd, 2 H, H_3), 3.04 (dd, 2 H, H_1), 2.77 (dd, 2 H, $H_{1'}$), $^3J_{1,2} = 4$, $^3J_{1',2} = 7.5$, $^2J_{1,1'} = 14$, $^3J_{2,3} = 5.5$, $^3J_{3,4} = 1.5$; ^{13}C NMR (D_2O) 77.9, 74.8 ($C_{2,3}$), 53.6 (C_1); MS (CI, NH_3) 164 (M^++1).

Isomerization of the piperidine 16a

***N*-Benzyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-2,6-di-*O*-methanesulfonyl-L-gulitol (21).** To a stirred solution of **16a** (100 mg, 0.23 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added NEt_3 (128 µL, 0.92 mmol) followed by methanesulfonyl chloride (42 mL, 0.53 mmol). After 10 min at 0 °C, the reaction was quenched by addition of water (7 mL) and diluted with CH_2Cl_2 (15 mL). After decantation and extraction (4 × 10 mL), the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The crude **21** was used in the next step without further purification. ^1H NMR 7.30 (m, 15 H, Ph), 5.0 (m, 1 H, H_2), 4.71–4.53 (m, 4 H, OCH_2Ph), 4.43 (m 2 H, $H_{6,6'}$), 3.96 (dd, 1 H, H_4), 3.83 (s, 2 H, NCH_2Ph), 3.69 (dd, 1 H, H_3), 3.40 (m, 1 H, H_5), 3.11 (m, 1 H, H_1), 2.94 (m, 1 H, $H_{1'}$), 2.86, 2.82 (2s, 6H, $MeSO_2$), $^3J_{3,4} = 8.5$, $^3J_{4,5} = 5$, $^3J_{2,3} = 3$.

Reaction of the dimesylated piperidine 21 with cesium acetate. To a stirred solution of **21** (130 mg, 0.22 mmol) in DMF (1 mL) was added AcOCs (423 mg, 2.2 mmol). After 24 h stirring at 40–50 °C, the mixture was concentrated in vacuo and diluted with CH_2Cl_2 (15 mL) and water (10 mL). After decantation and extraction (3 × 20 mL), the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was dissolved in MeOH (1 mL) and K_2CO_3 (311 mg, 2.2 mmol) was added. After 1 h stirring at 20 °C, the reaction mixture was concentrated in vacuo, and diluted with CH_2Cl_2 (15 mL) and water (10 mL). After decantation and extraction (3 × 20 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (CH_2Cl_2:acetone, 92:8) afforded 43 mg (45%) of **22a** (R_f 0.35), 17 mg (18%) of **16a** (R_f 0.30) and 8 mg (8%) of **17a** (R_f 0.25).

***N*-Benzyl-3,4-di-*O*-benzyl-2,5-dideoxy-2,5-imino-L-iditol (22a).** $[\alpha]_D$ − 19 (*c* 0.7, $CHCl_3$); ^1H NMR 7.30 (m, 15 H, Ph), 4.66, 4.59 (AB, 4 H, OCH_2Ph), 4.36 (m, 2 H, H_3), 3.97, 3.90 (AB, 2 H, NCH_2Ph), 3.74 (dd, 2 H, H_1), 3.67 (dd, 2 H, H_1'), 3.40 (m, 2 H, H_2), $^2J_{A,B\ (OCH_2Ph)} = 11.5$, $^2J_{A,B\ (NCH_2Ph)} = 14$, $^3J_{1,2} = 4.5$, $^3J_{1',2} = 2.5$, $^2J_{1,1'} = 12$; ^{13}C NMR 138.7, 137.8, 128.5, 128.1, 127.9, 127.7, 127.1 (Ph), 84.4 (C_3), 73.0 (OCH_2Ph), 61.5 (C_2), 59.4 (C_1), 52.4 (NCH_2Ph).

2,5-Dideoxy-2,5-imino-L-iditol (22). Hydrogenolysis of **22a** was carried out under identical conditions as for **4a** described above (100%). $[\alpha]_D$ +8 (*c* 0.6, H_2O), lit[24] +9.6 (*c* 0.6, H_2O); ^1H NMR (D_2O) 4.33 (d, 2 H, H_3), 3.90-3.75 (m, 6 H, $H_{1,1',2}$); ^{13}C NMR (D_2O) 78.5 (C_3), 64.3 (C_2); 61.7 (C_1); MS (CI, NH_3) 164 (M^++1), HRMS calcd for $C_5H_{10}NO_3$ ($M^+ - CH_2OH$) 132.0660; found 132.0660.

Mitsunobu reaction with 16a. To a solution of Ph_3P (448 mg, 1.708 mmol) in THF (4 mL) at 0 °C was dropwise added diethyl azodicarboxylate (DEAD) (270 µL, 1.708 mmol). After 5 min stirring, benzoic acid (208 mg, 1.708 mmol) in THF (500 µL) and **16a** (185 mg, 0.427 mmol) in THF (1 mL) were successively added dropwise. The reaction mixture was stirred for 15 h at 0 °C. If the reaction was not complete (monitoring by TLC), one equivalent or more of each

reagent was added. The reaction mixture was then concentrated in vacuo. The residue dissolved in AcOEt was filtered through a silica pad. Concentration in vacuo followed by flash chromatography (cyclohexane:AcOEt, 85:15) afforded a mixture of **22c** and **23b** (232 mg). To a solution of this mixture in MeOH (5 mL) was added K_2CO_3 (523 mg, 3.76 mmol). After 5 h stirring at 20 °C, the reaction mixture was concentrated in vacuo. The residue was diluted with CH_2Cl_2 (30 mL) and water (10 mL). After decantation and extraction (3 × 30 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (cyclohexane: AcOEt, 1:1) afforded 129 mg (70%) of **23a** (R_f 0.35) and 33 mg (18%) of **22a** (R_f 0.30).

***N*-Benzyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-L-iditol (23a)**. $[\alpha]_D$ +21 (*c* 0.5, $CHCl_3$); ^1H NMR 7.30 (m, 15 H, Ph), 4.83–4.54 (m, 4 H, OCH_2Ph), 3.95–3.57 (m, 7 H, $H_{2,3,4,6,6',NCH_2Ph}$), 3.03 (m, 1 H, H_5), 2.75–2.57 (m, 2 H, $H_{1,1'}$); ^{13}C NMR 138.7, 138.4, 137.4, 128.8, 128.7, 128.5, 128.3, 128.0, 127.9, 127.4 (Ph), 79.7, 79.2 ($C_{3,4}$), 74.2, 72.8 (OCH_2Ph), 68.0 (C_2), 60.3 (C_5), 59.2 (C_6), 58.4 (NCH_2Ph), 50.4 (C_1); HRMS calcd for $C_{26}H_{28}NO_3$ ($M^+ - CH_2OH$) 402.2069; found 402.2066.

1,5-Dideoxy-1,5-imino-L-iditol (23). Hydrogenolysis of **23a** was carried out under identical conditions as for **4a** described above (100%). $[\alpha]_D$ − 24 (*c* 0.7, H_2O); ^1H NMR (D_2O) 3.84-375 (m, 3 H, $H_{4,6,6'}$), 3.66 (m, 2 H, $H_{2,3}$), 3.24 (m, 1 H, H_5), 3.04 (br d, 1 H, H_1), 2.82 (dd, 2 H, $H_{1'}$), $^2J_{1,1'} = 12.5$, $^3J_{1',2} = 6$; ^{13}C NMR (D_2O) 75.0, 73.3, 72.7 ($C_{2\text{-}4}$), 60.6 (C_6), 59.2 (C_5), 46.9 (C_1); HMRS calcd for $C_5H_{10}NO_3$ ($M^+ - CH_2OH$) 132.0660; found 132.0660.

Isomerization of the piperidine 4a

***N*-Benzyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-2,6-di-*O*-methanesulfonyl-D-glucitol (24)**. Mesylation of **4a** was carried out under identical conditions as for **16a** described above (100%). ^1H NMR 7.30 (m, 15 H, Ph), 4.96–4.67 (m, 4 H, OCH_2Ph), 4.58–4.43 (m 3 H, $H_{6,6',2}$), 4.06 (AB, 1 H, NCH_2Ph), 3.70–3.55 (m, 2 H, $H_{3,4}$), 3.51 (AB, 1 H, NCH_2Ph), 3.23 (dd, 1 H, H_{1e}), 2.87, 2.78 (2s, 6H, $MeSO_2$), 2.60 (m, 1 H, H_5), 2.34 (t, 1 H, H_{1a}), $^2J_{A,B} = 14$, $^3J_{1e,2} = 5$, $^3J_{1a,2} = {}^2J_{1e,1a} = 11$.

Reaction of the dimesylated piperidine 24 with cesium acetate. To a stirred solution of **24** (145 mg, 0.246 mmol) in DMF (3 mL) was added AcOCs (472 mg, 2.46 mmol). After 24 h stirring at 35 °C, the mixture was concentrated in vacuo. Then water (7 mL) and CH_2Cl_2 (15 mL) were added, and after decantation and extraction (4 × 15 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (CH_2Cl_2:acetone, 99:1) afforded 65 mg (51%) of **1b** (R_f 0.35) and 40 mg (31%) of **4b** (R_f 0.30). This latter gives **4a** by methanolysis.

1,6-Di-*O*-acetyl-*N*-benzyl-3,4-di-O-benzyl-2,5-dideoxy-2,5-imino-D-mannitol (1b). $[\alpha]_D$ − 17 (*c* 1.2, $CHCl_3$); ^1H NMR 7.31 (m, 15 H, Ph), 4.53, 4.48 (AB, 4 H, OCH_2Ph), 4.22 (dd, 2 H, $H_{1'}$), 4.16 (dd, 2 H, $H_{1'}$), 4.07 (AB, 1 H, NCH_2Ph), 3.92 (br s, 2 H, H_3), 3.85 (AB, 1 H, NCH_2Ph), 3.35 (m, 2 H, H_2), 1.96 (s, 6 H, Ac), $^2J_{A,B\ (NCH_2Ph)} = 14$, $^2J_{A,B\ (OCH_2Ph)} = 12$, $^3J_{1,2} = 5$, $^3J_{1',2} = 6$, $^2J_{1,1'} = 11.5$; ^{13}C NMR 170.7 (CO), 138.9, 137.9, 128.4, 127.9, 127.7, 126.9 (Ph), 84.8 (C_3), 71.6 (OCH_2Ph), 64.2 (C_2), 63.0 (C_1), 51.3 (NCH_2Ph), 20.9 (CH_3CO).

2,6-Di-*O*-acetyl-*N*-benzyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (4b). $[\alpha]_D$ +20 (*c* 1.1, $CHCl_3$); ^1H NMR 7.27 (m, 15 H, Ph), 4.93 (dt 1 H, H_2), 4.89-4.54 (m, 4 H, OCH_2Ph), 4.56 (m, 1 H, H_6), 4.28 (dd, 1 H, $H_{6'}$), 4.00 (AB, 1 H, NCH_2Ph), 3.63 (t, 1 H, H_4), 3.52 (t, 1 H, H_3), 3.33 (AB, 1 H, NCH_2Ph), 2.95 (dd, 1 H, H_1), 2.51 (*br* d, 1 H, H_5), 2.00 (m, 1 H, $H_{1'}$), 2.00, 1.86 (2s, 6 H, Ac), $^2J_{A,B} = 13.5$, $^2J_{6,6'} = 12$, $^2J_{1,1'} = 11$, $^3J_{6',5} = 1$, $^3J_{3,4} = {}^3J_{2,3} = {}^3J_{4,5} = 9$, $^3J_{2,1} = {}^3J_{2,1'} = 4.5$.

***N*-Benzyl-3,4-di-*O*-benzyl-2,5-dideoxy-2,5-imino-D-mannitol (1a)**. To a stirred solution of **1b** (64 mg, 0.123 mmol) in MeOH (2 mL) was added K_2CO_3 (85 mg, 0.619 mmol). After 30 min stirring at 20 °C, the reaction mixture was concentrated in vacuo, then water (7 mL) and CH_2Cl_2 (20 mL) were added. After decantation and extraction (3 × 15 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (cyclohexane:AcOEt, 1:1) afforded 53 mg (100%) of **1a** (R_f 0.3). **1a** can also be obtained, in a higher yield, by Mitsunobu reaction with **4a** and subsequently methanolysis, see below. $[\alpha]_D$ − 5 (*c* 0.9, $CHCl_3$); ^1H NMR 7.31 (m, 15 H, Ph), 4.56, 4.50 (AB, 4 H, OCH_2Ph), 4.01 (br s, 2 H, H_3), 3.97 (br s, 2 H, NCH_2Ph), 3.79 (dd, 2 H, H_1), 3.58 (br d, 2 H, $H_{1'}$), 3.34 (m, 2 H, H_2), $^2J_{A,B} = 13$, $^3J_{1,2} = 3$, $^2J_{1,1'} = 11$; ^{13}C NMR 139.0, 137.3, 128.4, 128.0, 127.9, 127.7, 127.0 (Ph), 84.8 (C_3), 71.5 (OCH_2Ph), 67.9 (C_2), 61.0 (C_1), 51.0 (NCH_2Ph).

2,5-Dideoxy-2,5-imino-D-mannitol (1). Hydrogenolysis of **1a** was carried out under identical conditions as for **4a** described above (100%). Mp 112–114 °C, $[\alpha]_D$ +54 (*c* 0.5, H_2O), lit[25a] mp 115–117 °C, $[\alpha]_D$+53.8 (*c* 0.32, H_2O); ^1H NMR (D_2O) 3.92 (m, 2 H, H_3), 3.80 (dd, 2 H, H_1), 3.71 (dd, 2 H, $H_{1'}$), 3.16 (m, 2 H, H_2), $^3J_{1,2} = 4$, $^3J_{1',2} = 6$, $^2J_{1,1'} = 11$; ^{13}C NMR (D_2O) 80.2 (C_3), 64.6 (C_2); 64.3 (C_1); MS (CI, NH_3) 164 (M^++1), HRMS calcd for $C_5H_{10}NO_3$ ($M^+ - CH_2OH$) 132.0660; found 132.0660.

Mitsunobu reaction with 4a. Mitsunobu reaction with **4a** (140 mg, 0.323 mmol) was carried out under identical conditions as for **16a** described above, to give after flash chromatography (cyclohexane:AcOEt, 85:15) 128 mg (64%) of **1c** (R_f 0.35) and 58 mg (29%) of **4c** (R_f 0.30). By methanolysis, as above, **1c** (or **4c**) gives **1a** (or **4a**).

***N*-Benzyl-1,6-di-*O*-benzoyl-3,4-di-*O*-benzyl-2,5-dideoxy-2,5-imino-D-mannitol (1c).** $[\alpha]_D$ −26 (*c* 0.9, $CHCl_3$); ^1H NMR 7.96 (d, 4 H, Ph), 7.51–7.20 (m, 21 H, Ph), 4.54 (s, 4 H, OCH_2Ph), 4.51 (dd 2 H, H_1), 4.41 (dd, 2 H, $H_{1'}$), 4.19 (AB, 1 H, NCH_2Ph), 4.12 (br s, 2 H, H_3), 3.93 (AB, 1 H, NCH_2Ph), 3.56 (m, 2 H, H_2), $^2J_{A,B} = 14$, $^3J_{1,2} = 5.5$, $^3J_{1',2} = 4$, $^2J_{1,1'} = 11$; ^{13}C NMR 166.4 (CO), 138.8, 137.9, 132.9, 130.0, 129.7, 128.4, 128.3, 128.0, 127.7, 127.0 (Ph), 85.2 (C_3), 71.7 (OCH_2Ph), 64.4 (C_2), 63.5 (C_1), 51.3 (NCH_2Ph).

***N*-Benzyl-2,6-di-*O*-benzoyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (4c).** $[\alpha]_D$+38 (*c* 1.0, $CHCl_3$); ^1H NMR 8.05 (d, 2 H, Ph), 7.95 (d, 2 H, Ph), 7.65–7.17 (m, 21 H, Ph), 5.30 (m, 1 H, H_2), 4.95–4.80 (m, 2 H, $H_{6,6'}$), 4.80-4.56 (m, 4 H, OCH_2Ph), 4.17 (AB, 1 H, NCH_2Ph), 3.86 (t, 1 H, H_4), 3.77 (t, 1 H, H_3), 3.46 (d, 1 H, NCH_2Ph), 3.16 (dd, 1 H, H_1), 2.76 (br d, 1 H, H_5), 2.26 (t, 1 H, $H_{1'}$), $^3J_{3,4} = {}^3J_{4,5} = {}^3J_{2,3} = 8$, $^3J_{1',2} = {}^2J_{1,1'} = 10$, $^3J_{1,2} = 4$, $^2J_{A,B} = 14$.

Azasugars via the *N*-benzyloxycarbonyl piperidine 4e

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (4d). Palladium hydroxide (20%, 400 mg) in absolute EtOH (8 mL) was completely hydrogenated prior to the addition of **4a** (1.05 g, 2.42 mmol) in absolute EtOH (3 mL). After 2.5 h stirring, the catalyst was removed by filtration through a celite pad and the organic layer was concentrated in vacuo to afford crude **4d** (100%). It was used in the next step without further purification. ^1H NMR 7.30 (m, 10 H, Ph), 4.98–4.62 (m, 4 H, OCH_2Ph), 3.75-3.50 (m, 3 H, $H_{2,4,6}$), 3.36 (m, 2 H, $H_{3,6'}$), 3.17 (dd, 1 H, H_1), 2.65 (m, 1 H, H_5), 2.51 (t, 1 H, $H_{1'}$), $^3J_{1',2} = {}^2J_{1,1'} = 11$, $^3J_{1,2} = 4$; ^{13}C NMR 138.5, 138.0, 128.5, 128.4, 127.9, 127.8 (Ph), 87.1, 79.3 ($C_{3,4}$), 75.2, 74.9 (OCH_2Ph), 71.2 (C_2), 61.7 (C_6), 61.0 (C_5), 49.1 (C_1).

***N*-Benzyloxycarbonyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (4e).** To a solution of **4d** (831 mg, 2.42 mmol) in DMF was added K_2CO_3 (434 mg, 3.15 mmol). The mixture was cooled to 0 °C and benzylchloroformate (385 µL, 2.66 mmol) was added dropwise. After 30 min stirring at 0 °C, the reaction mixture was filtered through a celite pad and the organic layer was concentrated in vacuo. The residue was diluted in CH_2Cl_2 (40 mL) and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (AcOEt:cyclohexane, 6:4) afforded 1.05 g (90%) of **4e** (R_f 0.35). $[\alpha]_D$ −46 (*c* 0.7, $CHCl_3$); ^1H NMR 7.30 (m, 15 H, Ph), 5.16 (s, 2 H, CO_2CH_2Ph), 4.66 (m, 1 H, H_5), 4.63-4.43 (m, 4 H, OCH_2Ph), 4.17 (br d, 1 H, H_1), 3.91 (dd, 1 H, H_6), 3.80–3.53 (m, 4 H, $H_{6',2,3,4}$), 3.43 (d, 1 H, $H_{1'}$), $^2J_{1,1'} = 14$, $^3J_{6,5} = 7.5$, $^2J_{6,6'} = 11$; ^{13}C NMR 157.2 (CO), 137.1 136.6, 136.4, 129.6, 128.6, 128.5, 128.4, 128.1, 127.9, 127.8, 127.7, 127.6 (Ph), 74.1, 73.8 ($C_{3,4}$), 72.5, 71.7 (OCH_2Ph), 67.4 (CO_2CH_2Ph), 66.3 (C_2), 60.7 (C_6), 55.2 (C_5), 42.5 (C_1); Anal. calcd for $C_{28}H_{31}NO_6$: C, 70.42, H, 6.54, N, 2.93; found: C, 70.34, H, 6.56, N, 2.87.

***N*-Benzyloxycarbonyl-3,4-di-*O*-benzyl-2,6-di-*O*-benzoyl-1,5-dideoxy-1,5-imino-D-mannitol (25).** Mitsunobu reaction with **4e** (100 mg, 0.21 mmol) in presence of 4 equiv of [Ph_3P–DEAD–$PhCO_2H$] was carried out under identical conditions as for **16a** described above to give 131 mg (91%) of **25** (R_f 0.30, cyclohexane: AcOEt, 85:15). $[\alpha]_D$ −2 (*c* 1.6, $CHCl_3$); ^1H NMR 8.02 (d, 2 H, Ph), 7.91 (d, 2 H, Ph), 7.60–7.17 (m, 21 H, Ph), 5.39 (br d, 1 H, H_2), 5.20–4.95 (m, 2 H, CO_2CH_2Ph), 4.88 (m, 1 H, H_5), 4.76 (t, 1 H, H_6), 4.64–4.45 (m, 4 H, OCH_2Ph), 4.45 (dd, 1 H, $H_{6'}$), 4.41-4.28 (m, 1 H, H_{1e}), 4.12 (m, 1 H, H_3), 3.74 (m, 1 H, H_4), 3.52 (t, 1 H, H_{1a}), $^3J_{6,5} = {}^2J_{6,6'} = 10$, $^3J_{6',5'} = 6$, $^3J_{1a,2} = {}^2J_{1e,1a} = 12$; ^{13}C NMR 166.1, 165.3 (CO), 155.9 (NCO), 137.4 137.3, 136.3, 133.2, 132.9, 129.8, 129.7 129.6, 128.4, 127.8, 127.6 (Ph), 74.3, 73.3 ($C_{3,4}$), 73.7, 71.1 (OCH_2Ph), 68.2 (C_2), 67.5 (C_6), 61.6 (CO_2CH_2Ph), 52.8, 52.0 (C_5), 37.5 (C_1).

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-mannitol (5a). A mixture of **25** (85 mg, 0.123 mmol) and K_2CO_3 (256 mg, 1.84 mmol) in MeOH (4 mL), in a 20 mL flask, was concentrated in vacuo at 40 °C for 20 min. The reaction was monitored by TLC (CH_2Cl_2:MeOH, 85:15, R_f 0.9, R_f 0.35 for **25** and **5a**, respectively). If the reaction was not complete, the residue was diluted with MeOH and concentrated again in vacuo. The residue was then diluted with CH_2Cl_2 (20 mL) and water (8 mL). After decantation and extraction (4 × 15 mL), the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (CH_2Cl_2:MeOH, 85:15) afforded 40 mg (95%) of **5a**. $[\alpha]_D$ +3 (*c* 0.9, $CHCl_3$); ^1H NMR 7.30 (m, 10 H, Ph), 4.89-4.56 (m, 4 H, OCH_2Ph), 4.02 (br s, 1H, H_2), 3.80 (dd, 1 H, H_6), 3.60 (dd, 1 H, $H_{6'}$), 3.39–3.48 (m, 2 H, $H_{4,3}$), 3.16 (dd, 1 H, H_1), 2.63 (d, 1 H, $H_{1'}$), 2.50 (m, 1 H, H_5), $^3J_{6,5} = 3$, $^3J_{6',5} = 5$, $^2J_{6,6'} = 11$, $^3J_{1,2} = 2$, $^2J_{1,1'} = 14$; ^{13}C NMR 138.4 137.9, 128.5, 128.4, 128.0, 127.8, 127.7 (Ph), 83.6, 76.3 ($C_{3,4}$), 75.1, 71.7 (OCH_2Ph), 66.9 (C_2), 61.9 (C_6), 61.1 (C_5), 48.5 (C_1); HMRS calcd for $C_{19}H_{22}NO_3$ ($M^+ - CH_2OH$) 312.1599; found 312.1598.

1-Deoxymannojirimycin (5). Hydrogenolysis of **5a** was carried out under identical conditions as for **4a** described above (100%). Mp 185 °C, $[\alpha]_D$ −40 (*c* 0.9, H_2O), lit[27d] mp 185–187 °C, $[\alpha]_D$ −39 (H_2O); ^1H NMR (D_2O) 4.08 (m, 1 H, H_2), 3.83 (m, 2 H, $H_{6,6'}$), 3.69 (t, 1 H, H_4), 3.62 (dd, 1 H, H_3), 3.12 (br d, 1 H, H_1), 2.88 (d, 1 H, $H_{1'}$), 2.64 (m, 1 H, H_5), $^3J_{3,4} = {}^3J_{4,5} = 9.7$, $^3J_{2,3} = 3$, $^2J_{1,1'} = 14$; ^{13}C NMR (D_2O) 77.0, 71.5, 70.7 ($C_{2\text{-}4}$), 63.3 (C_5); 63.1 (C_6), 51.0 (C_1); MS (CI, NH_3) 164 (M^++1); HRMS calcd for $C_5H_{10}NO_3$ ($M^+ - CH_2OH$) 132.0660; found 132.0660.

3,4-Di-*O*-benzyl-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-D-glucitol (26). To a solution of **4e** (92 mg, 0.193 mmol) in MeOH (3 mL) was added K_2CO_3 (268 mg, 1.93 mmol). The reaction mixture was stirred for 45 min at 20 °C, and quenched by addition of water (7 mL), and diluted with CH_2Cl_2 (20 mL). After decantation and extraction (4 × 15 mL), the combined

organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (AcOEt:cyclohexane, 65:35) afforded 68 mg (96%) of **26** (R_f 0.35). Mp 131 °C; $[\alpha]_D$ +113 (*c* 1.0, $CHCl_3$); ^1H NMR 7.30 (m, 10 H, Ph), 4.98–4.58 (m, 4 H, OCH_2Ph), 4.24 (t, 1 H, H_6), 4.00 (dd, 1 H, H_{1e}), 3.73 (dd, 1 H, $H_{6'}$), 3.35 (m, 2 H, $H_{2,5}$), 3.40, 3.31 (2t, 2 H, $H_{3,4}$), 2.71 (t, 1 H, H_{1a}), $^3J_{3,4} = {}^3J_{4,5} = {}^3J_{2,3} = 9$, $^3J_{6,5} = {}^2J_{6,6'} = 8$, $^3J_{6',5} = 4.5$, $^3J_{1e,2} = 5$, $^3J_{1a,2} = {}^2J_{1e,1a} = 12$; ^{13}C NMR 156.7 (CO), 138.0 137.4, 128.7, 128.3, 128.1, 127.9 (Ph), 86.4, 80.2 ($C_{3,4}$), 75.7, 74.9 (OCH_2Ph), 69.2 (C_2), 65.6 (C_6), 57.0 (C_5), 44.3 (C_1); HMRS calcd for $C_{14}H_{16}NO_5$ ($M^+ - C_7H_7$) 278.1028; found 278.1030.

2-Azido-3,4-di-*O*-benzyl-*N*,6-*O*-carbonyl-1,2,5-trideoxy-1,5-imino-D-mannitol (27). To a solution of Ph_3P (127 mg, 0.486 mmol) in THF (1 mL) at 0 °C was dropwise added DEAD (77 µL, 0.486 mmol). After 5 min stirring, hydrazoic acid[28] (1.3 M in benzene, 374 µL, 0.486 mmol) and **26** (60 mg, 0.162 mmol) in THF (400 µL) were successively added dropwise. The reaction mixture was stirred for 1 h at 0 °C and 2 h at 20 °C. The reaction was monitored by TLC (CH_2Cl_2: acetone, 85:15, R_f 0.4, R_f 0.9 for **26** and **27**, respectively). If the reaction was not complete, one equivalent or more of each reagent was added. The reaction mixture was then concentrated in vacuo. Flash chromatography (CH_2Cl_2:acetone, 95:5) afforded 57 mg (90%) of **27** (R_f 0.25). $[\alpha]_D$+50 (*c* 0.6, $CHCl_3$); ^1H NMR 7.40-7.22 (m, 10 H, Ph), 4.96-4.61 (m, 4 H, OCH_2Ph), 4.26 (t, 1 H, H_6), 3.98 (m, 1 H, H_2), 3.90 (dd, 1 H, H_1), 3.81 (dd, 1 H, $H_{6'}$), 3.73 (t, 1 H, H_4), 3.66 (dd, 1 H, H_3), 3.47 (dt, 1 H, H_5), 2.93 (dd, 1 H, $H_{1'}$), $^3J_{3,4} = {}^3J_{4,5} = 9$, $^3J_{2,3} = 2.5$, $^3J_{6,5} = {}^2J_{6,6'} = 8.5$, $^3J_{6',5} = 4$, $^3J_{1,2} = 1.3$, $^3J_{1',2} = 0.6$, $^2J_{1,1'} = 14.5$; ^{13}C NMR 157.0 (CO), 137.6, 137.1, 128.6, 128.2, 127.9 (Ph), 82.7, 76.3 ($C_{3,4}$), 75.3, 72.5 (OCH_2Ph), 65.7 (C_6), 58.3, 57.0 ($C_{2,5}$), 43.2 (C_1); HMRS calcd for $C_{14}H_{15}N_4O_4$ ($M^+ - C_7H_7$) 303.1093; found 303.1093.

2-Azido-3,4-di-*O*-benzyl-1,2,5-trideoxy-1,5-imino-D-mannitol (28). Methanolysis of **27** was carried out under identical conditions as for **5a** described above (96%). R_f 0.4 (CH_2Cl_2:MeOH, 85:15); $[\alpha]_D$ +4 (*c* 0.9, $CHCl_3$); ^1H NMR 7.36–7.25 (m, 10 H, Ph), 4.91–4.59 (m, 4 H, OCH_2Ph), 3.91 (br s, 1 H, H_2), 3.75 (dd, 1 H, H_6), 3.68 (dd, 1 H, H_3), 3.63–3.56 (m, 2 H, $H_{4,6'}$), 3.03 (dd, 1 H, H_1), 2.65 (d, 1 H, $H_{1'}$), 2.53 (m, 1 H, H_5), $^3J_{3,4} = 9.5$, $^3J_{2,3} = 2.5$, $^3J_{6,5} = 2.5$, $^2J_{6,6'} = 11$, $^3J_{1,2} = 1$, $^2J_{1,1'} = 14$; ^{13}C NMR 138.2, 137.7, 128.5, 128.2, 127.8 (Ph), 83.8, 76.3 ($C_{3,4}$), 75.2, 72.3 (OCH_2Ph), 62.2 (C_6), 61.1, 60.3 ($C_{2,5}$), 47.4 (C_1); HMRS calcd for $C_{19}H_{21}N_4O_2$ ($M^+ - CH_2OH$) 337.1664; found 337.1664.

2-Amino-1,2,5-trideoxy-1,5-imino-D-mannitol (29). Hydrogenolysis of **28** was carried out under identical conditions as for **4a** described above (75%); $[\alpha]_D$ −14 (*c* 0.4, H_2O); ^1H NMR (D_2O) 3.86 (br d, 1 H, H_6), 3.74 (dd, 1 H, $H_{6'}$), 3.70 (dd, 1 H, H_3), 3.53 (t, 1 H, H_4), 3.32 (m, 1 H, H_2), 3.05 (br d, 1 H, H_1), 2.89 (br d, 1 H, $H_{1'}$), 2.58 (m, 1 H, H_5), $^3J_{3,4} = {}^3J_{4,5} = 9.5$, $^3J_{2,3} = 3.5$, $^2J_{6,6'} = 11$, $^3J_{6',5} = 5.5$, $^2J_{1,1'} = 14$; ^{13}C NMR (D_2O) 76.6, 71.0 ($C_{3,4}$), 63.9 (C_6); 63.8 (C_5), 53.9 (C_2), 49.9 (C_1); MS (CI, NH_3) 163 ($M^+ + 1$), HRMS calcd for $C_5H_{11}N_2O_2$ ($M^+ - CH_2OH$) 131.0820; found 131.0820.

(2*S*,3*R*,4*R*,5*S*)-*N*-Benzyloxycarbonyl-3,4-di-*O*-benzyl-3,4,5-trihydroxypipecolic acid (30a). To a stirred solution of **4e** (480 mg, 1 mmol) in diethylether (10 mL) was slowly added at 0 °C an aq solution of chromic acid (1.95 mL, 2 mmol).[30] After 1 h stirring at 0 °C, diethylether (20 mL) was added, and after decantation and extraction (4 × 20 mL Et_2O, then 4 × 30 mL CH_2Cl_2), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (CH_2Cl_2:MeOH, 92:8) afforded 246 mg (50%) of **30a** (R_f 0.3). ^1H NMR 7.25 (m, 15 H, Ph), 5.25–5.05 (m, 2 H, CO_2CH_2Ph), 4.9-4.0, 3.60 (2 m, 8 H and 2 H, OCH_2Ph, $H_{2\text{-}6'}$); ^{13}C NMR 174.6 (C_1), 158.5 (CO), 137.3, 136.6, 136.3, 128.6, 128.4, 128.1, 127.9, 127.8, 127.4 (Ph), 74.2, 72.9 ($C_{3,4}$), 72.0, 71.7 (OCH_2Ph), 67.7 (CO_2CH_2Ph), 66.9 (C_5), 55.2 (C_2), 44.4 (C_6); MS (CI, NH_3) 509 (M^++18), 492 (M^++1).

Methyl (2*S*,3*R*,4*R*,5*S*)-*N*-benzyloxy carbonyl-3,4-di-*O*-benzyl-3,4,5-trihydroxy pipecolate (30b). To a solution of **30a** (50 mg, 0.102 mmol) in MeOH:CH_2Cl_2 (1:1, 4 mL) was slowly added a solution of CH_2N_2 in diethylether until the yellow colour of the mixture was maintained. After 5 min stirring, and in vacuo concentration, flash chromatography (cyclohexane:AcOEt, 6:4) afforded 51 mg (100%) of **30b** (R_f 0.3). $[\alpha]_D$ −9 (*c* 0.7, $CHCl_3$); ^1H NMR (50 °C) 7.30 (m, 15 H, Ph), 5.29 (s, 1 H, H_2), 5.18 (m, 2 H, CO_2CH_2Ph), 4.78-4.13 (m, 5 H, OCH_2Ph, H_6), 3.80–3.55 (m, 4 H, $H_{5,3,4,6'}$), 3.50 (s, 3 H, CH_3); ^{13}C NMR mixture of atropoisomers 169.0 (C_1), 157.4, 156.5 (CO), 137.2, 136.5, 136.4, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.6, 127.4 (Ph), 74.7, 74.5, 72.9, 72.6 ($C_{3,4}$), 72.2, 72.1, 71.8 (OCH_2Ph), 67.6 (CO_2CH_2Ph), 66.5 (C_5), 55.1, 54.2 (C_2), 52.2 (CH_3), 44.1, 43.8 (C_6); MS (CI, NH_3) 523 (M^++18), 506 (M^++1); Anal. calcd for $C_{29}H_{31}NO_7$: C, 68.90, H, 6.18, N, 2.77; found: C, 68.88, H, 6.25, N, 2.80.

(2*S*,3*R*,4*R*,5*S*)-3,4,5-trihydroxypipecolic acid (30). Hydrogenolysis of **30a** was carried out under identical conditions as for **4a** described above, to give **30** (100%). Mp 226 °C, lit[31d] 228–230 °C; $[\alpha]_D$ +16 (*c* 0.3, H_2O), lit +14.1 (*c* 0.3, H_2O),[31c] +18.3 (*c* 1.0, H_2O);[31d] ^1H NMR (D_2O) 3.78 (m, 1 H, H_5), 3.68 (br t, 1 H, H_3), 3.53 (br t, 1 H, H_4), 3.48–3.40 (m, 2 H, $H_{2,6}$), 2.86 (br t, 1 H, $H_{6'}$), $^3J_{3,4} = {}^3J_{2,3} = 10$, $^3J_{6',5} = {}^2J_{6,6'} = 11$; ^{13}C NMR (D_2O) 174.9 (C_1), 78.6, 73.1, 69.9 ($C_{3\text{-}5}$), 64.0 (C_2), 48.1 (C_6); MS (CI, NH_3) 178 ($M^+ + 1$).

Isomerization of the azepane 17a or 18a

Mitsunobu reaction with 17a. To a solution of Ph_3P (55 mg, 0.213 mmol) in THF (500 µL) at 0 °C was dropwise added DEAD (34 µL, 0.213 mmol). After 5 min stirring, benzoic acid (26 mg, 0.213 mmol) in THF (200 µL) and **17a** (77 mg, 0.177 mmol) in THF

(300 μL) were successively added dropwise. The reaction mixture was stirred for 10 min at 0 °C and concentrated in vacuo. Flash chromatography (cyclohexane:AcOEt, 7:3) afforded 65 mg of a mixture of **17b** and **16c**. Methanolysis of this mixture, as above, and flash chromatography (CH_2Cl_2:acetone 90:10) afforded 18 mg (24%) of **16a** (R_f 0.35) and 28 mg (36%) of **17a** (R_f 0.30).

Mitsunobu reaction with 18a. To a solution of Ph_3P (157 mg, 0.6 mmol) in THF (1.5 mL) at 0 °C was dropwise added DEAD (95 μL, 0.6 mmol). After 5 min stirring, **18a** (200 mg, 0.462 mmol) in THF (500 μL) was added dropwise. The reaction mixture was stirred for 2 h at 20 °C and concentrated in vacuo. Flash chromatography (cyclohexane:AcOEt, 4:1) afforded 181 mg (94%) of [1*R*-(6-*endo*,7-*exo*)]-6,7-di-*O*-benzyl-3-benzyl-8-oxa-3-azabicyclo-[3.2.1]-octane-6,7-diol **31a**. $[\alpha]_D$ – 32 (*c* 1, $CHCl_3$); ^1H NMR 7.35–7.10 (m, 15 H, Ph), 4.63–4.48 (m, 4 H, OCH_2Ph), 4.32 (d, 1 H, H_7), 4.23 (br d, 1 H, H_5), 4.16 (dd, 1 H, H_6), 4.10 (s, 1 H, H_1), 3.53, 3.44 (AB, 2 H, NCH_2Ph), 2.86 (d, 1 H, H_{4endo}), 2.65 (d, 1 H, H_{2endo}), 2.44 (dd, 1 H, H_{2exo}), 2.26 (dd, 1 H, H_{4exo}), $^3J_{6,7} = 2.4$, $^3J_{6,5} = 6$, $^3J_{4exo,5} = 1$, $^3J_{2exo,1} = 0.8$, $^2J_{4exo,4endo} = 11.6$, $^2J_{2exo,2endo} = 11.2$, $^2J_{A,B} = 13$; ^{13}C NMR 138.2, 138.1, 138.0, 128.5, 128.3, 128.1, 127.8, 127.7, 127.6, 126.7 (Ph), 87.0, 86.3 ($C_{6,7}$), 79.1, 75.6 ($C_{1,5}$), 72.6, 71.4 (OCH_2Ph), 62.1 (NCH_2Ph), 56.0, 51.6 ($C_{2,4}$); Anal. calcd for $C_{27}H_{29}NO_3$: C, 78.04, H, 7.03, N, 3.37; found: C, 78.07, H, 7.06, N, 3.41.

[1*R*-(6-*endo*,7-*exo*)]-8-oxa-3-azabicyclo-[3.2.1]-octane-6,7-diol (31). Hydrogenolysis of **31a** was carried out under identical conditions as for **4a** described above (100%). $[\alpha]_D$ – 30 (*c* 0.8, MeOH), lit[33] – 4.4 (*c* 2.3, MeOH); ^1H NMR (CD_3OD) 4.24 (d, 1 H, H_6), 4.16 (br s, 1 H, H_7), 4.12 (br d, 1 H, H_5), 3.79 (br s, 1 H, H_1), 2.95 (br d, 1 H, H_4), 2.89 (br s, 1 H, $H_{2,2'}$), 2.78 (d, 1 H, $H_{4'}$), $^3J_{6,5} = 6.4$, $^2J_{4,4'} = 13.2$; ^{13}C NMR (CD_3OD) 83.6, 82.8, 82.0, 79.2 ($C_{6,7,1,5}$), 48.4, 45.6 ($C_{2,4}$); HRMS calcd for $C_6H_{11}NO_3$ (M^+) 145.0738; found 145.0739.

Partial hydrogenolysis of 31a. Palladium on charcoal (10%, 6 mg) in absolute EtOH (2 mL) was completely hydrogenated prior to the addition of **31a** (43 mg, 0.103 mmol) in absolute EtOH (1 mL). After 2 h stirring, the catalyst was removed by filtration through a celite pad and rinsed with EtOH. The organic layer was concentrated in vacuo. Flash chromatography (CH_2Cl_2:MeOH, 93:7) afforded 15 mg (43%) of **31b** (R_f 0.30) and 21 mg (55%) of **32** (R_f 0.95).

[1*R*-(6-*endo*,7-*exo*)]-6,7-Di-*O*-benzyl-8-oxa-3-azabicyclo-[3.2.1]-octane-6,7-diol (31b). $[\alpha]_D$ – 8 (*c* 0.7, $CHCl_3$), lit[33] – 6.4 (*c* 0.6, $CHCl_3$); ^1H NMR (C_6D_6) 7.20 (m, 10 H, Ph), 4.30 (m, 4 H, OCH_2Ph), 4.21 (br d, 1 H, H_6), 4.01 (br s, 2 H, $H_{7,5}$), 3.92 (br d, 1 H, H_1), 2.98 (d, 1 H, H_{4endo}), 2.93 (d, 1 H, H_{2endo}), 2.76 (d, 1 H, H_{2exo}), 2.32 (d, 1 H, H_{4exo}), $^3J_{6,5} = 6$, $^2J_{4endo,4exo} = {}^2J_{2endo,2exo} = 13$; ^{13}C NMR 137.7, 137.6, 128.4, 127.9 (Ph), 86.7, 86.0 ($C_{6,7}$), 79.2, 76.7 ($C_{1,5}$), 72.9, 71.4 (OCH_2Ph), 48.3, 45.1 ($C_{2,4}$); MS (CI, NH_3) 326 ($M^+ + 1$).

[1*R*-(6-*endo*,7-*exo*)]-6,7-Di-*O*-benzyl-3-ethyl-8-oxa-3-azabicyclo-[3.2.1]-octane-6,7-diol (32). ^1H NMR 7.30 (m, 10 H, Ph), 4.59, 4.49 (2 s, 4 H, OCH_2Ph), 4.24 (br s, 1 H, H_7), 4.20 (br d, 1 H, H_5), 4.12 (dd, 1 H, H_6), 4.08 (s, 1 H, H_1), 2.86 (d, 1 H, H_{4endo}), 2.69 (d, 1 H, H_{2endo}), 2.43–2.32 (m, 3 H, H_{2exo}, CH_2), 2.20 (dd, 1 H, H_{4exo}), 1.03 (t, 3 H, CH_3), $^3J_{6,5} = 6$, $^3J_{4,5} = 1.5$, $^2J_{4endo,4exo} = 11.5$, $^2J_{2endo,2exo} = 11.3$, $^3J_{4exo,5} = 1$; MS (CI, NH_3) 354 ($M^+ + 1$).

Inhibition analysis. α-D-Glucosidase from *Bacillus stearothermophilus*, β-D-glucosidase from almonds, α-D-mannosidase from Jack bean and α-L-fucosidase from bovine kidney were purchased from Sigma. K_i determinations were run at 37 °C using the corresponding *p*-nitrophenyl-α- (or β)-glycoside at the optimum pHs (citrate-phosphate buffer of pH 6.8, 5.0, 4.5 and 5.5 for α-D-glucosidase, β-D-glucosidase, α-D-mannosidase and α-L-fucosidase, respectively). For the inhibition studies, inhibitors were incorporated variously into each buffer to give a final concentration in the range 10^{-7}–10^{-3} mol L^{-1}. Dissociation constants for inhibition were calculated from the slopes of plots $1/v$ against $1/[S]$ from the rates of substrate hydrolysis in the absence and presence of inhibitor (Lineweaver–Burk plots).

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