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Synthesis of C_2-Symmetric Guanidino-Sugars as Potent Inhibitors of Glycosidases†

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Abstract—A series of enantiomerically pure C_2-Symmetric guanidino-sugars was synthesized from D-mannitol. The first method described involves direct opening of a bis-epoxide by guanidine, whereas the second one deals with a mercury-catalyzed transformation of a cyclic thiourea into a *N,N′,N″*-trisubstituted guanidine as a key step. The biological activity of these compounds towards several glycosidases has been evaluated. One of them (**5**) was found to selectively inhibit α-L-fucosidase of bovin kidney (2.8 μM).

Introduction

Glycosidases are enzymes which are responsible for the hydrolysis of the glycosyl bond; they play a key role in glycoprotein trimming, catabolism of glycoconjugates and degradation of polysaccharides. As a consequence, specific reversible inhibitors of those enzymes can have major therapeutic utility in the treatment of diabetes,[1] cancer[2] and viral infections.[3]

The strategy commonly encountered to design such inhibitors is to synthesize compounds that are able to mimick the oxocarbenium-type transition state,[4] which is supposed to arise during glycosyl bond hydrolysis. In most cases, azasugars[5–13] or amidine[14–21] derivatives have been chosen in order to resemble the transient oxonium. More recently, guanidino-sugars[22–24] have been proposed as a new class of glycosyl cation mimics.

Moreover, in the aim of synthesizing compounds capable of interacting with glycosidases, it has been shown that the aglycon part of the glycoside also plays an important role in the interaction. In particular, pseudo-disaccharides[25–29] or pseudo-sugars containing an alkyl aglycone part[30] deserve more consideration.

Here we report full results on both the synthesis of C_2-Symmetric guanidino-sugars **1**, **2** and **3**, **4**[31] from D-mannitol (Scheme 1), and the introduction on compound **4** of a *n*-butyl or glucopyranosyl group as an aglycon part (respectively, **5** and **6**). Results on the biological evaluation of those compounds as potent inhibitors of glycosidases will be presented.

Compounds **1**, **2** and **3**, **4** are respectively analogues of the azepanes **7**, **8** and of the pyrrolidines **9**, **10**, we precedently described and that inhibit glycosidases in low micromolar range.[32] Two retrosynthetic pathways (Scheme 2) have been imagined as a solution to this challenging synthesis. The first one involves the hetero-cyclization of bis-electrophiles derived from D-mannitol by guanidine. The use of bis-epoxydes will lead to cyclic guanidine **1** or **2** , while an activation at positions 2 and 5 of D-mannitol will lead to **3** or **4**. The second one involves the hetero-cyclization of a diamine as a bis-nucleophile.

Results and Discussion

The commercially available guanidine in salt form (hydrochloride, carbonate, nitrate or sulfate) has already been used as a nucleophile in reactions with α-diketones,[33] α,β-ethylenic esters[34] and alkyl halides,[35] and more recently in the opening of epoxides. For example, guanidine reacts with benzene trioxide[36] to lead cyclic guanidine, and with the 1,2:5,6-dianhydro-3,4-di-*O*-

Keywords: D-mannitol; guanidine; α-L-fucosidase inhibitor; mercuric chloride; thiourea.

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†Warmly dedicated to Professeur Pierre Sinaÿ on the occasion of his 62nd birthday.

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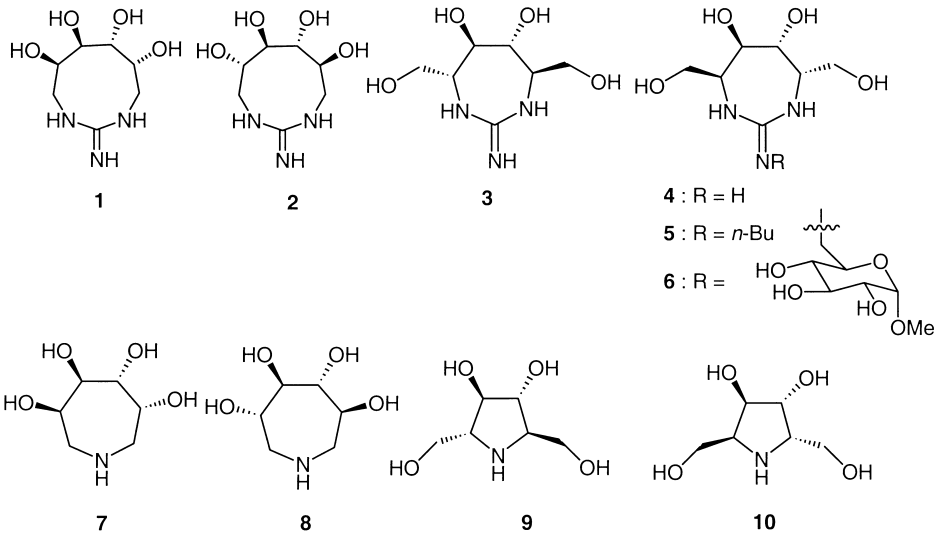
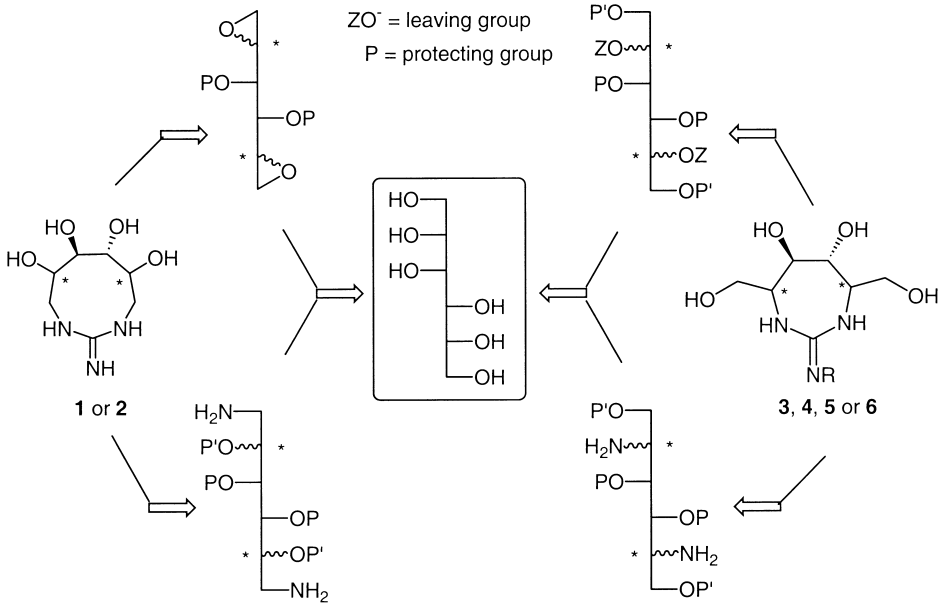


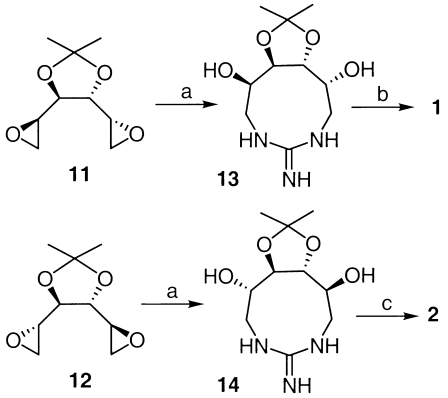
Scheme 1.



Scheme 2.

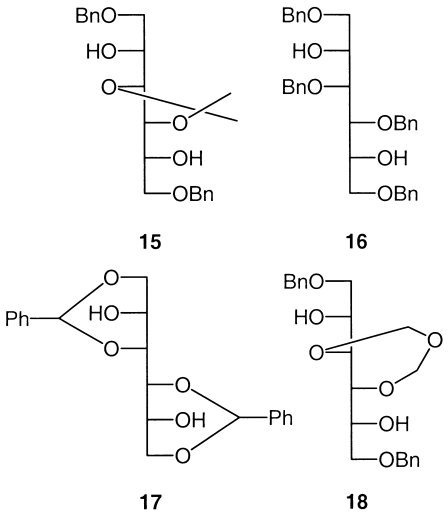
benzyl-L-iditol[37] to give the corresponding guanidinomethyl tetrahydrofuran by subsequent *O*-cyclization. In the latter case, considering that the protective groups play a decisive role in the selectivity of ring opening of the bis-epoxide, we chose to protect the 3,4-diol as an acetonide to prevent *O*-cyclization; the corresponding bis-epoxides **11** and **12** (Scheme 3) being easily prepared from D-mannitol.[38,39]

Thus, treatment of 1,2:5,6-dianhydro-3,4-*O*-methylethylidene-D-mannitol **11** (or L-iditol **12**) by 1 equivalent of guanidine (generated by ethanolic elution of its hydrochloride salt on Amberlite® IRA 400 (OH^-)[40]) in refluxing ethanol afforded the corresponding C_2-Symmetric cyclic guanidine **13** (or **14**) in 97% yield. Removal of the acetonide group was easily achieved with hydrogen chloride in methanol or with aqueous trifluoroacetic acid.



Scheme 3. (a) Guanidine, EtOH Δ, 97%; (b) HClg, MeOH, 70%; (c) TFA, H_2O, 70%.

According to the same strategy, the synthesis of cyclic guanidines **3**–**6** supposed the nucleophilic substitution of alcohols in positions 2 and 5 of D-mannitol or L-iditol, after protection of all the other alcohol functions. Thus, remaining secondary alcohols could be activated as mesylates or by the Mitsunobu reaction in order to react with guanidine.[41,42] Both approaches have been tried on different protected derivatives **15**, **16**, **17**, or **18** (Scheme 4), offering different spatial restraints. Diols **16**[43] and **17**[44,45] were prepared as already described, whereas the diol **15** was easily obtained from the commercially available 3,4-*O*-methylethylidene-D-mannitol **19** by selective benzylation of both primary hydroxyl groups through stannylidene activation with Bu_2SnO[46,47] (Scheme 5), and subsequent treatment with benzyl bromide (86%). Lastly, the diol **18** was prepared from the dicarbonate **20**[48,49] by protection of the alcohol functions in positions 3 and 4 as trioxepane[50] according to a method developed by Beck.[51] Reaction of dicarbonate **20** with paraformaldehyde and $BF_3.Et_2O$ led to an unseparable mixture of **21** and **22** (71% yield in 3:1 ratio according to ^1H NMR). Hydrolysis of carbonates in presence of pyridine yielded a mixture of the corresponding tetrols **23** and **24**. Final protection of both primary alcohols with Bu_2SnO and benzyl bromide, as described above, afforded the corresponding mixture of **18** and **25** which could be separated by flash chromatography (30 and 8% overall yield from **20**, respectively).



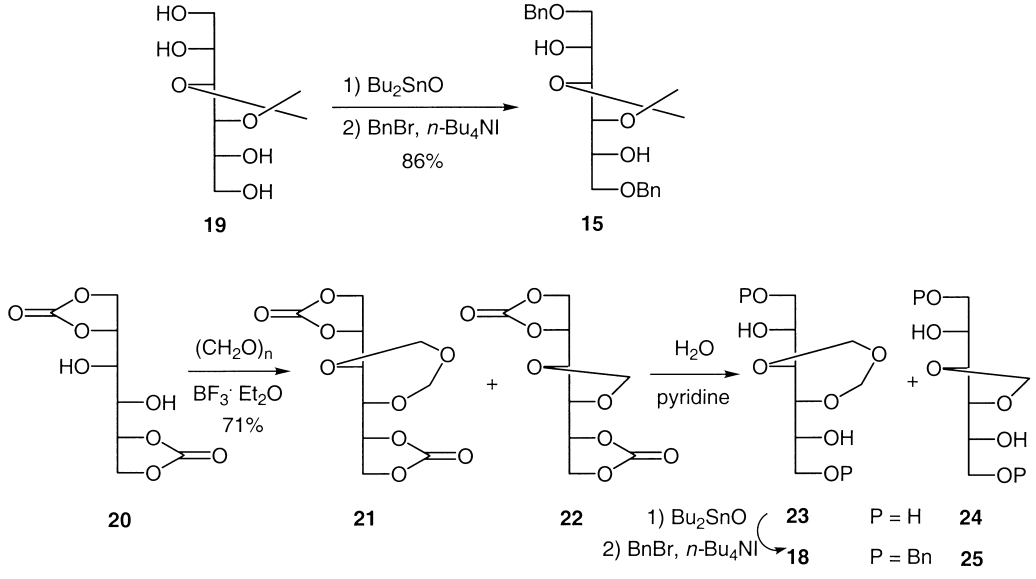
Scheme 4.

On one hand, the dimesylate **26**, **27** or **28**, issued, respectively, from diol **15**, **16** or **17** after treatment with methanesulfonyl chloride, failed to react with different sources of guanidine (free guanidine, acetyl-guanidine, *N,N′*-di-benzyloxy-carbonyl-guanidine), and on the other hand, Mitsunobu reaction involving *N,N′*-di-benzyloxy-carbonyl-guanidine on diol **16** or **18** led to the corresponding tetrahydrofuran **29** or **30** (Scheme 6). In the absence of the guanidine derivative, the yield of **29** or **30** could even be improved up to 91 or 68%, respectively.

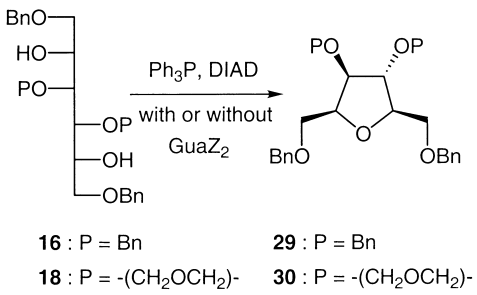
Thus, this first strategy involving the *N,N′*-dialkylation of guanidine revealed to only be efficient with a 1,6-bis activated derivative of D-mannitol. In order to obtain the cyclic guanidines **3**–**6** we turned our attention to the second strategy dealing with the cyclization of a 2,5-diamine derived from D-mannitol or L-iditol into thiourea and subsequent transformation into guanidine.

Synthesis of the readily available cyclic thiourea **33** via the L-*ido*-diamine **32** is depicted in Scheme 7. Nucleophilic substitution of the 2,5-dimesylate **26** by sodium azide afforded the diazido derivative **31** (57% overall yield from **15**) with inversion of configuration at C_2 and C_5, then subsequent heterogeneous catalytic reduction led to the corresponding diamine **32** (87%). Cyclization of **32** into thiourea **33** smoothly occurred by treatment with carbon disulfide[52,53] in pyridine (86%).

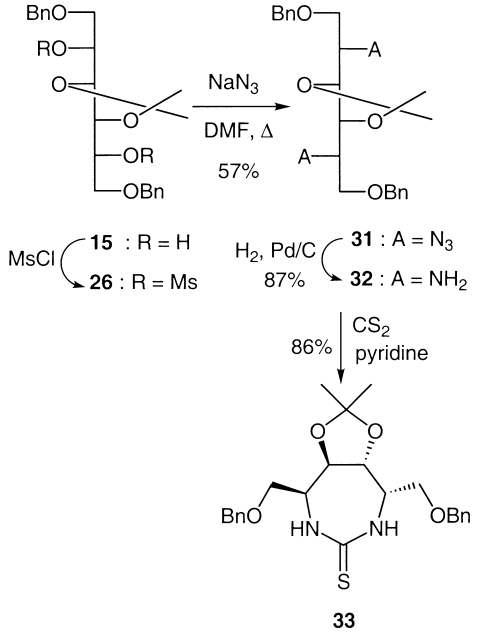
In order to transform the thiourea **33** into guanidine, the well-known method of thiourea alkylation into inter-



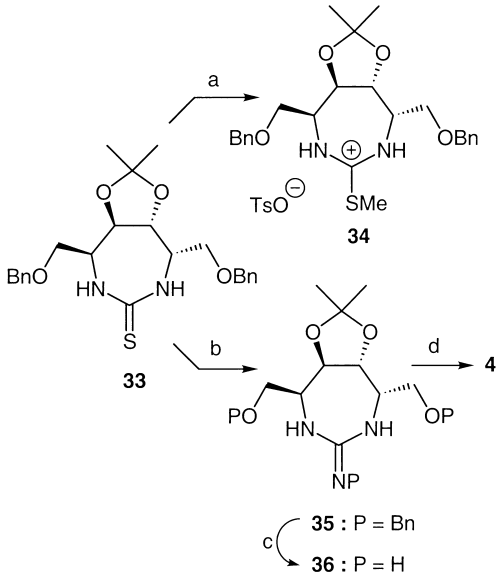
Scheme 5.



Scheme 6.



Scheme 7.

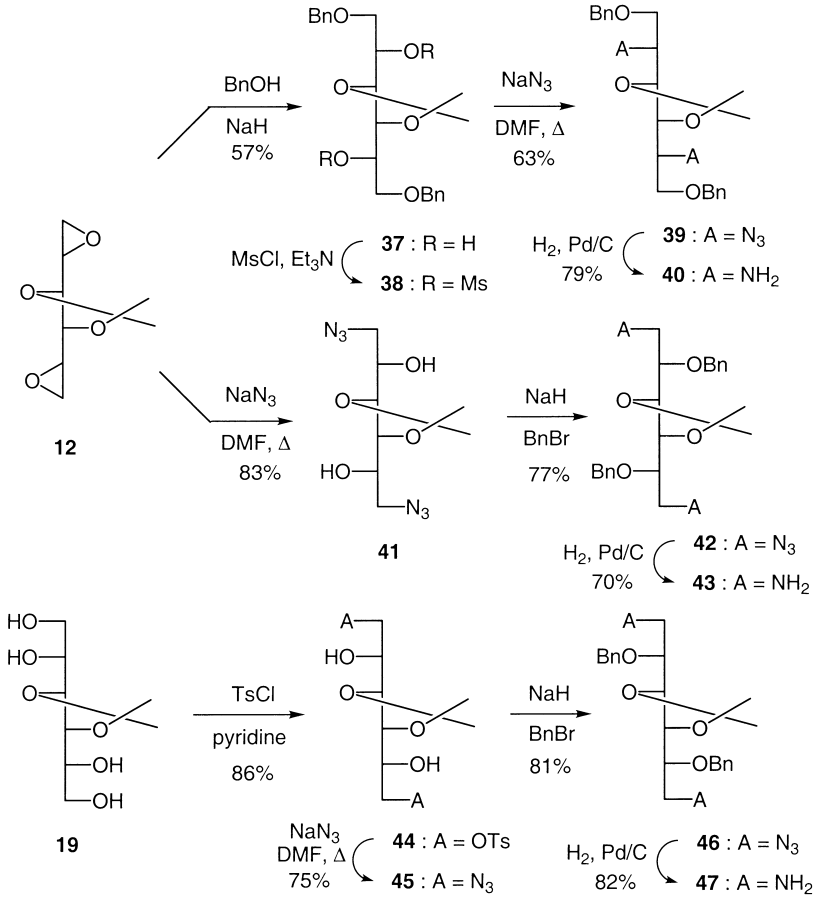


Scheme 8. (a) MeOTs, MeOH Δ, 88%; (b) $BnNH_2$, $HgCl_2$, Et_3N, CH_2Cl_2, 91%; (c) Na, NH_3, 74%; (d) TFA, H_2O, *quant*.

mediary methylisothiourea **34**[54–57] was first tried (Scheme 8). Although methylation at the exocyclic sulfur atom of **33** with methyl *para*-toluene-sulfonate[58] in refluxing methanol was easily achieved (88%), all attempts to substitute the thiomethyl group either with ammonia[59] or benzylamine[60] failed. We therefore turned to a more direct method using $HgCl_2$.[61,62] Such an approach had already successfully been used on *N-tert*-butyloxycarbonyl thioureas in DMF but was reported to be inefficient on unactivated thioureas.[63] Indeed, this method involving the thiourea **33** in the presence of benzylamine and CH_2Cl_2 as solvent,[64] revealed to efficiently afford the *N*-benzyl cyclic guanidine **35** (91%). The last step was the deprotection of cyclic guanidine **35**. Concerning reduction of benzyl ethers and *N*-benzyl guanidine, different attempts involving hydrogeneous catalytic reduction failed, while the use of sodium in liquid ammonia was successful. After 6 h, the reaction was quenched by addition of solid ammonium chloride. Then, an extraction with absolute ethanol was followed by discarding ammonium chloride in excess by an ethanolic elution on Amberlite® IRA 400 (OH^-). Final hydrolysis of the acetonide group was achieved in aqueous trifluoroacetic acid to yield the guanidino-sugar **4**.

This strategy could also be applied to the synthesis of cyclic guanidines **3**, **2** and **1** from corresponding diamines **40**, **43** and **47** (Scheme 9). Interestingly, this second way of synthesizing cyclic guanidines **1** and **2** offered a justification for their structures. In that purpose, D-manno diamine **40** and L-*ido* diamine **43** were obtained from L-*ido* bis-epoxide **12**. On one hand, opening of bis-epoxide **12** with sodium benzylate cleanly occurred to give the 1,6-di-*O*-benzyl derivative **37** (57%) which was then routinely converted into the 2,5-diamine **40** as described above for diamine **32** from diol **15**. On the other hand, opening of bis-epoxide **12** by sodium azide led to the diol **41** (83%) which was protected as dibenzyl ether **42**, by successive treatment with sodium hydride and benzyl bromide (77%). Finally, heterogeneous catalytic reduction in ethanol led to the diamine **43** (70%). The last diamine **47** was obtained from tetrol **19** as follows: selective tosylation of both primary hydroxyl groups with *para*-toluenesulfonyl chloride in pyridine[39] (86%), then nucleophilic substitution with sodium azide (75%) and heterogeneous catalytic reduction (82%). Cyclization of diamines **40**, **43** and **47** into thioureas **48**, **51** and **53** and subsequent transformations into the corresponding guanidino-sugars are summarized in Table 1.

Furthermore, this strategy which involves transformation of a cyclic thiourea into guanidine with benzylamine could be extended to other primary amines such as *n*-butylamine or methyl 6-amino-6-deoxy-2,3,4-tri-*O*-benzyl-D-gluco-pyranoside[65] (Table 2). Thus, *n*-butylamine treatment of thiourea **33** in CH_2Cl_2 in the presence of mercuric chloride at 20 °C led to the cyclic *N*-butyl guanidine **55** (65%), while reaction with the 6-amino-6-deoxy derivative of D-glucose in 1,2-dichloroethane at 80°C afforded the protected pseudo-disaccharide **57** (86%). By sodium reduction and subsequent acidic hydrolysis, as above, **55** and **57** yielded the corresponding deprotected guanidino-sugars **5** and **6**.



Scheme 9.

Biological activity of synthesized guanidino-sugars towards different glycosidases (α- and β-D-glucosidases, α-D-mannosidase and α-L-fucosidase) was evaluated (Table 3). The results show that guanidino-sugars are weak inhibitors of glycosidases. For example, **3** is a less potent inhibitor of α- and β-D-glucosidases than its parent aza-sugar **9** (DMDP). The best results observed concerned the *N*-butyl and the *N*-glucosyl derivatives **5** and **6** which competitively inhibit α-L-fucosidase, $K_i = 2.8$ and 500 μM, respectively. Selective strong inhibition of α-L-fucosidase by compound **5**, and more weakly by compound **6** confirms that the aglycon part plays a critical role in recognition. In particular, an alkyl aglycon moiety may be decisive in order to inhibit α-L-fucosidase.

Experimental[66]

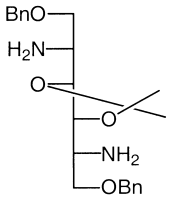
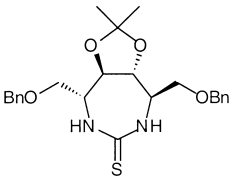
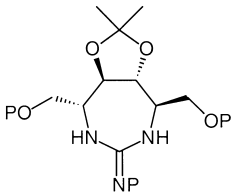
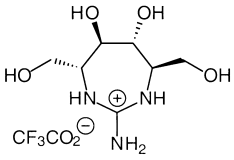
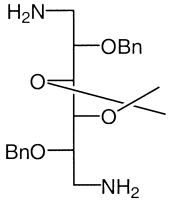
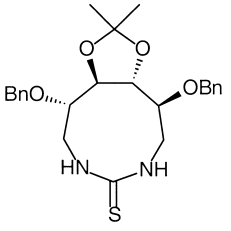
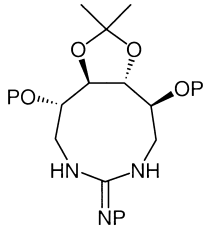
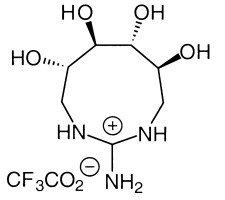
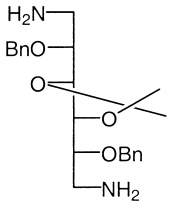
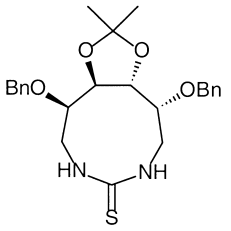
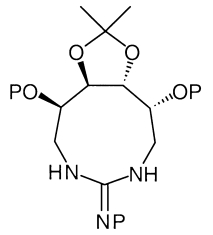
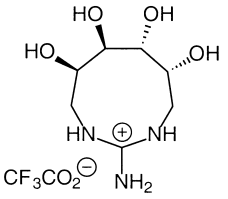
General methods

^{1}H NMR (250 MHz) and ^{13}C NMR (63 MHz) spectra were recorded in $CDCl_3$ (unless otherwise indicated) on a Bruker ARX 250 spectrometer. Optical rotations were measured on a Perkin–Elmer 241C polarimeter with sodium lamp (589 nm) at 20 °C. IR spectra were recorded on a Perkin–Elmer 783 spectrophotometer and wave-numbers of characteristic absorption bands are given in cm^{-1}. Elemental analyses were performed by the 'Service Régional de Microanalyse de l'Université Pierre et Marie Curie', Paris, France. Mass spectra were performed by the 'Service de Spectrométrie de Masse de l'Ecole Normale Supérieure', Paris, France. All reactions were monitored by thin-layer chromatography with Merck 60F 254 precoated silica (0.2 mM) on glass. Flash chromatography was performed with Merck Kieselgel 60H (5–40 μM). Prior to use, THF and Et_2O were distilled from benzophenone-sodium, and CH_2Cl_2 from CaH_2. Spectroscopic (^{1}H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

(5*R*,6*R*,7*R*,8*R*)-5,6,7,8-Tetrahydroxy-1,3-diazonan-2-iminium chloride (1). A solution of the guanidine **13** (50 mg, 21 μmol) in gazeous hydrogen chloride saturated methanol (1 mL) was heated at 60 °C during 1 h. After cooling to 20 °C, the solid was filtered and washed with ethanol to yield the guanidinium chloride **1** (35 mg, 70%) as a white hygroscopic solid. [α] +5 (*c* 0.8, H_2O); ^{1}H NMR (D_2O): 3.35–3.50 (m, 2H, $H_{5,8}$), 3.60–3.75 (m, 2H, $H_{6,7}$), 3.75–4.05 (m, 4H, $H_{4,9}$); ^{13}C NMR (D_2O): 47.9 ($C_{4,9}$), 71.6, 72.2 ($C_{5,6,7,8}$), 160.4 (C_2); HRMS (FAB$^+$) for $C_7H_{16}O_4N_3$: (MH^+) calcd 206.1141, found: 206,1118.

(5*S*,6*R*,7*R*,8*S*)-5,6,7,8-Tetrahydroxy-1,3-diazonan-2-iminium trifluoroacetate (2). A solution of the guanidine **14** (180 mg, 76 μmol) in 10% aq trifluoroacetic acid (4 mL) was heated at 60 °C during 1 h. After concentration in vacuo, the resulting oil was triturated with diethylether to leave a white solid collected by filtration and washed with

Table 1.

Diamine	Thiourea	Protected guanidine	Guanidino-sugar
			
40	**48** (81%)	**49**: P = Bn (78%) **50**: P = H (75%)	**3** (100%)
			
43	**51** (100%)	**52**: P = Bn (94%) **14**: P = H (80%)	**2** (70%)
			
47	**53** (100%)	**54**: P = Bn (94%) **13**: P = H (77%)	**1** (70%)

diethylether to yield the guanidinium trifluoroacetate **2** (177 mg, 70%) as a white hygroscopic solid. [α] +19 (*c* 0.3, H_2O); ^{1}H NMR (D_2O): 3.25–3.40 (m, 2H, $H_{6,7}$), 3.45–4.10 (m, 6H, $H_{4,5,8,9}$); ^{13}C NMR (D_2O): 54.7 ($C_{4,9}$), 74.2, 76.1 ($C_{5,6,7,8}$), 159.6 (C_2).

(4*R*,5*R*,6*R*,7*R*)-5,6-Dihydroxy-4,7-dihydroxy methyl-1,3-diazepan-2-iminium trifluoroacetate (3). The guanidinium trifluoroacetate **3** (40 mg) was quantitatively obtained as a whitish hygroscopic solid from the guanidine **50** on a 0.12 mmol scale, according to the procedure described above for the guanidino-sugar **2**. [α] +8 (*c* 1.3, H_2O); ^{1}H NMR (D_2O): 3.40–3.50 (m, 2H, $H_{4,7}$), 3.60–3.70 (m, 2H, $H_{5,6}$), 3.93 (dd, 2H, $J_{4,CHOH} = 6.4$, $J_{CH_2OH} = 12.0$ Hz, CH_2OH), 4.06 (dd, 2H, $J_{4,CH'OH} = 3.6$, $J_{CH2\,OH} = 12.0$ Hz, CH_2OH); ^{13}C NMR (D_2O): 60.7 ($C_{4,7}$), 63.2 (CH_2OH), 75.3 ($C_{5,6}$); HRMS (FAB^+) for $C_7H_{16}N_3O_4$: (MH^+) calcd 206.1141, found 206.1095.

(4*S*,5*R*,6*R*,7*S*)-5,6-Dihydroxy-4,7-dihydroxy methyl-1,3-diazepan-2-iminium trifluoroacetate (4). The guanidinium trifluoroacetate **4** (27 mg) was quantitatively obtained as a whitish hygroscopic solid from the guanidine **36** on a 0.08 mmol scale, according to the procedure described above for the guanidino-sugar **2**. [α] +12 (*c* 1.0, H_2O); ^{1}H NMR (D_2O): 3.65–4.10 (m, 8H, $H_{4,5,6,7}$, CH_2OH); ^{13}C NMR (D_2O): 59.6 ($C_{4,7}$), 63.9 (CH_2OH), 72.3 ($C_{5,6}$), 160.6 (C_2); HRMS (FAB^+) for $C_7H_{16}N_3O_4$: (MH^+) calcd 206.1141, found 206.1165.

(4*S*,5*R*,6*R*,7*S*)-5,6-Dihydroxy-4,7-dihydroxy methyl-1,3-diazepan-2-(*N*-butyl)-iminium trifluoroacetate (5). The guanidino-sugar **5** (120 mg, 96%) was obtained as a whitish hygroscopic solid from the guanidine **58** on a 0.33 mmol scale, according to the procedure described above for the guanidino-sugar **2**. [α] +2 (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD): 0.97 (t, 3H, $J_{3',4'} = 7.3$ Hz, $H_{4'}$), 1.37 (m, 2H, $H_{3'}$), 1.64 (m, 2H, $H_{2'}$), 3.65–4.00 (m, 8H, $H_{4,7,1'}$, CH_2OH), 4.17 (m, 2H, $H_{5,6}$); ^{13}C NMR (CD_3OD): 15.8 ($C_{4'}$), 22.8 ($C_{3'}$), 33.7 ($C_{2'}$), 45.2 ($C_{1'}$), 59.4 ($C_{4,7}$), 65.8 (CH_2OH), 80.0 ($C_{5,6}$), 160.6 (C_2); MS (NH_3): 262 (MH^+).

Methyl (4′*S*,5′*R*,6′*R*,7′*S*)-6-deoxy-D-gluco pyranoside-6-(4′,7′-dihydroxy methyl-5′,6′-dihydroxy-1′,3′-diazepan-2′-yl)-iminium trifluoroacetate (6). The guanidino-sugar **6** (160 mg, 98%) was obtained as a whitish hygroscopic solid from the guanidine **60** on a 0.33 mmol scale according to the procedure described above for guanidino-sugar **2**. [α] +25 (*c* 0.9, CH_3OH); ^{1}H NMR (CD_3OD): 3.35–3.43 (m, 11H, $H_{4,7}$, CH_2N, OCH_3, CH_2OH), 3.69–3.77

Table 2.

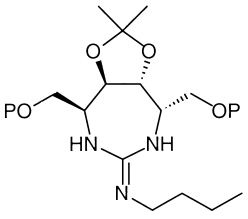
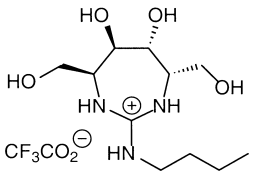
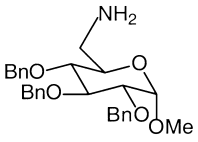
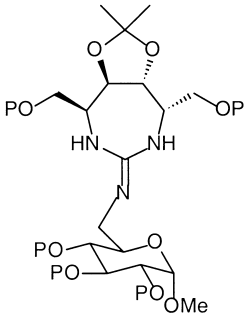
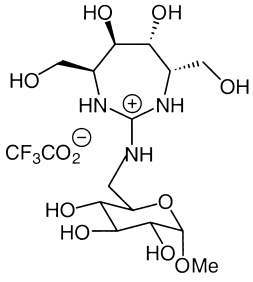
Reactants	Protected guanidine	Guanidino-sugars
33 + nBuNH$_2$, $HgCl_2$,CH_2Cl_2, 20 °C	 **55**: P = Bn (65%) **56**: P = H (73%)	 **5** (96%)
33 +  $HgCl_2$,$ClCH_2CH_2Cl$, 80 °C	 **57**: P = Bn (86%) **58**: P = H (79%)	 **6** (98%)

Table 3.

Enzyme	Inhibitors (%)[a]					
	1	**2**	**3**	**4**	**5**	**6**
α-D-glucosidase[b]	24	36	14	37	41	14
β-D-glucosidase[c]	7	34	10	16	NI	6
α-D-mannosidase[d]	10	41	4	4	18	12
α-L-fucosidase[e]	21	31	12	32	94	96
					2.8 μM[f]	500 μM[f]

[a]% Inhibition determined at 1 mM concentration of inhibitor; NI for no inhibition.
[b]*Bacillus stearothermophilus*, pH 6.8.
[c]Almond, pH 5.0.
[d]Jack beans, pH 4.5.
[e]Bovine kidney, pH 5.5.
[f]Inhibition constants (K_i in μM) determined by the Lineweaver–Burk method.

(m, 6H, $H_{5,6,2',3',4',5'}$), 4.77 (m, 1H, $H_{1'}$); ^{13}C NMR (CD_3 OD): 46.0 (CH_2N), 52.5, 58.7 ($C_{4,7}$, OCH_3), 66.0 (CH_2 OH), 71.8, 74.3, 74.9, 75.8, 77.1 ($C_{5,6,2',3',4',5'}$), 103.8 ($C_{1'}$); MS (FAB$^+$): 382 (MH^+).

(5*R*,6*R*,7*R*,8*R*)-5,6,7,8-Tetrahydroxy-6,7-*O*-methylethylidene-2-imino-1,3-diazonane (13)

From 1,2:5,6-dianhydro-3,4-*O*-methylethylidene-D-mannitol (11). A solution of guanidinium chloride (83 mg, 87 μmol, 0.95 equiv) in a minimum of 95% ethanol:water was neutralized on Amberlite® IRA 400 (OH^-), then eluted with absolute ethanol. After concentration in vacuo, free guanidine was dissolved in absolute ethanol (1 mL), the bis-epoxide **11**[39] (170 mg, 92 μmol) was added and the resulting mixture was heated under reflux during 1 h. After concentration in vacuo, water and CH_2Cl_2 were added. The organic layer was washed with water and the combined aqueous layers were concentrated in vacuo to yield the guanidine **13** (208 mg, 97%) as an hygroscopic solid.

From (5*R*,6*R*,7*R*,8*R*)-5,8-dibenzyloxy-7,8-dihydroxy-7,8-di-*O*-methylethylidene-2-benzylimino-1,3-diazonane (54). A solution of the benzylated guanidine **54** (50 mg, 97 μmol) in a minimum of anhydrous tetrahydrofuran was added into liquid ammonia (5 mL). After addition of sodium until persistance of a dark blue color, the reaction mixture was stirred under refluxing ammonia during 6 h. Then, careful addition of solid ammonium chloride resulted in decoloration and was followed by ammonia evaporation. The resulting solid was washed with CH_2Cl_2 and extracted with absolute ethanol. The combined alcoholic layers were concentrated in vacuo, neutralized over Amberlite® IRA 400 (OH^-), eluted with ethanol and concentrated in vacuo to yield the guanidine **13** (23 mg, 77%) as an hygroscopic solid. [α] +24 (*c* 1.0, MeOH); ^{1}H NMR (D_2O): 1.47 (s, 6H, CH_3), 3.38–3.58 (m, 4H, $H_{4,9}$), 3.68–4.00 (m, 4H, $H_{5,6,7,8}$); ^{13}C NMR (CD_3OD): 27.3 (CH_3), 58.3 ($C_{4,9}$), 73.4 ($C_{5,8}$), 82.5 ($C_{6,7}$), 110.5 (CMe_2), 161.2 (C_2); MS (NH_3): 246 (MH^+), 263 ($M + NH_4^+$).

(5*S*,6*R*,7*R*,8*S*)-5,6,7,8-Tetrahydroxy-6,7-*O*-methylethylidene-2-imino-1,3-diazonane (14). As described above for **13**, the protected guanidino-sugar **14** was obtained as an hygroscopic solid on one hand, from the bis-epoxide **12** (92 μmol scale, 97%), and on the other hand by *N,O*-debenzylation of **52** (97 μmol scale, 80%). [α] +27 (*c*

0.9, MeOH); ^{1}H NMR (D_2O): 1.49 (s, 6H, CH_3), 3.42 (dd, 2H, $J_{4,5}=5.8$, $J_{4,4'}=15.6$ Hz, $H_{4,9}$), 3.64 (m, 2H, $H_{4',9'}$), 3.75–4.10 (m, 4H, $H_{5,6,7,8}$); ^{13}C NMR (CD_3OD): 27.3 (CH_3), 55.5 ($C_{4,9}$), 72.4 ($C_{5,8}$), 82.3 ($C_{6,7}$), 110.6 (CMe_2), 161.7 (C_2); MS (NH_3): 246 (MH^+).

1,6-Di-*O*-benzyl-3,4-*O*-methylethylidene-D-mannitol (15). In a flask equipped with a Dean–Stark, a suspension of 3,4-*O*-methylethylidene-D-mannitol (500 mg, 2.25 mmol) and dibutyl-tin oxide (1.15 g, 4.7 mmol, 2.1 equiv) in toluene (23 mL) was heated under reflux during 15 h. After concentration in vacuo, to a solution of the residue in toluene (11 mL), benzyl bromide (1.1 mL, 9 mmol, 4 equiv) and tetrabutylammonium iodide (805 mg, 2.25 mmol, 1 equiv) were added and the mixture was stirred at 70 °C for 15 h. Concentration in vacuo and subsequent chromatography of the resulting residue (EtOAc:cyclohexane, 3:7) afforded the diol **15** (777 mg, 86%) as an oil. [α] +21 (*c* 1.2, $CHCl_3$); ^{1}H NMR: 1.36 (s, 6H, CH_3), 3.57 (dd, 2H, $J_{1,2}=6.2$, $J_{1,1'}=9.7$ Hz, $H_{1,6}$), 3.71–3.85 (m, 4H, $H_{1',2,5,6'}$), 3.85–3.95 (m, 2H, $H_{3,4}$), 4.57 (s, 4H, OCH_2Ph), 7,32 (s, 10H, CH_{Ph}); ^{13}C NMR: 26.9 (CH_3), 71.7 ($C_{1,6}$), 72.0 ($C_{2,5}$), 73.5 (OCH_2Ph), 79.9 ($C_{3,4}$), 109.4 (CMe_2), 127.8, 128.4 (CH_{Ph}), 138.1 (C_{Ph}). Anal. calcd for $C_{23}H_{30}O_6$: C, 68.62; H, 7.52. Found: C, 68.77; H, 7.41.

(4*R*,5*R*,1′*R*,1″*R*)-4,5-Di-(2′-benzyloxy-1′-hydroxyethyl)-1,3,6-trioxepan (18) and 1,6-di-*O*-benzyl-3,4-*O*-methylene-D-mannitol (25). The diols **18** and **25** were obtained from the mixture of the tetrols **23** and **24** on a 0.22 mmol scale, as described above for the diol **15**. Flash chromatography of the residue (cyclohexane:EtOAc, 6:4) respectively afforded **18** (40 mg, 30%) and **25** (10 mg, 8%).

18. [α] −2 (*c* 0.7, $CHCl_3$); ^{1}H NMR: 3.60–3.67 (m, 6H, $H_{1,3,4,6}$), 4.01 (m, 2H, $H_{2,5}$), 4.50, 4.55 (AB, 4H, $J_{AB}=11.0$ Hz, OCH_2Ph), 4.78, 4.95 (2d, 4H, $J=6.0$ Hz, OCH_2O), 4.95 (d, 2H, $J_{2,2}=6.0$ Hz, OCH_2O), 7.30 (s, 10H, CH_{Ph}); ^{13}C NMR: 69.4 ($C_{2,5}$), 70.7 ($C_{1,6}$), 73.4 (OCH_2Ph), 83.0 ($C_{3,4}$), 91.9 (OCH_2O), 127.8, 128.5 (CH_{Ph}), 137.9 (C_{Ph}); MS (NH_3) 422 ($M+NH_4^+$).

25. [α] +11 (*c* 0.4, $CHCl_3$); ^{1}H NMR: 3.57 (dd, 2H, $J_{1,2}=6.0$, $J_{1,1'}=10.0$ Hz, $H_{1,6}$), 3.71 (dd, 2H, $J_{1',2}=3.2$, $J_{1,1'}=10.0$ Hz, $H_{1',6'}$), 3.80 (m, 2H, $H_{2,5}$), 3.97 (m, 2H, $H_{3,4}$), 4.56 (s, 4H, OCH_2Ph), 4.93 (s, 2H, OCH_2O), 7.32 (s, 10H, CH_{Ph}); MS (NH_3): 392 ($M+NH_4^+$).

(4*S*,5*S*,4′R,4″*R*)-4,5-Di-(2′-oxo-1′,3′-dioxol-4′-yl)-1,3,6-trioxepan (21) and 1,2:5,6-di-*O*-carbonyl-3,4-*O*-methylene-D-mannitol (22). Boron trifluoride etherate (215 μL) was dropwise added to a suspension of both the diol **20** (163 mg, 0.69 mmol) and paraformaldehyde (62 mg) in ethyl acetate (1.6 mL) at 0 °C. Then, the temperature was allowed to warm up to 20 °C and stirring was continued for 15 h. After addition of a saturated aqueous solution of $NaHCO_3$, the pH was adjusted to 8 by addition of solid $NaHCO_3$. Then the mixture was extracted with ethyl acetate and the combined organic layers were dried ($MgSO_4$), concentrated in vacuo and chromatographied (acetone:dichloromethane, 5:95) to yield a mixture of the trioxepane **21** and of the methylene acetal **22** (75:25 according to ^{1}H NMR, 137 mg, ~71%) as a solid.

21. ^{1}H NMR: 3.78 (m, 2H, $H_{4,5}$), 4.43 (dd, 2H, $J_{4',5'}=6.3$, $J_{5',5''}=9.0$ Hz, $H_{5'}$), 4.55 (dd, 2H, $J_{5',5''}=9.0$, $J_{4',5''}=8.2$ Hz, $H_{5''}$), 4.78–4.86 (m, 2H, $H_{4'}$), 4.90 (d, 2H, $J_{2,2'}=6$ Hz, $H_{2,7}$), 5.07 (d, 2H, $J_{2,2'}=6.0$ Hz, $H_{2,7}$); MS (NH_3): 277 (MH^+), 294 ($M+NH_4^+$).

22. ^{1}H NMR: 4.11 (m, 2H, $H_{3,4}$), 4.42 (dd, 2H, $J_{1,2}=5.3$, $J_{1,1'}=8.7$ Hz, $H_{1,6}$), 4.58 (dd, 2H, $J_{1',2}=9.5$, $J_{1,1'}=8.7$ Hz, $H_{1',6'}$), 4.70–4.75 (m, 2H, $H_{2,5}$), 5.10 (s, 2H, OCH_2O); MS (NH_3): 264 ($M+NH_4^+$).

(4*R*,5*R*,1′*R*,1″*R*)-4,5-Di-(1′,2′-dihydroxyethyl)-1,3,6-trioxepan (23) and 3,4-*O*-methylene-D-mannitol (24). A solution of the mixture of carbonates **21** and **22** (137 mg, ~0.5 mmol) in a 1:1 pyridine:water solution (26 mL) was heated under reflux during 1 h to yield a quantitative mixture of tetrols **23** and **24** (110 mg, ~75:25), after concentration in vacuo.

23. ^{1}H NMR (D_2O): 3.64–3.81 (m, 4H, $H_{2',2''}$), 3.86 (m, 2H, $H_{1',1''}$), 3.99 (m, 2H, $H_{4,5}$), 5.01 (d, 2H, $J_{2,2'}=8.0$ Hz, $H_{2,7}$), 5.18 (d, 2H, $J_{2,2'}=8.0$ Hz, $H_{2',7'}$).

24. ^{1}H NMR (D_2O): 3.64–3.81 (m, 4H, $H_{1,6}$), 3.86 (m, 2H, $H_{2,5}$), 4.18 (m, 2H, $H_{3,4}$), 5.08 (s, 2H, OCH_2O).

1,6-Di-*O*-benzyl-2,5-di-*O*-methane sulfonyl-3,4-*O*-methylethylidene-D-mannitol (26). Methane sulfonyl chloride (150 μL, 1.9 mmol, 3 equiv) was dropwise added to a solution of the diol **15** (250 mg, 0.62 mmol) and triethylamine (350 μL, 2.5 mmol, 4 equiv) in dichloromethane (1 mL) at 0 °C. After stirring at 20 °C for 5 min, water was added and the mixture was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to quantitatively yield the dimesylate **26** (345 mg). ^{1}H NMR 1.38 (s, 6H, CH_3), 3.03 (s, 6H, SO_3Me), 3.70 (dd, 2H, $J_{1,2}=6.9$, $J_{1,1'}=11.3$ Hz, $H_{1,6}$), 3.85 (dd, 2H, $J_{1',2}=3.2$, $J_{1,1'}=11.3$ Hz, $H_{1',6'}$), 4.33 (m, 2H, $H_{3,4}$), 4.51, 4.57 (AB, 4H, $J_{AB}=11.7$ Hz, OCH_2Ph), 4.86 (m, 2H, $H_{2,5}$), 7.30 (m, 10H, CH_{Ph}).

1,3,4,6-Tetra-*O*-benzyl-2,5-di-*O*-methane sulfonyl-D-mannitol (27). The dimesylate **27** (130 mg) was quantitatively obtained from the diol **16** as described above for the dimesylate **26** on a 0.18 mmol scale. ^{1}H NMR 2.96 (s, 6H, SO_2CH_3), 3.80 (dd, 2H, $J_{1,2}=7.0$, $J_{1,1'}=11.0$ Hz, $H_{1,6}$), 3.92 (dd, 2H, $J_{1',2}=3.0$, $J_{1,1'}=11.0$ Hz, $H_{1',6'}$), 4.03 (m, 2H, $H_{3,4}$), 4.45, 4.52 (AB, 4H, $J_{AB}=12.0$ Hz, OCH_2Ph), 4.62, 4.68 (AB, 4H, $J_{AB}=11.0$ Hz, OCH_2Ph), 4.93 (m, 2H, $H_{2,5}$), 7.32 (m, 20H, CH_{Ph}).

1,3:4,6-Di-*O*-benzylidene-2,5-di-*O*-methanesulfonyl-D-mannitol (28). The dimesylate **28** (157 mg, 79%) was obtained from the diol **17** as described above for the

dimesylate **26** on a 0.28 mmol scale. ^{1}H NMR: 3.03 (s, 6H, SO_2CH_3), 3.84 (dd, 2H, $J_{1,2}=10.5$, $J_{1,1'}=10.6$ Hz, $H_{1,6}$), 4.13 (d, 1H, $J_{2,3}=9.0$ Hz, $H_{3,4}$), 4.55 (dd, 2H, $J_{1',2}=5.5$, $J_{1',1}=10.6$ Hz, $H_{1',6'}$), 5.05 (m, 2H, $H_{2,5}$), 5.50 (s, 2H, OCHPh), 7.35 (m, 6H, CH_{Ph}), 7.47 (m, 4H, CH_{Ph}).

1,3,4,6-Tetra-*O*-benzyl-2,5-anhydro-D-glucitol (29). Diisopropyl azodicarboxylate (55 μL, 0.27 mmol, 3 equiv) was dropwise added to a solution of both the diol **16** (50 mg, 0.09 mmol) and triphenylphosphine (55 mg, 0.27 mmol, 3 equiv) in toluene (1 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was concentrated in vacuo and the residue was chromatographied (EtOAc:cyclohexane, 1:9) to yield the tetrahydrofuran **29** (44 mg, 91%). [α] +21 (*c* 1.2, $CHCl_3$) {lit.[67] $[\alpha]_D^{20}$ +24.9 (*c* 4.28, $CHCl_3$)}; ^{1}H NMR: 3.54 (dd, 1H, $J_{1,2}=6.8$, $J_{1,1'}=9.9$ Hz, H_1), 3.65 (dd, 1H, $J_{1',2}=5.7$, $J_{1,1'}=9.9$ Hz, $H_{1'}$), 3.73 (dd, 1H, $J_{5,6}=6.0$, $J_{6,6'}=11.3$ Hz, H_6), 3.79 (dd, 1H, $J_{5,6'}=5.3$, $J_{6,6'}=11.3$ Hz, $H_{6'}$), 3.96 (br.d, 1H, $J_{2,3}=3.0$ Hz, H_3), 3.98 (br.d, 1H, $J_{4,5}=3.9$ Hz, H_4), 4.12 (ddd, 1H, $J_{2,3}=3.0$, $J_{1',2}=5.7$, $J_{1,2}=6.8$ Hz, H_2), 4,26 (ddd, 1H, $J_{4,5}=3.9$, $J_{5,6'}=5.3$, $J_{5,6}=6.0$ Hz, H_5), 4.39, 4.62 (AB, 2H, $J_{AB}=12.0$ Hz, OCH_2Ph), 4.61–4.47 (m, 6H, OCH_2Ph), 7.29 (br.s, 20H, CH_{Ph}); ^{13}C NMR: 68.3, 70.5 ($C_{1,6}$), 71.5, 73.4 (OCH_2Ph), 80.1, 82.8, 83.8 ($C_{2,3,4,5}$), 127.6, 128.4, 129.7, 133.5 (CH_{Ph}), 137.9 (C_{Ph}); MS (NH_3): 542 ($M+NH_4^+$).

(1*R*,7*R*,8*S*,10*R*)-8,10-Dibenzyloxy methyl-2,4,6,9-tetraoxa-bicyclo[5.3.0] decane (30). The tetrahydrofuran **30** was obtained from the diol **18** as described above for the tetrahydrofuran **29** on a 0.1 mmol scale. After flash chromatography (cyclohexane:EtOAc, 8:2), the compound **30** (26 mg, 68%) was obtained as an oil. [α] −4 (*c* 1.0, $CHCl_3$); ^{1}H NMR: 3.53 (dd, 1H, $J_{10,CHOBn}=4.8$, $J_{CH_2OBn}=10.6$ Hz, CH_2OBn), 3.60–3.69 (m, 3H, CH_2OBn), 4.03 (m, 1H, H_{10}), 4.25–4.36 (m, 2H, $H_{1,8}$), 4.45 (dd, 1H, $J_{7,8}=8.3$, $J_{1,7}=8.1$ Hz, H_7), 4.53 (s, 2H, OCH_2Ph), 4.58 (s, 2H, OCH_2Ph), 4.82 (d, 1H, $J_{3,3'}=6.2$ Hz, H_3), 4.95 (d, 1H, $J_{5,5'}=6.2$ Hz, H_5), 5.11 (d, 2H, $J_{3,3'}=J_{5,5'}=6.2$ Hz, $H_{3,5}$), 7.31 (s, 10H, CH_{Ph}); ^{13}C NMR: 69.7, 69.9 (CH_2OBn), 73.5 (OCH_2Ph), 76.4, 77.5, 80.1, 82.3 ($C_{1,7,8,10}$), 95.5, 95.9 ($C_{3,5}$), 127.5, 127.6, 129.7, 133.0 (CH_{Ph}), 138.3 (C_{Ph}); MS (NH_3): 404 ($M+NH_4^+$).

2,5-Diazido-1,6-di-*O*-benzyl-2,5-dideoxy-3,4-*O*-methylethylidene-L-iditol (31). A solution of the dimesylate **26** (345 mg, 0.62 mmol) and sodium azide (405 mg, 6.2 mmol, 10 equiv) in DMF (7.5 mL) was heated at 120 °C during 15 h. After concentration in vacuo and addition of water, the mixture was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and chromatographied (cyclohexane:dichloromethane, 2:8) to yield the diazido compound **31** (160 mg, 57%) as a colorless oil. [α] +67 (*c* 1.7, $CHCl_3$); ^{1}H NMR: 1.41 (s, 6H, CH_3), 3.67 (dd, 2H, $J_{1,2}=4.7$, $J_{1,1'}=10$ Hz, $H_{1,6}$), 3.75 (dd, 2H, $J_{1'2}=7.8$, $J_{1,1'}=10$ Hz, $H_{1',6'}$), 4.13 (br.s, 2H, $H_{3,4}$), 4.46 (m, 2H, $H_{2,5}$), 4.55 (s, 4H, OCH_2Ph), 7.34 (s, 10H, CH_{Ph}); ^{13}C NMR: 26.9 (CH_3), 60.1 ($C_{2,5}$), 69.9, 73.6 ($C_{1,6}$, OCH_2Ph), 77.1 ($C_{3,4}$), 110.5 (CMe_2), 127.8, 127.9, 128.5 (CH_{Ph}), 137.5 (C_{Ph}); MS (NH_3): 425 (MH^+-N_2), 470 ($M+NH_4^+$). Anal. calcd for $C_{23}H_{28}O_4N_6$: C, 61.03; H, 6.24; N, 18.58. Found: C, 61.14; H, 6.18; N, 18.56.

2,5-Diamino-1,6-di-*O*-benzyl-2,5-dideoxy-3,4-*O*-methylethylidene-L-iditol (32). Palladium (10%) on charcoal (125 mg) in ethanol (3 mL) was completely hydrogenated under 1 atm of H_2 at 20 °C prior to the addition of the diazido derivative **31** (189 mg, 0.42 mmol) in ethanol (2 mL). After 2 h, the catalyst was removed through a celite pad and the filtrate was concentrated in vacuo and purified by flash chromatography (CH_2Cl_2:MeOH:ammonium hydroxide, 94:3:3) to yield the diamine **32** (146 mg, 87%) as an oil. [α] +14 (*c* 0.8, $CHCl_3$); ^{1}H NMR: 1.38 (s, 6H, CH_3), 2.93 (m, 2H, $H_{2,5}$), 3.80 (dd, 2H, $J_{1,2}=7.3$, $J_{1,1'}=9.2$ Hz, $H_{1,6}$), 3.49 (dd, 2H, $J_{1',2}=5$, $J_{1,1'}=9.2$ Hz, $H_{1',6'}$), 4.06 (br.s, 2H, $H_{3,4}$), 4.49 (s, 4H, OCH_2Ph), 7.30 (s, 10H, CH_{Ph}); ^{13}C NMR ($CDCl_3$): 19.7 (CH_3), 51.9 ($C_{2,5}$), 73.3, 73.8 ($C_{1,6}$, OCH_2Ph), 78.2 ($C_{3,4}$), 108.8 (CMe_2), 127.7, 128.4 (CH_{Ph}), 138.1 (C_{Ph}).

(4*S*,5*R*,6*R*,7*S*)-4,7-Dibenzyloxymethyl-5,6-dihydroxy-5,6-*O*-methylethylidene-1,3-diazepan-2-thione (33). Carbon disulfide (118 μL, 1.96 mmol, 2 equiv) was added to a solution of the diamine **32** (391 mg, 0.98 mmol) in pyridine (800 μL). After stirring at 60 °C for 15 h, the pH was adjusted to 2–3 by the addition of a 1 M aq HCl solution. The mixture was extracted with dichloromethane and the combined organic layers were washed with a 1 M aq NaOH solution, dried ($MgSO_4$) and concentrated in vacuo to yield the thiourea **33** (372 mg, 86%) as a yellow foam. [α] +21 (*c* 1.0, $CHCl_3$); ^{1}H NMR: 1.35 (s, 6H, CH_3), 3.30–3.80 (m, 4H, CH_2OBn), 3.80–4.20 (m, 4H, $H_{4,5,6,7}$), 4.20–4.60 (m, 4H, OCH_2Ph), 7.24 (m, 10H, CH_{Ph}); ^{13}C NMR: 27.0 (CH_3), 53.0 ($C_{4,7}$), 69.5 ($C_{5,6}$), 73.1 (CH_2OBn, OCH_2Ph), 110.2 (CMe_2), 127.8, 128.4 (CH_{Ph}), 136.3 (C_{Ph}), 184.0 (C_2); IR (neat): 1230 ($\nu_{C=S}$); HRMS (NH_3): for $C_{24}H_{31}N_2O_4S$ (MH^+) calcd 443.2004, found 443.1983.

(4*R*,5*R*,6*R*,7*R*)-4,7-Dibenzyloxymethyl-5,6-dihydroxy-2-methylthio-4,5,6,7-tetrahydro-1,3-diazepinium *para*-toluene sulfonate (34). A solution of the thiourea **33** (40 mg, 0.09 mmol) and methyl *para*-toluenesulfonate (24 μL, 0.16 mmol, 1.7 equiv) in methanol (200 μL) was heated under reflux during 30 min. After concentration in vacuo, the resulting oil was triturated with diethylether to yield the isothiourea **34** (47 mg, 88%) as an hygroscopic solid. [α] +109 (*c* 0.4, $CHCl_3$); ^{1}H NMR: 2.29 (br.s, 3H, SCH_3), 2.44 (br.s, 3H, $ArCH_3$), 3.80 (m, 6H, $H_{4,7}$, CH_2OBn), 4.40 (m, 6H, $H_{5,6}$, OCH_2Ph), 7.09 (br.s, 2H, CH_{Ar}), 7.24 (br.s, 10H, CH_{Ar}), 7.72 (br.s, 2H, CH_{Ar}); ^{13}C NMR: 15.4 (SCH_3), 21.3 ($ArCH_3$), 60.6 ($C_{4,7}$), 69.6 (CH_2OBn), 71.6 ($C_{5,6}$), 73.4 (OCH_2Ph), 126.0, 127.8, 128.0, 128.5, 128.9, 129.9 (CH_{Ar}), 137.5, 140.3, 141.9 (C_{Ar}); MS (FAB+): 417 (MH^+).

(4*S*,5*R*,6*R*,7*S*)-4,7-Dibenzyloxymethyl-5,6-dihydroxy-5,6-*O*-methylethylidene-2-(*N*-benzyl)-imino-1,3-diazepane (35). Benzylamine (57 μL, 0.52 mmol, 1.1 equiv) and triethylamine (63 μL, 0.94 mmol, 2 equiv) were successively added to a solution of both the thiourea **33** (208 mg, 0.47 mmol) and mercuric chloride (160 mg,

0.61 mmol, 1.3 equiv) in dichloromethane (6.5 mL). After stirring at 20 °C during 15 h, mercuric salts were removed by filtration through a celite pad and washed with dichloromethane. The combined organic layers were successively washed with a 1 M aq HCl solution and a 1 M aq NaOH solution then dried ($MgSO_4$) and concentrated in vacuo to yield the guanidine **35** (220 mg, 91%). [α] +32 (*c* 0.5, $CHCl_3$); ^1H NMR: 1.25 (br.s, 6H, CH_3), 3.30–3.70 (m, 4H, CH_2OBn), 3.70–4.00 (m, 6H, $H_{4,5,6,7}$, NCH_2Ph), 4.00–4.38 (m, 4H, OCH_2Ph), 7,24 (br.s, 15H, CH_{Ph}); ^{13}C NMR: 27.1 (CH_3), 53.4 ($C_{4,7}$), 56.3 (C5,6), 71.5, 73.0 (NCH_2Ph, CH_2OBn, OCH_2Ph), 109.5 (CMe_2), 127.7, 128.4 (CH_{Ph}), 138.0 (C_{Ph}); IR (neat): 1625 ($\nu_{C=N}$); HRMS (NH_3) for $C_{31}H_{38}N_3O_4$: (MH^+) calcd 516.2862, found 516.2845.

(4*S*,5*R*,6*R*,7*S*)-5,6-Dihydroxy-4,7-dihydroxy methyl-5,6-*O*-methylethylidene-2-imino-1,3-diazepane (36). A solution of the benzylated guanidine **35** (191 mg, 0.42 mmol) in a minimum of anhydrous THF was poured into liquid ammonia (10 mL). Then, sodium was added until persistance of a dark blue color and the mixture was stirred in refluxing ammonia during 6 h. After careful addition of solid ammonium chloride until decoloration, ammonia was evaporated and the solid residue was washed with dichloromethane and extracted with absolute ethanol. The combined alcoholic layers were concentrated in vacuo. Neutralization of the resulting residue by ethanolic elution through an Amberlite® IRA 400 (OH^-) packed column followed by concentration in vacuo afforded the guanidine **36** (67 mg, 74%) as an hygroscopic solid. ^1H NMR (D_2O): 1.60 (m, 6H, CH_3), 3.70–4.30 (m, 8H, $H_{4,5,6,7}$, CH_2OH); ^{13}C NMR (D_2O): 28.9 (CH_3), 57.0 ($C_{4,7}$), 64.6 (CH_2OH), 79.3 ($C_{5,6}$), 113.4 (CMe_2), 160.2 (C_2).

1,6-Di-*O*-benzyl-3,4-*O*-methylethylidene-L-iditol (37). Benzylic alcohol (4.2 mL, 40.3 mmol, 2.5 equiv) was added to a suspension of sodium hydride (851 mg, 35.5 mmol, 2.2 equiv) in DMF (32 mL) and the reaction mixture was stirred at 20 °C during 3 h. Then, a solution of the bis-epoxide **12**[39] (3 g, 16.11 mmol) in a minimum of DMF was dropwise added at 0 °C. After stirring at 20 °C during 20 h, methanol was added and the reaction mixture was concentrated in vacuo prior to the addition of water. The mixture was then extracted with dichloromethane and the combined organic layers were dried ($MgSO_4$), concentrated in vacuo and chromatographied (cyclohexane:AcOEt, 70:30) to yield the diol **37** (3.7 g, 57%) as an oil. [α] −19 (*c* 5.1, CH_2Cl_2); ^1H NMR: 1.43 (s, 6H, CH_3), 3.51 (dd, 2H, $J_{1,2}=5.5$, $J_{1,1'}=10.0$ Hz, $H_{1,6}$), 3.56 (dd, 2H, $J_{1',2}=6.0$, $J_{1,1'}=10.0$ Hz, $H_{1',6'}$), 3.78 (m, 2H, $H_{2,5}$), 4.11 (m, 2H, $H_{3,4}$), 4.52 (s, 4H, OCH_2Ph), 7.33 (s, 10H, CH_{Ph}). Anal. calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found: C, 68.54; H, 7.50.

1,6-Di-*O*-benzyl-2,5-di-*O*-methane sulfonyl-3,4-*O*-methylethylidene-L-iditol (38). The dimesylate **38** (2.57 g) was quantitatively obtained from the diol **37** as described above for the dimesylate **26** on a 4.59 mmol scale. ^1H NMR: 1.40 (s, 6H, CH_3), 3.02 (s, 6H, SO_3CH_3), 3.70 (dd, 2H, $J_{1,2}=3.3$, $J_{1,1'}=11.0$ Hz, $H_{1,6}$), 3.87 (dd, 2H, $J_{1,2}=8.5$, $J_{1,1'}=11.0$ Hz, $H_{1',6'}$), 4.13 (m, 2H, $H_{3,4}$), 4.48, 4.54 (AB, 4H, $J_{AB}=11.5$ Hz, OCH_2Ph), 4.92 (m, 2H, $H_{2,5}$), 7.33 (m, 10H, CH_{Ph}).

2,5-Diazido-1,6-di-*O*-benzyl-2,5-dideoxy-3,4-*O*-methylethylidene-D-mannitol (39). The diazido compound **39** was obtained from the dimesylate **38** as described above for the diazide **31** on a 4.6 mmol scale. After flash chromatography (dichloromethane:cyclohexane, 8:2), the product **39** (1.3 g, 63% yield) was obtained as an oil. [α] +8 (*c* 0.8, $CHCl_3$); ^1H NMR: 1.35 (s, 6H, CH_3), 3.61 (dd, 2H, $J_{1,1'}=8.3$, $J_{1,2}=9.4$ Hz, $H_{1,6}$), 3.69–3.75 (m, 2H, $H_{2,5}$), 3.81 (dd, 2H, $J_{1',2}=3.0$, $J_{1,1'}=8.3$ Hz, $H_{1',6'}$), 4.01 (m, 2H, $H_{3,4}$), 4.57 (s, 4H, OCH_2Ph), 7.33 (s, 10H, CH_{Ph}); ^{13}C NMR: 27.4 (CH_3), 63.1 ($C_{2,5}$), 70.0, 73.6 ($C_{1,6}$, OCH_2Ph), 78.0 ($C_{3,4}$), 110.7 (CMe_2), 126.5, 127.8, 128.5 (CH_{Ph}), 137.6 (C_{Ph}); IR (neat): 2100 (ν_{N_3}). Anal. calcd for $C_{23}H_{28}O_4N_6$: C, 61.05; H, 6.24; N, 18.57. Found: C, 61.02; H, 6.35; N, 18.47.

2,5-Diamino-1,6-di-*O*-benzyl-2,5-dideoxy-3,4-*O*-methylethylidene-D-mannitol (40). The diamine **40** was obtained from the diazido compound **39** as described above for the diamine **32** on a 0.89 mmol scale. After flash chromatography (CH_2Cl_2:MeOH:ammonium hydroxide, 94:3:3), the compound **40** (280 mg, 79%) was obtained as an oil. [α] +7 (*c* 0.7, $CHCl_3$); ^1H NMR: 1.33 (s, 6H, CH_3), 3.07 (m, 2H, $H_{2,5}$), 3.46 (dd, 2H, $J_{1,2}=7.1$, $J_{1,1'}=9.1$ Hz, $H_{1,6}$), 3.69 (dd, 2H, $J_{1',2}=3.5$, $J_{1,1'}=9.1$ Hz, $H_{1',6'}$), 3.85 (m, 2H, $H_{3,4}$), 4.52 (s, 4H, OCH_2Ph), 7.32 (s, 10H, CH_{Ph}); ^{13}C NMR: 27.3 (CH_3), 54.0 ($C_{2,5}$), 72.6, 73.3 ($C_{1,6}$, OCH_2Ph), 81.1 ($C_{3,4}$), 108.9 (CMe_2), 127.7, 128.4 (CH_{Ph}), 138.3 (C_{Ph}).

1,6-Diazido-1,6-dideoxy-3,4-*O*-methyl ethylidene-L-iditol (41). A solution of the bis-epoxide **12**[39] (688 mg, 3.7 mmol), ammonium chloride (870 mg, 16.3 mmol, 4.4 equiv) and sodium azide (2.4 g, 36.9 mmol, 10 equiv) in methanol:water 8:1 (15 mL) was stirred at 20 °C during 15 h. After concentration in vacuo, water was added and the mixture was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and chromatographied (dichloromethane:ether, 80:20) to yield the diazido-diol **41** (835 mg, 83%) as an oil. [α] −4 (*c* 1.0, CH_2Cl_2); ^1H NMR: 1.43 (s, 6H, CH_3), 3.35 (dd, 2H, $J_{1,2}=5.2$, $J_{1,1'}=12.6$ Hz, $H_{1,6}$), 3.45 (dd, 2H, $J_{1',2}=6.9$, $J_{1,1'}=12.6$ Hz, $H_{1',6'}$), 3.73 (m, 2H, $H_{2,5}$), 4.04 (s, 2H, $H_{3,4}$); ^{13}C NMR: 27.0 (CH_3), 54.2 ($C_{1,6}$), 68.9 ($C_{2,5}$), 77.0 ($C_{3,4}$), 110.3 (CMe_2); IR (neat): 2100 (ν_{N_3}). Anal. calcd for $C_9H_{16}N_6O_4$: C, 39.70; H, 5.92; N, 30.87. Found: C, 39.83; H, 3.17; N, 30.11.

1,6-Diazido-2,5-di-*O*-benzyl-1,6-dideoxy-3,4-*O*-methylethylidene-L-iditol (42). A solution of the diol **41** (748 mg, 2.75 mmol) in THF (4.5 mL) was dropwise added to a suspension of sodium hydride (195 mg, 8.1 mmol, 3 equiv) in THF (4.5 mL) at 0 °C. After stirring at 20 °C for 3 h, benzyl bromide (4 mL, 8.1 mmol, 3 equiv) was added and the mixture was stirred at 20 °C for an additional 15 h. Then, methanol was added and the reaction mixture was concentrated in vacuo. After addition of water and extraction with dichloromethane, the combined organic layers were washed with brine,

dried ($MgSO_4$), and concentrated in vacuo. Flash chromatograpy (dichloromethane:cyclohexane, 8:2) afforded the compound **42** (957 mg, 77%) as an oil. [α] +34 (*c* 1.0, $CHCl_3$); ^1H NMR: 1.37 (s, 6H, CH_3), 3.41 (br.s, 6H, $H_{1,2,5,6}$), 4.04 (s, 2H, $H_{3,4}$), 4.51, 4. 71 (AB, 4H, $J_{AB}=11.7$ Hz, OCH_2Ph), 7.32 (br.s, 10H, CH_{Ph}); ^{13}C NMR: 26.9 (CH_3), 51.8 ($C_{1,6}$), 73.4 (OCH_2Ph), 76.0, 76.2 ($C_{2,3,4,5}$), 109.5 (CMe_2), 128.1, 128.2, 128.5 (CH_{Ph}), 137.5 (C_{Ph}); IR (neat) 2100 (ν_{N_3}). Anal. calcd for $C_{23}H_{28}N_3O_4$: C,61.0; H, 6.24; N, 18.57. Found: C, 61.00; H, 6.25; N, 18.43.

1,6-Diamino-2,5-di-*O*-benzyl-1,6-dideoxy-3,4-*O*-methylethylidene-L-iditol (43). The diamine **43** was obtained from the diazido compound **42** as described above for the diamine **32** on a 0.85 mmol scale. After flash chromatography (CH_2Cl_2:MeOH:ammonium hydroxide, 90:7:3), the compound **43** (240 mg, 70%) was obtained as an oil. [α] +12 (*c* 0.4, $CHCl_3$); ^1H NMR: 1.40 (s, 6H, CH_3), 2.77 (dd, 2H, $J_{1,2}=5.9$, $J_{1,1'}=13.3$ Hz, $H_{1,6}$), 2.89 (dd, 2H, $J_{1',2}=5.0$, $J_{1,1'}=13.3$ Hz, $H_{1',6'}$), 3.34 (m, 2H, $H_{2,5}$), 4.14 (br.s, 2H, $H_{3,4}$), 4.57, 4.64 (AB, 4H, $J_{AB}=11.8$ Hz, OCH_2Ph), 7.30 (br.s, 10H, CH_{Ph}); ^{13}C NMR: 27.1 (CH_3), 42.3 ($C_{1,6}$), 72.7 (OCH_2Ph), 77.7, 78.8 ($C_{2,3,4,5}$), 109.1 (CMe_2), 127.8, 128.0, 128.4 (CH_{Ph}), 138.2 (C_{Ph}).

1,6-Diazido-1,6-dideoxy-3,4-*O*-methyl ethylidene-D-mannitol (45). A solution of the ditosylate **44**[39] (5 g, 9.5 mmol) and sodium azide (2.5 g, 38 mmol, 4 equiv) in DMF (38 mL) was heated at 70 °C during 3 h. After concentration in vacuo and addition of water, the mixture was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and chromatographied (dichloromethane:ether, 90:10) to yield the diazido-diol **45** (2 g, 75%) as an oil. [α] +45 (*c* 2.0, CH_2Cl_2); ^1H NMR: 1.35 (s, 6H, CH_3), 3.44 (dd, 2H, $J_{1,2}=4.6$, $J_{1,1'}=12.2$ Hz, $H_{1,6}$), 3.64 (d, 2H, $J_{1,1'}=12.2$ Hz, $H_{1',6'}$), 3.78 (m, 4H, $H_{2,3,4,5}$); ^{13}C NMR: 26.7 (CH_3), 54.2 ($C_{1,6}$), 72.2 ($C_{2,5}$), 80.1 ($C_{3,4}$), 109.9 (CMe_2); IR (neat) 2100 (ν_{N3}). Anal. calcd for $C_9H_{16}N_6O_4$: C, 39.70; H, 5.92; N, 30.87. Found: C, 39.72; H, 6.23; N, 29.93.

1,6-Diazido-2,5-di-*O*-benzyl-1,6-dideoxy-3,4-*O*-methylethylidene-D-mannitol (46). The dibenzyl-ether **46** was obtained from the diol **45** as described above for the dibenzyl-ether **42** on a 1.78 mmol scale. After flash chromatography (dichloromethane:cyclohexane, 8:2), the compound **46** (223 mg, 81%) was obtained as an oil. ^1H NMR: 1.34 (s, 6H, CH_3), 3.39 (dd, 2H, $J_{1,2}=5.8$, $J_{1,1'}=13.2$ Hz, $H_{1,6}$), 3.49 (dd, 2H, $J_{1',2}=3.3$, $J_{1,1'}=13.2$ Hz, $H_{1',6'}$), 3.61 (m, 2H, $H_{2,5}$), 4.06 (m, 2H, $H_{3,4}$), 4.53, 4.66 (AB, 4H, $J_{AB}=11.5$ Hz, OCH_2Ph), 7.29 (m, 10H, CH_{Ph}); ^{13}C NMR: 27.2 (CH_3), 51.1 ($C_{1,6}$), 72.8 (OCH_2Ph), 78.3, 79.3 ($C_{2,3,4,5}$), 110.2 (CMe_2), 128.0, 128.5 (CH_{Ph}), 137.5 (C_{Ph}). Anal. calcd for $C_{23}H_{28}N_6O_4$: C, 61.05; H, 6.24; N, 18.57. Found: C, 61.21; H, 6.16; N, 18.51.

1,6-Diamino-2,5-di-*O*-benzyl-1,6-dideoxy-3,4-*O*-methylethylidene-D-mannitol (47). The diamine **47** was obtained from the diazido compound **46** as described above for the diamine **32** on a 0.29 mmol scale. After flash chromatography (CH_2Cl_2:MeOH:ammonium hydroxide, 90:7:3), the compound **47** (94 mg, 82%) was obtained as an oil. [α] +16 (*c* 1.0, $CHCl_3$); ^1H NMR: 1.36 (s, 6H, CH_3), 2.93 (m, 4H, $H_{1,6}$), 3.51 (m, 2H, $H_{2,5}$), 4.14 (m, 2H, $H_{3,4}$), 4.56 (s, 4H, OCH_2Ph), 7.27 (br.s, 10H, CH_{Ph}); ^{13}C NMR: 27.3 (CH_3), 41.2 ($C_{1,6}$); 72.1 (OCH_2Ph), 78.7, 81.4 ($C_{2,3,4,5}$), 109.7 (CMe_2), 127.9, 128.4 (CH_{Ph}), 138.2 (C_{Ph}).

(4*R*,5*R*,6*R*,7*R*)-4,7-Dibenzyloxymethyl-5,6-dihydroxy-5,6-*O*-methylethylidene-1,3-diazepan-2-thione (48). The thiourea **48** (125 mg, 81%) was obtained as a yellow foam from the diamine **40** on a 0.35 mmol scale, according to the procedure described above for the thiourea **33**. [α] +40 (*c* 0.4, $CHCl_3$); ^1H NMR: 1.34 (s, 6H, CH_3), 3.44 (m, 6H, $H_{4,7}$, CH_2OBn), 3.74 (m, 2H, $H_{5,6}$), 4.55 (s, 4H, OCH_2Ph), 7.33 (s, 10H, CH_{Ph}); ^{13}C NMR: 26.8 (CH_3), 56.7 ($C_{4,7}$), 69.0, 73.4 (CH_2OBn, OCH_2Ph), 78.9 ($C_{5,6}$), 111.6 (CMe_2), 127.0, 128.6 (CH_{Ph}), 137.2 (C_{Ph}), 187.3 (C_2); IR (neat) 1230 ($\nu_{C=S}$); HRMS (NH_3) for $C_{24}H_{31}N_2O_4S$: (MH^+) calcd 443.2004, found 443.2003.

(4*R*,5*R*,6*R*,7*R*)-4,7-Dibenzyloxymethyl-5,6-dihydroxy-5,6-*O*-methylethylidene-2-(*N*-benzyl)-imino-1,3-diazepane (49). The guanidine **49** (45 mg, 78%) was obtained as a yellow foam from the thiourea **48** on a 0.11 mmol scale, according to the procedure described above for the guanidine **35**. [α] +37 (*c* 0.4, $CHCl_3$); ^1H NMR: 1.33 (s, 6H, CH_3), 3.42–3.72 (m, 6H, $H_{4,7}$, CH_2OBn), 3.80 (m, 2H, $H_{5,6}$), 4.18–4.41 (m, 2H, NCH_2Ph), 4.54 (m, 4H, OCH_2Ph), 7.14–7.25 (m, 15H, CH_{Ph}); ^{13}C NMR: 26.7 (CH_3), 55.5 ($C_{4,7}$), 68.4, 73.5 (NCH_2Ph, CH_2OBn, OCH_2Ph), 78.2 ($C_{5,6}$), 111.6 (CMe_2), 127.0, 128.0, 128.3, 128.5, 129.0, 129.1 (CH_{Ph}), 135.2, 137.4 (C_{Ph}), 159.8 (C_2); IR (neat): 1635 (ν_{CN}); HRMS (NH_3) for $C_{31}H_{38}N_3O_4$: (MH^+) calcd 516.2862, found 516.2872.

(4*R*,5*R*,6*R*,7*R*)-5,6-Dihydroxy-4,7-dihydroxy methyl-5,6-*O*-methylethylidene-2-imino-1,3-diazepane (50). The guanidino-sugar **50** (21 mg, 75%) was obtained as an hygroscopic solid from the guanidine **49** on a 0.13 mmol scale, according to the procedure described above for the guanidino-sugar **36**. ^1H NMR (D_2O): 1.52 (s, 6H, CH_3), 3.55 (m, 2H, $H_{4,7}$), 3.79 (dd, 2H, $J_{4,CHOH}=5.6$, $J_{CH_2OH}=12.1$ Hz, CH_2OH), 3.91–3.99 (m, 4H, $H_{5,6}$, $CH'OH$); ^{13}C NMR (D_2O): 28.7 (CH_3), 59.2 ($C_{4,7}$), 63.4 (CH_2OH), 80.4 ($C_{5,6}$), 115.4 (CMe_2), 162.8 (C_2).

(5*S*,6*R*,7*R*,8*S*)-5,8-Dibenzyloxy-6,7-dihydroxy-6,7-*O*-methylethylidene-1,3-diazonan-2-thione (51). The thiourea **51** (335 mg) was quantitatively obtained as a yellow foam from the diamine **43** on a 0.77 mmol scale according to the procedure described above for thiourea **33**. [α] +21 (*c* 1.1, $CHCl_3$); ^1H NMR: 1.36 (br.s, 6H, CH_3), 3.43 (m, 4H, $H_{4,9}$), 3.65 (m, 2H, $H_{5,8}$), 4.01 (br.s, 2H, $H_{6,7}$), 4.43, 4.58 (AB, 4H, $J_{AB}=11.8$ Hz, OCH_2Ph), 7.25 (s, 10H, CH_{Ph}); ^{13}C NMR: 27.0 (CH_3), 44.9 ($C_{4,9}$), 72.3 (OCH_2Ph), 73.8, 77.4 ($C_{5,6,7,8}$), 109.5 (CMe_2), 128.3 (CH_{Ph}), 137.5 (C_{Ph}), 182.6 (C_2); IR (neat): 1215 ($\nu_{C=S}$); HRMS (NH_3) for $C_{24}H_{31}N_2O_4S$: (MH^+) calcd 443.2004, found 443.2003.

(5*S*,6*R*,7*R*,8*S*)-5,8-Dibenzyloxy-6,7-dihydroxy-6,7-*O*-methylethylidene-2-(*N*-benzyl)-imino-1,3-diazonane (52). The guanidine **52** (55 mg, 94%) was obtained as a yellow

foam from the thiourea **51** on a 0.11 mmol scale according to the procedure described above for the guanidine **35**. [α] +21 *c* 1.1, $CHCl_3$); ^1H NMR: 1.25 (br.s, 6H, CH_3), 3.15–3.82 (m, 8H, $H_{4,5,8,9}$, NCH_2Ph), 3.8–4.30 (m, 4H, $H_{6,7}$), 4.30–4.80 (m, 4H, OCH_2Ph), 7.20 (br.s, 15H, CH_{Ph}); ^{13}C NMR: 27.0 (CH_3), 43.6 ($C_{4,9}$, NCH_2Ph), 73.5 (OCH_2Ph), 77.7 ($C_{5,6,7,8}$), 109.9 (CMe_2), 128.1, 128.5 (CH_{Ph}), 137.6 (C_{Ph}), 156 (C_2); IR (neat): 1630 ($\nu_{C=N}$); HRMS (NH_3) for $C_{31}H_{38}N_3O_4$: (MH^+) calcd 516.2862, found 516.2872.

(5*R*,6*R*,7*R*,8*R*)-5,8-Dibenzyloxy-6,7-dihydroxy-6,7-*O*-methylethylidene-1,3-diazonan-2-thione (53). The thiourea **53** (145 mg) was quantitatively obtained as a yellow foam from the diamine **47** on a 335 μmol scale, according to the procedure described above for the thiourea **33**. [α] +20 (*c* 0.4, $CHCl_3$); ^1H NMR: 1.34 (s, 6H, CH_3), 3.65 (m, 6H, $H_{4,5,8,9}$), 4.06 (m, 2H, $H_{6,7}$), 4.54 (m, 4H, OCH_2Ph), 7.26 (br.s, 10H, CH_{Ph}); ^{13}C NMR: 27.0 (CH_3), 44.3 ($C_{4,9}$), 72.3 (OCH_2Ph), 77.9, 78.4 ($C_{5,6,7,8}$), 110.1 (CMe_2), 127.9, 128.2, 129.4 (CH_{Ph}), 137.7 (C_{Ph}), 182.7 (C_2); IR (neat): 1210 ($\nu_{C=S}$); HRMS (NH_3) for $C_{24}H_{31}N_2O_4S$: (MH^+) calcd 443.2004, found 443.2009.

(5*R*,6*R*,7*R*,8*R*)-5,8-Dibenzyloxy-6,7-dihydroxy-6,7-*O*-methylethylidene-2-(*N*-benzyl)-imino-1,3-diazonane (54). The guanidine **54** (139 mg, 94%) was obtained as a yellow foam from the thiourea **53** on a 287 μmol scale, according to the procedure described above for the guanidine **35**. [α] −8 (*c* 0.5, $CHCl_3$); ^1H NMR: 1.26 (br.s, 6H, CH_3), 3.30–3.56 (m, 4H, $H_{4,9}$), 3.75 (m, 2H, NCH_2Ph), 4.07–4.58 (m, 8H, $H_{5,6,7,8}$, OCH_2Ph), 7.22 (br.s, 15H, CH_{Ph}); ^{13}C NMR: 26.8 (CH_3), 43.1, 46.0 ($C_{4,9}$, NCH_2Ph), 72.2 (OCH_2Ph), 79.0 ($C_{5,6,7,8}$), 109.8 (CMe_2), 128.0, 128.5 (CH_{Ph}), 137.3 (C_{Ph}); IR (neat): 1630 ($\nu_{C=N}$); HRMS (NH_3) for $C_{31}H_{38}O_4N_3$: (MH^+) calcd 516.2862, found 516.2877.

(4*S*,5*R*,6*R*,7*S*)-4,7-Dibenzyloxymethyl-5,6-dihydroxy-5,6-*O*-methylethylidene-2-(*N*-butyl)-imino-1,3-diazepane (55). The guanidine **55** (318 mg, 65%) was obtained as a yellow foam from the thiourea **33** on a 1.02 mmol scale, according to the procedure described above for the guanidine **35** using *n*-butylamine. [α] +42 (*c* 0.7, $CHCl_3$); ^1H NMR: 0.84 (m, 3H, $H_{4'}$), 1.24–1.40 (m, 10H, $H_{2',3'}$, CH_3), 3.20–4.20 (m, 10H, $H_{4,5,6,7,1'}$, CH_2OBn), 4.19 (m, 4H, OCH_2Ph), 7.23 (m, 10H, CH_{Ph}); ^{13}C NMR: 13.6 ($C_{4'}$), 19.9 ($C_{3'}$), 27.1 (CH_3), 30.7 ($C_{2'}$), 41.0 ($C_{1'}$), 52.8 ($C_{4,7}$), 73.1 (CH_2OBn, OCH_2Ph), 77.5 ($C_{5,6}$), 109.9 (CMe_2), 127.6, 128.3 (CH_{Ph}), 138.0 (C_{Ph}), 159.0 (C_2); IR (neat): 1625 ($\nu_{C=N}$); HRMS (NH_3) for $C_{28}H_{40}O_4N_3$: (MH^+) calcd 482.3019, found 482.2986.

(4*S*,5*R*,6*R*,7*S*)-5,6-Dihydroxy-4,7-hydroxy methyl-5,6-*O*-methylethylidene-2-(*N*-butyl)-imino-1,3-diazepane (56). The guanidine **56** (140 mg, 73%) was obtained as an hygroscopic solid from the guanidine **55** on a 0.64 mmol scale, according to the procedure described above for the guanidino-sugar **36**. [α] +45 (*c* 0.7, MeOH); ^1H NMR (CD_3OD): 0.93 (t, 3H, $J_{3',4'}=7.1$ Hz, $H_{4'}$), 1.39–1.45 (m, 8H, $H_{3'}$, CH_3), 1,55 (m, 2H, $H_{2'}$), 3.14 (m, 2H, $H_{1'}$), 3.55–3.80 (m, 6H, $H_{4,7}$, CH_2OH), 4.05 (br.s, 2H, $H_{5,6}$); ^{13}C NMR (CD_3OD): 16.2 ($C_{4'}$), 23.2 ($C_{3'}$), 29.3 (CH_3), 35.3 ($C_{2'}$), 45.9 ($C_{1'}$), 58.6 ($C_{4,7}$), 67.7 (CH_2OH), 80.9 ($C_{5,6}$), 112.1 (CMe_2), 159.5 (C_2); MS (NH_3): 302 (MH^+).

Methyl (4′*S*,5′*R*,6′*R*,7′*S*)-6-deoxy-6-(4′,7′-dibenzyloxymethyl-5′,6′-dihydroxy-5′,6′-*O*-methylethylidene-1′,3′-diazepan-2′-yl)-imino-2,3,4-tri-*O*-benzyl-D-glucopyranoside (57). The guanidine **57** (327 mg, 86%) was obtained as a yellow foam from the thiourea **33** on a 0.79 mmol scale, according to the procedure described above for the guanidine **35** using methyl 6-amino-6-deoxy-2,3,4-tri-*O*-benzyl-D-glucopyranoside. [α] +36 (*c* 0.5, $CHCl_3$); ^1H NMR: 1.37 (m, 6H, CH_3), 3.25–4.10 (m, 17H, $H_{4,5,6,7,2',3',4',5'}$, CH_2N, OCH_3, CH_2OBn), 4.39–5.00 (m, 11H, OCH_2Ph, $H_{1'}$), 7.24 (m, 25H, CH_{Ph}); ^{13}C NMR: 27.0 (CH_3), 46.0 (CH_2N), 54.0, 55.3 ($C_{4,7}$, OCH_3), 69.5 ($C_{5,6}$), 73.3, 74.9, 75.7 (CH_2OBn, OCH_2Ph), 77.3, 78.8, 80.1, 81.3 ($C_{2',3',4',5'}$), 98.0 ($C_{1'}$), 110.0 (CMe_2), 127.7, 128.0, 128.4 (CH_{Ph}), 138.1, 138.7 (C_{Ph}), 158.0 (C_2); IR (neat): 1635 ($\nu_{C=N}$); HRMS (NH_3) for $C_{52}H_{62}O_9N_3$: (MH^+) calcd 872.4486, found 872.4501.

Methyl (4′*S*,5′*R*,6′*R*,7′*S*)-6-deoxy-6-(4′,7′-dihydroxymethyl-5′,6′-dihydroxy-5′,6′-*O*-methylethylidene-1′,3′-diazepan-2′-yl)-imino-D-glucopyranoside (58). The guanidine **58** (209 mg, 79%) was obtained as an hygroscopic solid from the guanidine **57** on a 0.62 mmol scale according to the procedure described above for the guanidino-sugar **36**. [α] +55 (*c* 0.75, CH_3OH); ^1H NMR (CD_3OD): 1.38 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.42 (m, 5H, CH_2N, OCH_3), 3.55–3.85 (m, 8H, $H_{4,5,6,7}$, CH_2OH), 3.90–4.40 (m, 4H, $H_{2',3',4',5'}$), 4.68 (m, 1H, $H_{1'}$); ^{13}C NMR (CD_3OD): 30.0 (CH_3), 47.0 (CH_2N), 51.8, 58.3 ($C_{4,7}$, OCH_3), 66.0 (CH_2OH), 76.1, 76.9, 77.4, 79.8, 81.7 ($C_{5,6,2',3',4',5'}$), 103.8 ($C_{1'}$), 112.0 (CMe_2), 159.9 (C_2).

Inhibition analysis of compounds 1, 2, 3, 4, 5 and 6 against various glycosidases. α-D-glucosidase from *bacillus stearothermophilus* (11×10^{-3} unit, EC 3.2.1.20), β-D-glucosidase from almonds (15×10^{-3} unit, EC 3.2.1.21), α-D-mannosidase from Jack beans (10×10^{-3} unit, EC 3.2.1.24) or α-L-fucosidase from bovine kidney (4×10^{-3} unit, EC 3.2.1.111) were purchased from Sigma-Aldrich Chimie. Incubation mixtures (1 mL) contained 0.05 M citrate–phosphate buffer at a pH of 6.8, 5.0, 4.5 and 5.5, respectively, according to the enzyme, 4-nitrophenyl-α-D-glucopyranoside (2 mM), or 4-nitrophenyl-β-D-glucopyranoside (2 mM), or 4-nitrophenyl-α-D-mannopyranoside (2 mM) or 4-nitrophenyl α-L-fucopyranoside (0.25 mM), the potential inhibitor **1**, **2**, **3**, **4**, **5**, or **6** at a final concentration of 1 mM and finally, the enzyme α-D-glucosidase, 11×10^{-3} unit; β-D-glucosidase, 15×10^{-3} unit; α-D-mannosidase, 10×10^{-3} unit; or α-L-fucosidase, 4×10^{-3} unit per sample). After a 10 min incubation period at 37 °C, the reaction was quenched by the addition of a 0.2 M glycine–sodium hydroxide buffer at pH 10 (1 mL). The optical absorbance at 400 nm was measured to determine the amount of liberated 4-nitrophenol and the percentage of inhibition was calculated.

When the percentage of inhibition was greater than 50%, as it was the case for the compounds **5** and **6** against α-L-fucosidase, the assay was performed in presence of

variable amounts of the 4-nitrophenyl-α-L-fucopyranoside (in the range of 0.05 to 0.5 mM) and in the absence or in the presence of the inhibitor (at a constant final concentration of 1 mM) in 0.05 M citrate–phosphate buffer at pH 5.5. Lineweaver–Burk plots were then constructed for both reactions (with and without inhibitor) and the K_i was calculated from the two Michaelis–Menten constants (K_m) thus obtained.

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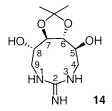
66. To facilitate the notation in the attribution of ^{1}H NMR signals of C_2 symmetric molecules, the coupling constants are reported only for the half of the molecule while all the protons are attributed. For example, in the molecule **14**, H_4 and H_9 have the same chemical shift as well as $H_{4'}$ and $H_{9'}$. The corresponding notation for these protons is: 3.42 (dd, 2H, $J_{4,5} = 5.8$, $J_{4,4'} = 15.6$ Hz, $H_{4,9}$), 3.64 (m, 2H, $H_{4',9'}$).



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