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Synthesis and glycosidase inhibitory activity of aminocyclitols with a C6- or a C7-ring

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Abstract—The synthesis of carbasugars and various aminocyclitols, related to voglibose and acarbose used in the treatment of non-insulino-dependant diabetes, is described from C_2-symmetrical bis-epoxides derived from D-mannitol. The methodology involves two key steps: a domino alkylation–cyclization with 2-lithio-1,3-dithiane derivatives, and reduction or reductive amination with a primary amine. These compounds have been evaluated as inhibitors of several glycosidases, and this study indicates notably that the L-*ido* or D-*manno* 1-aminocycloheptane-3,4,5,6-tetrol are inhibitors of α-D-glucosidase with K_i in the micromolar range.

1. Introduction

Interest in diabetes is currently blowing up as the number of people with diabetes is expected to rise from the current estimate of 150 million to 220 million in 2010 and 300 million in 2025.[1] There are two main forms of diabetes. Type 1 diabetes[2] is the most common chronic disease of children and is due to auto-immune-mediated destruction of pancreatic β-cell islets resulting in absolute insulin deficiency. It can be treated by supplying exogenous insulin. Type 2 diabetes or non-insulinodependant *mellitus* diabetes (NIDMD), which represents 90% of cases, is a multifactorial disease and is characterized by insulin resistance in peripheral tissues and/or abnormal insulin secretion from the pancreas and increasing blood glucose levels.[3] The NIDMD is taking an increasing place both in developed and developing countries and is associated with sedentary lifestyle and obesity.[4] Many complications such as retino-, neuro- and nephro-pathies are associated with NIDMD and lowering blood glucose may be an effective mechanism for preventing the development of diabetic complications.[5]

At present, therapies for NIDMD are directed towards the reduction of hyperglycemia itself. Thus, sulfonylureas and related insulin secretagogues[6] increase insulin release from pancreatic islets; the biguanide metformin[7] delays the absorption of dietary carbohydrates by inhibiting the glucose transporter found on the brush border of the epithelial lining of the intestines and so acts to reduce hepatic glucose production. Thiazolidinediones[8] which are peroxisome proliferator-activated receptor-γ (PPARγ) agonists enhance insulin action. Insulin itself stops glucose production and increases glucose utilization.[9] Alpha-glucosidase inhibitors such as the pseudo-oligosaccharide acarbose[10] can decrease post-prandial glucose elevation by decreasing the intestinal absorption of glucose. However, although these drugs are effective, due to the frequent need of long-term therapies, they often have to be used successively or simultaneously as the disease progresses so that limited tolerability and side-effects may be observed. In that context, it is obvious that there is still a need for new therapies to complement and even improve on existing ones.

Our investigations concern α-glucosidase inhibitors, the activity of acarbose,[11] voglibose[12] and miglitol[13] having already been demonstrated as inhibitors of intestinal digestive enzymes (Fig. 1) and these compounds being approved for use in humans.[14] Both the naturally occurring voglibose and acarbose are believed, in the same way as other carbohydrate mimics such as polyhydroxylated piperidines (like miglitol), pyrrolidines, indolizidines and pyrrolizidines, to mimic the charge of the presumed transition state for enzymatic glycoside hydrolysis, due to

Keywords: aza-disaccharide; aminocyclitol; bis-epoxide; carbasugar; cyclization; glycosidases; reductive amination.

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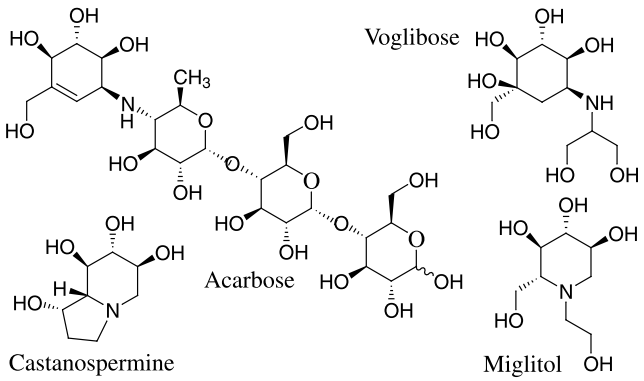


Figure 1. Inhibitors of α-glucosidases.

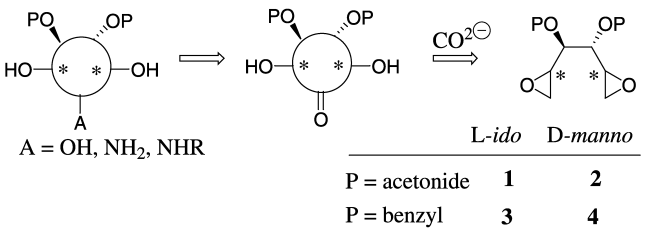


Figure 2. Retrosynthetic analysis.

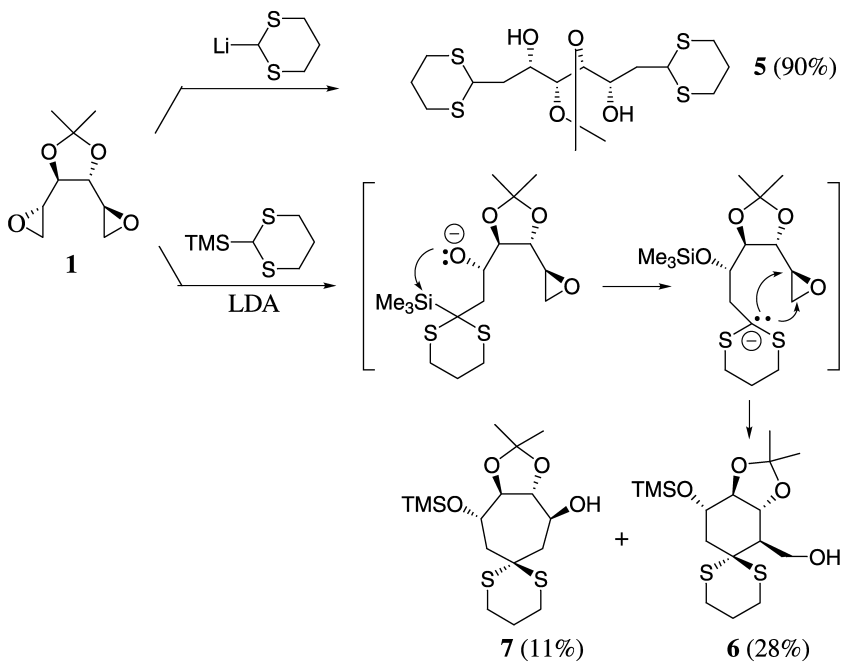
the protonation of their nitrogen atom in the enzyme active site.

If considerable synthetic efforts have been devoted to the synthesis of iminosugar analogs[15] and have sometimes shown interesting inhibitory activitiy,[16] to our knowledge, aminocyclitols with a C6- or C7-ring have been less studied in the field of glycosidase inhibitors. We report here full results concerning the synthesis of these compounds and their evaluation as glycosidase inhibitors.[17] To access to the target molecules, our retrosynthetic analysis (Fig. 2) involves the carbacyclization of enantiomerically pure C_2-symmetric bis-epoxides derived from D-mannitol by a formal carbonyl dianion.[18] Subsequent reduction or reductive amination of the introduced carbonyl group lead to the corresponding cyclitols or aminocyclitols.

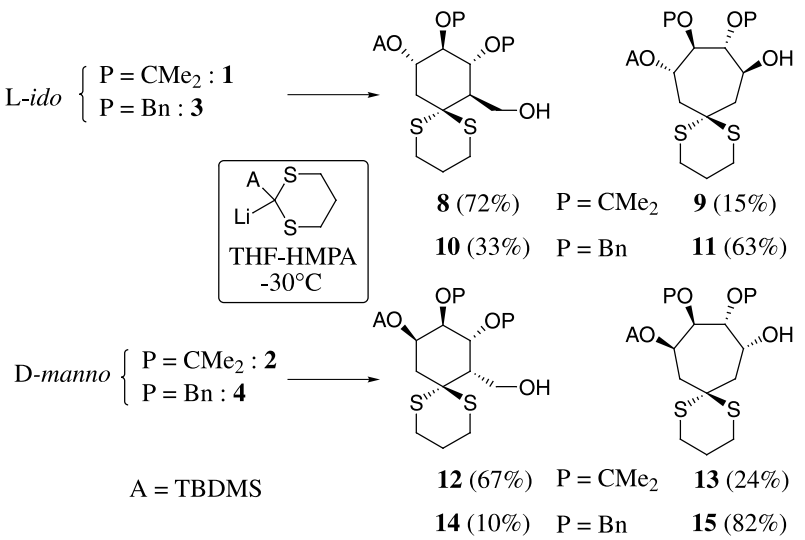
2. Results and discussion

We have studied the nucleophilic opening of the easily available 1,2:5,6-dianhydro-3,4-*O*-methylethylidene-L-iditol **1** or D-mannitol **2** and their 3,4-di-*O*-benzyl analogs **3** and **4** with lithiated derivatives of 1,3-dithiane. Treatment of bis-epoxide **1** with lithiated 1,3-dithiane afforded the C_2-symmetric acyclic compound **5** (Scheme 1). The yield of **5** was improved to 90% with 2.4 equiv. of lithiated 1,3-dithiane. This result proved that the alkoxide anion resulting from the first epoxide opening by the organometallic is not sufficiently basic to remove the second hydrogen atom of the introduced 1,3-dithiane, and in this way to generate the second nucleophily of the dihiane.

To circumvent this difficulty and to promote the C-cyclization we turned our attention to the use of 2-trimethylsilyl-1,3-dithiane. An organometallic derivative of this commercially available reagent has been recently used in a bis-alkylation reaction with two equivalents of epoxide through Brook's rearrangement.[19] Treatment of the bis-epoxide **1** with the lithio derivative of 2-TMS-1,3-dithiane, generated by LDA, afforded the expected carbocycles **6** and **7**, in only 28 and 11% yield, respectively, after separation by chromatography. This poor isolated yield was attributed to partial hydrolysis of the *O*-silyl bond during the chromatography. It should be noted that the desilylation of the crude reaction mixture with tetrabutylammonium fluoride afforded the corresponding diols, which could not be separated by chromatography. Nevertheless, formation of the C6- and C7-rings in this reaction confirms that the expected 1,4-Brook rearrangement occurs, transferring the



Scheme 1.



Scheme 2. *Reagents and conditions*: see Table 1.

silyl group to alkoxide and generating the second nucleophile of the 1,3-dithiane. Subsequently, this anion promotes the intramolecular opening of the second epoxide at the less subsituted side (7-*endo-tet* process) and at the more substituted side (6-*exo-tet* process). Furthermore, these results show that the intramolecular silyl migration and C-cyclization are faster than the intermolecular reaction which should evolve towards the C_2-symmetric acyclic compound **5**.

To increase the stability of the resulting *O*-silyl derivative, we then turned our attention towards 2-*tert*-butyldimethylsilyl-1,3-dithiane for which the lithio derivative has already been used in the sequential opening of two different epoxides.[20] Reactivity of this organometallic species has been studied on bis-epoxides **1**–**4** (Scheme 2) under different experimental conditions (Table 1).

The conjugate base of 2-TBDMS-1,3-dithiane was generated either at −78°C by addition of *tert*-butyllithium, or at room temperature by addition of a mixture of *n*-BuLi/*n*-Bu_2Mg.[21] In each case, the reaction was carried out with the bis-epoxide in a THF/HMPA mixture and afforded enantiomerically pure carbacycles, in good yield, 63 to 82%, for the main product (after chromatographic purification). Whatever the method used for the formation of the 2-metallated 2-TBDMS-1,3-dithiane, the yield was comparable. However, it should be noted that with *t*-BuLi, the reaction mixture was cleaner, justifying the use of these conditions on a large scale of bis-epoxide (up to 4 g).

Table 1. Screening of conditions for the carbacyclization

bis-Epoxide	Conditions	Product[a]	
		C6-ring	C7-ring
1	A	**8** (72%)	**9** (15%)
1	B	**8** (52%)	**9** (30%)
3	A	**10** (21%)	**11** (43%)
3	B	**10** (33%)	**11** (63%)
2	A	**12** (39%)	**13** (13%)
2	B	**12** (67%)	**13** (24%)
4	A	**14** (13%)	**15** (73%)
4	B	**14** (10%)	**15** (82%)

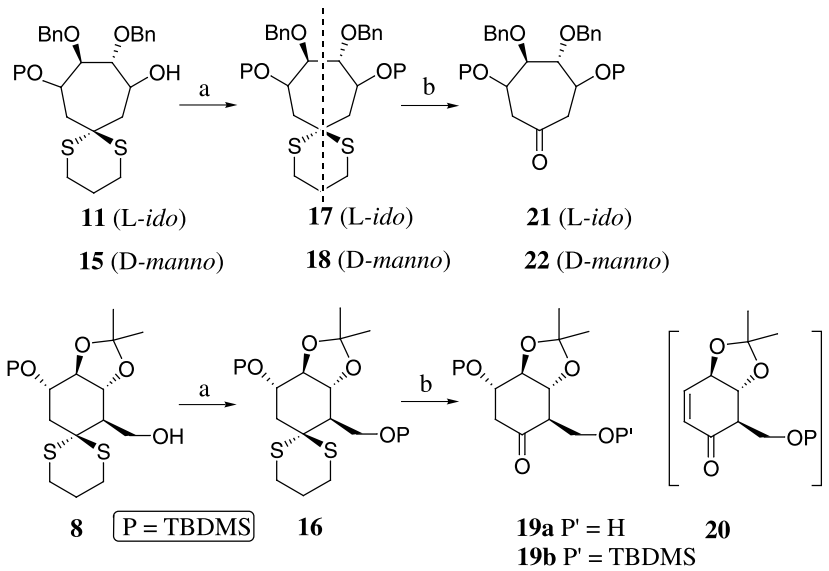
A: *t*-BuLi, THF, HMPA, −78°C then −30°C and bis-epoxide addition; B: *n*-BuLi, *n*-Bu_2Mg, THF, HMPA, rt, then bis-epoxide addition.
[a] Isolated yield after flash chromatographic purification.

Results from the Table 1 show that, on one hand depending on the 3,4-*O*-protective group of the bis-epoxide, benzyl ether or acetonide, the cyclization is directed to the major formation of either the C7- or the C6-ring, respectively. On the other hand, analogous results are obtained independent of the D-*manno* or L-*ido* configuration of the bis-epoxide.[22]

Silylation of the free alcohol function of **8**, **11** or **15** (Scheme 3) was accomplished by treatment with *tert*-butyldimethylsilyl chloride in the presence of imidazole in DMF at 70°C. The ^1H and ^{13}C NMR spectra of the resulting bis-silylated C7-cyclitols **17** and **18** exhibited a simplification consistent with the presence of a C_2-symmetric axis.

Next, attention was focused on the dithioketal hydrolysis (Scheme 3). Treatment of **17** or **18** with bis(trifluoroacetoxy) iodobenzene[23] in aqueous acetonitrile at 20°C yielded the corresponding cycloheptanone **21** or **22** in a yield varying from 50 to 80% depending of the attempts (Table 2, entries 1, 2). Furthermore, from **16**, the cyclohexanone **19b** was isolated in only 34% yield (entry 3). Considerable effort was made to improve the yield of the desired cycloalcanone by running the reaction under various experimental conditions.

For example, from dithioketal **16** we found that triethyloxonium tetrafluoroborate[24] (entry 4), or 2,3-dichloro-5,6-dicyanobenzoquinone[25] (entry 5) only led to decomposition giving an inextractable mixture. Moreover, treatment with mercury(II) perchlorate[26] (entry 7) in the presence of K_2CO_3 at room temperature afforded the expected cyclohexanone **19b** in a low yield (28%). A small amount of a slightly higher running product was also isolated which turned out to be enone **20**, probably resulting from **19b** by a β-elimination. Reaction with *N*-bromosuccinimide[27] at room temperature in aqueous acetone (entry 8) resulted in 34% of the desired ketone **19b**. When carried out at −30°C,



Scheme 3. *Reagents and conditions*: (a) TBDMSCl, ImH, DMF, 70°C; (b) see text.

the reaction proved to be more interesting and synthetically useful. Indeed, we isolated the ketone **19b**, **21** or **22** in an excellent yield (80%, entries 9, 10 and 11).

Having found suitable conditions for the dithioketal hydrolysis, we now proceeded to the reduction of the cycloalkanone (Scheme 4). Thus, reduction of **22** with lithium aluminium hydride in refluxing THF, yielded the corresponding alcohol **23** (50%). Fortunately, the reduction performed with sodium borohydride in EtOH afforded **23** in quantitative yield.

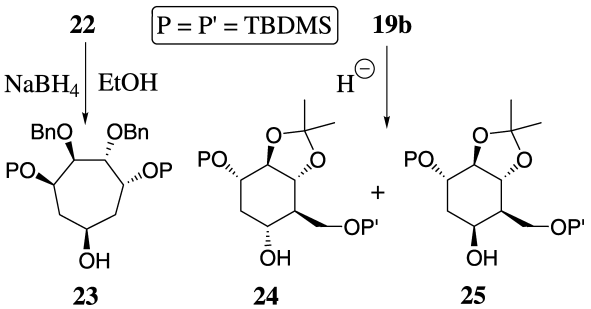
Reduction of the crude cyclohexanone **19b** by $NaBH_4$ in EtOH at 20°C afforded a 82:18 mixture of the alcohols **24/25** in 80% yield. These products were easily separated by flash chromatography and the absolute configuration at the newly created asymmetric carbon was assigned by ^1H NMR. The observed coupling constants for the H-1 protons: $J_{1,2b}=J_{1,6}=9.1$ Hz for **24** and $J_{1,2b}=J_{1,6}=3.0$ Hz for **25** are consistent with an axial–axial and an axial–equatorial relationship, respectively. The reduction of **19b** with $NaBH_4$ was also carried out at −78°C, and the diastereoselectivity was improved up to 96:4 in favour of the equatorial hydroxyl group in the same yield (80%) as above. To reverse the diastereoselectivity, attempts were made in the presence of bulkier hydride sources such as di-*iso*-butylaluminium hydride (DIBAL-H), L- or K-selectride® in THF at −78°C. With DIBAL-H, we observed the formation of the same major epimer as above (**24/25** 78:22, 43%), whereas with L- or K-selectride® we observed the expected inversion of the diastereoselectivity (**24/25** 36:64, 50%). In order to examine the eventual influence of the primary free alcohol function of **19a** this compound was submitted to $NaBH_4$ reduction (EtOH at −78°C). A 75:25 mixture of the corresponding diols (like **24** and **25** with P′=H) revealing no significative modification of the diastereoselectivity.

We next turned to the preparation of the targeted aminocyclitols via the reductive amination of the cycloalkanones with various primary amines such as benzylamine, *n*-butylamine, bis-*O*-*tert*-butyldimethyl silylserinol[28] or methyl 6-amino-6-deoxy-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside,[29] respectively chosen to afford unsubstituted aminocyclitols, *N*-butylaminocyclitols

Table 2. Deprotection of the dithioketal group

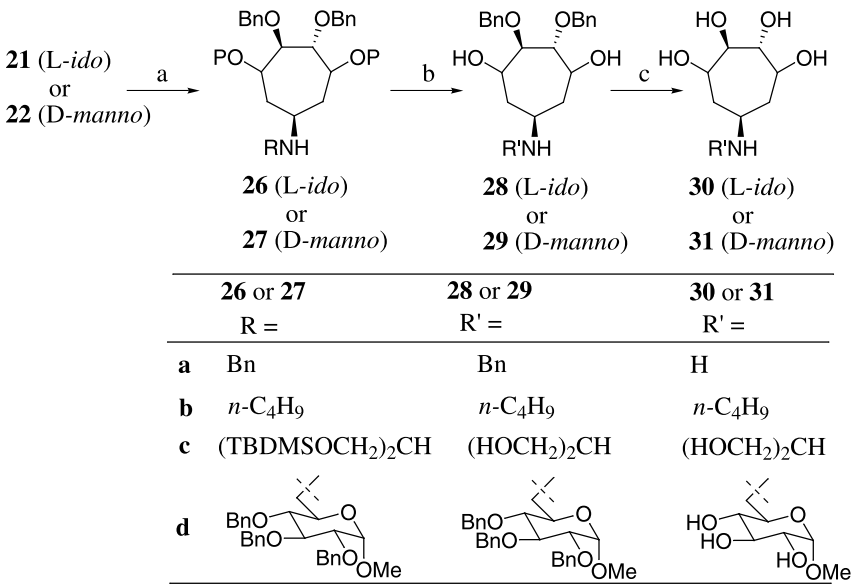
Entry	Thioketal	Conditions	Result
1	**17**	$(CF_3CO_2)_2PhI$, MeCN, H_2O	**21** (63%)
2	**18**	$(CF_3CO_2)_2PhI$, MeCN, H_2O	**22** (54%)
3	**16**	$(CF_3CO_2)_2PhI$, MeCN, H_2O	**19b** (34%)
4	**16**	Et_3OBF_4, CH_2Cl_2, rt	Dec.[a]
5	**16**	DDQ, MeCN, H_2O	Dec.[a]
6	**16**	$HgCl_2$, K_2CO_3	n.r.[b]
7	**16**	$Hg(ClO_4)_2$, K_2CO_3	**19b** (28%)+**20**
8	**16**	NBS, Me_2CO, H_2O, rt	**19b** (34%)
9	**16**	NBS, Me_2CO, H_2O, −30°C	**19b** (77%)
10	**17**	NBS, Me_2CO, H_2O, −30°C	**21** (79%)
11	**18**	NBS, Me_2CO, H_2O, −30°C	**22** (77%)

[a] Decomposition of the reaction mixture.
[b] No reaction.



$H^{\ominus}$	ratio **24/25**	Yield (%)
$NaBH_4$, EtOH, 20°C	82/18	80
$NaBH_4$, EtOH, -78°C	96/4	80
DIBAL-H, THF, -78°C	78/22	43
L-Selectride, THF, -78°C	39/61	50
K-Selectride, THF, -78°C	36/64	50

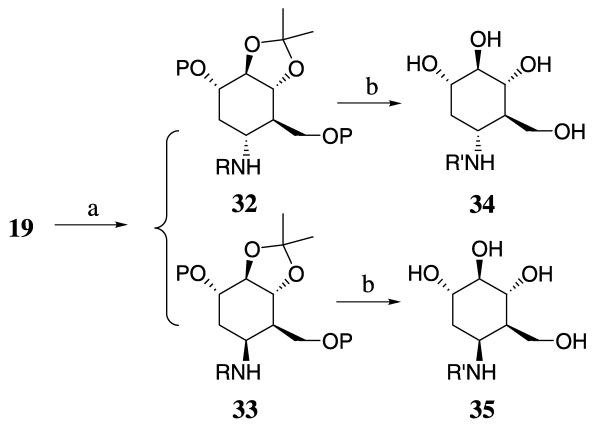
Scheme 4. Reduction of the cycloalkanones **19b** and **22**.

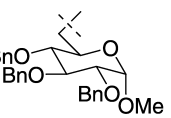
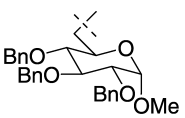
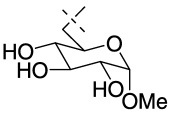


	26 or 27 R =	28 or 29 R' =	30 or 31 R' =
a	Bn	Bn	H
b	*n*-C_4H_9	*n*-C_4H_9	*n*-C_4H_9
c	$(TBDMSOCH_2)_2CH$	$(HOCH_2)_2CH$	$(HOCH_2)_2CH$
d			

Scheme 5. *Reagents and conditions*: (a) RNH_2, Ti(O*i*-Pr)$_4$, then $NaBH_3CN$, EtOH, rt; (b) TBAF, THF, rt; (c) H_2, Pd, AcOH for **30a**,**b**,**c** or **31a**,**b**,**c**, or Na, NH_3, −33°C for **30d**.

analogs of voglibose, or analogs of disaccharide displaying partial acarbose structure. The reductive amination carried out under the conditions of Mattson et al.[30] involved imine formation catalyzed by titanium(IV) *iso*propoxide followed by in situ reduction with sodium cyanoborohydride. In the cycloheptanone series (Scheme 5), the expected *N*-substituted aminocycloheptanols (**26a**,**b**,**c**,**d** or **27a**,**b**,**c**,**d**) were isolated after flash chromatographic purification in yields ranging from 47 to 91%. In the cyclohexanone series (Scheme 6), the reductive amination provided a mixture of the two possible aminocyclitols **32**/**33** in moderate to good yield (61–82%), which could be easily separated by flash chromatography. In all cases, the diastereoselectivity (60:40 to 70:30) was in favor of **32** which presents the amino group in an equatorial direction, as precedently observed for the $NaBH_4$ reduction of the



	32 or 33 R =	34 R' =	35 R' =
a	Bn	H	—
b	$(TBDMSOCH_2)_2CH$	$(HOCH_2)_2CH$	$(HOCH_2)_2CH$
c			—
d	H		—

Scheme 6. *Reagents and conditions*: (a) RNH_2, Ti(O*i*-Pr)$_4$, then $NaBH_3CN$, EtOH, rt; (b) TFA, H_2O for **32d→34a**, or for **32b→34b**, or for **33b→35b**, or TFA, H_2O, THF for **32c→34c**; (c) H_2, $Pd(OH)_2$, EtOH for **32a→32d**, (d) H_2, Pd black, AcOH for **34c→34d**.

Table 3. Comparison of inhibitory activities for aminocyclitols **30**, **31**, **34** and **35** and iminosugars **36**–**38**. Percentage of inhibitions at 1 mM and K_i in μM (in bold) when measured[33]

Enzyme	**30a**	**30b**	**30c**	**30d**	**31a**	**31b**	**31c**	**34a**	**34b**	**34d**	**35b**	**36**	**37**	**38**
α-D-Glu	**25** μM	21%	8%	n.i.[a]	**70** μM	16%	19%	2%	15%	15%	n.i.[a]	**4.8** μM	**70** μM	**0.44** μM
β-D-Glu	n.i.[a]	33%	8%	4%	11%	15%	5%	3%	6%	9%	30%	**17** μM	1%	
α-D-Man	37%	n.i.[a]	n.i.[a]	n.i.[a]	39%	n.i.[a]	7%	n.i.[a]	n.i.[a]	n.i.[a]	n.i.[a]	25%	1%	
α-L-Fuc	14%	10%	11%	7%	4%	10%	8%	n.i.[a]	12%	4%	10%	4%	**28** μM	

[a] No inhibition detected.

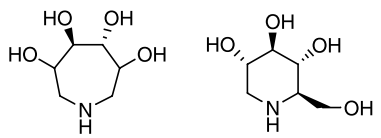
cyclohexanone **19**. The axial or equatorial position of the amino group was determined by the coupling constants between the H-1 and the H-neighbors, for example $J_{1,2b}$=10 Hz, $J_{1,2a}$=4.5 Hz, $J_{1,6}$=11.8 Hz for **32a**, and $J_{1,2b}$=$J_{1,2a}$=$J_{1,6}$=3.0 Hz for **33a**. No evidence for epimerization adjacent to the ketone was observed in each case.

Finally, the following steps concerned the removal of the protecting groups. In the C7-series, removal of the *tert*-butyldimethylsilyl groups was achieved by an excess of *n*-tetrabutylammonium fluoride in THF to give the corresponding alcohols **28** or **29**, and the deprotection of benzyl ethers, and *N*-benzyl amines for **28a** and **29a**, involved hydrogenolysis in the presence of palladium black in acetic acid. For compounds **28d** and **29d**, the last reaction was carried out by sodium in liquid ammonia. In the C6-series, acidic hydrolysis (TFA, H_2O) of both acetonide and silyl ether of **32b** or **33b** led to the aminocyclitol **34b** or **35b**. Hydrogenolysis of **32a** in the presence of Pearlman catalyst (**32a→32d**), followed by acidic hydrolysis (TFA, H_2O) furnished the *N*-unsubstituted aminocyclitol **34a** while for the disaccharide analog **32c**, deprotections required acidic hydrolysis (TFA, THF, H_2O) of both acetonide and the silyl ethers (**32c→34c**), then hydrogenolysis of the benzyl ethers (Pd black, AcOH) to give **34d**. In all cases, subsequent purification by ion exchange chromatography afforded the targeted pure aminocyclitols.

3. Inhibition studies

The new aminocyclitols (**30**, **31**, **34** and **35**) were screened against four common glycosidases (α-D-glucosidase from baker's yeast, β-D-glucosidase from almonds, α-D-*manno*-sidase from Jack beans and α-L-fucosidase from bovine kidney). The observed results are gathered in Table 3 and compared with the reported activity of the parent imino-sugar:[31] 3,4,5,6-tetrahydroxy-L-*ido*- or D-*manno*azepane, **36** or **37**, or 1-deoxynojirimycin **38** (Fig. 3).

The aminocyclitols are weakly or no-potent on the four commercially available enzymes. Among them, the best



36 (L-*ido*)
37 (D-*manno*)

38 (DNJ)

Figure 3.

results are for the *N*-unsubstituted aminocycloheptanols **30a** and **31a** which competitively inhibits the α-D-glucosidase (K_i=25 and 70 μM, respectively). However, no significative difference was observed, on one hand between the L-*ido* or D-*manno* configuration, and on the other hand by comparison with the parent iminosugars (K_i=4.8 and 70 μM for **36** and **37**, respectively). *N*-substitution of these compounds by a *n*-butyl group, a bis-hydroxymethylmethylene, the aglycon part of the voglibose, or a methyl glucoside reduce or prevent inhibition. Furthermore, the aminocyclohexanols (**34**, **35**) are weak inhibitors or inactive towards all glycosidases studied.

In order to extend the biological evaluation of the precedent aminocyclitols, they were also tested on α-D-galactosidase from green coffee beans, β-D-galactosidase from *Thermus thermophilus*, and on pancreatic porcine α-amylase. The synthesized aminocyclitols were totally inactive towards these latter enzymes, except *N*-unsubstituted amino-L-idocycloheptane-tetrol **30a** and the structural analog of voglibose **34b** which were weak inhibitors of β-D-galactosidase (K_i=200 and 600 μM, respectively), and *N*-butylamino-L-idocycloheptane-tetrol **30b** which moderately inhibits α-amylase (IC_{50}=600 μM). Finally, even if voglibose, actually used in the treatment of diabetes NID, is a powerful inhibitor of intestinal sucrase (K_i=67 nM), its activity on β-D-glucosidase from almonds is weak (IC_{50} (1.5 mM). In this context, evaluation of the synthetized aminocyclitols on such an enzyme will later be performed.

4. Conclusion

In conclusion, we have developed an efficient and versatile synthetic strategy for the preparation of enantiopure carbasugars and aminocyclitols with a C6- or C7-ring, from easily available bis-epoxides. The key steps involved the one-pot domino alkylation–cyclization which can be directed either to the C6 or C7 polyhydroxylated cyclo-alkanone by selecting the appropriate *O*-protecting groups of the bis-epoxide derived from D-mannitol, and the reduction or the reductive amination in the presence of a primary amine. According to this strategy, the synthesized aminocyclitols can be *N*-substituted by various R groups, notably R=$CH(CH_2OH)_2$ or methyl glucoside as, respectively, voglibose or acarbose analogs or unsubstituted to serve as a reference concerning the biological effect of N-substitution. Interestingly, biological studies indicate that the L-*ido* or D-*manno* 1-aminocycloheptane-3,4,5,6-tetrol are inhibitors of α-D-glucosidase with the K_i values in the low micromolar range.

5. Experimental

^{1}H NMR (250 MHz) and ^{13}C NMR (63 MHz) spectra were recorded on a Bruker AM250 in $CDCl_3$ (unless indicated). Chemical shifts (δ) are reported in ppm and coupling constants are given in Hz. IR spectra were recorded on a Perkin–Elmer 783 Infrared Spectrophotometer. Optical rotations were measured on a Perkin–Elmer 241C polarimeter with sodium (589 nm) or mercury (365 nm) lamp. Mass spectra, chemical ionization (CI), and high resolution (HRMS) were recorded by the Service de Spectrométrie de Masse, Ecole Normale Supérieure, Paris. All reactions were carried out under an argon atmosphere, and were monitored by thin-layer chromatography with Merck 60F–254 precoated silica (0.2 mm) on glass. Flash chromatography was performed with Merck Kieselgel 60 (200–500 μm); the solvent system were given v/v spectroscopic (^{1}H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatography homogeneous samples.

5.1. General procedure for carbacyclization

Method A. To a −78°C cooled solution of 2-*tert*-butyldimethylsilyl-1,3-dithiane (34.2 g, 146.2 mmol, 5.2 equiv.) in a 9:1 mixture of THF/HMPA (887 mL) was slowly added *tert*-butyllithium (1.5 M in hexanes, 97.5 mL, 146.2 mmol, 5.2 equiv.). The temperature was then increased to −30°C and a solution of the epoxide **1**, **2**, **3** or **4** (5.23 g, 28.1 mmol) in THF (86 mL) was added. After stirring at −30°C for 15 min, a saturated NH_4Cl aqueous solution was added. After ether extractions, the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the crude (cyclohexane/EtOAc) afforded the expected carbacycles.

Method B. To a solution of 2-*tert*-butyldimethylsilyl-1,3-dithiane (3.6 g, 15.3 mmol, 4.7 equiv.) in a 9:1 mixture of THF/HMPA (92.5 mL), at 20°C, was slowly added a mixture of *n*-butyllithium (1.6 M in hexanes, 9.6 mL, 15.3 mmol, 4.7 equiv.) and dibutylmagnesium (1.0 M in hexane, 3.8 mL, 3.8 mmol, 1.2 equiv.). The mixture was stirred for 1 h at 20°C prior to the addition of a solution of the epoxide **1**, **2**, **3** or **4** (607 mg, 3.3 mmol) in THF (7.7 mL). After stirring for 15 min, a saturated NH_4Cl aqueous solution was added and the same protocol as above was followed.

5.1.1. [3*S*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-6-hydroxymethyl-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (8). R_f 0.35 (cyclohexane/EtOAc 8:2); mp 95°C; $[\alpha]_D$=+15 (*c* 0.81, CH_2Cl_2); ^{1}H NMR (500 MHz) δ 4.21 (ddd, 1H, $J_{7a,7b}$=11.6 Hz, $J_{7a,OH}$=10.0 Hz, $J_{7a,6}$=4.0 Hz, H_{7a}), 4.06 (ddd, 1H, $J_{7b,7a}$=11.6 Hz, $J_{7b,6}$=7.3 Hz, $J_{7b,OH}$=3.4 Hz, H_{7b}), 4.02 (ddd, 1H, $J_{3,4}$=$J_{3,2b}$=9.2 Hz, $J_{3,2a}$~4.0 Hz, H_3), 3.76 (dd, 1H, $J_{5,6}$=11.3 Hz, $J_{5,4}$=9.2 Hz, H_5), 3.44 (dd, 1H, $J_{4,5}$=$J_{4,3}$=9.2 Hz, H_4), 3.25–3.17 (m, 1H, $H_{1'a}$), 3.02 (dd, 1H, $J_{2a,2b}$=14.0 Hz, $J_{2a,3}$=4.0 Hz, H_{2a}), 3.06–2.98 (m, 1H, $H_{3'a}$), 2.76–2.67 (m, 2H, $H_{1'b,3'b}$), 2.62 (dd, 1H, $J_{7a,OH}$=10.0 Hz, $J_{7b,OH}$=3.4 Hz, OH), 2.18–2.11 (m, 1H, $H_{2'a}$), 2.07 (ddd, 1H, $J_{5,6}$=11.3 Hz, $J_{7b,6}$=7.3 Hz, $J_{7a,6}$=4.0 Hz, H_6), 1.95–1.82 (m, 1H, $H_{2'b}$), 1.88 (dd, 1H, $J_{2b,2a}$=14 Hz, $J_{2b,3}$=10 Hz, H_{2b}), 1.44, 1.43 (2s, 6H, CMe_2), 0.94 (s, 9H, *t*Bu); 0.15 (s, 6H, $SiMe_2$); ^{13}C NMR δ 109.4 (CMe_2), 84.7 (C_4), 76.7 (C_5), 69.0 (C_3), 62.7 (C_7), 51.7 ($C_{1,6}$), 46.2 (C_2), 27.0, 25.8 (CMe_2), 26.8, 25.8, 25.5 ($C_{1',2',3'}$), 25.8, 18.3 (*t*Bu), −4.6, −4.8 ($SiMe_2$); MS (CI, CH_4) 421 (M^++1); HRMS for $C_{19}H_{37}O_4S_2Si$ (M^++1) calcd 421.1902; found 421.1898. Anal. calcd for $C_{19}H_{36}O_4S_2Si$: C, 54.25; H, 8.63; found: C, 54.17, H, 8.72.

5.1.2. [3*S*,4*S*,5*R*,6*S*]-3-*O*-*tert*-Butyldimethylsilyl-4,5-*O*-methylethylidene-3,4,5,6-tetrahydroxycycloheptan-1-one 1,3-propanedithioketal (9). R_f 0.25 (cyclohexane/EtOAc 8:2); $[\alpha]_D$=+14 (*c* 0.5, CH_2Cl_2); ^{1}H NMR δ 4.01–3.98 (m, 3H, $H_{3,5,6}$), 3.85 (dd, 1H, $J_{4,5}$=$J_{4,3}$=9.0 Hz, H_4), 2.90–2.84 (m, 4H, $H_{1'a,1'b,3'a,3'b}$), 2.52 (dd, 1H, $J_{2a,2b}$=14.7 Hz, $J_{2a,3}$=5.4 Hz, H_{2a}), 2.36 (dd, 1H, $J_{7b,7a}$=15.0 Hz, $J_{7b,6}$=5.0 Hz, H_{7b}), 2.26 (dd, 1H, $J_{7a,7b}$=15.0 Hz, $J_{7a,6}$=4.8 Hz, H_{7a}), 2.10 (dd, 1H, $J_{2b,2a}$=14.7 Hz, $J_{2b,3}$=7.0 Hz, H_{2b}), 2.00–1.90 (m, 3H, $H_{2'a,2'b,OH}$), 1.36 (s, 6H, CMe_2); 0.90 (s, 9H, *t*Bu), 0.08 (s, 6H, $SiMe_2$); ^{13}C NMR δ 109.0 (CMe_2), 80.5 ($C_{4,5}$), 71.7, 71.0 ($C_{3,6}$), 48.0 (C_1), 47.5, 45.5 ($C_{2,7}$), 27.2, 27.0, 24.9 ($C_{1',2',3'}$), 27.1 (CMe_2), 25.8, 18.2 (*t*Bu), −4.4, −4.7 ($SiMe_2$); MS (CI, CH_4) 421 (M^++1); HRMS for $C_{19}H_{37}O_4S_2Si$ (M^++1) calcd 421.1902; found 421.1890.

5.1.3. [3*S*,4*S*,5*R*,6*R*]-4,5-Di-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-6-hydroxymethyl-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (10). R_f 0.4 (cyclohexane/EtOAc 85:15); $[\alpha]_D$=+23 (*c* 0.67, CH_2Cl_2); ^{1}H NMR (500 MHz) δ 7.39–7.28 (m, 10H, H_{ar}), 5.01, 4.75 (AB, 2H, J_{AB}=11.5 Hz, OCH_2Ph), 4.92, 4.89 (AB, 2H, J_{AB}=10.8 Hz, O–CH_2–Ph), 4.28 (d, 1H, $J_{7a,7b}$=10.5 Hz, H_{7a}), 4.12 (dd, 1H, $J_{7b,7a}$=10.5 Hz, $J_{7b,6}$=4.0 Hz, H_{7b}), 4.07 (dd, 1H, $J_{5,6}$=$J_{5,4}$=9.2 Hz, H_5), 3.98 (ddd, 1H, $J_{3,2b}$=11.6 Hz, $J_{3,4}$=9.2 Hz, $J_{3,2a}$=4.1 Hz, H_3), 3.46 (dd, 1H, $J_{4,5}$=$J_{4,3}$=9.2 Hz, H_4), 3.30–3.19 (m, 1H, $H_{1'a}$), 3.14 (dd, 1H, $J_{2a,2b}$=13.5 Hz, $J_{2a,3}$=4.1 Hz, H_{2a}), 3.03–3.00 (m, 1H, $H_{3'a}$), 2.78–2.68 (m, 1H, $H_{1'b}$), 2.60–2.52 (m, 1H, $H_{3'b}$), 2.15–2.08 (m, 1H, $H_{2'a}$), 1.92–1.80 (m, 2H, $H_{6,2'b}$), 1.75 (dd, 1H, $J_{2b,2a}$=13.5 Hz, $J_{2b,3}$=11.7 Hz, H_{2b}), 0.96 (s, 9H, *t*Bu); 0.21, 0.15 (s, 6H, $SiMe_2$); ^{13}C NMR δ 138.9, 138.8, 128.6, 128.4, 127.8, 127.5 (C_{ar}), 89.7 (C_4), 77.5 (C_5), 75.3, 74.6 (OCH_2Ph), 69.4 (C_3), 59.1 (C_7), 54.4 (C_6), 51.9 (C_1), 42.2 (C_2), 27.0, 25.7 ($C_{1',2',3'}$), 26.2, 18.3 (*t*Bu), −4.9, −5.1 ($SiMe_2$).

5.1.4. [3*S*,4*S*,5*R*,6*S*]-4,5-Di-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-3,4,5,6-tetrahydroxycycloheptan-1-one 1,3-propanedithioketal (11). R_f 0.3 (cyclohexane/EtOAc 85:15); $[\alpha]_D$=+11 (*c* 1.1, CH_2Cl_2); ^{1}H NMR δ 7.30–7.20 (m, 10H, H_{ar}), 4.96, 4.56 (AB, 2H, J_{AB}=11.2 Hz, OCH_2Ph), 4.84, 4.75 (AB, 2H, J_{AB}=11.9 Hz, OCH_2Ph), 4.00–3.94 (m, 1H, H_3), 3.83–3.76 (m, 1H, H_6), 3.70–3.60 (m, 2H, $H_{4,5}$), 3.07–2.86 (m, 2H, $H_{1'a,3'a}$), 2.80–2.70 (m, 2H, $H_{1'b,3'b}$), 2.55 (dd, 1H, $J_{2a,2b}$=15 Hz, $J_{2b,3}$=10.5 Hz, H_{2b}), 2.21 (d, 1H, $J_{2a,2b}$=15 Hz, H_{2a}), 2.12–1.80 (m, 4H, $H_{2'a,2'b,7a,7b}$), 0.91 (s, 9H, *t*Bu), 0.13, 0.08 (2s, 6H, $SiMe_2$); ^{13}C NMR δ 138.9, 138.2, 128.5, 128.2, 127.8, 127.7, 127.1, 126.4 (C_{ar}), 88.9, 88.0 ($C_{4,5}$), 75.5, 75.0 (OCH_2Ph), 69.5, 67.7 ($C_{3,6}$), 47.2 (C_1), 46.0, 42.2 ($C_{2,7}$), 26.7, 25.1 ($C_{1',2',3'}$), 26.0, 17.9 (*t*Bu), −4.3, −4.5 ($SiMe_2$).

5.1.5. [3*R*,4*S*,5*R*,6*S*]-3-*O*-*tert*-Butyldimethylsilyl-6-hydroxymethyl-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (12).

R_f 0.2 (cyclohexane/EtOAc 8:2); $[\alpha]_D=-28$ (*c* 1.05, CH_2Cl_2); ^1H NMR δ 4.82 (dd, 1H, $J_{5,4}=10.2$ Hz, $J_{5,6}=4.6$ Hz, H_5), 4.35–4.31 (m, 1H, H_3), 4.01–3.88 (m, 2H, $H_{7a,7b}$), 3.71 (dd, 1H, $J_{4,5}=10.2$ Hz, $J_{4,3}=2.5$ Hz, H_4), 3.28–3.20 (m, 1H, H_6), 3.15–3.04 (m, 2H, $H_{1'a,3'a}$), 2.69–2.57 (m, 2H, $H_{1'b,3'b}$), 2.20 (dd, 1H, $J_{2a,2b}=15.1$ Hz, $J_{2a,3}=1.5$ Hz, H_{2a}), 2.15–2.06 (m, 1H, $H_{2'a}$), 1.88 (dd, 1H, $J_{2b,2a}=15.1$ Hz, $J_{2b,3}=2.6$ Hz, H_{2b}), 1.87–1.81 (m, 1H, $H_{2'b}$), 1.47, 1.45 (2s, 6H, CMe_2), 0.94 (s, 9H, *t*Bu), 0.11, 0.10 (2s, 6H, $SiMe_2$); ^{13}C NMR δ 109.8 (CMe_2), 75.8 (C_4), 73.5 (C_5), 67.4 (C_3), 61.0 (C_7), 50.7 (C_1), 43.8 (C_6), 43.7 (C_2), 27.1, 24.5 ($C_{1',2',3'}$), 26.8, 26.6 (CMe_2), 25.8, 18.2 (*t*Bu), −4.6, −5.1 ($SiMe_2$); MS (CI, CH_4) 421 (M^++1); HRMS for $C_{19}H_{37}O_4S_2Si$ (M^++1) calcd 421.1902; found 421.1897.

5.1.6. [3*R*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-4,5-*O*-methylethylidene-3,4,5,6-tetrahydroxycycloheptan-1-one 1,3-propanedithioketal (13). R_f 0.4 (cyclohexane/EtOAc 8:2); $[\alpha]_D=+48$ (*c* 0.97, CH_2Cl_2); ^1H NMR δ 4.78 (dd, 1H, $J_{5,4}=9.7$ Hz, $J_{5,6}=5$ Hz, H_5), 4.35–4.26 (m, 1H, H_3), 4.25–3.14 (m, 1H, H_6), 4.09 (dd, 1H, $J_{4,5}=9.7$ Hz, $J_{4,3}=1.8$ Hz, H_4), 3.32–3.08 (m, 2H, $H_{1'a,3'a}$), 2.87–2.53 (m, 4H, $H_{1'b,3'b,2a,OH}$), 2.25–2.15 (m, 1H, H_{7a}), 2.12–1.99 (m, 1H, $H_{2'b}$), 1.98–1.77 (m, 3H, $H_{2'a,\ 2b,\ 7b}$), 1.43, 1.41 (2s, 6H, CMe_2), 0.97 (s, 9H, *t*Bu), 0.11, 0.08 (2s, 6H, $SiMe_2$); ^{13}C NMR δ 109.4 (CMe_2), 78.2 (C_4), 76.0 (C_5), 75.1 (C_3), 73.8 (C_6), 48.4 (C_2), 48.4 (C_1), 42.7 (C_2), 27.4, 26.8, 25.6 ($C_{1',2',3'}$), 27.1 (CMe_2), 25.8, 18.2 (*t*Bu), −4.4, −4.7 ($SiMe_2$).

5.1.7. [3*R*,4*S*,5*R*,6*S*]-4,5-Di-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-6-hydroxymethyl-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (14). R_f 0.3 (cyclohexane/EtOAc 8:2); $[\alpha]_D=+23$ (*c* 0.67, CH_2Cl_2); ^1H NMR δ 7.45–7.05 (m, 10H, H_{ar}), 4.93–4.25 (m, 4H, OCH_2Ph), 4.30–3.60 (m, 5H, $H_{7a,\ 7b,3,4,5}$), 3.35–3.40 (m, 5H, $H_{2a,1'a,1'b,3'a,3'b}$), 2.18–1.63 (m, 4H, $H_{2b,6,2'a,2'b}$), 0.91 (s, 9H, *t*-Bu), 0.10, 0.09 (2s, 6H, $SiMe_2$); ^{13}C NMR δ 139.1, 138.3, 128.4, 128.3, 127.8, 127.4 (C_{ar}), 89.7 (C_4),77.5 (C_5), 68.5 (C_3), 74.4, 72.8 (OCH_2Ph), 60.6 (C_7), 52.2 (C_1), 47.8 (C_6), 39.8 (C_2), 26.6, 25.0 ($C_{1',2',3'}$), 26.0, 18.3 (*t*-Bu), −3.6, −4.7 ($SiMe_2$).

5.1.8. [3*R*,4*S*,5*R*,6*R*]-4,5-Di-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-3,4,5,6-tetrahydroxycycloheptan-1-one 1,3-propanedithioketal (15). R_f 0.35 (cyclohexane/EtOAc 8:2); $[\alpha]_D=-20$ (*c* 0.96, CH_2Cl_2); ^1H NMR δ 7.35–7.25 (m, 10H, H_{ar}), 4.85, 4.44 (AB, 2H, $J_{AB}=12$ Hz, OCH_2Ph), 4.60, 4.57 (AB, 2H, $J_{AB}=12$ Hz, OCH_2Ph), 4.16–4.08 (m, 1H, H_3), 4.00–3.90 (m, 1H, H_6), 3.70–3.60 (m, 2H, $H_{4,5}$), 3.01–2.62 (m, 5H, $H_{1'a,1'b,3'a,3'b,OH}$), 2.55 (dd, 1H, $J_{2a,2b}=15$ Hz, $J_{2b,3}=10.5$ Hz, H_{2b}), 2.21 (d, 1H, $J_{2a,2b}=15$ Hz, H_{2a}), 2.12–1.80 (m, 4H, $H_{2'a,2'b,7a,7b}$), 0.91 (s, 9H, *t*Bu), 0.13, 0.08 (2s, 6H, $SiMe_2$), ^{13}C NMR δ 138.9, 138.3, 128.6, 128.4, 127.8, 127.7, 126.4 (C_{ar}), 81.5 (C_4), 80.2 (C_5), 74.0, 73.2 (OCH_2Ph), 68.1, 67.0 ($C_{3,6}$), 47.3 (C_1), 42.1, 41.5 ($C_{2,7}$), 27.0, 25.3 ($C_{1',2',3'}$), 26.0, 18.0 (*t*Bu), −4.5, −4.7 ($SiMe_2$).

5.2. General procedure for silylation

To a solution of cycloalcanol (5.82 mmol) in DMF (131 mL) at 20°C, were successively added imidazole (22.1 mmol, 3.7 equiv.) and *tert*-butyldimethylsilyl chloride (15.6 mmol, 2.7 equiv.). The temperature was then raised to 70°C and the mixture was stirred for 24 h. After cooling to 20°C, a saturated NH_4Cl aqueous solution was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were then dried ($MgSO_4$), filtered and concentated in vacuo. Flash chromatography of the crude led to the pure silylated derivatives.

5.2.1. [3*S*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-6-*tert*-butyldimethylsilyloxymethyl-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (16). Isolated yield: 88%; R_f 0.4 (cyclohexane/EtOAc 97.5:2.5); mp 77°C; $[\alpha]_D=+17$ (*c* 1.0, CH_2Cl_2); ^1H NMR δ 4.12 (dd, 1H, $J_{7a,7b}=10.0$ Hz, $J_{7a,6}=4.3$ Hz, H_{7a}), 4.05–3.90 (m, 2H, $H_{7b,3}$), 3.76 (dd, 1H, $J_{5,6}=11.3$ Hz, $J_{5,4}=9.2$ Hz, H_5), 3.35 (dd, 1H, $J_{4,5}=J_{4,3}=9.2$ Hz, H_4), 3.30–3.01 (m, 1H, $H_{1'a}$), 3.05–2.85 (m, 2H, $H_{2a,3'a}$), 2.71–2.55 (m, 2H, $H_{1'b,3'b}$), 2.13–2.03 (m, 1H, $H_{2'a}$), 2.00–1.75 (m, 3H, $H_{2'a,2b,6}$), 1.41, 1.36 (2s, 6H, CMe_2), 0.90, 0.89 (2s, 18H, *t*Bu), 0.11, 0.08, 0.07 (3s, 12H, $SiMe_2$); ^{13}C NMR δ 110.8 (CMe_2), 84.7 (C_4), 74.9 (C_5), 69.1 (C_3), 61.0 (C_7), 52.7 (C_1), 52.2 (C_6), 45.9 (C_2), 26.9, 25.9 (CMe_2), 26.9, 25.9 ($C_{1',2',3'}$), 25.9, 18.3 (*t*Bu), −4.5, −4.7, −5.2 ($SiMe_2$). Anal. calcd for $C_{25}H_{50}O_4S_2Si_2$: C, 56.13; H, 9.42; found: C, 56.23; H, 9.47.

5.2.2. [3*S*,4*S*,5*S*,6*S*]-4,5-Dibenzyloxy-3,6-di-*tert*-butyldimethylsilyloxycycloheptan-1-one 1,3-propanedithioketal (17). Isolated yield: 100%; R_f 0.5 (cyclohexane/EtOAc 95:5); mp 104°C; $[\alpha]_D=-9$ (*c* 0.98, CH_2Cl_2); ^1H RMN δ 7.24–7.16 (m, 10H, H_{ar}), 4.76, 4.66 (AB, 4H, $J_{AB}=11.6$ Hz, OCH_2Ph), 4.05 (dd, 1H, $J_{3,2b}=9.3$ Hz, $J_{3,4}=7.0$ Hz, $H_{3,6}$), 3.51–3.42 (m, 2H, $H_{4,5}$), 2.93–2.71 (m, 4H, $H_{1'a,1'b,3'a,3'b}$), 2.38 (d, 2H, $J_{2a,2b}=15.1$ Hz, $H_{2a,7a}$), 2.13 (dd, 2H, $J_{2a,2b}=15$ Hz, $J_{2b,3}=9.3$ Hz, $H_{2b,7b}$), 2.06–1.93 (m, 2H, $H_{2'a,2'b}$), 0.88 (s, 18H, *t*-Bu), 0.14, −0.02 (2s, 12H, $SiMe_2$); ^{13}C NMR δ 139.0, 128.0, 127.0 (C_{ar}), 87.6 ($C_{4,5}$), 74.4 (OCH_2Ph), 70.1 ($C_{3,6}$), 47.9 (C_1), 44.8 ($C_{2,7}$), 26.9, 25.3 ($C_{1',2',3'}$), 26.0, 18.0 (*t*-Bu), −4.3, −4.6 ($SiMe_2$).

5.2.3. [3*R*,4*S*,5*S*,6*R*]-4,5-Dibenzyloxy-3,6-di-*tert*-butyldimethylsilyloxycycloheptan-1-one 1,3-propanedithioketal (18). Isolated yield: 100%; R_f 0.5 (cyclohexane/EtOAc 95:5); $[\alpha]_D=-20$ (*c* 0.96, CH_2Cl_2); ^1H NMR δ 7.39–7.24 (m, 10H, H_{ar}), 4.85, 4.58 (AB, 4H, $J_{AB}=12.2$ Hz, OCH_2Ph), 4.15–3.96 (m, 2H, $H_{3,6}$), 3.62 (s, 2H, $H_{4,5}$), 2.93–2.82 (m, 4H, $H_{1'a,1'b,3'a,3'b}$), 2.76 (dd, 2H, $J_{2a,2b}=J_{7a,7b}=15.3$ Hz, $J_{2b,3}=J_{7b,6}=10.1$ Hz, $H_{2b,7b}$), 2.17 (d, 2H, $J_{2a,2b}=J_{7a,7b}=15.3$ Hz, $H_{2a,7a}$), 2.08–1.96 (m, 2H, $H_{2'a,2'b}$), 0.95 (s, 18H, *t*Bu), 0.18, 0.14 (2s, 12H, $SiMe_2$); ^{13}C NMR δ 139.1, 128.2, 127.4 (C_{ar}), 81.8 ($C_{4,5}$), 73.9 (OCH_2Ph), 68.0 ($C_{3,6}$), 47.5 (C_1), 41.6 ($C_{2,7}$), 26.9, 25.4 ($C_{1',2',3'}$), 25.9, 18.0 (*t*Bu), −4.8 ($SiMe_2$). Anal. calcd for $C_{36}H_{58}O_4S_2Si$: C, 64.04; H, 8.66; found: C, 64.05, H, 8.79.

5.3. General procedure for dithioketal hydrolysis

To a −25°C cooled solution of *N*-bromosuccinimide (2.66 g, 14.96 mmol, 8 equiv.) in a 98:2 mixture of acetone/H_2O (80 mL), was added the dithioketal (1.00 g, 1.87 mmol) in acetone (27 mL) and the mixture was stirred

for 30 min prior to the addition, at −25°C, of a saturated $Na_2S_2O_3$ aqueous solution (17.8 mL). After increasing the temperature to 20°C and removing the acetone in vacuo, the resulting residue was extracted with ether and the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude ketone was then purified by flash chromatography.

5.3.1. [3*S*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-6-*tert*-butyldimethylsilyloxymethyl-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one (19b). Isolated yield: 77%; R_f 0.43 (cyclohexane/EtOAc 95:5); mp 46°C; $[\alpha]_D$=+7 (*c* 1.03, CH_2Cl_2); ^{1}H NMR δ 4.10 (dd, 1H, $J_{7a,7b}$=9.9 Hz, $J_{7a,6}$=2.2 Hz, H_{7a}), 4.05–3.95 (m, 1H, H_3), 3.90–3.65 (m, 3H, $H_{4,5,7b}$), 2.74 (dd, 1H, $J_{2a,2b}$=16.8 Hz, $J_{2a,3}$=6.8 Hz, H_{2a}), 2.41–2.29 (m, 1H, H_6), 2.34 (dd, 1H, $J_{2b,2a}$=16.8 Hz, $J_{2b,3}$=8.0 Hz, H_{2b}), 1.41, 1.43 (2s, 6H, CMe_2), 0.87, 0.85 (2s, 18H, *t*Bu), 0.11, 0.10, 0.04, 0.03 (4s, 12H, $SiMe_2$); ^{13}C NMR δ 205.7 (C_1), 111.7 (CMe_2), 83.6 (C_4), 73.3 (C_5), 67.6 (C_3), 58.4 (C_7), 55.5 (C_6), 49.6 (C_2), 29.7, 25.8 (CMe_2), 27.1, 27.0, 18.3, 18.1 (*t*Bu), −4.6, −5.0, −5.6 ($SiMe_2$). Anal. calcd for $C_{22}H_{44}O_5Si_2$: C, 59.41; H, 9.97; found: C, 59.34; H, 10.00.

5.3.2. [3*S*,4*S*,5*S*,6*S*]-4,5-Dibenzyloxy-3,6-di-*tert*-butyldimethylsilyloxycycloheptan-1-one (21). Isolated yield: 79%; R_f 0.3 (cyclohexane/EtOAc 95:5); $[\alpha]_D$=−18 (*c* 1.03, CH_2Cl_2); ^{1}H NMR δ 7.40–7.20 (m, 10H, H_{ar}), 4.57, 4.49 (AB, 4H, J_{AB}=11.9 Hz, OCH_2Ph), 4.15 (ddd, 2H, $J_{3,2a}$=7.9 Hz, $J_{3,4}$=5.3 Hz, $J_{3,2b}$=1.6 Hz, H_3), 3.68 (d, 1H, $J_{4,3}$=5.3 Hz, H_4), 2.95 (dd, 2H, $J_{2a,2b}$=14.8 Hz, $J_{2a,3}$=1.6 Hz, H_{2a}), 2.61 (dd, 1H, $J_{2b,2a}$=14.8 Hz, $J_{2b,3}$=7.9 Hz, H_{2b}), 0.83 (s, 18H, *t*Bu), 0.00, −0.04 (2s, 12H, $SiMe_2$); ^{13}C NMR δ 208.1 (C_1), 138.3, 128.3, 127.8, 127.7 (C_{ar}), 82.9 ($C_{4,5}$), 72.9 (OCH_2Ph), 69.1 ($C_{3,6}$), 47.7 ($C_{2,7}$), 25.2, 17.9 (*t*Bu), −5.0, −5.2 ($SiMe_2$). Anal. calcd for $C_{33}H_{52}O_5Si_2$: C, 67.76; H, 8.96; found: C, 67.65; H, 9.09.

5.3.3. [3*R*,4*S*,5*S*,6*R*]-4,5-Dibenzyloxy-3,6-di-*tert*-butyldimethylsilyloxycycloheptan-1-one (22). Isolated yield: 77%; R_f 0.38 (cyclohexane/EtOAc 95:5); mp 52°C; $[\alpha]_D$=−13 (*c* 1.1, CH_2Cl_2); ^{1}H NMR δ 7.40–7.23 (m, 10H, H_{ar}); 4.70 (s, 4H, OCH_2Ph), 4.29–4.20 (m, 2H, $H_{3,6}$), 3.76 (s, 2H, $H_{4,5}$), 2.72–2.70 (m, 2H, $H_{2a,7a}$), 2.63–2.49 (m, 2H, $H_{2b,7b}$), 0.83 (s, 18H, *t*Bu), 0.05, 0.02 (2s, 12H, $SiMe_2$); ^{13}C NMR δ 207.9 (C_1), 145.1, 138.7, 128.2, 127.8, 127.4 (C_{ar}), 82.9 ($C_{4,5}$), 73.8 (OCH_2Ph), 68.6 ($C_{3,6}$), 47.5 ($C_{2,7}$), 25.8, 18.0 (*t*Bu), −4.6, −5.2 ($SiMe_2$). Anal. calcd for $C_{33}H_{52}O_5Si_2$: C, 67.76; H, 8.96; found: C, 67.13; H, 9.20.

5.4. Reduction of cycloalkanone

Method A. To a solution of the cycloheptanol **22** (119.9 mg, 0.21 mmol) in absolute ethanol (3.9 mL), at 0°C, was added sodium cyanoborohydride (15.5 mg, 0.72 mmol, 3.4 equiv.) and the mixture was stirred at 20°C for 2 h. A saturated NH_4Cl aqueous solution was then added and the mixture was extracted with CH_2Cl_2. The combined organic layers were then dried ($MgSO_4$), filtered and concentrated in vacuo to give the cyclitol **23** (123.1 mg) as an oil, in quantitative yield.

Method B. To the crude cyclohexanone **19b** (obtained from **16** (0.17 mmol)) in THF (4 mL) at −78°C was added K-selectride® (1 M in THF, 1.1 mL, 1.1 mmol, 6.5 equiv.) and the mixture was stirred for 1.5 h prior to the addition of a saturated NH_4Cl aqueous solution. After ether extractions, the combined organic layers were then dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatographic purification of the crude (cyclohexane/EtOAc 95:5) led to the alcohols **24** (5.6 mg) and **25** (16.9 mg) as colorless oils in 50% yield.

5.4.1. [3*R*,4*S*,5*S*,6*R*]-4,5-Dibenzyloxy-3,6-di-*tert*-butyldimethylsilyloxy-1-cycloheptanol (23). Prepared according to the method A. R_f 0.4 (cyclohexane/EtOAc 95:5); ^{1}H NMR δ 7.28–7.25 (m, 10H, H_{ar}); 4.78, 4.77, 4.60, 4.58 (2AB, 4H, $J_{A,B}$=11.8 Hz, OCH_2Ph), 4.35–4.25 (m, 1H, H_3), 4.23–4.15 (m, 1H, H_6), 4.10–3.95 (m, 1H, H_1), 3.65–3.55 (m, 2H, $H_{4,5}$), 2.40–2.35 (m, 1H, H_{2b}), 2.35–2.10 (m, 1H, H_{7b}), 2.00–1.90 (m, 1H, H_{7a}), 1.70–1.60 (m, 1H, H_{2a}), 0.88 (s, 18H, *t*Bu), 0.06 (s, 12H, $SiMe_2$); ^{13}C NMR δ 139.0, 138.8, 128.2, 127.7, 127.6, 127.4, 127.3 (C_{ar}), 83.2, 83.0 ($C_{4,5}$), 74.0, 73.8 (OCH_2Ph), 70.2, 68.1, 66.4 ($C_{1,3,6}$), 39.6, 39.4 ($C_{2,7}$), 25.9, 18.1 (*t*Bu), −4.6, −4.7, −4.9 ($SiMe_2$).

5.4.2. [1*R*,3*S*,4*S*,5*R*,6*S*]-3-*O*-*tert*-Butyldimethylsilyl-6-*tert*-butyldimethylsilyloxymethyl-4,5-*O*-methylethylidenecyclohexan-1,3,4,5-tetrol (24). Prepared according to the method A, excepted that the reaction was carried out at −78°C (80% yield R_f 0.2 (cyclohexane/EtOAc 95:5); $[\alpha]_D$=+29 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 4.07 (dd, 1H, $J_{7a,b}$=10.0 Hz, $J_{6,7b}$=9.1 Hz, H_{7b}), 3.98 (s, 1H, OH), 3.79–3.63 (m, 2H, $H_{3,1}$), 3.63 (dd, 1H, $J_{7a,b}$=10.0 Hz, $J_{6,7a}$=3.7 Hz, H_{7a}), 3.42 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9.1 Hz, H_4), 2.97 (dd, 1H, $J_{5,6}$=11.1 Hz, $J_{5,4}$=9.1 Hz, H_5), 2.17 (ddd, 1H, $J_{2a,b}$=13.1 Hz, $J_{2a,3}$=$J_{2a,1}$=4.9 Hz, H_{2a}), 1.83 (dddd, 1H, $J_{6,5}$=11.1 Hz, $J_{6,7b}$=$J_{6,1}$=9.1 Hz, $J_{6,7a}$=3.7 Hz, H_6), 1.61 (ddd, 1H, $J_{2b,2a}$=13.1 Hz, $J_{2b,3}$=$J_{2b,1}$=11.1 Hz, H_{2b}), 1.37, 1.34 (2s, 6H, CMe_2), 0.88, 0.87 (2s, 18H, *t*Bu), 0.09, 0.08, 0.07, 0.06 (4s, 12H, $SiMe_2$); ^{13}C NMR δ 110.8 (CMe_2), 83.9 (C_4), 77.0 (C_5), 75.1 (C_3), 71.5 (C_1), 65.3 (C_7), 46.9 (C_6), 42.2 (C_2), 30.1, 26.9 (CMe_2), 25.7, 18.2, 18.0 (*t*Bu), −4.6, −4.9, −5.6, −5.7 ($SiMe_2$); MS (CI, CH_4) 446 (M^+); HRMS for $C_{22}H_{46}O_5Si_2$ (M^++1) calcd 446.2884; found 446.2884.

5.4.3. [1*S*,3S,4*S*,5*R*,6*S*]-3-*O*-*tert*-Butyldimethylsilyl-6-*tert*-butyldimethylsilyloxymethyl-4,5-*O*-methylethylidenecyclohexan-1,3,4,5-tetrol (25). Prepared according to the method B; R_f 0.4 (cyclohexane/EtOAc 95:5); $[\alpha]_D$=+12 (*c* 0.6, CH_2Cl_2); ^{1}H NMR δ 4.31 (d, 1H, $J_{1,2}$=2.6 Hz, H_1), 4.13 (ddd, 1H, $J_{3,2a}$=$J_{3,4}$=9.1 Hz, $J_{3,2b}$=4.8 Hz, H_3), 4.06 (dd, 1H, $J_{7a,b}$=10.4 Hz, $J_{7a,6}$=3.0 Hz, H_{7a}), 3.97 (dd, 1H, $J_{7a,b}$=10.4 Hz, $J_{7b,6}$=3.0 Hz, H_{7b}), 3.88 (s, 1H, OH), 3.83 (dd, 1H, $J_{5,6}$=11.6 Hz, $J_{5,4}$=9.1 Hz, H_5), 3.25 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9.1 Hz, H_4), 2.11 (ddd, 1H, $J_{2a,b}$=16.1 Hz, $J_{2a,3}$=4.8 Hz, $J_{2a,1}$=2.6 Hz, H_{2a}), 1.83 (dddd, 1H, $J_{6,5}$=11.1 Hz, $J_{6,7b}$=$J_{6,1}$=$J_{6,7a}$=3.0 Hz, H_6), 1.47–1.38 (m, 1H, H_{2b}), 1.38, 1.37 (2s, 6H, CMe_2), 0.89, 0.88 (2s, 18H, *t*Bu), 0.09, 0.08, 0.06, 0.05 (4s, 12H, $SiMe_2$); ^{13}C NMR δ 109.3 (CMe_2), 84.9 (C_4), 72.6 (C_5), 71.4 (C_3), 68.7 (C_1), 63.0 (C_7), 44.5 (C_6), 41.3 (C_2), 27.0, 26.8 (CMe_2), 25.9, 25.7, 18.3, 18.1 (*t*Bu), −4.6, −4.9, −5.6, −5.7 ($SiMe_2$); MS (CI, NH_3) 446 (M^+); HRMS for $C_{22}H_{46}NO_5Si_2$ (M^++1) calcd 446.2884; found 446.2883.

5.5. Reductive amination in C7 series

To the neat cycloalkanone (0.53 mmol) at 20°C, were successively added titanium tetra-isopropoxide (0.66 mmol, 1.25 equiv.) and the primary amine (1.06 mmol, 2 equiv.). After 2 h stirring, absolute ethanol (500 μL) and sodium cyanoborohydride (2.79 mmol, 5.3 equiv.) were added and the resulting mixture was further stirred for 14 h. Addition of H_2O (300 μL) resulted in the formation of a off-white precipitate which was filtered off and washed with absolute ethanol. Concentration of the filtrate was followed by extraction of the resulting residue with ethyl acetate, filtration and concentration in vacuo. The oily residue was then dissolved in CH_2Cl_2 and stirred in the presence of sodium hydrogencarbonate. Filtration and concentration in vacuo afforded the crude aminocyclitol which was then purified by flash chromatography.

5.5.1. [3*S*,4*S*,5*R*,6*S*]-4,5-Dibenzyloxy-3,6-di-*tert*-butyldimethylsilyloxy-1-*N*-cycloheptanyl-*N*-benzylamine (26a). Isolated yield: 80%; R_f 0.3 (cyclohexane/EtOAc 95:5); $[\alpha]_D=-1$ (*c* 1.0, CH_2Cl_2); ^1H NMR δ 7.50–7.10 (m, 15H, H_{ar}), 4.78, 4.35 (AB, 2H, $J_{AB}=12.1$ Hz, OCH_2Ph), 4.56, 4.52 (AB, 2H, $J_{AB}=11.8$ Hz, OCH_2Ph), 4.20–4.02 (m, 2H, $H_{3,6}$), 3.87, 3.78 (AB, 2H, $J_{AB}=13.3$ Hz, $NHCH_2Ph$), 3.56 (dd, 1H, $J_{4,5}=1.3$ Hz, $J_{4,3}=6.1$ Hz, H_4), 3.45 (dd, 1H, $J_{5,4}=1.3$ Hz, $J_{5,6}=8.2$ Hz, H_5), 3.03–2.80 (m, 1H, H_1), 2.04–1.66 (m, 4H, $H_{7a,2a,2b,7b}$), 0.89, 0.83 (2s, 18H, *t*Bu), 0.05, 0.01, −0.04 (3s, 12H, $SiMe_2$); ^{13}C NMR δ 139.7, 139.2, 138.4, 128.5, 128.3, 128.0, 127.8, 127.5, 127.1, 127.0 (C_{ar}), 88.0, 82.3 ($C_{4,5}$), 73.9, 72.9 (OCH_2Ph), 71.8, 69.5 ($C_{3,6}$), 50.9 ($NHCH_2Ph$), 50.5 (C_1), 40.6, 36.4 ($C_{2,7}$), 26.0, 25.8, 18.1, 17.9 (*t*Bu), −4.4, −4.7, −5.2 ($SiMe_2$).

5.5.2. [3*S*,4*S*,5*S*,6*S*]-4,5-Dibenzyloxy-3,6-di-*tert*-butyldimethylsilyloxy-1-*N*-cycloheptanyl-*N*-butylamine (26b). Isolated yield: 63%; R_f 0.2 (cyclohexane/EtOAc 8:2); $[\alpha]_D=+5$ (*c* 1.0, CH_2Cl_2); ^1H NMR δ 7.34–7.22 (m, 10H, H_{ar}); 4.68, 4.56 (AB, 2H, $J_{AB}=11.9$ Hz, OCH_2Ph), 4.50, 4.33 (AB, 2H, $J_{AB}=11.6$ Hz, OCH_2Ph), 4.21–4.05 (m, 2H, $H_{3,6}$), 3.56 (dd, 1H, $J_{4,3}=6.2$ Hz, $J_{4,5}=1.5$ Hz, H_4), 3.58 (dd, 1H, $J_{5,6}=8.2$ Hz, $J_{5,4}=1.5$ Hz, H_5), 2.95–2.76 (m, 1H, H_1), 2.73–2.48 (m, 2H, $H_{1'}$), 1.95–1.54 (m, 4H, $H_{2a,b,7a,b}$), 1.53–1.23 (m, 4H, $H_{2',3'}$), 0.99–0.75 (m, 21H, *t*Bu, $H_{4'}$), 0.06, 0.01, −0.02 (3s, 12H, $SiMe_2$); ^{13}C NMR δ 139.3, 138.5, 128.3, 128.0, 127.8, 127.5, 127.2 (C_{ar}), 88.0, 82.3 ($C_{4,5}$), 74.1, 73.2 (OCH_2Ph), 72.8, 69.8 ($C_{3,6}$), 51.5 (C_1), 47.1 ($C_{1'}$), 40.8, 36.9 ($C_{2,7}$), 32.5 ($C_{2'}$), 26.0, 25.8, 18.1, 18.0 (*t*Bu), 20.6 ($C_{3'}$), 14.0 ($C_{4'}$), −4.4, −4.8, −5.0 ($SiMe_2$); MS (CI, CH_4) 642 (M^++1); HRMS for $C_{37}H_{64}NO_4Si_2$ (M^++1) calcd 642.4374; found 642.4371.

5.5.3. [3*S*,4*S*,5*S*,6*S*]-4,5-Dibenzyloxy-3,6-di-*tert*-butyldimethylsilyloxy-1-*N*-cycloheptanyl-*N*-(1′,2′-di-*tert*-butyldimethylsilyloxy)-2′-propylamine (26c). Isolated yield: 72%; R_f 0.46 (cyclohexane/EtOAc 9:1); $[\alpha]_D=+0$ (*c* 1.0, CH_2Cl_2); $[\alpha]_{Hg}=+0$ (*c* 1.0, CH_2Cl_2); ^1H NMR δ 7.40–7.15 (m, 10H, H_{ar}), 4.68, 4.55 (AB, 2H, $J_{AB}=11.8$ Hz, OCH_2Ph), 4.50, 4.21 (AB, 2H, $J_{AB}=11.9$ Hz, OCH_2Ph), 4.20–4.02 (m, 2H, $H_{3,6}$), 3.67–3.39 (m, 6H, $H_{4,5,1',3'}$), 2.98–2.81 (m, 1H, H_1), 2.75–2.62 (m, 1H, $H_{2'}$), 1.88–1.62 (m, 4H, $H_{2a,b,7a,b}$), 0.88 (s, 36H, *t*Bu), 0.06, 0.03, 0.00, −0.03 (4s, 24H, $SiMe_2$); ^{13}C NMR δ 139.3, 138.5, 128.3, 128.0, 127.8, 127.4, 127.1 (C_{ar}), 88.3, 82.0 ($C_{4,5}$), 73.5, 71.7 (OCH_2Ph), 72.6, 69.7 ($C_{3,6}$), 62.9, 62.0 ($C_{1',3'}$), 58.6 ($C_{2'}$), 49.2 (C_1), 42.1, 37.4 ($C_{2,7}$), 25.9, 25.8, 18.2, 18.1 (*t*Bu), −4.4, −4.6, −5.2, −5.4 ($SiMe_2$); MS (CI, CH_4) 888 (M^++1); HRMS for $C_{48}H_{90}NO_6Si_4$ (M^++1) calcd 888.5877; found 888.5845.

5.5.4. Methyl [3′*S*,4′*S*,5′*S*,6′*S*]-6-deoxy-(4′,5′-dibenzyloxy-3′,6′-di-*tert*-butyldimethylsilyloxy-cycloheptanyl)-amino-2,3,4-tri-*O*-benzyl-D-glucopyranoside (26d). Isolated yield: 43%; R_f 0.3 (cyclohexane/EtOAc 7:3); $[\alpha]_D=+0.3$ (*c* 2.0, CH_2Cl_2); ^1H NMR δ 7.34–7.22 (m, 25H, H_{ar}), 5.00–4.20 (m, 10H, OCH_2Ph), 4.53 (d, 1H, $J_{1,2}=3.5$ Hz, H_1), 4.21–4.05 (m, 2H, $H_{3',6'}$), 3.97 (dd, 1H, $J_{3,2}=J_{3,4}=9.2$ Hz, H_3), 3.80–3.70 (m, 1H, H_5), 3.62–3.40 (m, 4H, $H_{4,5',4',2}$), 3.37 (s, 3H, OMe), 3.06 (dd, 1H, $J_{6a,b}=12.0$ Hz, $J_{6a,5}=2.7$ Hz, H_{6a}), 2.95–2.80 (m, 1H, $H_{1'}$), 2.68 (dd, 1H, $J_{6a,b}=12.0$ Hz, $J_{6b,5}=5.8$ Hz, H_{6b}), 1.90–1.60 (m, 4H, $H_{2'a,b,7'a,b}$), 0.86, 0.84 (2s, 18H, *t*Bu), 0.03 (s, 12H, $SiMe_2$); ^{13}C NMR δ 139.3, 138.9, 138.5, 138.4, 138.3, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.6, 127.5, 127.2 (C_{ar}), 98.1 (C_1), 88.0, 82.0 ($C_{4',5'}$), 82.3, 80.1, 73.3 ($C_{2,3,4}$), 75.7, 75.1, 73.5, 73.4, 71.8 (OCH_2Ph), 72.6, 69.7 ($C_{3',6'}$), 70.1 (C_5), 55.3 (OMe), 51.7 ($C_{1'}$), 47.6 (C_6), 40.8, 36.8 ($C_{2',7'}$), 26.0, 25.0, 18.1, 18.0 (*t*Bu), −4.5, −4.6, −5.1 ($SiMe_2$); MS (CI, CH_4) 1032 (M^++1); HRMS for $C_{61}H_{86}NO_9Si_2$ (M^++1) calcd 1032.5841; found 1032.5824.

5.5.5. [3*R*,4*S*,5*S*,6*R*]-4,5-Dibenzyloxy-3,6-di-*tert*-butyldimethylsilyloxy-1-*N*-cycloheptanyl-*N*-benzylamine (27a). Isolated yield: 93%; R_f 0.3 (cyclohexane/EtOAc 95:5); $[\alpha]_D=-16$ (*c* 1.09, CH_2Cl_2); ^1H NMR δ 7.47–7.10 (m, 15H, H_{ar}), 4.84, 4.59 (AB, 2H, $J_{AB}=11.8$ Hz, OCH_2Ph), 4.76, 4.57 (AB, 2H, $J_{AB}=12.0$ Hz, OCH_2Ph), 4.56–4.20 (m, 1H, H_3), 4.18–4.08 (m, 1H, H_6), 3.79 (s, 2H, $NHCH_2Ph$), 3.64 (dd, 1H, $J_{4,5}=5.5$ Hz, $J_{4,3}=1.1$ Hz, H_4), 3.58 (dd, 1H, $J_{5,4}=5.5$ Hz, $J_{5,6}=1.9$ Hz, H_5), 3.06–2.89 (m, 1H, H_1), 2.23 (ddd, 1H, $J_{2a,b}=14.3$ Hz, $J_{2a,3}=9.4$ Hz, $J_{2a,1}=5.8$ Hz, H_{2a}), 2.10 (ddd, 1H, $J_{7b,a}=14.0$ Hz, $J_{7b,6}=J_{7b,1}=9.8$ Hz, H_{7b}), 1.84–1.71 (m, 1H, H_{7a}), 1.53 (ddd, 1H, $J_{2b,a}=14.3$ Hz, $J_{2b,1}=6.5$ Hz, $J_{2b,3}=2.2$ Hz, H_{2b}), 0.89, 0.87 (2s, 18H, *t*Bu), 0.04, 0.03 (2s, 12H, $SiMe_2$); ^{13}C NMR δ 139.7, 139.2, 138.4, 128.5, 128.3, 128.0, 127.8, 127.5, 127.1, 127.0 (C_{ar}), 88.0, 82.3 ($C_{4,5}$), 73.9, 72.9 (OCH_2Ph), 71.8, 69.5 ($C_{3,6}$), 50.9 ($NHCH_2Ph$), 50.5 (C_1), 40.6, 36.4 ($C_{2,7}$), 26.0, 25.8, 18.1, 17.9 (*t*Bu), −4.4, −4.7, −5.2 ($SiMe_2$); MS (CI, CH_4) 676 (M^++1); HRMS for $C_{40}H_{62}NO_4Si_2$ (M^++1) calcd 676.4217; found 676.4202.

5.5.6. [3*R*,4*S*,5*S*,6*R*]-4,5-Dibenzyloxy-3,6-di-*tert*-butyldimethylsilyloxy-1-*N*-cycloheptanyl-*N*-butylamine (27b). Isolated yield: 47%; R_f 0.2 (cyclohexane/EtOAc 75:25); $[\alpha]_D=-21$ (*c* 1.03, CH_2Cl_2); ^1H NMR δ 7.30–7.20 (m, 10H, H_{ar}), 4.83, 4.58 (AB, 2H, $J_{AB}=11.9$ Hz, OCH_2Ph), 4.74, 4.57 (AB, 2H, $J_{AB}=12.0$ Hz, OCH_2Ph), 4.28–4.05 (m, 2H, $H_{3,6}$), 3.63 (dd, 1H, $J_{4,5}=5.4$ Hz, H_4), 3.56 (d, 1H, $J_{5,4}=5.4$ Hz, H_5), 2.98–2.74 (m, 1H, H_1), 2.56 (t, 2H, $J_{1',2'}=7.0$ Hz, $H_{1'}$), 2.19 (ddd, 1H, $J_{2a,b}=14.6$ Hz, $J_{2a,3}=9.3$ Hz, $J_{2a,1}=6.0$ Hz, H_{2a}), 1.99 (ddd, 1H, $J_{7b,a}=13.9$ Hz, $J_{7b,6}=J_{7b,1}=9.9$ Hz, H_{7b}), 1.80–1.55 (m, 1H, H_{7a}), 1.55–1.23 (m, 5H, $H_{2b,2',3'}$), 0.94–0.82 (m, 21H, *t*Bu, $H_{4'}$), 0.06, 0.04 (2s, 12H, $SiMe_2$); ^{13}C NMR δ 139.4, 139.1,

128.1, 127.5, 127.4, 127.2 (C_{ar}), 83.7, 82.7 ($C_{4,5}$), 74.1, 73.2 (OCH_2Ph), 70.7, 68.8 ($C_{3,6}$), 51.9 (C_1), 47.0 ($C_{1'}$), 37.4, 37.0 ($C_{2,7}$), 32.5 ($C_{2'}$), 26.0, 25.9, 18.1, 18.0 (*t*Bu), 20.6 ($C_{3'}$), 14.1 ($C_{4'}$), −4.7, −4.8, −5.0 ($SiMe_2$); MS (CI, CH_4) 642 (M^++1); HRMS for $C_{37}H_{64}NO_4Si_2$ (M^++1) calcd 642.4374; found 642.4371.

5.5.7. [3*R*,4*S*,5*S*,6*R*]-4,5-Dibenzyloxy-3,6-di-*tert*-butyldimethylsilyloxy-1-*N*-cycloheptanyl-*N*-(1′,3′-di-*tert*-butyldimethylsilyloxy)-2′-propylamine (27c). Isolated yield: 91%; R_f 0.56 (cyclohexane/EtOAc 9:1); $[\alpha]_D$=−13 (*c* 1.0, CH_2Cl_2); ^1H NMR δ 7.40–7.10 (m, 10H, H_{ar}), 4.86, 4.59 (AB, 2H, J_{AB}=11.9 Hz, OCH_2Ph), 4.72, 4.55 (AB, 2H, J_{AB}=12.0 Hz, OCH_2Ph), 4.32–4.18 (m, 1H, H_3), 4.16–4.04 (m, 1H, H_6), 3.70–3.40 (m, 6H, $H_{4,5,1'a,b,3'a,b}$), 3.07–2.89 (m, 1H, $H_{2'}$), 2.75–2.60 (m, 1H, H_1), 2.14 (ddd, 1H, $J_{2a,b}$=14.5 Hz, $J_{2a,3}$=8.7 Hz, $J_{2a,1}$=5.5 Hz, H_{2a}), 2.01 (ddd, 1H, $J_{7b,a}$=13.5 Hz, $J_{7b,6}$=$J_{7b,1}$=10.5 Hz, H_{7b}), 1.71–1.48 (m, 2H, $H_{2b,7a}$), 0.88, 0.87 (2s, 36H, *t*Bu), 0.06, 0.04, 0.03, 0.02 (4s, 24H, $SiMe_2$); ^{13}C NMR δ 139.5, 139.2, 128.2, 128.1, 127.6, 127.4, 127.2 (C_{ar}), 84.0, 82.8 ($C_{4,5}$), 74.3, 73.2 (OCH_2Ph), 70.5, 68.9 ($C_{3,6}$), 62.1, 61.6 ($C_{1',3'}$), 57.7 ($C_{2'}$), 49.0 (C_1), 38.6, 38.1 ($C_{2,7}$), 25.9, 18.3, 18.1 (*t*Bu), −4.7, −5.4 ($SiMe_2$); MS (CI, CH_4) 888 (M^++1); HRMS for $C_{48}H_{90}NO_6Si_4$ (M^++1): calcd 888.5877; found 888.5855.

5.6. General procedure for the hydrolysis of the silyl ethers (26) or (27)

To a solution of the silylated diol **26** (or **27**) (0.47 mmol) in THF (11.8 mL) was added tetra-*n*-butylammonium fluoride (1 M in THF, 1.64 mL, 1.64 mmol, 3.5 equiv.). After 24 h stirring at 20°C, the mixture was concentrated in vacuo and the crude diol **28** (or **29**) was purified by flash chromatography.

5.6.1. [3*S*,4*R*,5*R*,6*S*]-4,5-Di-*O*-benzyl-1-*N*-(-3,4,5,6-tetrahydroxycycloheptanyl)-*N*-benzylamine (28a). Isolated yield: 100%; R_f 0.3 (CH_2Cl_2/MeOH 96:4); $[\alpha]_D$=−2 (*c* 0.93, CH_2Cl_2); ^1H NMR δ 7.50–7.10 (m, 15H, H_{ar}), 4.85, 4.61 (AB, 2H, J_{AB}=11.3 Hz, OCH_2Ph), 4.75, 4.64 (AB, 2H, J_{AB}=11.4 Hz, OCH_2Ph), 4.19 (ddd, 1H, $J_{3,2b}$=$J_{3,4}$=8.6 Hz, $J_{3,2a}$=2.3 Hz, H_3), 4.05 (ddd, 1H, $J_{6,7b}$=8.7 Hz, $J_{6,5}$=5.6 Hz, $J_{6,7a}$=3.0 Hz, H_6), 3.91, 3.77 (AB, 2H, J_{AB}=12.7 Hz, $NHCH_2Ph$), 3.74 (dd, 1H, $J_{5,4}$=$J_{5,6}$=5.6 Hz, H_5), 3.46 (dd, 1H, $J_{4,5}$=5.6 Hz, $J_{4,3}$=8.6 Hz, H_4), 3.23–3.07 (m, 1H, H_1), 2.14–1.76 (m, 2H, $H_{2a,7a}$), 1.42–1.20 (m, 2H, $H_{2b,7b}$); ^{13}C NMR δ 139.7, 139.2, 138.4, 128.5, 128.3, 128.0, 127.8, 127.5, 127.1, 127.0 (C_{ar}), 88.0, 82.3 ($C_{4,5}$), 73.9, 72.9 (OCH_2Ph), 71.8, 69.5 ($C_{3,6}$), 50.9 ($NHCH_2Ph$), 50.5 (C_1), 40.6, 36.4 ($C_{2,7}$), 26.0, 25.8, 18.1, 17.9 (*t*Bu), −4.4, −4.7, −5.2 ($SiMe_2$); MS (CI, CH_4) 448 (M^++1); HRMS for $C_{28}H_{34}NO_4$ (M^++1) calcd 448.2488; found 448.2483.

5.6.2. [3*S*,4*R*,5*R*,6*S*]-4,5-Di-*O*-benzyl-1-*N*-(3,4,5,6-tetrahydroxycycloheptanyl)-*N*-butylamine (28b). Isolated yield: 85%; R_f 0.3 (EtOAc/EtOH 95:5); $[\alpha]_D$=+21 (*c* 1.0, CH_2Cl_2); ^1H NMR δ 7.37–7.23 (m, 10H, H_{ar}), 4.85, 4.60 (AB, 2H, J_{AB}=11.2 Hz, OCH_2Ph), 4.71, 4.63 (AB, 2H, J_{AB}=11.3 Hz, OCH_2Ph), 4.19 (ddd, 1H, $J_{3,2b}$=10.4 Hz, $J_{3,4}$=8.5 Hz, $J_{3,2a}$=1.9 Hz, H_3), 4.09 (ddd, 1H, $J_{6,7b}$=7.3 Hz, $J_{6,5}$=5.3 Hz, $J_{6,7a}$=1.8 Hz, H_6), 3.76 (dd, 1H, $J_{5,4}$=$J_{5,6}$=5.3 Hz, H_5), 3.45 (dd, 1H, $J_{4,5}$=5.3 Hz, $J_{4,3}$=8.5 Hz, H_4), 3.17–3.02 (m, 1H, H_1), 2.79–2.50 (m, 2H, $H_{1'}$), 2.21–1.74 (m, 4H, $H_{2a,b,7a,b}$), 1.63–1.20 (m, 4H, $H_{2',3'}$), 0.91 (t, 3H, $J_{4',3'}$=7.1 Hz, $H_{4'}$); ^{13}C NMR δ 138.2, 128.5, 127.9, 127.8 (C_{ar}), 88.6, 86.2 ($C_{4,5}$), 73.8, 73.0 (OCH_2Ph), 71.0, 66.1 ($C_{3,6}$), 52.7 (C_1), 47.0 ($C_{1'}$), 39.2 ($C_{2'}$), 32.1, 31.1 ($C_{2,7}$), 20.4 ($C_{3'}$), 14.0 ($C_{4'}$); MS (CI, CH_4) 414 (M^++1); HRMS for $C_{25}H_{36}NO_4$ (M^++1) calcd 414.2644; found 414.2640.

5.6.3. [3*S*,4*R*,5*R*,6*S*]-4,5-Di-*O*-benzyloxy-1-*N*-(1′,3′-dihydroxycycloheptanyl-*N*-(1′,2′-dihydroxy)-2′-propylamine (28c). This product was submitted without purification to the hydrogenolysis reaction.

5.6.4. Methyl [3′*S*,4′*R*,5′*R*,6′*S*]-6-deoxy-(4′,5′-dibenzyloxy-3′,6′-dihydroxycycloheptanyl)-amino-2,3,4-tri-*O*-benzyl-D-glucopyranoside (28d). Isolated yield: 87%; R_f 0.2 (EtOAc/EtOH 95:5); $[\alpha]_D$=+0.5 (*c* 0.2, CH_2Cl_2); ^1H NMR δ 7.32–7.20 (m, 25H, H_{ar}), 5.00–4.52 (m, 10H, OCH_2Ph), 4.53 (d, 1H, $J_{1,2}$=3.5 Hz, H_1), 4.15–3.90 (m, 3H, $H_{3',6',3}$), 3.79–3.62 (m, 2H, $H_{5,5'}$), 3.46 (dd, 1H, $J_{2,3}$=9.6 Hz, $J_{2,1}$=3.5 Hz, H_2), 3.42–3.30 (m, 2H, $H_{4,4'}$), 3.33 (s, 3H, OMe), 3.00–2.95 (m, 1H, $H_{1'}$), 2.90 (dd, 1H, $J_{6a,6b}$=12.0 Hz, $J_{6a,5}$=2.7 Hz, H_{6a}), 2.58 (dd, 1H, $J_{6b,6a}$=12.0 Hz, $J_{6b,5}$=7.1 Hz, H_{6b}), 1.90–1.60 (m, 4H, $H_{2'a,b,7'a,b}$); ^{13}C NMR δ 138.8, 138.3, 138.1, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 127.6, 126.8 (C_{ar}), 98.0 (C_1), 88.5, 86.2 ($C_{4',5'}$), 82.0, 80.1, 79.4 ($C_{2,3,4}$), 75.7, 75.0, 74.0, 73.4 (OCH_2Ph), 70.5, 69.3, 66.2 ($C_{3',6',5}$), 55.3 (OMe), 53.4 ($C_{1'}$), 48.0 (C_6), 38.1, 32.4 ($C_{2',7'}$); MS (CI, CH_4) 804 (M^++1); HRMS for $C_{49}H_{57}NO_9$ (M^++1) calcd 804.4105; found 804.4111.

5.6.5. [3*R*,4*R*,5*R*,6*R*]-4,5-Di-*O*-benzyl-1-*N*-(-3,4,5,6-tetrahydroxycycloheptanyl)-*N*-benzylamine (29a). Isolated yield: 74%; R_f 0.3 (CH_2Cl_2/MeOH 96:4); $[\alpha]_D$=−8 (*c* 1.0, CH_2Cl_2); ^1H NMR δ 7.34–7.21 (m, 15H, H_{ar}), 4.72, 4.70, 4.62 (AB, 4H, J_{AB}=11.6 Hz, OCH_2Ph), 4.28 (ddd, 1H, $J_{3,2a}$=8.9 Hz, $J_{3,2b}$=$J_{3,4}$=2.3 Hz, H_3), 4.15 (ddd, 1H, $J_{6,7b}$=8.9 Hz, $J_{6,7a}$=$J_{6,5}$=2.6 Hz, H_6), 3.81 (dd, 1H, $J_{4,5}$=6.1 Hz, $J_{4,3}$=2.3 Hz, H_4), 3.81, 3.74 (AB, 2H, J_{AB}=13.0 Hz, $NHCH_2Ph$), 3.67 (dd, 1H, $J_{5,4}$=6.1 Hz, $J_{5,6}$=2.6 Hz, H_5), 3.07 (dddd, 1H, $J_{1,2b}$=7.3 Hz, $J_{1,7b}$=6.2 Hz, $J_{1,2a}$=5.5 Hz, $J_{1,7a}$=4.4 Hz, H_1), 2.24 (ddd, 1H, $J_{2a,b}$=14.3 Hz, $J_{2a,3}$=8.9 Hz, $J_{2a,1}$=5.5 Hz, H_{2a}), 2.00 (ddd, 1H, $J_{7b,a}$=14.1 Hz, $J_{7b,6}$=8.9 Hz, $J_{7b,1}$=6.2 Hz, H_{7b}), 1.84 (ddd, 1H, $J_{7a,b}$=14.1 Hz, $J_{7a,1}$=4.4 Hz, $J_{7a,6}$=2.6 Hz, H_{2a}), 1.65 (ddd, 1H, $J_{2b,a}$=14.3 Hz, $J_{2b,1}$=7.3 Hz, $J_{2b,3}$=2.3 Hz, H_{2b}); ^{13}C NMR δ 138.4, 138.3, 136.0, 129.1, 128.8, 128.5, 128.0, 127.8 (C_{ar}), 82.3, 82.0 ($C_{4,5}$), 73.4, 73.1 (OCH_2Ph), 68.7, 66.9 ($C_{3,6}$), 51.1 (NH–CH_2–Ph), 50.9 (C_1), 34.8, 33.9 ($C_{2,7}$).

5.6.6. [3*R*,4*R*,5*R*,6*R*]-4,5-Di-*O*-benzyl-1-*N*-(3,4,5,6-tetrahydroxycycloheptanyl)-*N*-butylamine (29b). Isolated yield: 88%; R_f 0.3 (EtOAc/EtOH 95:5); $[\alpha]_D$=−28 (*c* 1.0, CH_2Cl_2); ^1H NMR δ 7.30–7.26 (m, 10H, H_{ar}), 4.72, 4.67, 4.62 (AB, 2H, J_{AB}=11.6 Hz, OCH_2Ph), 4.27 (ddd, 1H, $J_{3,2a}$=8.9 Hz, $J_{3,2b}$=$J_{3,4}$=2.3 Hz, $H_{3'}$), 4.17 (ddd, 1H, $J_{6,7b}$=8.9 Hz, $J_{6,7a}$=$J_{6,5}$=2.5 Hz, H_6), 3.81 (dd, 1H, $J_{4,5}$=6.1 Hz, $J_{4,3}$=2.5 Hz, H_4), 3.65 (dd, 1H, $J_{5,4}$=6.1 Hz, $J_{5,6}$=2.5 Hz, H_5), 3.11–2.96 (m, 1H, H_1), 2.90–2.70 (m, 2H, OH),

2.70–2.48 (m, 2H, $H_{1'}$), 2.22 (ddd, 1H, $J_{2a,b}$=14.2 Hz, $J_{2a,3}$=8.9 Hz, $J_{2a,1}$=5.5 Hz, H_{2a}), 2.07–1.88 (m, 1H, H_{7b}), 1.79 (ddd, 1H, $J_{7a,b}$=14.2 Hz, $J_{7a,1}$=3.9 Hz, $J_{7a,6}$=2.0 Hz, H_{2a}), 1.63 (ddd, 1H, $J_{2b,a}$=14.2 Hz, $J_{2b,1}$=7.4 Hz, $J_{2b,3}$=2.0 Hz, H_{2b}), 1.52–1.20 (m, 4H, $H_{2',3'}$), 0.90 (t, 3H, $J_{4',3'}$=7.1 Hz, $H_{4'}$); ^{13}C NMR δ 138.4, 128.5, 127.8 (C_{ar}), 83.2, 82.8 ($C_{4,5}$), 73.5, 72.9 (OCH_2Ph), 69.3, 67.1 ($C_{3,6}$), 51.7 (C_1), 46.8 ($C_{1'}$), 36.6 ($C_{2'}$), 34.8, 32.0 ($C_{2,7}$), 20.4 ($C_{3'}$), 13.9 ($C_{4'}$); MS (CI, CH_4) 414 (M^++1); HRMS for $C_{25}H_{36}NO_4$ (M^++1) calcd 414.2644; found 414.2646.

5.6.7. [3*R*,4*R*,5*R*,6*R*]-4,5-Di-*O*-benzyloxy-1-*N*-(1′,3′-dihydroxycycloheptanyl-*N*-(1′,2′-dihydroxy)-2′-propylamine (29c). This product was submitted without purification to the hydrogenolysis reaction.

5.7. Hydrogenolysis in the C7 series

For **28a**,**b**,**c** or **29a**,**b**,**c**. A suspension of palladium black (37.3 mg) in acetic acid (1 mL) was saturated with dihydrogen. A solution of the substrate (90 μmol) in acetic acid (2 mL) was then added and was followed by 14 h stirring. The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated in vacuo. Subsequent purification by ion exchange chromatography (Dowex® 50X8-100, 3% aqueous ammonium hydroxide) afforded the pure targeted aminocyclitol.

For **28d**. To a solution of the benzylated derivative **28** (93 mg, 11.6 μmol) in THF (500 μL) was condensed liquid ammonia (60 mL) at −78°C. Sodium was then added until persistance of a dark blue color and the mixture was stirred in refluxing ammonia for 6 h. After careful addition of solid ammonium chloride until decoloration, ammonia was evaporated and the solid residue was washed with CH_2Cl_2 and extracted with MeOH. The combined alcoholic layers were then concentrated in vacuo, and purification by ion-exchange chromatography (Dowex® 50X8-100, 1% aqueous ammonium hydroxide) gave the expected **30d** (17.5 mg) as a hygroscopic solid, in 43% yield.

5.7.1. [3*S*,4*R*,5*R*,6*S*]-1-Aminocycloheptane-3,4,5,6-tetrol (30a). Isolated yield: 60%; $[\alpha]_D$=+9 (*c* 1, H_2O); ^{1}H NMR (D_2O) δ 3.98–3.84 (m, 1H, H_6), 3.76–3.53 (m, 2H, $H_{3,1}$), 3.49–3.35 (m, 2H, $H_{4,5}$), 2.21 (ddd, 1H, $J_{2a,b}$=13.5 Hz, $J_{2a,1}$=5 Hz, $J_{2a,3}$=2.4 Hz, H_{2a}), 2.15–1.93 (m, 2H, $H_{7a,b}$), 1.73 (ddd, 1H, $J_{2b,a}$=13.5 Hz, $J_{2b,1}$=$J_{2b,3}$=11.2 Hz, H_{2b}); ^{13}C NMR (D_2O) 80.8, 80.1 ($C_{4,5}$), 72.0, 70.5 ($C_{3,6}$), 46.7 (C_1), 40.4, 39.4 ($C_{2,7}$); SM (CI, CH_4) 178 (M^++1); HRMS for $C_7H_{16}O_4N$ (M^++1) calcd 178.1079, found 178.1084.

5.7.2. [3*S*,4*R*,5*R*,6*S*]-1-*N*-(3,4,5,6-Tetrahydroxycycloheptanyl)-*N*-butylamine (30b). Isolated yield: 62%; $[\alpha]_D$=+1 (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 3.92 (ddd, 1H, $J_{3,2b}$=$J_{3,4}$=11.2 Hz, $J_{3,2a}$=3.8 Hz, H_3), 3.80–3.62 (m, 1H, H_6), 3.57–3.34 (m, 3H, $H_{1,4,5}$), 3.13 (t, 2H, $J_{1',2'}$=7.7 Hz, $H_{1'}$), 2.27 (ddd, 1H, $J_{2a,b}$=13.5 Hz, $J_{2a,3}$=3.8 Hz, $J_{2a,1}$=2.4 Hz, H_{2a}), 2.15–2.03 (m, 2H, $H_{7a,b}$), 1.78 (ddd, 1H, $J_{2b,a}$=13.5 Hz, $J_{2b,1}$=$J_{2b,3}$=11.2 Hz, H_{2b}), 1.71–1.56 (m, 2H, $H_{2'}$), 1.43 (qt, 2H, $J_{3',4'}$=$J_{3',2'}$=7.3 Hz, $H_{3'}$), 0.97 (t, 3H, $J_{4',3'}$=7.3 Hz, $H_{4'}$); ^{13}C NMR (D_2O) 82.4, 81.6 ($C_{4,5}$), 74.1, 72.5 ($C_{3,6}$), 55.6 (C_1), 48.5 ($C_{1'}$), 41.5, 40.2 ($C_{2,7}$), 34.3 ($C_{2'}$), 23.9 ($C_{3'}$), 16.7 ($C_{4'}$); SM (CI, CH_4) 234 (M^++1); HRMS for $C_{11}H_{24}O_4N$ (M^++1) calcd 234.1705; found 234.1709.

5.7.3. [3*S*,4*R*,5*R*,6S]-1-*N*-(1′,3′-Dihydroxy-2′-*N*-propyl)-3,4,5,6-tetrahydroxycycloheptylamine (30c). Overall yield from **26c**: 50%; $[\alpha]_D$=+5 (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 3.85–3.73 (m, 1H, H_6), 3.72–3.47 (m, 5H, $H_{3,1'a,b,3'a,b}$), 3.40–3.23 (m, 2H, $H_{4,5}$), 3.20–3.04 (m, 1H, H_1), 2.93–2.81 (m, 1H, $H_{2'}$), 2.06 (ddd, 1H, $J_{2a,b}$=13.6 Hz, $J_{2a,3}$=4.2 Hz, $J_{2a,1}$=2.4 Hz, H_{2a}), 1.92–1.77 (m, 2H, $H_{7a,b}$), 1.45 (dt, 1H, $J_{2b,a}$=13.6 Hz, $J_{2b,3}$=$J_{2b,1}$=11.2 Hz, H_{2b}); ^{13}C NMR (D_2O) δ 80.7, 80.2 ($C_{4,5}$), 72.6, 70.9 ($C_{3,6}$), 63.2, 62.8 ($C_{1',3'}$), 59.2 ($C_{2'}$), 49.6 (C_1), 40.7, 39.2 ($C_{2,7}$); SM (CI, CH_4) 252 (M^++1); HRMS for $C_{10}H_{22}NO_6$ (M^++1) calcd 252.1447; found 252.1445.

5.7.4. Methyl [3′*S*,4′*R*,5′*R*,6′*S*]-6-deoxy-(3′,4′,5′,6′-tetrahydroxycycloheptanyl)-6-amino-D-glucopyranoside (30d). Isolated yield: 43%; $[\alpha]_D$=+71 (*c* 0.7, H_2O); ^{1}H NMR (D_2O) δ 4.87 (d, 1H, $J_{1,2}$=3.6 Hz, H_1), 3.92–3.67 (m, 4H, $H_{3',6',5,3}$), 3.62 (dd, 1H, $J_{2,3}$=9.8 Hz, $J_{2,1}$=3.6 Hz, H_2), 3.49 (s, 3H, OMe), 3.45–3.20 (m, 4H, $H_{4,5',4',1'}$), 3.21 (dd, 1H, $J_{6a,6b}$=12.7 Hz, $J_{6a,5}$=2.2 Hz, H_{6a}), 2.94 (dd, 1H, $J_{6b,a}$=12.7 Hz, $J_{6b,5}$=9.1 Hz, H_{6b}), 2.19 (ddd, 1H, $J_{2'a,b}$=13.6 Hz, $J_{2'a,3'}$=4.6 Hz, $J_{2'a,1'}$=2.5 Hz, $H_{2'a}$), 2.08–1.93 (m, 2H, $H_{7'a,b}$), 1.65 (ddd, 1H, $J_{2'b,a}$=13.6 Hz, $J_{2'b,3'}$=$J_{2'b,1'}$=11.0 Hz, $H_{2'b}$); ^{13}C NMR (D_2O) δ 102.2 (C_1), 80.8, 80.1 ($C_{4',5'}$), 75.7, 74.7, 74.0 ($C_{2,3,4}$), 72.5, 71.8, 70.8 ($C_{3',6',5}$), 58.2 (OMe), 52.7 ($C_{1'}$), 49.5 (C_6), 39.0, 38.0 ($C_{2',7'}$); SM (CI, CH_4) 354 (M^++1); HRMS for $C_{14}H_{28}NO_9$ (M^++1) calcd 354.1764; found 354.1768.

5.7.5. [3*R*,4*R*,5*R*,6*R*]-1-Aminocycloheptane-3,4,5,6-tetrol (31a). Isolated yield: 85%; $[\alpha]_D$=−2 (*c* 0.93, H_2O); ^{1}H NMR (D_2O) δ 4.31–4.21 (m, 1H, H_3), 4.19–4.08 (m, 1H, H_6), 3.96–3.86 (m, 2H, $H_{4,5}$), 2.38 (ddd, 1H, $J_{2a,b}$=14.5 Hz, $J_{2a,3}$=8.8 Hz, $J_{2a,1}$=6.3 Hz, H_{2a}), 2.20–1.92 (m, 2H, $H_{7a,b}$), 1.81 (ddd, 1H, $J_{2b,a}$=14.5 Hz, $J_{2b,1}$=7.8, $J_{2b,3}$=2.5 Hz, H_{2b}); ^{13}C NMR (D_2O) δ 77.6, 76.3 ($C_{4,5}$); 70.4, 69.8 ($C_{3,6}$); 47.8 (C_1); 36.7, 36.1 ($C_{2,7}$); SM (CI, CH_4) 178 (M^++1); HRMS for $C_7H_{16}O_4N$ (M^++1) calcd 178.1079; found 178.1080.

5.7.6. [3*R*,4*R*,5*R*,6*R*]-1-*N*-(3,4,5,6-Tetrahydroxycycloheptanyl)-*N*-butylamine (31b). Isolated yield: 50%; $[\alpha]_D$=−2 (*c* 0.9, H_2O); ^{1}H NMR (D_2O) δ 4.34–4.25 (m, 1H, H_3), 4.17–4.09 (m, 1H, H_6), 3.92 (s, 2H, $H_{4,5}$), 3.71–3.55 (m, 1H, H_1), 3.13 (t, 2H, $J_{1',2'}$=7.7 Hz, $H_{1'}$), 2.44 (ddd, 1H, $J_{2a,b}$=15 Hz, $J_{2a,3}$=9.2 Hz, $J_{2a,1}$=6.7 Hz, H_{2a}), 2.33–2.00 (m, 2H, $H_{7a,b}$), 1.89 (ddd, 1H, $J_{2b,a}$=15 Hz, $J_{2b,1}$=7.6 Hz, $J_{2b,3}$=3.8 Hz, H_{2b}), 1.80–1.62 (m, 2H, $H_{2'}$), 1.68 (qt, 2H, $J_{3',4'}$=$J_{3',2'}$=7.3 Hz, $H_{3'}$), 0.99 (t, 3H, $J_{4',3'}$=7.3 Hz, $H_{4'}$); ^{13}C NMR (D_2O) δ 77.9, 76.3 ($C_{4,5}$), 70.8, 69.9 ($C_{3,6}$), 54.8 (C_1), 48.0 ($C_{1'}$), 35.0, 34.5 ($C_{2,7}$), 31.0 ($C_{2'}$), 22.2 ($C_{3'}$), 15.6 ($C_{4'}$); SM (CI, CH_4) 234 (M^++1); HRMS for $C_{11}H_{24}O_4N$ (M^++1) calcd 234.1705; found 234.1704.

5.7.7. [3*R*,4*R*,5*R*,6*R*]-1-*N*-(1′,3′-Dihydroxy-2′-*N*-propyl)-3,4,5,6-tetrahydroxycycloheptylamine (31c). Overall yield from **27c**: 75%; $[\alpha]_D$=−5 (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 4.25 (dd, 1H, $J_{3,2a}$=8.8 Hz, $J_{3,2b}$=2.8 Hz, H_3), 4.18–4.06 (m, 1H, H_6), 3.92 (d, 2H, $J_{4,5}$=7.6 Hz, $H_{4,5}$), 3.80

(dd, 2H, $J_{1'a,b}=J_{3'a,b}=11.9$ Hz, $J_{1'a,2'}=J_{3'a,2'}=5.2$ Hz, $H_{1'a,3'a}$), 3.71 (dd, 2H, $J_{1'b,a}=J_{3'b,a}=11.9$ Hz, $J_{1'b,2'}=J_{3'b,2'}=5.4$ Hz, $H_{1'b,3'b}$), 3.44 (dddd, 1H, $J_{1,2a}=J_{1,7b}=7.8$ Hz, $J_{1,2a}=J_{1,7b}=5.8$ Hz, H_1), 3.24–3.09 (m, 1H, $H_{2'}$), 2.30 (ddd, 1H, $J_{2a,2b}=14.5$ Hz, $J_{2a,3}=8.8$ Hz, $J_{2a,1}=5.8$ Hz, H_{2a}), 2.06–1.91 (m, 2H, $H_{7a,b}$), 1.75 (ddd, 1H, $J_{2b,a}=14.5$ Hz, $J_{2b,1}=7.8$ Hz, $J_{2b,3}=2.8$ Hz, H_{2b}); ^{13}C NMR (D_2O) δ 78.3, 76.4 ($C_{4,5}$), 71.0, 70.2 ($C_{3,6}$), 62.6, 62.4 ($C_{1',3'}$), 59.9 ($C_{2'}$), 51.6 (C_1), 37.1, 36.5 ($C_{2,7}$); SM (CI, CH_4) 252 (M^++1); HRMS for $C_{10}H_{22}NO_6$ (M^++1) calcd 252.1447; found 252.1449.

5.8. Reductive amination in C6 series

The reductive amination was performed according to the procedure described above in C7 series.

5.8.1. (1*R*,3*S*,4*S*,5*R*,6*S*)-3-*O*-*tert*-Butyldimethylsilyl-6-*tert*-butyldimethylsilyloxymethyl-4,5-*O*-methylethylidene-1-*N*-(3,4,5-trihydroxycyclohexanyl)-*N*-benzylamine (32a). Isolated yield: 54%; R_f 0.22 (cyclohexane/EtOAc 95:5); $[\alpha]_{Hg}=-17$ (*c* 1.1, CH_2Cl_2); ^{1}H NMR δ 7.40–7.20 (m, 5H, H_{ar}), 3.98 (dd, 1H, $J_{7a,b}=10.2$ Hz, $J_{7a,6}=2.4$ Hz, H_{7a}), 3.88, 3.69 (AB, 2H, $J_{AB}=13$ Hz, NCH_2Ph), 3.75–3.59 (m, 2H, $H_{3,7b}$), 3.34 (dd, 1H, $J_{4,3}=J_{4,5}=9.0$ Hz, H_4), 3.21 (dd, 1H, $J_{5,6}=10.6$ Hz, $J_{5,4}=9.0$ Hz, H_5), 2.74 (ddd, 1H, $J_{1,6}=11.8$ Hz, $J_{1,2b}=10$ Hz, $J_{1,2a}=4.5$ Hz, H_1), 2.24 (ddd, 1H, $J_{2a,b}=13$ Hz, $J_{2a,3}=J_{2a,1}=4.5$ Hz, H_{2a}), 1.66–1.52 (m, 1H, H_6), 1.38, 1.33 (2s, 6H, CMe_2), 1.31–1.22 (m, 1H, H_{2b}), 0.88, 0.87 (2s, 18H, *t*Bu), 0.08, 0.07, 0.03, 0.02 (4s, 12H, $SiMe_2$); ^{13}C NMR δ 140.7, 128.4, 128.1, 126.9 (C_{ar}), 110.0 (CMe_2), 84.1 (C_4), 75.3 (C_5), 69.5 (C_3), 60.5 (C_7), 54.0 (C_1), 51.8 (NCH_2Ph), 46.6 (C_6), 40.5 (C_2), 26.9 (CMe_2), 25.8, 18.2 (*t*Bu), −4.5, −4.8, −5.5 ($SiMe_2$); SM (CI, CH_4) 536 (M^++1); HRMS for $C_{29}H_{54}NO_4Si_2$ (M^++1) calcd 536.3591; found 536.3597.

5.8.2. (1*R*,3*S*,4*S*,5*R*,6*S*)-3-*O*-*tert*-Butyldimethylsilyl-6-*tert*-butyldimethylsilyloxymethyl-4,5-*O*-methylethylidene-1-*N*-(3,4,5-trihydroxycyclohexanyl)-*N*-(1′,3′-di-*tert*-butyldimethylsilyloxy)-2″-propylamine (32b). Isolated yield: 28%; R_f 0.4 (cyclohexane/EtOAc 97:3); $[\alpha]_D=-9$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 3.95 (dd, 1H, $J_{7a,b}=9.9$ Hz, $J_{7a,6}=1.8$ Hz, H_{7a}), 3.75–3.60 (m, 3H, $H_{3,7b,3'a}$), 3.56 (dd, 1H, $J_{1'a,b}=10$ Hz, $J_{1'a,2'}=4.8$ Hz, $H_{1'a}$), 3.44 (dd, 1H, $J_{1'a,b}=10$ Hz, $J_{1'b,2'}=6.1$ Hz, $H_{1'b}$), 3.39–3.25 (m, 2H, $H_{4,5}$), 2.80–2.63 (m, 2H, $H_{1,2'}$), 2.29–2.17 (m, 1H, H_{2a}), 1.42–1.30 (m, 1H, H_6), 1.37, 1.33 (2s, 6H, CMe_2), 1.26–1.20 (m, 1H, H_{2b}), 0.87 (s, 36H, *t*Bu), 0.08, 0.03, 0.02 (3s, 24H, $SiMe_2$); ^{13}C NMR δ 109.9 (CMe_2), 84.1 (C_4), 74.9 (C_5), 69.5 (C_3), 63.2 ($C_{1',3'}$), 59.6 ($C_{2'}$), 58.2 (C_7), 50.6 (C_6), 47.9 (C_1), 42.0 (C_2), 27.1 (CMe_2), 25.8, 18.2 (*t*Bu), −4.5, −4.9, −5.4 ($SiMe_2$). Anal. calcd for $C_{37}H_{81}NO_6Si_4$: C, 59.38; H, 10.91; N, 1.87; found: C, 59.24; H, 10.84; N, 1.95.

5.8.3. Methyl [1′*R*,3′*S*,4′*S*,5′*R*,6′*S*]-6-Deoxy-6-[3′-*tert*-butyldimethylsilyloxy-6′-*tert*-butyldimethylsilyloxymethyl-4′,5′-*O*-methylethylidene-1′-*N*-(3′,4′,5′-trihydroxycyclohexanyl)]-amino-2,3,4-tri-*O*-benzyl-D-glucopyranoside (32c). Isolated yield: 46%; R_f 0.16 (cyclohexane/EtOAc 85:15); $[\alpha]_D=+27$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.40–7.12 (m, 15H, H_{ar}), 5.01–4.55 (m, 6H, OCH_2Ph), 4.50 (d, 1H, $J_{1,2}=3.5$ Hz, H_1), 3.95 (dd, 1H, $J_{3,2}=J_{3,4}=9.2$ Hz, H_3), 3.87 (dd, 1H, $J_{7'a,b}=10$ Hz, $J_{7'a,6'}=2$ Hz, $H_{7'a}$), 3.78–3.62 (m, 3H, $H_{5,7'b,3'}$), 3.51 (dd, 1H, $J_{4,3}=J_{4,5}=9.2$ Hz, H_4), 3.45 (dd, 1H, $J_{2,3}=9.6$ Hz, $J_{2,1}=3.5$ Hz, H_2), 3.34 (s, 3H, OMe), 3.31–3.28 (m, 2H, $H_{4',5'}$), 2.93 (dd, 1H, $J_{6a,b}=11.7$ Hz, $J_{6a,5}=2.9$ Hz, H_{6a}), 2.74–2.58 (m, 1H, $H_{1'}$), 2.61 (dd, 1H, $J_{6a,b}=11.7$ Hz, $J_{6b,5}=5.7$ Hz, H_{6b}), 2.13 (ddd, 1H, $J_{2'a,b}=12.8$ Hz, $J_{2'a,3'}=J_{2'a,1'}=4.4$ Hz, $H_{2'a}$), 1.55–1.44 (m, 1H, $H_{6'}$), 1.36, 1.32 (2s, 6H, CMe_2), 1.28–0.93 (m, 1H, $H_{2'b}$), 0.87, 0.80 (2s, 18H, *t*Bu), 0.07, 0.05, −0.01, −0.06 (4s, 12H, $SiMe_2$); ^{13}C NMR δ 138.9, 138.3, 128.4, 128.1, 128.0, 127.7, 127.6 (C_{ar}),109.9 (CMe_2), 97.9 (C_1), 84.1, 80.1, 79.1 ($C_{2,3,4,4'}$), 75.7, 75.1, 73.4 (OCH_2Ph), 75.1 ($C_{5'}$), 70.3, 69.5 ($C_{3',5}$), 59.1 ($C_{7'}$), 55.2 (OMe), 53.0 ($C_{6'}$), 47.1 (C_6), 46.1 ($C_{1'}$), 40.5 ($C_{2'}$), 27.0 (CMe_2), 25.9, 18.3 (*t*Bu), −4.4, −4.8, −5.6 ($SiMe_2$).

5.8.4. (1*S*,3*S*,4*S*,5*R*,6*S*)-3-*O*-*tert*-Butyldimethylsilyl-6-*tert*-butyldimethylsilyloxymethyl-4,5-*O*-methylethylidene-1-*N*-(3,4,5-trihydroxycyclohexanyl)-*N*-benzylamine (33a). Isolated yield: 20%; R_f 0.6 (cyclohexane/EtOAc 95:5); $[\alpha]_D=+33$ (*c* 1.3, CH_2Cl_2); ^{1}H NMR δ 7.40–7.20 (m, 5H, H_{ar}), 4.10 (ddd, 1H, $J_{3,2b}=10.1$ Hz, $J_{3,4}=9.1$ Hz, $J_{3,2a}=4.4$ Hz, H_3), 3.84, 3.61 (AB, 2H, $J_{AB}=15.2$ Hz, NCH_2Ph), 3.75–3.59 (m, 2H, $H_{7a,b}$), 3.74 (dd, 1H, $J_{5,6}=11.5$ Hz, $J_{5,4}=9.1$ Hz, H_5), 3.29 (dd, 1H, $J_{4,3}=J_{4,5}=9.1$ Hz, H_4), 3.24–3.15 (m, 1H, H_1), 2.14 (ddd, 1H, $J_{2a,b}=14.0$ Hz, $J_{2a,3}=4.4$ Hz, $J_{2a,1}=2.7$ Hz, H_{2a}), 1.81 (dddd, 1H, $J_{6,5}=11.5$ Hz, $J_{6,7b}=8.2$ Hz, $J_{6,7a}=6.6$ Hz, $J_{6,1}=4.4$ Hz, H_6), 1.37, 1.34 (2s, 6H, CMe_2), 1.31–1.22 (m, 1H, H_{2b}), 0.91, 0.84 (2s, 18H, *t*Bu), 0.1, 0.02 (2s, 12H, $SiMe_2$); ^{13}C NMR δ 140.7, 128.3, 128.2, 126.8 (C_{ar}), 110.0 (CMe_2), 85.2 (C_4), 74.3 (C_5), 68.8 (C_3), 61.8 (C_7), 55.2 (C_1), 52.3 (NCH_2Ph), 45.6 (C_6), 37.6 (C_2), 26.9 (CMe_2), 25.9, 18.1 (*t*Bu), −4.5, −4.7, −5.5, −5.6 ($SiMe_2$); SM (CI, CH_4) 536 (M^++1); HRMS for $C_{29}H_{54}NO_4Si_2$ (M^++1) calcd 536.3591; found 536.3587.

5.8.5. (1*S*,3*S*,4*S*,5*R*,6*S*)-3-*O*-*tert*-Butyldimethylsilyl-6-*tert*-butyldimethylsilyloxymethyl-4,5-*O*-methylethylidene-1-*N*-(3,4,5-trihydroxycyclohexanyl)-*N*-(1′,3′-di-*tert*-butyldimethylsilyloxy)-2′-propylamine (33b). Isolated yield: 28%; R_f 0.62 (cyclohexane/EtOAc 95:5); $[\alpha]_D=-13$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 3.95 (ddd, 1H, $J_{3,2b}=10.2$ Hz, $J_{3,4}=9.0$ Hz, $J_{3,2a}=4.4$ Hz, H_3), 3.75 (dd, 1H, $J_{7a,b}=14.2$ Hz, $J_{7a,6}=5.5$ Hz, H_{7a}), 3.74 (dd, 1H, $J_{7b,a}=14.2$ Hz, $J_{7b,6}=10.2$ Hz, H_{7b}), 3.62–3.42 (m, 5H, $H_{1',3',5}$); 3.32–3.25 (m, 1H, H_1), 3.20 (dd, 1H, $J_{4,3}=J_{4,5}=9.0$ Hz, H_4), 2.76–2.64 (m, 1H, $H_{2'}$), 1.98 (ddd, 1H, $J_{2a,b}=14.2$ Hz, $J_{2a,3}=4.4$ Hz, $J_{2a,1}=2.6$ Hz, H_{2a}), 1.83–1.60 (m, 2H, $H_{6,2b}$), 1.36, 1.34 (2s, 6H, CMe_2), 0.88, 0.87 (2s, 36H, *t*Bu), 0.08, 0.07, 0.03, 0.02 (4s, 24H, $SiMe_2$); ^{13}C NMR δ 109.2 (CMe_2), 85.1 (C_4), 74.8 (C_5), 69.0 (C_3), 62.2, 61.9 ($C_{1',3'}$), 60.8 (C_7), 58.7 ($C_{2'}$), 51.3 (C_6), 46.9 (C_1), 39.8 (C_2), 26.9 (CMe_2), 25.9, 18.2, 18.1 (*t*Bu), −4.4, −4.8 ($SiMe_2$). Anal. calcd for $C_{37}H_{81}NO_6Si_4$: C, 59.38; H, 10.91; N, 1.87; found: C, 59.42; H, 10.74; N, 1.71.

5.8.6. Methyl [1′*S*,3′*S*,4′*S*,5′R,6′*S*]-6-Deoxy-6-[3′-*tert*-butyldimethylsilyloxy-6′-*tert*-butyldimethylsilyloxymethyl-4′,5′-*O*-methylethylidene-1′-*N*-(3′,4′,5′-trihydroxycyclohexanyl)]-amino-2,3,4-tri-*O*-benzyl-D-glucopyranoside (33c). Isolated yield: 13%; R_f 0.46 (cyclohexane/EtOAc 85:15); $[\alpha]_D=+51$ (*c* 1.0, CH_2Cl_2);

^{1}H NMR δ 7.36–7.23 (m, 15H, H_{ar}), 4.84 (AB, 2H, J_{AB}=10.7 Hz, OCH_2Ph), 4.76 (AB, 2H, J_{AB}=10.9 Hz, OCH_2Ph), 4.71 (AB, 2H, J_{AB}=12.2 Hz, OCH_2Ph), 4.50 (d, 1H, $J_{1,2}$=3.5 Hz, H_1), 4.02–3.89 (m, 2H, $H_{3,3'}$), 3.85–3.65 (m, 3H, $H_{5,7'a,b}$), 3.59 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9.3 Hz, H_4), 3.58 (dd, 1H, $J_{5',6'}$=11.3 Hz, $J_{5',4'}$=9.0 Hz, $H_{5'}$), 3.45 (dd, 1H, $J_{2,3}$=9.6 Hz, $J_{2,1}$=3.5 Hz, H_2), 3.34 (s, 3H, OMe), 3.22 (dd, 1H, $J_{4',3'}$=$J_{4',5'}$=9.0 Hz, $H_{4'}$), 3.15–3.07 (m, 1H, $H_{1'}$), 2.90 (dd, 1H, $J_{6a,b}$=11.9 Hz, $J_{6a,5}$=4.7 Hz, H_{6a}), 2.73 (dd, 1H, $J_{6a,b}$=11.9 Hz, $J_{6b,5}$=2.6 Hz, H_{6b}), 2.10 (ddd, 1H, $J_{2'a,b}$=14.2 Hz, $J_{2'a,3'}$=4.8 Hz, $J_{2'a,1'}$=3.0 Hz, $H_{2'a}$), 1.92–1.79 (m, 1H, $H_{6'}$), 1.35 (s, 6H, CMe_2), 1.30–1.20 (m, 1H, $H_{2'b}$), 0.84, 0.77 (2s, 18H, *t*Bu), 0.00, −0.02, −0.03 (3s, 12H, $SiMe_2$); ^{13}C NMR δ 138.8, 138.4, 128.4, 128.1, 127.9, 127.7 (C_{ar}), 109.2 (CMe_2), 97.9 (C_1), 85.3, 82.2, 80.1, 78.6 ($C_{2,3,4,4'}$), 75.9, 74.9, 73.4 (OCH_2Ph), 74.5 ($C_{5'}$), 69.5, 69.0 ($C_{3',5}$), 61.7 ($C_{7'}$), 55.1 (OMe), 55.0 ($C_{6'}$), 48.4 (C_6), 45.9 ($C_{1'}$), 37.6 ($C_{2'}$), 27.0 (CMe_2), 25.8, 18.2 (*t*Bu), −4.3, −4.8, −5.5, −5.6 ($SiMe_2$). Anal. calcd for $C_{50}H_{77}NO_9Si_2$: C, 67.30; H, 8.70; N, 1.57; found: C, 67.31; H, 8.83; N, 1.52.

5.9. Deprotection of the aminocyclohexanols

5.9.1. (1*R*,3*S*,4*S*,5*R*,6*S*)-3-*O*-*tert*-Butyldimethylsilyl-6-*tert*-butyldimethylsilyloxymethyl-4,5-*O*-methylethylidene-3,4,5-trihydroxy-1-cyclohexylamine (32d). To a suspension of palladium hydroxide (58 mg) in absolute ethanol (2 mL) saturated with dihydrogen was added a solution of the *N*-benzylamine **32a** (144 mg, 0.269 mmol) in EtOAc (0.7 mL). After stirring for 14 h, the catalyst was removed by filtration through a Celite pad and the filtrate was concentrated in vacuo. Flash chromatographic purification (CH_2Cl_2/MeOH 98:2) led to amine **32d** (71.9 mg) as an oil in 60% yield. R_f 0.3 (CH_2Cl_2/MeOH 98:2); $[\alpha]_D$=+24 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 3.91 (dd, 1H, $J_{7a,b}$=10.4 Hz, $J_{7a,6}$=2.6 Hz, H_{7a}), 3.74 (dd, 1H, $J_{7b,a}$=10.4 Hz, $J_{7b,6}$=4.1 Hz, H_{7b}), 3.89–3.75 (m, 1H, H_3), 3.34 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9.1 Hz, H_4), 3.21 (dd, 1H, $J_{5,6}$=10.6 Hz, $J_{5,4}$=9.1 Hz, H_5), 2.89 (ddd, 1H, $J_{1,6}$=12 Hz, $J_{1,2b}$=9.6 Hz, $J_{1,2a}$=4.5 Hz, H_1), 2.07 (ddd, 1H, $J_{2a,b}$=13.1 Hz, $J_{2a,3}$=$J_{2a,1}$=4.5 Hz, H_{2a}), 1.63–1.20 (m, 1H, $H_{6,2b}$), 1.38, 1.36 (2s, 6H, CMe_2), 0.88, 0.87 (2s, 36H, *t*Bu), 0.08, 0.07, 0.06, 0.05 (4s, 24H, $SiMe_2$); ^{13}C NMR δ 110.2 (CMe_2), 84.2 (C_4), 75.2 (C_5), 69.4 (C_3), 60.2 (C_7), 48.9, 48.1 ($C_{1,6}$), 43.9 (C_2), 27.0, 26.9 (CMe_2), 25.8, 18.2 (*t*Bu), −4.5, −4.9, −5.5, −5.6 ($SiMe_2$); SM (CI, CH_4) 446 (M^++1); HRMS for $C_{22}H_{48}NO_4Si_2$ (M^++1) calcd 446.3122; found 446.3128.

5.9.2. (1*R*,3*S*,4*R*,5*R*,6*R*)-1-Amino-6-hydroxymethylcyclohexane-3,4,5-triol (34a). The acetonide **32d** (69.3 mg, 0.16 mmol) was stirred in a 9:1 solution of trifluoroacetic acid/H_2O at 20°C for 15 h. After concentrating in vacuo, the resulting oil was triturated in diethyl ether and the supernatant was discarded to afford a brownish solid which was then purified by ion-exchange chromatography (Dowex® 5 X8-100, 3% aqueous ammonium hydroxide) to give the aminocyclitol **34a** (25 mg) as a solid in 90% yield. $[\alpha]_D$=+11 (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 4.01–3.86 (m, 2H, $H_{7a,b}$), 3.58 (ddd, 1H, $J_{3,2b}$=11.4 Hz, $J_{3,4}$=9.0 Hz, $J_{3,2a}$=3.7 Hz, H_3), 3.46–3.26 (m, 2H, $H_{4,5}$), 2.93 (ddd, 1H, $J_{1,6}$=$J_{1,2b}$=11.4 Hz, $J_{1,2a}$=3.7 Hz, H_1), 2.20 (ddd, 1H, $J_{2a,b}$=12.1 Hz, $J_{2a,3}$=$J_{2a,1}$=3.7 Hz, H_{2a}), 1.57–1.26 (m, 1H, H_6), 1.39 (ddd, 1H, $J_{2b,a}$=12.1 Hz, $J_{2b,3}$=$J_{2b,1}$=11.4 Hz, H_{2b}); ^{13}C NMR (D_2O) δ 81.8 (C_4), 73.3 (C_5), 72.3 (C_3), 61.0 (C_7), 52.6 (C_1), 47.7 (C_6), 42.3 (C_2); SM (CI, NH_3) 178 (M^++1); HRMS for $C_7H_{16}NO_4$ (M^++1) calcd 178.1079; found 178.1075.

5.9.3. (1*R*,3*S*,4*R*,5*R*,6*R*)-1-(1′,3′-Dihydroxy-2′-propylamine)-6-hydroxymethylcyclohexane-3,4,5-triol (34b). The protected aminocyclitol **32b** (97 mg, 0.13 mmol) was reacted under the same conditions as above to afford the aminocyclitol **34b** (28 mg) as a brownish solid in 86% yield. $[\alpha]_D$=−23 (*c* 1.4, H_2O); ^{1}H NMR (D_2O) δ 4.05 (dd, 1H, $J_{7a,b}$=11.4 Hz, $J_{7a,6}$=2.9 Hz, H_{7a}), 3.84 (dd, 1H, $J_{7b,a}$=11.4 Hz, $J_{7b,6}$=6.4 Hz, H_{7b}), 3.79–3.59 (m, 4H, $H_{1'a,b,3'a,b}$), 3.52 (ddd, 1H, $J_{3,2b}$=11.5 Hz, $J_{3,4}$=8.8 Hz, $J_{3,2a}$=3.7 Hz, H_3), 3.41–3.22 (m, 2H, $H_{4,5}$); 3.07–2.94 (m, 1H, $H_{2'}$), 2.92 (ddd, 1H, $J_{1,6}$=$J_{1,2b}$=11.4 Hz, $J_{1,2a}$=3.7 Hz, H_1), 2.39 (ddd, 1H, $J_{2a,b}$=12.3 Hz, $J_{2a,3}$=$J_{2a,1}$=3.7 Hz, H_{2a}), 1.71–1.53 (m, 1H, H_6), 1.48 (ddd, 1H, $J_{2b,a}$=12.3 Hz, $J_{2b,3}$=$J_{2b,1}$=11.4 Hz, H_{2b}); ^{13}C NMR (D_2O) δ 81.6 (C_4), 73.6 (C_5), 72.3 (C_3), 64.5, 63.7, 63.3 ($C_{7,1',3'}$), 60.2 ($C_{2'}$), 54.8 (C_1), 51.0 (C_6), 40.2 (C_2); SM (CI, CH_4) 252 (M^++1); HRMS for $C_{10}H_{22}NO_6$ (M^++1) calcd 252.1447; found 252.1443.

5.9.4. (1*S*,3*S*,4*R*,5*R*,6*R*)-1-(1′,3′-Dihydroxy-2′-propylamine)-6-hydroxymethylcyclohexane-3,4,5-triol (35b). The protected aminocyclitol **33b** (99 mg, 0.132 mmol) was reacted under the same conditions as above to afford the aminocyclitol **35b** (32.2 mg) as a brownish solid in 98% yield. $[\alpha]_D$=+58 (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 3.90 (dd, 1H, $J_{7a,b}$=11.4 Hz, $J_{7a,6}$=3.7 Hz, H_{7a}), 3.86 (dd, 1H, $J_{7b,a}$=11.4 Hz, $J_{7b,6}$=5.9 Hz, H_{7b}), 3.76 (dd, 1H, $J_{3,2b}$=13.2 Hz, $J_{3,4}$=9.4 Hz, $J_{3,2a}$=3.7 Hz, H_3), 3.68 (dd, 1H, $J_{1'a,b}$=11.4 Hz, $J_{1'a,2'}$=5.0 Hz, $H_{1'a}$), 3.63 (dd, 1H, $J_{5,6}$=11.4 Hz, $J_{5,4}$=9.4 Hz, H_5), 3.62 (dd, 1H, $J_{3'b,a}$=11.5 Hz, $J_{3'b,2'}$=5.5 Hz, $H_{3'b}$), 3.57 (dd, 1H, $J_{3'a,b}$=11.5 Hz, $J_{3'a,2'}$=4.9 Hz, $H_{3'a}$), 3.50 (dd, 1H, $J_{1'b,a}$=11.4 Hz, $J_{1'b,2'}$=6.9 Hz, $H_{1'b}$), 3.32–3.27 (m, 1H, H_1), 3.28 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9.4 Hz, H_4); 2.88–2.78 (m, 1H, $H_{2'}$), 2.16 (ddd, 1H, $J_{2a,b}$=13.2 Hz, $J_{2a,3}$=$J_{2a,1}$=3.7 Hz, H_{2a}), 1.71 (dddd, 1H, $J_{6,5}$=11.4 Hz, $J_{6,7b}$=5.9 Hz, $J_{6,7a}$=$J_{6,1}$=3.7 Hz, H_6), 1.48 (ddd, 1H, $J_{2b,a}$=$J_{2b,3}$=13.2 Hz, $J_{2b,1}$=3.4 Hz, H_{2b}); ^{13}C NMR (D_2O) δ 82.3 (C_4), 72.3 (C_5), 71.3 (C_3), 64.2, 63.4 ($C_{7,1',3'}$), 61.4 ($C_{2'}$), 55.3 (C_1), 48.6 (C_6), 37.5 (C_2); SM (CI, CH_4) 252 (M^++1); HRMS for $C_{10}H_{22}NO_6$ (M^++1) calcd 252.1447; found 252.1446.

5.9.5. Methyl [1′*R*,3′*S*,4′*R*,5′*R*,6′*R*]-6-Deoxy-6-[6′-hydroxymethyl-1′-*N*-(3′,4′,5′-trihydroxycyclohexanyl)]-amino-2,3,4-tri-*O*-benzyl-D-glucopyranoside (34c). To a cooled solution of the silylated diol **32c** (90 mg, 99 μmol) in THF (2.7 mL) at 0°C were successively added H_2O (0.9 mL) and trifluoroacetic acid (0.9 mL). After stirring for 40 h at 20°C, CH_2Cl_2 (3 mL) and a saturated $NaHCO_3$ aqueous solution (0.9 mL) were added, then the pH was adjusted to 7 by addition of K_2CO_3. The mixture was extracted with CH_2Cl_2, and the organic layers were dried ($MgSO_4$) and concentrated in vacuo. After flash chromatography (CH_2Cl_2/MeOH 85:15), the compound **34c** was obtained in quantitative yield as an yellow oil. R_f 0.44 (CH_2Cl_2/MeOH 8:2); $[\alpha]_D$=+28 (*c* 1.1, CH_2Cl_2); ^{1}H NMR δ 7.30–7.20 (m, 15H, H_{ar}), 5.00–4.56 (m, 7H, OCH_2Ph, H_1), 4.08–3.83 (m, 2H, $H_{3,7'a}$), 3.72–3.52 (m, 3H, $H_{5,7'b,3'}$), 3.50–3.40 (m, 2H, $H_{4,2}$), 3.29 (s, 3H, OMe), 3.17–2.95 (m,

3H, $H_{4',5',6a}$), 2.47–2.29 (m, 2H, $H_{6b,1'}$), 2.24–2.11 (m, 1H, $H_{2'a}$), 1.72–1.51 (m, 1H, $H_{6'}$), 1.37–1.15 (m, 1H, $H_{2'b}$); ^{13}C NMR δ 129.9, 128.6, 128.5, 128.4, 128.2, 128.0, 127.7 (C_{ar}), 98.0 (C_1), 81.8, 80.0, 79.3, 78.9 ($C_{2,3,4,4'}$), 76.0, 75.1, 74.3 (OCH_2Ph), 71.8 ($C_{5'}$), 69.2, 69.0 ($C_{3',5}$), 64.3 ($C_{7'}$), 57.7 ($C_{6'}$), 55.5 (OMe), 47.6 ($C_{1'}$), 47.2 (C_6), 37.0 ($C_{2'}$); SM (CI, CH_4) 624 (M^++1); HRMS for $C_{35}H_{46}NO_9$ (M^++1) calcd 624.3173; found 624.3170.

5.9.6. Methyl [1′*R*,3′*S*,4′*R*,5′*R*,6′*R*]-6-Deoxy-6-[6′-hydroxymethyl-1′-*N*-(3′,4′,5′-trihydroxycyclohexanyl)]-amino-D-glucopyranoside (34d). To a suspension of palladium black (37.3 mg) in acetic acid (1 mL) saturated with dihydrogen was added a solution of the benzylated derivative **34c** (74.1 mg, 90 μmol) in acetic acid (2 mL). After stirring for 14 h, the catalyst was removed by filtration through a Celite pad and the filtrate was concentrated in vacuo. Purification by ion-exchange chromatography (Dowex® 5X8-100, 3% aqueous ammonium hydroxide) gave the aminocyclitol **34d** (29.3 mg) as an ocher solid in 70 % yield. $[\alpha]_D$=+15 (*c* 1.1, H_2O); ^1H NMR (D_2O) δ 4.87 (d, 1H, $J_{1,2}$=3.4 Hz, H_1), 4.12 (dd, 1H, $J_{7'a,b}$=11.4 Hz, $J_{7'a,6'}$= 3 Hz, $H_{7'a}$), 3.82 (dd, 1H, $J_{7'b,a}$=11.4 Hz, $J_{7'b,6'}$=7.9 Hz, $H_{7'b}$), 3.79–3.66 (m, 2H, $H_{3,5}$), 3.63 (dd, 1H, $J_{2,3}$=9.7 Hz, $J_{2,1}$=3.4 Hz, H_2), 3.58–3.48 (m, 1H, $H_{3'}$), 3.45 (s, 3H, OMe), 3.37 (dd, 1H, $J_{6a,b}$=11.5 Hz, $J_{6a,5}$=4.1 Hz, H_{6a}), 3.36 (dd, 1H, $J_{4',3'}$=$J_{4',5'}$=9.1 Hz, $H_{4'}$), 3.35 (dd, 1H, $J_{4,3}$= $J_{4,5}$=9.3 Hz, H_4), 3.25 (dd, 1H, $J_{5',6}$=10.1 Hz, $J_{5',4'}$=9.1 Hz, $H_{5'}$), 3.04–2.87 (m, 1H, $H_{1'}$), 2.78 (dd, 1H, $J_{6a,b}$=$J_{6b,5}$=11.7 Hz, H_{6b}), 2.13 (ddd, 1H, $J_{2'a,b}$=12.8 Hz, $J_{2'a,3'}$=$J_{2'a,1'}$=4.2 Hz, $H_{2'a}$), 1.84–1.60 (m, 1H, $H_{6'}$), 1.45 (ddd, 1H, $J_{2'a,b}$=12.8 Hz, $J_{2'b,3'}$=$J_{2'b,1'}$=10.9 Hz, $H_{2'b}$); ^{13}C NMR (D_2O) δ 98.0 (C_1), 81.8, 80.0, 79.3, 78.9 ($C_{2,3,4,4'}$), 71.8 ($C_{5'}$), 69.2, 69.0 ($C_{3',5}$), 64.3 ($C_{7'}$), 57.7 ($C_{6'}$), 55.5 (OMe), 47.6 ($C_{1'}$), 47.2 (C_6), 37.0 ($C_{2'}$); SM (CI, NH_3) 354 (M^++1); HRMS for $C_{14}H_{28}NO_9$ (M^++1) calcd 354.1754; found 354.1769.

5.10. Inhibition studies[32]

α-D-Glucosidase from *Bacillus stearothermophilus* (EC 3.2.1.20), β-D-glucosidase from almonds (EC 3.2.1.21), α-D-*manno*sidase from Jack beans (EC 3.2.1.24), α-L-fucosidase from bovine kidney (EC 3.2.1.51), α-D-galactosidase from green coffee bean (EC 3.2.1.22), and pancreatic porcine α-amylase (EC 3.2.1.1) and all substrates were purchased from Sigma. β-D-galactosidase from *Thermus thermophilus*[33] was a generous gift from Dr M. Dion. Inhibition studies with α-D-glucosidase, β-D-glucosidase, α-D-*manno*sidase and α-L-fucosidase were displayed as previously reported.[31] Briefly, assays were run at 37°C in 50 mM citrate-phosphate buffer, pH 6.8, 5.0, 4.5 and 5.5 respectively, according to the enzyme, using the corresponding 4-nitrophenyl-glycoside in a total volume of 0.1 mL. After an incubation time of 10 min at 37°C, the reaction was quenched by the addition of a 0.2 M glycine-sodium hydroxide buffer at pH 10 (0.1 mL). The optical absorbance at 400 nm was measured to determine the amount of liberated 4-nitrophenol and the percentage of inhibition was calculated. α-Amylase kinetics were performed in MES buffer 100 mM, NaCl 100 mM, $CaCl_2$ 10 mM, NaN_3 1.6 g L^{-1}, KSCN 0.8 M, pH 6.0 by monitoring the release of CNP at 405 nm on an ELISA plate reader (iEMS-Labsystems) for 7 min. α-D-Galactosidase and β-D-galactosidase kinetics were performed likewise in 50 mM phosphate buffer pH 7.0 by monitoring the release of 2-nitrophenol and 4-nitrophenol from the corresponding 2- or 4-nitrophenyl substrates, respectively. The potential inhibitors were tested at a final concentration of 1 mM and the amount of enzyme in each assay was adjusted so that less than 10% of the substrate would be consummed. When the percentage of inhibition was higher than 70 %, the K_i was determined according to the Lineweaver-Burk method. Substrates were at a concentration range of 0.2–5 K_M and inhibitors were added to final concentration between 10^{-3} and 10^{-8} M. In all cases, the inhibitors displayed typical competitive inhibition kinetics. The K_i was then calculated from the two Michaelis–Menten (K_M and $K_{M'}$) constants obtained in the absence or presence of inhibitor.

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