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N- and *C*-functionalisation of seven-membered iminosugars with long alkyl chains generate potent glycosidase inhibitors and F508del-CFTR correctors

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The glycosidase inhibitory properties of synthetic *C*-alkyl and *N*-alkyl six-membered iminosugars have been extensively studied leading to therapeutic candidates. The related seven-membered iminocyclitols have been less examined despite the report of promising structures. Using an in house ring enlargement/*C*-alkylation as well as cross-metathesis methodologies as the key steps, we have undertaken the synthesis and biological evaluation of a library of fourteen 2*C*- and eight *N*-alkyl tetrahydroxylated azepanes starting from an easily available glucopyranose-derived azidolactol. Four, six, nine and twelve carbon atoms alkyl chains have been introduced. Study of two distinct D-*gluco* and L-*ido* stereochemistries for the tetrol pattern as well as *R* and *S* configurations for the C-2 carbon bearing the C-alkyl chain is reported. We observed that *C*-alkylation of the L-*ido* tetrahydroxylated azepane converts it from a α-L-fucosidase to a β-glucosidase and β-galactosidase inhibitor while *N*-alkylation of the D-*gluco* iminosugar significantly improves its inhibition profile leading to potent β-glucosidase, β-galactosidase, α-L-rhamnosidase and β-glucuronidase inhibitors whatever the stereochemistry of the alkyl chain. Interestingly, *N*-alkyl chain length usually parallels the azepane inhibitor potency as exemplified by the identification of a potent glucocerebrosidase inhibitor (K_i 1 μM) bearing a twelve carbon atoms chain. Additionally, several *C*-alkyl azepanes demonstrated promising F508del-CFTR correction unlike the parent tetrahydroxyazepanes. None of the *C*-alkyl and *N*-alkyl azepanes did inhibit ER α-glucosidases I or II.

Introduction

Glycosidase inhibitors are enjoying much interest, as they are finding applications in an increasing number of therapies.[1,2] Iminoalditols rank among the most powerful glycosidase inhibitors and the scaffold of natural product deoxynojirimycin (DNJ), its most famous representative, is found in two approved medicines.[3,4] Both exhibit an alkyl substituent on the nitrogen that improves their selectivity and lipophilic balance. Introduction of long alkyl chains on the nitrogen has been a major advance for the therapeutic development of iminosugars.[5] Moving the alkyl chain from the endocyclic nitrogen to the pseudoanomeric carbon leads to another class of important carbohydrate analogues, the iminosugar C-glycosides that can be seen as glycoconjugates with a stable substituent at the C-1 position. Most of the work in this area has been devoted to the synthesis and biological evaluation of five-[6] and six-membered[7] iminosugars that closely resemble the parent sugars processed by glycosidases. Other ring sizes including four-,[8] seven-[9] and eight-membered[10] iminosugars have been less investigated, the tetrahydroxylated azepanes being the most studied. As early as 1967, Paulsen reported their synthesis[11] but their glycosidase inhibitory potential was only disclosed in the 90's by Wong.[12] As some azepanes displayed comparable inhibition potency compared to polyhydroxylated pyrrolidines and piperidines, several synthetic strategies toward these iminosugars have been reported[13] but only a few *N*-alkyl[14] and *C*-alkyl[15] tetrahydroxyazepanes has been described. Amongst them, some *N*-alkyl derivatives[14a, d] demonstrated significant potential as pharmacological chaperones for the treatment of Gaucher disease. To get insights into the impact of alkylation on the biological profile of tetrahydroxylated azepanes, we report herein the synthesis of a library of *C*- and *N*-alkyl azepanes and their biological evaluation on a panel of iminosugar-relevant proteins including F508del-CFTR, ER α-glucosidases I and II, glucocerebrosidase, as well as commercial glycosidases.

Our interest in seven-membered iminosugars[16] prompted us to recently develop a general strategy towards piperidine- and azepane-based iminosugar C-glycosides exploiting the C-alkylation of a seven-membered electrophilic iminosugar.[17a] We have used this strategy here and explored two configurations for the tetrahydroxylated azepane motif, namely 3S, 4R, 5R, 6R

and 3S, 4R, 5R, 6S, corresponding to azepanes **A** and **B** respectively, a choice guided by their promising glycosidase inhibition profile[8d] and by their rapid access using our methodology. Four different alkyl chain lengths usually studied in the iminosugar field, namely butyl, hexyl, nonyl and dodecyl, have been introduced on the azepane scaffold (Figure 1).

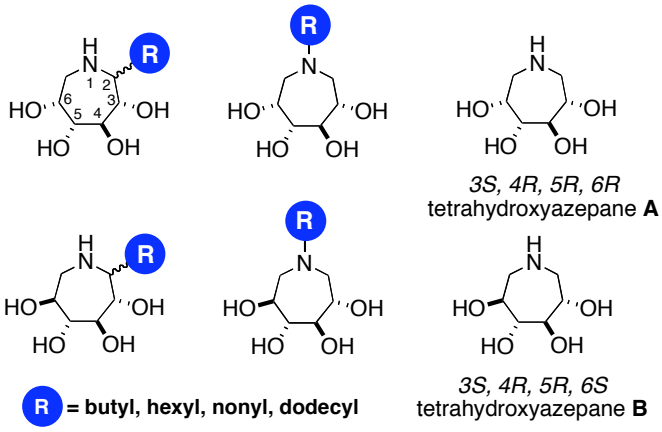


Figure 1: Structures of tetrahydroxyazepanes **A** and **B** and *N*- and 2*C*-alkyl derivatives studied in this work

Results and discussion

Synthesis of the *C*-alkyl derivatives

To construct the library of *C*-alkyl azepanes, we exploited the electrophilic *N,O*-acetal **2** easily available from the known azidolactol **1** via a Staudinger/azaWittig-based cyclisation. Treatment of **2** with the butyl, hexyl, nonyl and dodecyl-based organomagnesium reagents afforded the corresponding *3S, 4R, 5R, 6R* azepanes **3a-d** (35-50% yield over 3 steps from azidolactol **1**) as single diastereoisomers. A small $J_{2,3}$ coupling constant (0 Hz < $J_{2,3}$ < 0.5 Hz) supported a *cis* relationship between C-2 and C-3 substituents corresponding to a *R* configuration for the C-2 carbon atom bearing the alkyl chain. The stereochemical outcome of this alkylation can be rationalized by a delivery of the organometallic reagent guided by the 6-OH group released during imine formation.[17b, 18] Final hydrogenolysis under mild acidic conditions furnished the azepanes **4a-d** as their hydrochloride salt (Scheme 1). Structure of compound **4d** was confirmed by X-ray crystallography (Figure 2).

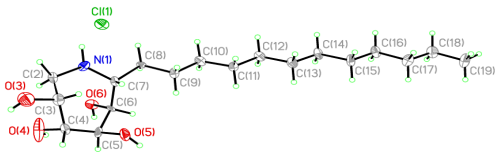
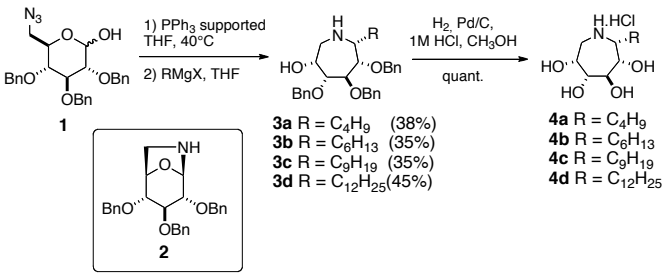
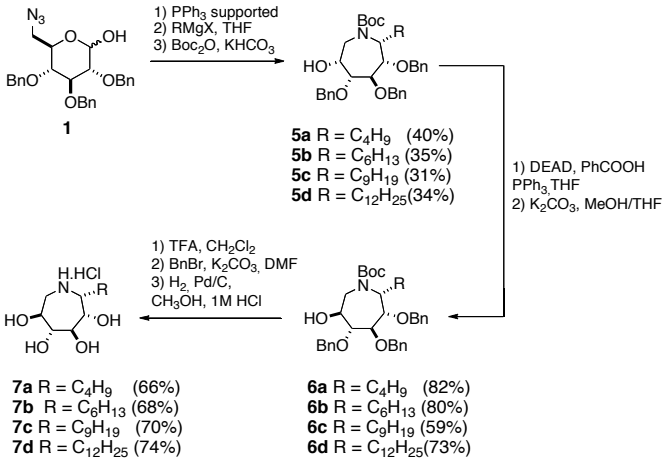


Figure 2: X-Ray crystallography of compound **4d** (CCDC 970784)



Scheme 1: Synthesis of 2*C*-alkyl tetrahydroxyazepanes **4a-d**

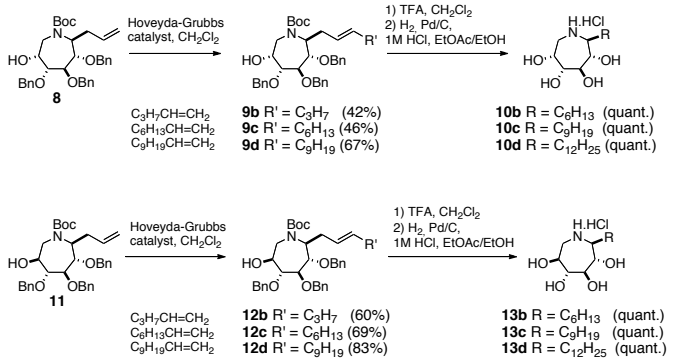
We were also interested in the diastereomeric 2*C*-alkyl *6S* tetrahydroxylated azepanes as the parent seven-membered iminosugar **B** has been reported to inhibit several glycosidases in the micromolar range.[9d] Such iminocyclitols can be accessed via inversion of the 6-OH group in **A** that requires protection of the intracyclic nitrogen with an electron-withdrawing group to avoid nitrogen anchimeric participation. Starting from azidolactol **1**, the Staudinger/azaWittig/alkylation sequence followed by protection of the intracyclic nitrogen of the crude azepane with $(Boc)_2O$ furnished the expected hydroxyazepanes **5a-d** (31-40% yield over three steps). Inversion of the 6-OH group under Mitsunobu conditions (p-nitrobenzoic acid, PPh_3, DEAD, THF) followed by ester hydrolysis (NaOMe, MeOH) provided the corresponding 6*R*-hydroxyazepanes **6a-d** (59-82% yield over two steps). To avoid tedious amine purification after Boc deprotection using TFA, the crude amines were protected as their N-benzyl derivatives (BnBr, K_2CO_3, DMF) and purified by flash chromatography. Final hydrogenolysis under mild acidic conditions (H_2, Pd/C, CH_3OH, 1M aq. HCl) furnished the target azepanes **7a-d** (66-74% yield over three steps) as their hydrochloride salt (Scheme 2).



Scheme 2: Synthesis of 2*C*-alkyl tetrahydroxyazepanes **7a-d**

The orientation of the alkyl chain in the C-alkyl derivatives might be of importance regarding glycosidase anomeric selectivity as this substituent can be seen as a pseudoanomeric lipophilic aglycon. So the study of the epimeric 2S *C*-alkyl azepanes displaying an alkyl chain pointing above the azepane ring was also planned. Such compounds except the four carbons derivative should be accessible from the known 2S *C*-allyl azepane[17a] using a cross metathesis elongation strategy.[19] The *C*-allyl azepane **8**[17a] easily available from azidolactol **1** was treated with pent-1-ene, oct-1-ene and undec-1-ene

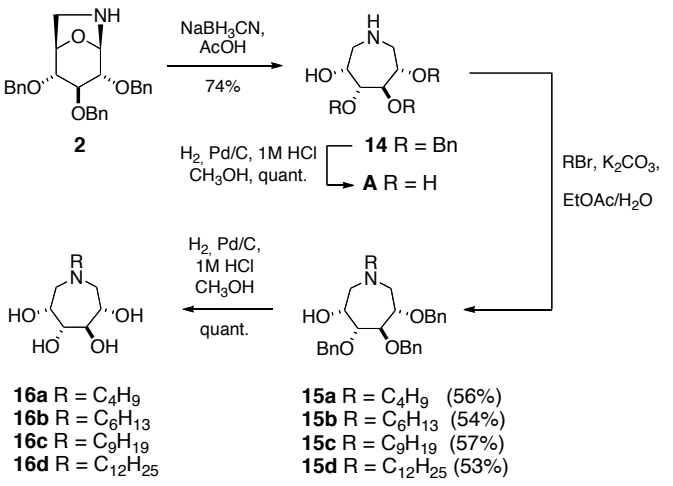
in the presence of Hoveyda-Grubbs catalyst to give the corresponding unsaturated iminosugar C-glycosides **9b-d** (42-67% yield). Stepwise removal of the Boc and benzyl groups furnished the corresponding 2*C*-alkyl azepanes **10b-d**. Uneventful inversion of O-OH group as described above gave the *C*-allyl azepane **11**. The same elongation strategy was then applied to deliver the unsaturated iminosugar *C*-glycosides **12b-d** (60-83% yield) and the corresponding *C*-alkyl azepanes **13b-d** after acidic hydrolysis (TFA) and hydrogenolysis (Scheme 3).



Scheme 3: Synthesis of *C*-alkyl azepanes **10b-d** and **13b-d**

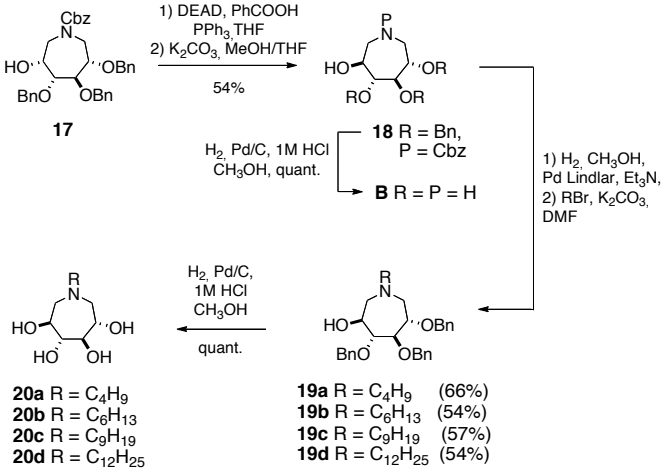
Synthesis of the *N*-alkyl derivatives

The most promising six-membered iminosugars reported in the literature display an alkyl chain on the nitrogen. This structural modification appears as essential to obtain therapeutic hits. To this end, we once more exploited the *N,O* acetal **2** to build up a library of *N*-alkyl azepanes. As with organometallic species, ring opening of **2** with hydride species should furnish the corresponding 6-hydroxyazepane that could be further *N*-alkylated and deprotected. Treatment of **2** with $NaBH_3CN$ afforded aminoalcohol **14** in 74% yield. Hydrogenolysis of **14** furnished the known tetrahydroxylated azepane **A**.[9d] Subsequent *N*-alkylation under basic conditions (alkyl bromide, K_2CO_3, 85°C) provided the N-butyl, -hexyl, -nonyl and -dodecyl derivatives **15a-d** (53-57% yield). Removal of the benzyl groups under mild acidic conditions (H_2, Pd/C, 1M aq. HCl) furnished the known **16a** [14b,d] and new **16b-d** iminosugars as their hydrochloride salt.



Scheme 4: Synthesis of **A** and *N*-alkyl *3S, 4R, 5R, 6R* tetrahydroxyazepanes **16a-d**

To access the complementary diastereomeric *N*-alkyl *3S, 4R, 5R, 6S* azepanes, we capitalized on our inversion strategy. Epimerisation of the 6-OH group in the available hydroxyazepane **17**[20b] under Mitsunobu conditions produced the hydroxyazepane **18** after ester hydrolysis. Its hydrogenolysis furnished the tetrahydroxylated azepane **B**.[9d] Chemoselective hydrogenolysis of the Cbz group in **18** (H_2, Pd Lindlar, Et_3N) followed by *N*-alkylation of the resulting crude hydroxyazepane gave the corresponding *N*-alkyl azepanes **19a-d**. Final deprotection yielded the target azepanes **20a-d** as their hydrochloride salt.



Scheme 5: Synthesis of azepane **B** and *N*-alkyl *3S,4R,5R,6S* tetrahydroxyazepanes **20a-d**

Biological evaluation

The library of tetrahydroxylated azepanes **A-B**, **4a-d**, **7a-d**, **10b-d**, **13b-d**, **16a-d** and **20a-d** was submitted to a series of biological evaluations, including glycoenzyme inhibition profiling, inactivation of glucocerebrosidase involved in Gaucher's disease, as well as correction of defective F508del-CFTR function.

Cellular glycoenzymes inhibition

Compounds were used at the highest non-cytotoxic concentration, as determined by MTS[21] cell proliferation assay, for endoplasmic reticulum (ER) α-glucosidase inhibition, using a free oligosaccharide (FOS) analysis following a 3-day incubation with the compound in HL-60 cells.

ER α-glucosidase inhibition

Compounds **4a-b, 7a-b, 10b-c, 13b-c, 16a-c, 20a-c** were non-toxic at 100 µM over a 24h incubation time. Compounds **4c** (CC_{50} = 37 µM), **4d** (CC_{50} = 120 µM), **7c** (CC_{50} = 120 µM), **7d** (CC_{50} = 34 µM), **10d** (CC_{50} = 124 µM), **13d** (CC_{50} = 117 µM), **16d** (CC_{50} = 50 µM), **20d** (CC_{50} = 125 µM) were evaluated at the highest non-toxic concentration, 50 and 5 µM respectively. FOS analysis in HL-60 cells was used to evaluate level of ER α-glucosidases I and II inhibition as determined by the amount of $Glc_3Man_5GlcNAc_1$ and $Glc_1Man_4GlcNAc_1$ oligosaccharide, respectively, produced in the cytosol as a result of endoplasmic reticulum-associated protein degradation (ERAD). These FOS species are the major tri- and

mono-glucosylated FOS species produced in response to ER α-glucosidases I and II inhibition in the ER, as a result of retrotranslocation via an ERAD pathway and the actions of PNGase and cytosolic α-mannosidase.[22] None of the azepanes demonstrated inhibition of glucosidases at the highest dose as no glucosylated oligosaccharides were detected. In control untreated HL-60 cells, no $Glc_3Man_5GlcNAc_1$ was produced and using 100μM NB-DNJ treatment for 24hrs significant quantities of tri-glucosylated FOS species was observed.

Glycoenzyme inhibition profiling:

Azepanes **4a-d, 7a-d, 10b-d, 13b-d, 16a-d** and **20a-d** were assayed as inhibitors of a collection of glycosidases, including glucosidases, galactosidases and mannosidases, in comparison with known tetrahydroxyazepanes **A** and **B**.

We first focused on the C-2 position and whether adding the alkyl chain at this position could influence the inhibition activities of *3S, 4R, 5R, 6R* and *3S, 4R, 5R, 6S* tetrahydroxyazepanes (azepanes **A** and **B**). As shown in Table 1, the basic structure, azepane **A** was a specific inhibitor against bovine kidney α-L-fucosidase, with IC_{50} value of 62 μM. In contrast, azepane **B**, epimeric at C-6 of azepane **A**, was completely inactive toward this enzyme, whereas it showed inhibition activities against almond, *Aspergillus niger*, human lysosome β-glucosidases (IC_{50} = 38, 59, and 287 μM) and *E. coli* β-glucuronidase (IC_{50} = 886 μM). This study revealed that introduction of an alkyl chain at C-2 could influence the inhibition activities against β-glucosidases and β-galactosidase. *C*-Alkyl azepanes **4a-d** and **7a-d** with the alkyl chain *cis* to the C-3 OH group increased the inhibition potency of the parent azepane in a length-dependent manner (Table 1). We next tested the *C*-alkyl azepanes **10b-d** and **13b-d** with the alkyl chain *trans* to the C-3 OH group (Table 2). A very similar inhibition profile was observed for these derivatives suggesting that the stereochemistry of the alkyl chain is not crucial for glycosidase inhibition. Finally, *N*-alkyl azepanes derived from **A** and **B** were examined in order to increase our understanding of the effect of the alkyl substituent on the glycosidase inhibition profile (Table 3). The introduction of an *N*-alkyl substituent into azepanes **A** and **B** (**16a-d** and **20a-d**) improved their inhibitory potency against β-glucosidases and β-galactosidase. This behavior is similar to that of *C*-alkyl azepanes. Especially, *N*-dodecyl-azepane **20d** showed potent inhibition against all types of β-glucosidases (IC_{50} = 2.5 μM for almond, 9.2 μM for bovine liver, 52 μM for *A. niger*, 1.1 μM for human lysosome). It is notable that introduction of a *N*-alkyl chain in azepane **A** to give iminosugars **16a-c** does not affect significantly the inhibition activity against α-L-fucosidase. This tendency obviously differs from *C*-alkyl azepanes **4a-c** derived from **A**. Comparison of *C*-alkyl azepanes **7a-d** and *N*-alkyl azepanes **20a-d** derived from **B** suggested that introduction of a *N*-alkyl chain drastically reduced the inhibition selectivities since they showed broad inhibition not only against β-glucosidases and β-galactosidase but also against jack beans α-mannosidase, *P. decumbens* α-L-rhamnosidase, *E. coli* β-glucuronidase.

CFTR correction

Iminosugars have been identified as pharmacological chaperones that can stabilize or correct the structure of misfolded proteins. The protein cystic fibrosis transmembrane conductance regulator (CFTR) is glycosylated, even though it does not involve any sugar metabolism; CFTR is an ABC transporter-class protein and ion channel that transports chloride ions across the apical membrane of epithelial cells. Mutations of the *CFTR* gene affect folding and/or functioning of the CFTR chloride channels in these cell membranes, causing cystic fibrosis. The most common CF mutation F508del causes misfolding of the protein and intracellular retention by the endoplasmic reticulum quality control and premature degradation; iminosugars may help in the correction of structure of the misfolded protein. Miglustat is an inhibitor of glucosyl ceramide transferase leading to its use in substrate reduction therapy (SRT) for the treatment of Gaucher's disease.[23] Both miglustat[24] (an α-glucosidase inhibitor), its multivalent derivatives[25] and isoLAB[26] have been found to show significant rescue of the defective F508del-CFTR function as assessed by single-cell fluorescence imaging and sensitivity to the CFTR selective inhibitor $CFTR_{inh}$-172.[27] Azepanes were compared to miglustat for their corrector effect on CFTR function in CF-KM4 cells[28] using single-cell fluorescence imaging (Figure 3).[29] Some *C*-alkyl azepanes **4a**, **7c** and **7d** show significant rescue of F508del-CFTR activity unlike the unsubstituted azepanes **A** and **B**, despite being less efficient than miglustat. The most interesting structures are the D-*gluco* configured *C*-alkyl azepanes **13b-d** that demonstrate F508del-CFTR rescue to miglustat whatever the alkyl chain length. The mechanism by which these iminosugars show such effects is not clear but may involve binding to the glycosylated site of the protein. ER glucosidase I inhibition by miglustat is a major concern regarding long term treatments as this cellular glycosidase is involved in the maturation of the glycan moiety of glycoproteins. Therefore these potent *C*-alkyl azepanes that can selectively restore F508del-CFTR activity without inhibiting α-1,2 glucosidase are of interest.

Conclusions

In summary, exploiting a skeletal rearrangement approach and a cross metathesis elongation strategy, we have synthesized a library of fourteen *C*-alkyl and eight *N*-alkyl seven-membered iminosugars and studied their biological effects. *C*-Alkylation, and to a lesser extend *N*-alkylation, broaden the glycosidase inhibition profile of the parent tetrahydroxylated azepanes providing new potent β-glucosidase, β-galactosidase, α-L-rhamnosidase and β-glucuronidase inhibitors. Long alkyl chains produce better inhibitors as illustrated by the *N*-dodecyl derivative **20d**, a low micromolar inhibitor of glucocerebrosidase involved in Gaucher's disease. Interestingly, some of these iminosugars **13b-d** were also found to significantly correct F508del-CFTR responsible for cystic fibrosis. This study emphasizes the potential of polyhydroxylated azepanes as biologically active compounds and gives structural clues for further modification of these scaffolds that could lead to improved glycosidase inhibitors.

Experimental section

General experimental methods

All commercial reagents were used as supplied. Solvents (DMF, THF) were distilled under anhydrous conditions. TLC plates were visualized under 254 nm UV light and/or by dipping the TLC plate into a solution of 3 g of phosphomolybdic acid in 100 mL of ethanol followed by heating with a heat gun. Flash column chromatography was performed using silica gel 60 (15-40 μm). NMR experiments were recorded with a 400 Bruker spectrometer at 400 MHz for 1H nuclei and at 100 MHz for 13C nuclei. The chemical shifts are expressed in part per million (ppm) relative to TMS (δ = 0

ppm) and the coupling constant J in hertz (Hz). NMR multiplicities are reported using the following abbreviations: b = broad, s = singulet, d = doublet, t = triplet, q = quadruplet, m = multiplet. HRMS were obtained with a Q-TOF spectrometer. Compounds names in the experimental section are given according to IUPAC nomenclature; numbering for some of them is different from the one used in the manuscript.

(3R,4S,5S,6R,7S)-4,5,6-Tris(benzyloxy)-8-oxa-1-aza-bicyclo[3.2.1]octane (2). Triphenylphosphine polymer bound (2.8 g, 3.2 mmol.g-1, 8.96 mmol) was added to a solution of azidolactol **1** (2.8 g, 5.89 mmol) in anhydrous THF (60 mL). The reaction mixture was stirred at 40 °C overnight, then filtered on Celite and the solvent removed under reduced pressure. The residue was purified by flash chromatography (EtOAc/EP 30% then EtOAc) to give a colorless oil (1.6 g, 62%); $[\alpha]_D$ = 32.5 (c 0.4, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35-7.23 (m, 15H, ArH), 5.06 (s, 1H, H-7), 4.57-4.52 (m, 5H, 2 x OCH_2Ph, H-3), 4.43 (br. s, 2H, OCH_2Ph), 3.57 (br. s, 1H, H-5), 3.31 (br. s, 1H, H-6), 3.25 (br. s, 1H, H-4), 3.08-2.98 (m, 2H, H-2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.3, 138.2, 138.0 (aromatic C ipso), 128.6, 128.56, 128.52, 128.06, 128.00, 127.9, 127.8 (aromatic CH), 88.7 (C-7), 77.7 (C-6), 77.3 (C-4), 75.9 (C-5), 73.9 (C-3), 72.1, 71.5, 71.01 (3 x OCH_2Ph), 45.9 (C-2); HRMS (ESI) m/z: [M+H]+ calcd for $C_{27}H_{30}NO_4$: 432.2175; found: 432.2182.

(3R,4R,5R,6S,7R)-4,5,6-Tris(benzyloxy)-7-butylazepan-3-ol (3a). Triphenylphosphine polymer bound (3.2 mmol.g-1, 145 mg, 0.46 mmol) was added to a solution of azidolactol **1** (147 mg, 0.31 mmol) in anhydrous THF (4 mL). The reaction mixture was stirred at 40 °C overnight, then filtered on Celite and the solvent removed under reduced pressure. The residue was diluted with Et_2O, filtered again and the filtrate concentrated. A solution of the crude bicyclic *N,O*-acetal **2** (134 mg, 0.31 mmol) in Et_2O (6 mL) was added to a solution of n-butylmagnesium chloride (1.5 mL, 3.1 mmol, 2M solution in Et_2O), at 0 °C. The reaction was stirred at room temperature for 1 h (monitored by TLC, EtOAc), quenched with saturated aqueous NH_4Cl (30 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure after filtration. The residue was purified by flash chromatography (EtOAc/PE 80:20) to afford **3a** as a light yellow oil (58 mg, 38% over 2 steps); $[\alpha]_D$ = -16 (c 1.1, CH_3OH); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.27 (m, 15H, aromatic H), 4.73 (m, 3H, OCHPh, OCH_2Ph), 4.62 (m, 2H, OCH_2Ph,), 4.38 (d, J = 11.3 Hz, 1H, OCHPh), 4.00 (m, 1H, H-3), 3.98 (dd, J = 6.3 Hz, J = 2.0 Hz, 1H, H-5), 3.58 (dd, J = 6.3, J = 1.5 Hz, 1H, H-4), 3.47 (d, J = 2.0 Hz, 1H, H-6), 3.14 (dd, J = 14.8 Hz, J = 4.5 Hz, 1H, H-2), 2.76 (d, J = 14.8 Hz, 1H, H-2), 2.68 (t, J = 6.7 Hz, 1H, H-7), 1.42-1.09 (m, 6H, 3 x CH_2), 0.85 (t, J = 8.0, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.4, 138.1, 136.5 (aromatic C ipso), 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.7 (aromatic CH), 87.3 (C-4), 82.2 (C-5), 79.0 (C-6), 73.1, 72.7, 72.6 (3 x OCH_2Ph), 72.0 (C-3), 56.3 (C-7), 52.2 (C-2), 35.6 (CH_2), 28.8 (CH_2), 22.5 (CH_2), 14.0 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{31}H_{40}NO_4$: 490.2957; found: 490.2944.

(3R,4R,5R,6S,7R)-4,5,6-Tris(benzyloxy)-7-hexylazepan-3-ol (3b). The reaction was carried out, as for compound **3a**, using 257 mg (0.541 mmol) of azidolactol **1** in the first step and hexylmagnesium chloride (5.4 mmol, 2M in Et_2O) in the second step. Purification was performed by flash chromatography (EP/EtOAc : 1:1) affording **3b** as a pale yellow oil (99 mg, 35 % over 2 steps); [α]D = -21 (c 2.0, CH_3OH); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35-7.26 (m, 15H, aromatic H), 4.74 (m, 3H, OCHPh, OCH_2Ph), 4.63 (m, 2H, OCH_2Ph), 4.35 (d, J = 11.3 Hz, 1H, OCHPh), 3.97 (m, 1H, H-3), 3.94 (dd, J = 6.3 Hz, J = 2.0 Hz, 1H, H-5), 3.69 (dd, J = 6.3 Hz, J = 1.4 Hz, 1H, H-4), 3.45 (d, J = 2.0 Hz, 1H, H-6), 3.12 (dd, J = 14.8 Hz, J = 4.8 Hz, 1H, H-2), 2.72 (d, J = 14.8 Hz, 1H, H-2), 2.65 (t, J = 6.7 Hz, 1H, H-7), 1.40-1.10 (m, 10H, 5 x CH_2), 0.85 (t, J = 7.6, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.1, 138.0, 136.5 (aromatic C ipso), 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.4, 127.7 (aromatic CH), 87.4 (C-4), 82.2 (C-5), 79.1 (C-6), 73.2, 72.7, 72.2 (3 x OCH_2Ph), 72.0 (C-3), 56.4 (C-7), 52.3 (C-2), 36.3 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 26.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{33}H_{44}NO_4$: 518.3270; found: 518.3280.

(3R,4R,5R,6S,7R)-4,5,6-Tris(benzyloxy)-7-nonylazepan-3-ol (3c). The reaction was carried out, as for compound **3a**, using 114 mg (0.240 mmol) of azidolactol **1** in the first step and nonylmagnesium bromide (1M in Et_2O, 2.4 mmol) in the second step. Purification by flash chromatography (EtOAc/PE : 1:1) affording **3c** as a pale yellow oil (47 mg, 35 % over 2 steps); $[\alpha]_D$ = -5 (c 0.94, CH_3OH); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39-7.26 (m, 15H, aromatic H), 4.72 (m, 3H, OCHPh, OCH_2Ph), 4.58 (m, 2H, OCH_2Ph), 4.35 (d, J = 11.3 Hz, 1H, OCHPh), 3.97 (m, 1H, H-3), 3.94 (dd, J = 6.2 Hz, J = 2.1 Hz, 1H, H-5), 3.69 (dd, J = 6.2 Hz, J = 1.2 Hz, 1H, H-4), 3.45 (d, J = 2.1 Hz, 1H, H-6), 3.11 (dd, J = 14.8 Hz, J = 4.8 Hz, 1H, H-2), 2.74 (d, J = 14.8 Hz, 1H, H-2), 2.65 (t, J = 6.9 Hz, 1H, H-7), 1.28-1.20 (m, 16H, 8 x CH_2), 0.85 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.5, 138.1, 136.6 (aromatic C), 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.7 (aromatic CH), 87.3 (C-4), 82.2 (C-5), 79.0 (C-6), 73.3, 72.8, 72.4 (3 x OCH_2Ph), 72.0 (C-3), 56.5 (C-7), 52.3 (C-2), 36.0, 32.0, 29.7, 29.7, 29.6, 29.5, 26.8, 22.8 (8 x CH_2), 14.2 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{36}H_{50}NO_4$: 560.3739; found: 560.3585. [M+Na]+ calcd for $C_{36}H_{49}NO_4Na$: 582.3559; found: 582,3585.

(3R,4R,5R,6S,7R)-4,5,6-Tris(benzyloxy)-7-dodecylazepan-3-ol (3d). The reaction was carried out, as for compound **3a**, using 105 mg (0.220 mmol) of azidolactol **1** in the first step and dodecylmagnesium bromide (1M in Et_2O, 2,2 mmol) in the second step. Purification was performed by flash chromatography (EtOAc/PE 1:1) affording **3d** as a pale yellow oil (59 mg, 45 %, 2 steps); $[\alpha]_D$ = -24 (c 1.2, CH_3OH); 1H-NMR (400 MHz, $CDCl_3$): δ 7.35-7.26 (m, 15H, ArH), 4.72 (m, 3H, OCHPh, OCH_2Ph), 4.58 (m, 2H, OCH_2Ph), 4.35 (d, J = 11.3 Hz, 1H, OCHPh), 3.96 (m, 1H, H-3), 3.94 (dd, J = 6.2 Hz, J = 2.0 Hz, 1H, H-5), 3.68 (dd, J = 6.2 Hz, 1.2 Hz, 1H, H-4), 3.44 (d, J = 2.0 Hz, 1H, H-6), 3.12 (dd, J = 14.8 Hz, J = 4.7 Hz, 1H, H-2), 2.72 (d, J = 14.8 Hz, 1H, H-2), 2.65 (t, J = 6.9 Hz, 1H, H-7), 1.30-1.16 (m, 22H, 11 x CH_2), 0.89 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.4, 138.2, 136.6 (aromatic C ipso), 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.7 (aromatic CH), 87.3 (C-4), 82.2 (C-5), 79.0 (C-6), 73.3, 72.2, 72.4 (3 x OCH_2Ph), 71.9 (C-3), 56.5 (C-7), 52.3 (C-2), 35.9, 32.0, 29.7, 29.7, 29.6, 29.6, 29.5, 26.8 22.8 (11 x CH_2), 14.3 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{39}H_{56}NO_4$: 602.4209; found: 602.4207. [M+Na]+ calcd for $C_{39}H_{55}NO_4Na$: 624.4029; found 624.4042.

(2R,3S,4R,5R,6R)-2-butylazepane-3,4,5,6-tetraol (4a). To a solution of protected compound **3a** (58 mg, 0.120 mmol) in CH_3OH (7 mL) was added 10% Pd/C (58 mg) and a 1M HCl aqueous solution (0.3 mL, 0.30 mmol). The solution was purged with H_2. After stirring overnight at room temperature, the reaction mixture was purged with N_2, filtered on Celite eluted with CH_3OH. The solution was concentrated to give **4a** as its hydrochloride salt (33 mg, quantitative yield); $[\alpha]_D$ = -17 (c 0.6, CH_3OH); ^{1}H-NMR (400 MHz, D_2O): δ 4.25 (d, J = 6.9 Hz, 1H, H-6), 3.96 (m, 3H, H-3, H-4, H-5), 3.44 (m, 2H, H-2, H-7), 3.28 (dd, J = 13.7 Hz, J = 2.3 Hz, 1H, H-7), 1.72 (m, 2H, CH_2), 1.33 (m, 4H, 2 x CH_2), 0.87 (t, J = 7.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, D_2O): δ 76.5, 74.1, 70.8 (C-3, C-4, C-5), 67.7 (C-6), 56.7 (C-2), 47.2 (C-7), 30.6 (CH_2), 26.7 (CH_2), 21.6 (CH_2), 12.8 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{10}H_{22}NO_4$: 220.1549; found: 220.1547.

(2R,3S,4R,5R,6R)-2-hexylazepane-3,4,5,6-tetraol (4b). Azepane **3b** (99 mg, 0.19 mmol) was deprotected as described for compound **4a** to afford compound **4b** as its hydrochloride salt (45 mg, quantitative yield); $[\alpha]_D$ = -12 (c 0.8, CH_3OH); ^{1}H NMR (400 MHz, D_2O): δ 4.25 (d, J = 6.0 Hz, 1H, H-6), 3.96 (m, 3H, H-3, H-4, H-5), 3.43 (m, 2H, H-2, H-7), 3.30 (dd, J = 13.7 Hz, J = 2.3 Hz, 1H, H-7), 1.72 (m, 2H, CH_2), 1.32 (m, 8H, 4 x CH_2), 0.85 (t, J = 7.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, D_2O): δ 76.5, 74.1, 70.8 (C-3, C-4, C-5), 67.7 (C-6), 56.7 (C-2), 47.2 (C-7), 30.8 (CH_2), 30.6, 27.8, 24.6, 21.8 (4 x CH_2), 13,2 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{12}H_{26}NO_4$: 248.1861; found: 248.1862.

(2R,3S,4R,5R,6R)-2-nonylazepane-3,4,5,6-tetraol (4c). Azepane **3c** (47 mg, 0.084 mmol) was deprotected as described for compound **4a** to afford compound **4c** as its hydrochloride salt (33 mg, quantitative yield); $[\alpha]_D$ = -4 (c 0.7, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 4.25 (d, J = 6.0 Hz, 1H, H-6), 3.95 (m, 3H, H-3, H-4, H-5), 3.45 (m, 2H, H-2, H-7), 3.30 (dd, J = 13.7, 2.0 Hz, 1H, H-7), 1.71 (m, 2H, CH_2), 1.26 (m, 14H, 7 x CH_2), 0.85 (t, J = 7.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, D_2O): δ 76.5, 74.1, 70.7 (C-3, C-4, C-5), 67.7 (C-6), 56.7 (C-2), 47.2 (C-7), 31.1, 30.8, 30.2, 28.5, 28.3, 28.1, 24.6, 22.0 (11 x CH_2), 13.4 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{15}H_{32}NO_4$: 290.2331; found: 290.2332.

(2R,3S,4R,5R,6R)-2-docecylazepane-3,4,5,6-tetraol (4d). Azepane **3d** (59 mg, 0.098 mmol) was deprotected as described for compound **4a** to afford compound **4d** as its hydrochloride salt (34 mg, quantitative yield); $[\alpha]_D$ = -12 (c 0.7, CH_3OH); ^{1}H NMR (400 MHz, MeOD): δ 4.25 (dd, J = 8.3 Hz, J = 3.5 Hz, 1H, H-3), 3.95 (m, 2H, H-3, H-5), 3.87 (t, J = 2.2 Hz, 1H, H-4), 3.45 (m, 2H, H-2, H-7), 3.20 (dd, J = 13.0 Hz, J = 3.4 Hz, 1H, H-7), 1.71 (m, 2H, CH_2), 1.26 (m, 20H, 10 x CH_2), 0.85 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, MeOD): δ 79.1, 73.6 (C-3, C-5), 73.1 (C-4), 76.4 (C-6), 57.4 (C-2), 47.6 (C-7), 33.0, 32.6, 30.8, 30.7, 30.6, 30.5, 30.3, 26.6, 23.7 (11x CH_2), 14.4 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{18}H_{38}NO_4$: 332.2800; found: 332.2798.

(2R,3S,4R,5R,6R)-tert-butyl-3,4,5-tris(benzyloxy)-2-butyl-6-hydroxyazepane-1-carboxylate (5a). Triphenylphosphine polymer bound (1 g, 3.2 mmol.g-1, 3.2 mmol) was added to a solution of azidolactol **1** (1 g, 2.10 mmol) in anhydrous THF (40 mL). The reaction mixture was stirred at 40 °C overnight, then filtered over Celite and the solvent removed under reduced pressure. The residue was diluted with Et_2O, filtered again and the filtrate concentrated. The resulting crude bicyclic N,O-acetal **2** (852 mg, 1.97 mmol) dissolved in THF (40 mL) was added to a solution of n-butylmagnesium chloride (5.8 mL, 9.9 mmol, 20% in THF/toluene) at 0 °C. The reaction was stirred at room temperature for 1 h, quenched with saturated aqueous NH_4Cl and extracted with EtOAc to afford the expected crude azepane (967 mg, 1.97 mmol). Some $KHCO_3$ (2 g, 20.0 mmol) and di-tert-butyl dicarbonate (1.3 g, 6.0 mmol) in EtOAc/H_2O (1:1, 50 mL) were added to the solution. The mixture was stirred over night at room temperature. After extraction with EtOAc, the organic layer was washed with water, dried, filtered and concentrated. The residue was purified by flash chromatography (EtOAc/PE 10:90) to afford azepane **5a** as a colorless oil (498 mg, 40% over 3 steps); $[\alpha]_D$ = -9 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 7.34-7.26 (m, 15H, aromatic H), 4.72-4.49 (m, 6H, 3 x OCHPh), 4.44, 4.30 (2 x m, 1H, H-2), 4.19-3.84 (m, 3H, H-6, H-7, H-4), 3.72-3.68 (m, 1H, H-5), 3.57 (dd, J = 6.1 Hz, J = 4.1 Hz, 0.5H, H-3), 3.53 (dd, J = 6.0, 4.0 Hz, 0.5H, H-3'), 3.11 (m, 1H, H-7), 2.82 (m, 0.5H, OH), 2.60 (br. d, J = 7.1 Hz, OH), 1.88-1.50 (m, 2H, CH_2), 1.42, 1.41 (2 x s, 9H, tBu), 1.35-1.14 (m, 4H, 2 x CH_2), 0.86 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 155.1 (2 x C=O), 138.4, 138.3, 138.1, 138.0, 137.8, 137.4 (aromatic C), 128.5–127.7 (aromatic CH), 83.3, 83.2 (C-5, C-5'), 82.9, 82.5 (C-3, C-3'), 81.4, 80.7 (C-4, C-4'), 80.1 and 79.9 (Boc), 73.8, 73.6, 73.5, 73.3, 72.9, 72.7 (3 x CH_2Ph, 3 x CH2'Ph), 69.4 and 69.0 (C-6, C-6'), 54.7, 53.8 (C-2, C-2'), 43.7, 43.2 (C-7, C-7'), 28.4, 28.3 (CH_3 Boc, CH_2), 26.4, 26.2 (CH_2, CH_2'), 22.5, 22.4 (CH_2, CH_2'), 14.0 (CH_3). HRMS (ESI) m/z: [M+H]+ calcd for $C_{36}H_{47}NO_6$: 590.3482; found: 590.3480.

(2R,3S,4R,5R,6R)-tert-butyl-3,4,5-tris(benzyloxy)-2-hexyl-6-hydroxyazepane-1-carboxylate (5b). The reaction was carried out, as for compound **5a**, in 3 steps, using 1 g (3.2 mmol) of azidolactol **1** in the first step and hexylmagnesium chloride (2M in THF, 4.2 mmol) in the second step. After Boc protection, the residue was purified by flash chromatography (EtOAc/PE 10:90) to afford azepane **5b** as a colorless oil (457 mg, 35% over 3 steps); $[\alpha]_D$ = -9 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 7.32-7.26 (m, 15H, ArH), 4.72-4.49 (m, 6H, 3 x OCH_2Ph), 4.44 and 4.30 (2 x m, 1H, H-2), 4.19-3.84 (m, 3H, H-6, H-7, H-4), 3.73-3.70 (m, 1H, H-5), 3.58 (dd, J = 6.1 Hz, J = 4.1 Hz, 0.5H, H-3), 3.53 (dd, J = 6.0 Hz, 4.0 Hz, 0.5H, H-3'), 3.12 (m, 1H, H-7), 2.90 (m, 0.5H, OH), 2.66 (br. d, J = 7.1 Hz, OH'), 1.90-1.49 (m, 2H, CH_2), 1.42 and 1.41 (2 x s, 9H, tBu), 1.28-1.24 (m, 8H, 4 x CH_2), 0.89-0.84 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 155.2 (2 x C=O), 138.4, 138.3, 138.1, 138.0, 137.9, 137.6 (aromatic C), 128.5–127.7 (aromatic CH), 83.3, 83.2 (C-5, C-5'), 83.1, 82.7 (C-3, C-3'), 81.5, 80.8 (C-4, C-4'), 80.1, 79.9 (Boc), 73.8, 73.6, 73.5, 73.3, 72.9, 72.8 (3 x CH_2Ph, 3 x CH_2'Ph), 69.5, 69.1 (C-6, C-6'), 54.7, 53.8 (C-2, C-2'), 43.7, 43.1 (C-7, C-7'), 31.8 (CH_2), 29.2, 29.0 (CH_2, CH_2'), 28.4 (CH_3 Boc), 26.5, 26.4 (CH_2, CH_2'), 26.14, 26.11 (CH_2, CH_2'), 22.7, 22.6 (CH_2, CH_2'), 14.1 (CH_3). HRMS (ESI) m/z: [M+H]+ calcd for $C_{38}H_{52}NO_6$: 618.3795; found: 618.3789.

(2R,3S,4R,5R,6R)-tert-butyl-3,4,5-tris(benzyloxy)-6-hydroxy-2-nonylazepane-1-carboxylate (5c). The reaction was carried out, as for compound **5a**, in 3 steps, using 1 g (3.2 mmol) of azidolactol **1** in the first step and nonylmagnesium bromide (1M in Et_2O, 12 mmol) in the second step. After Boc protection, the residue was purified by flash chromatography

(EtOAc/PE 10:90) to afford azepane **5c** as a colorless oil (429 mg, 31% over 3 steps); $[\alpha]_D$ = -5 (c 0.8, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 7.33-7.27 (m, 15H, ArH), 4.67-4.49 (m, 6H, 3 x OCH_2Ph), 4.45 and 4.30 (2 x m, 1H, H-2), 4.19-3.84 (m, 3H, H-6, H-7, H-4), 3.71 (m, 1H, H-5), 3.58 (dd, J = 6.0 Hz, J = 4.0 Hz, 0.5H, H-3), 3.53 (dd, J = 5.9 Hz, J = 4.0 Hz, 0.5H, H-3'), 3.11 (m, 1H, H-7), 2.80 (m, 0.5H, OH), 2.60 (m, 0.5H, OH'), 1.90-1.49 (m, 2H, CH_2), 1.42, 1.41 (2 x s, 9H, tBu), 1.24 (m, 14H, 7 x CH_2), 0.89 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 155.1 (2 x C=O), 138.35, 138.31, 138.1, 138.0, 137.8, 137.4 (aromatic C), 128.5–127.7 (aromatic CH), 83.3, 83.2 (C-5, C-5'), 82.9, 82.6 (C-3, C-3'), 81.4, 80.7 (C-4, C-4'), 80.1, 79.8 (Boc), 73.8, 73.6, 73.5, 73.3, 72.9, 72.7 (3 x CH_2Ph, 3 x CH_2'Ph), 69.4, 68.9 (C-6, C-6'), 54.6, 53.8 (C-2, C-2'), 43.7, 43.1 (C-7, C-7'), 31.9 (CH_2, CH_2'), 29.6, 29.5, 29.4, 29.3 (4 x CH_2, 4 x CH_2'), 28.4 (CH_3 Boc), 26.6, 26.4, 26.1 (2 x CH_2, 2 x CH_2'), 22.7 (CH_2, CH_2'), 14.1 (CH_3). HRMS (ESI) m/z: [M+H]+ calcd for $C_{41}H_{58}NO_6$: 660.4264; found: 660.4259.

(2R,3S,4R,5R,6R)-tert-butyl-3,4,5-tris(benzyloxy)-2-dodecyl-6-hydroxyazepane-1-carboxylate (5d). The reaction was carried out, as for compound **5a**, in 3 steps, using 1 g (3.2 mmol) of azidolactol **1** in the first step and dodecylmagnesium bromide (1M in Et_2O, 12 mmol) in the second step. After Boc protection, the residue was purified by flash chromatography (EtOAc/PE 10:90) to afford azepane **5d** as a colorless oil (506 mg, 34% over 3 steps); $[\alpha]_D$ = -3 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 7.33-7.23 (m, 15H, ArH), 4.71-4.49 (m, 6H, 3 x OCH_2Ph), 4.44, 4.29 (2 x m, 1H, H-2), 4.19-3.84 (m, 3H, H-6, H-7, H-4), 3.71 (m, 1H, H-5), 3.57 (dd, J = 6.2 Hz, J = 4.2 Hz, 0.5H, H-3), 3.53 (dd, J = 6.0 Hz, J = 4.0 Hz, 0.5H, H-3'), 3.11 (m, 1H, H-7), 2.80 (m, 0.5H, OH), 2.60 (m, 0.5H, OH'), 1.90-1.48 (m, 2H, CH_2), 1.42, 1.41 (2 x s, 9H, tBu), 1.25 (m, 20H, 10 x CH_2), 0.89 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 155.1 (2 x C=O), 138.37, 138.33, 138.1, 138.0, 137.8, 137.4 (aromatic C), 128.5–127.7 (aromatic CH), 83.3, 83.2 (C-5, C-5'), 82.9, 82.6 (C-3, C-3'), 81.4, 80.7 (C-4, C-4'), 80.1, 79.8 (Boc), 73.8, 73.6, 73.5, 73.3, 72.9, 72.7 (3 x CH_2Ph, 3 x CH_2'Ph), 69.4, 69.0 (C-6, C-6'), 54.7, 53.8 (C-2, C-2'), 43.7, 43.2 (C-7, C-7'), 31.9 (CH_2), 29.7, 29.66, 29.57, 29.36, 29.31 (CH2, CH2'), 28.4 (CH3 Boc), 26.6, 26.4 (CH_2, CH_2'), 26.1(CH_2), 22.7 (CH_2), 14.1 (CH_3). HRMS (ESI) m/z: [M+H]+ calcd for $C_{44}H_{64}NO_6$: 702.4734; found: 702.4728.

(2R,3S,4R,5R,6S)-tert-butyl-3,4,5-tris(benzyloxy)-2-butyl-6-hydroxyazepane-1-carboxylate (6a).
Diethyl azodicarboxylate (40% in toluene, 0.76 ml, 1.67 mmol) was added to a solution of azepane **5a** (492 mg, 0.835 mmol), triphenylphosphine (438 mg, 1.67 mmol) and *p*-nitrobenzoic acid (209 mg, 1.25 mmol) in anhydrous THF (15 mL) at 0 °C. The mixture was stirred at room temperature for 2 h and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/PE 5:95) to afford the inverted ester (561 mg, 91%); $[\alpha]_D$ = 64 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 8.18-8.04 (m, 4H, ArH), 7.36-7.19 (m, 15H, ArH), 5.40, 5.30 (2 x m, 1H, H-6, H-6'), 4.69-4.55 (m, 6.5H, 3 x OCH_2Ph, 3 x OCH_2'Ph, H-2), 4.46-4.40 (m, 0.5H, H-2'), 4.32 (dd, J = 15.3 Hz, J = 4.0 Hz, 0.5H, H-7), 4.17 (dd, J = 15.8 Hz, J = 3.9 Hz, 0.5H, H-7'), 4.02 (dd, J = 7.0 Hz, J = 3.3 Hz, 0.5H, H-5), 3.94-3.88 (m, 1.5H, H-5', H-4, H-4'), 3.80 (dd, J = 6.8 Hz, J = 3.5 Hz, 0.5H, H-3), 3.77 (dd, J = 6.8 Hz, J = 3.7 Hz, 0.5H, H-3'), 3.60 (dd, J = 15.8 Hz, J = 2.6 Hz, 0.5H, H-7'), 3.53 (dd, J = 15.3 Hz, J = 3.0 Hz, 0.5H, H-7), 1.93-1.60 (m, 2H, CH_2), 1.41-1.21 (m, 13H, $C(CH_3)_3$, 4 x CH_2), 0.88, 0.87 (2 x t, 3H, J = 7.0 Hz, CH_3, CH_3'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 163.6 (2 x C=O), 155.9, 155.6 (2 x C=O), 150.5, 150.3, 138.31, 138.27, 138.0, 137.9, 137.6, 135.5, 135.4, (aromatic C ipso), 130.9, 130.8, 128.4-127.6, 123.5, 123.3 (aromatic CH), 83.3, 83.2 (C-4), 81.8, 81.6 (C-3), 80.1, 80.0 (C-5), 79.9 (Boc), 73.5, 73.4, 73.3, 73.2 (2 x OCH_2Ph, 2 x OCH_2'Ph), 73.2, 73.0 (C-4), 72.9, 72.5 (OCH_2Ph, OCH_2'Ph), 54.7, 53.4 (C-2, C-2'), 40.1, 39.6 (C-7, C-7') 28.41, 28.34, 28.32, 28.21 (CH_3 Boc, CH_2), 25.7, 25.1 (CH_2, CH_2'), 22.5, 22.3 (CH_2, CH_2'), 14.0 (CH_3). HRMS (ESI) m/z: [M+H]+ calcd for $C_{43}H_{51}N_2O_9$: 739.3595; found: 739.3594. Potassium carbonate (447 mg, 3.19 mmol) was added to a solution of this ester (236 mg, 0.319 mmol) in MeOH/THF (10 mL/5 mL). The mixture was stirred at room temperature for 2 h, extracted with EtOAc. The organic layer was washed with H_2O, dried over $MgSO_4$ and concentrated after filtration. The residue was purified by flash chromatography (EtOAc/PE 10:90) to afford azepane **6a** as a colorless oil (169 mg, 90%; 82% for 2 steps); $[\alpha]_D$ = -13 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 7.32-7.26 (m, 15H, ArH), 4.77-4.26 (m, 7H, 3 x OCH_2Ph, H-2), 4.04-3.54 (m, 6H, H-3, H-4, H-5, H-6, 2 x H-7), 2.75 (br. s, 1H, OH), 1.67-1.59 (m, 2H, CH_2), 1.47, 1.45 (2 x s, 9H, tBu), 1.32-1.14 (m, 4H, 2 x CH_2), 0.86 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 155.6 (2 x C=O), 138.5, 138.3, 138.2, 138.1 (aromatic Cipso), 128.4–127.6 (aromatic CH), 84.4, 83.8, 82.9, 82.8, 81.1, 80.6 (C-3, C-4, C-5), 80.2, 80.0 (Boc), 74.4, 74.0, 73.8, 73.5, 73.2, 73.0 (3 x OCH_2Ph, 3 x OCH_2'Ph), 71.5, 70.6 (C-6, C-6'), 54.9, 53.8 (C-2, C-2'), 44.1, 43.3 (C-7, C-7'), 28.53, 28.45, 28.39, 28.35 (CH_3 Boc, CH_2), 26.7 (CH_2), 22.5, 22.3 (CH_2, CH_2'), 14.0 (CH_3). HRMS (ESI) m/z: [M+H]+ calcd for $C_{36}H_{47}NO_6$: 590.3482; found: 590.3480.

(2R,3S,4R,5R,6S)-tert-butyl-3,4,5-tris(benzyloxy)-2-hexyl-6-hydroxyazepane-1-carboxylate (6b). The same procedure as for compound **6a** was applied to compound **5b** to afford the inverted ester (467 mg, 89%); $[\alpha]_D$ = 63 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 8.17-8.03 (m, 4H, ArH), 7.38-7.20 (m, 15H, ArH), 5.40, 5.30 (2 x m, 1H, H-6, H-6'), 4.73-4.41 (m, 6.5H, 3 x OCH_2Ph, 3 x OCH_2'Ph, H-2), 4.46-4.41 (m, 0.5H, H-2'), 4.33 (dd, J = 15.3 Hz, J = 4.0 Hz, 0.5H, H-7), 4.19 (dd, J = 15.7 Hz, J = 3.9 Hz, 0.5H, H-7'), 4.03 (dd, J = 6.9 Hz, J = 3.2 Hz, 0.5H, H-5), 3.95-3.89 (m, 1.5H, H-5', H-4, H-4'), 3.80 (dd, J = 6.9 Hz, J = 3.4 Hz, 0.5H, H-3), 3.78 (dd, J = 6.9 Hz, J = 3.6 Hz, 0.5H, H-3'), 3.59 (dd, J = 15.7 Hz, J = 2.4 Hz, 0.5H, H-7'), 3.54 (dd, J = 15.3 Hz, J = 2.9 Hz, 0.5H, H-7), 1.93-1.63 (m, 2H, CH_2), 1.41-1.26 (m, 17H, $C(CH_3)_3$, 4 x CH_2), 0.88, 0.87 (2t, 3H, J = 7.0 Hz, CH_3, CH_3'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 163.6 (2 x C=O), 155.8, 155.5 (2 x C=O), 150.4, 150.3, 138.3, 138.2, 138.0, 137.9, 137.7, 135.8, 135.4 (aromatic Cipso), 130.8, 130.7, 128.4-127.6, 123.5, 123.2 (aromatic CH), 83.3 (C-4), 81.9, 81.6 (C-3), 80.1, 80.0 (C-5), 79.9, 79.8 (Boc), 73.4, 73.3, 73.2, 73.1 (2 x OCH_2Ph, 2 x OCH_2'Ph), 73.2, 73.0 (C-6), 72.9, 72.4 (OCH_2Ph, OCH_2'Ph), 54.5, 53.4 (C-2, C-2'), 40.1, 39.5 (C-7, C-7'), 31.7 (CH_2, CH_2'), 29.0, 28.8 (CH_2, CH_2'), 28.3, 28.2 (CH_3 Boc), 26.2, 26.1 (CH_2, CH_2'), 25.9, 25.4 (CH_2, CH_2'), 22.7, 22.6 (CH_2, CH_2'), 14.0 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{45}H_{55}N_2O_9$: 767.3908; found: 767.3902. The same ester hydrolysis procedure than above furnished azepane **6b** as a colorless oil (323 mg, 90 %; 80% for 2 steps); $[\alpha]_D$ = -12.2 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (presence of 2

rotamers) 7.32-7.25 (m, 15H, ArH), 4.77-4.28 (m, 7H, 3 x OCH_2Ph, H-2), 4.04-3.49 (m, 6H, H-3, H-4, H-5, H-6, 2 x H-7), 2.80 (br. s, 1H, OH), 1.71-1.60 (m, 2H, CH_2), 1.48, 1.45 (2 x s, 9H, tBu), 1.25 (m, 8H, 4 x CH_2), 0.86 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 155.7 (2 x C=O), 138.6, 138.5, 138.4, 138.3, 138.28, 138.2 (aromatic Cipso), 128.5-127.7 (aromatic CH), 84.4, 83.9, 82.9, 81.2, 80.7 (C-3, C-4, C-5), 80.3, 80.0 (Boc), 74.4, 74.0, 73.8, 73.6, 73.3, 73.1 (3 x OCH_2Ph, 3 x OCH_2'Ph), 71.6, 70.6 (C-6, C-6'), 54.9, 53.9 (C-2, C-2'), 44.2, 43.3 (C-7, C-7'), 31.8 (CH_2), 29.2, 29.0 (CH_2, CH_2'), 28.54, 28.49 (CH_3 Boc), 27.0, 26.9 (CH_2, CH_2'), 26.4, 26.2 (CH_2, CH_2'), 22.72, 22.68 (CH_2, CH_2'), 14.0 (CH_3). HRMS (ESI) m/z: [M+H]+ calcd for $C_{38}H_{52}NO_6$: 618.3795; found: 618.3789.

(2R,3S,4R,5R,6S)-tert-butyl-3,4,5-tris(benzyloxy)-2-nonyl-6-hydroxyazepane-1-carboxylate (6c). The same procedure as for compound **6a** afforded the inverted ester (384 mg, 84%); $[\alpha]_D$ = 58 (c 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 8.18-8.04 (m, 4H, ArH), 7.36-7.20 (m, 15H, ArH), 5.38, 5.29 (2 x m, 1H, H-6, H-6'), 4.72-4.54 (m, 6.5H, 3 x OCH_2Ph, 3 x OCH_2'Ph, H-2), 4.44-4.40 (m, 0.5H, H-2'), 4.33 (dd, J = 15.3 Hz, J = 4.0 Hz, 0.5H, H-7), 4.18 (dd, J = 15.7 Hz, J = 3.9 Hz, 0.5H, H-7'), 4.02 (dd, J = 6.9 Hz, J = 3.2 Hz, 0.5H, H-5), 3.94-3.88 (m, 1.5H, H-5', H-4, H-4'), 3.79 (dd, J = 6.8 Hz, J = 3.4 Hz, 0.5H, H-3), 3.78 (dd, J = 6.7 Hz, J = 3.6 Hz, 0.5H, H-3'), 3.58 (dd, J = 15.7 Hz, J = 2.5 Hz, 0.5H, H-7'), 3.53 (dd, J = 15.3 Hz, J = 2.9 Hz, 0.5H, H-7), 1.88-1.61 (m, 2H, CH_2), 1.40-1.20 (m, 23H, $C(CH_3)_3$, 7 x CH_2), 0.89, 0.87 (2 x t, 3H, J = 7.0 Hz, CH_3, CH_3'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 163.6 (2 x C=O), 155.9, 155.5 (2 x C=O), 150.4, 150.3, 138.3, 138.2, 138.0, 137.7, 137.6, 135.8, 135.4 (aromatic Cipso), 130.8, 130.7, 128.4-127.6, 123.5, 123.3 (aromatic CH), 83.2, (C-4), 81.9, 81.6 (C-3), 80.1, 79.9 (C-5), 80.0, 79.8 (Boc), 73.43, 73.4, 73.3, 73.2 (2 x OCH_2Ph, 2 x OCH_2'Ph), 73.16, 73.0 (C-6), 72.9, 72.4 (OCH_2Ph, OCH_2'Ph), 54.5, 53.4 (C-2, C-2'), 40.1, 39.5 (C-7, C-7'), 31.9 (CH_2, CH_2'), 29.64, 29.58, 29.54, 29.4, 29.3, 29.2 (4 x CH_2, 4 x CH_2'), 28.3, 28.2 (CH_3 Boc), 26.2, 26.1 25.9, 25.4 (2 x CH_2, 2 x CH_2'), 22.7 (CH_2, CH_2'), 14.1 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{48}H_{61}N_2O_9$: 809.4377; found: 809.4372. The same ester hydrolysis procedure than above afforded azepane **6c** as a colorless oil (219 mg, 70 %; 59% for 2 steps); $[\alpha]_D$ = -6 (c 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 7.31-7.27 (m, 15H, ArH), 4.78-4.27 (m, 7H, 3 x OCH_2Ph, H-2), 4.04-3.49 (m, 6H, H-3, H-4, H-5, H-6, 2 x H-7), 1.69-1.54 (m, 2H, CH_2), 1.47, 1.45 (2 x s, 9H, tBu), 1.24 (m, 14H, 7 x CH_2), 0.88 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 155.6 (2 x C=O), 138.6, 138.5, 138.4, 138.3, 138.28, 138.2 (aromatic Cipso), 128.5-127.7 (aromatic CH), 84.4, 83.9, 82.9, 81.1, 80.5 (C-3, C-4, C-5), 80.2, 80.0 (Boc), 74.4, 74.0, 73.8, 73.6, 73.3, 73.0 (3 x OCH_2Ph, 3 x OCH_2'Ph), 71.5, 70.6 (C-6, C-6'), 54.9, 53.8 (C-2, C-2'), 44.2, 43.3 (C-7, C-7'), 31.9 (CH_2), 29.64, 29.60, 29.56, 29.35, 29.32 (CH_2, CH_2'), 28.46, 28.41 (CH_3 Boc), 27.0, 26.9 (CH_2, CH_2'), 26.4, 26.2 (CH_2, CH_2'), 22.7 (CH_2), 14.1 (CH_3). HRMS (ESI) m/z: [M+H]+ calcd for $C_{41}H_{58}NO_6$: 660.4264; found: 660.4259.

(2R,3S,4R,5R,6S)-tert-butyl-3,4,5-tris(benzyloxy)-2-dodecyl-6-hydroxyazepane-1-carboxylate (6d). The same procedure as for compound **6a** afforded the inverted ester (161 mg, 84%); $[\alpha]_D$ = 59 (c 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 8.19-8.04 (m, 4H, ArH), 7.37-7.19 (m, 15H, ArH), 5.38, 5.29 (2 x m, 1H, H-6, H-6'), 4.71-4.54 (m, 6.5H, 3 x OCH_2Ph, 3 x OCH_2'Ph, H-2), 4.42 (m, 0.5H, H-2'), 4.31 (dd, J = 15.4 Hz, J = 4.08 Hz, 0.5H, H-7), 4.17 (dd, J = 15.7 Hz, J = 3.8 Hz, 0.5H, H-7'), 4.02 (dd, J = 6.9 Hz, J = 3.2 Hz, 0.5H, H-5), 3.94-3.88 (m, 1.5H, H-5', H-4, H-4'), 3.78 (dd, J = 6.8 Hz, J = 3.4 Hz, 0.5H, H-3), 3.76 (dd, J = 6.8 Hz, J = 3.7 Hz, 0.5H, H-3'), 3.58 (dd, J = 15.7 Hz, J = 2.6 Hz, 0.5H, H-7'), 3.53 (dd, J = 15.4 Hz, J = 2.9 Hz, 0.5H, H-7), 1.87-1.61 (m, 2H, CH_2), 1.40-1.20 (m, 29H, $C(CH_3)_3$, 10 x CH_2), 0.88 (t, 3H, J = 7.0 Hz, CH_3, CH_3'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 163.6 (2 x C=O), 155.9, 155.5 (2 x C=O), 150.5, 150.3, 138.3, 138.2, 138.0, 137.9, 137.7, 137.6, 135.8, 135.4 (aromatic Cipso), 130.9, 130.8, 128.4-127.6, 123.5, 123.3 (aromatic CH), 83.2, (C-4), 81.9, 81.6 (C-3), 80.1, 80.0 (C-5), 79.9, 79.8 (Boc), 73.44, 73.42, 73.3, 73.2 (2 x OCH_2Ph, 2 x OCH_2'Ph), 73.1, 73.0 (C-6), 72.9, 72.5 (OCH_2Ph, OCH_2'Ph), 54.5, 53.4 (C-2, C-2'), 40.1, 39.5 (C-7, C-7'), 31.9 (CH_2, CH_2'), 29.72, 29.69, 29.58, 29.45, 29.40, 29.3, (CH_2, CH_2'), 28.3, 28.2 (CH_3 Boc), 26.3, 26.2 25.9, 25.4 (CH_2, CH_2'), 22.7 (CH_2, CH_2'), 14.1 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{51}H_{67}N_2O_9$: 851.4847; found: 851.4841. The same ester hydrolysis procedure than above afforded azepane **6d** as a colorless oil (100 mg, 87 %; 73% for 2 steps); $[\alpha]_D$ = -11 (c 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 7.33-7.23 (m, 15H, ArH), 4.78-4.46 (m, 6.5H, 3 x OCH_2Ph, H-2'), 4.28 (m, 0.5H, H-2), 4.04-3.49 (m, 6H, H-3, H-4, H-5, H-6, 2 x H-7), 1.69-1.57 (m, 2H, CH_2), 1.47, 1.45 (2 x s, 9H, tBu), 1.25 (m, 20H, 10 x CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 155.6 (2 x C=O), 138.6, 138.5, 138.3, 138.2 (aromatic Cipso), 128.5-127.6 (aromatic CH), 84.4, 83.83, 83.81, 81.1, 80.5 (C-3, C-4, C-5), 80.2, 80.1 (Boc), 74.4, 74.0, 73.8, 73.6, 73.3, 73.0 (3 x OCH_2Ph, 3 x OCH_2'Ph), 71.6, 70.6 (C-6, C-6'), 54.9, 53.8 (C-2, C-2'), 44.2, 43.3 (C-7, C-7'), 31.9 (CH_2), 29.73, 29.70, 29.61, 29.55, 29.4, 29.3 (CH_2, CH_2'), 28.5, 28.4 (CH_3 Boc), 27.0, 26.4, 26.2 (CH_2, CH_2'), 22.7 (CH_2), 14.1 (CH_3). HRMS (ESI) m/z: [M+H]+ calcd for $C_{44}H_{64}NO_6$: 702.4734; found: 702.4728.

(2R,3S,4R,5R,6S)-2-butylazepane-3,4,5,6-tetraol (7a). Trifluoroacetic acid (1 mL) was added to a solution of azepane **6a** (169 mg, 0.287 mmol) in anhydrous dichloromethane (10 mL) at 0 °C. The mixture was stirred at room temperature for 3 h and concentrated in vacuo. The residue was diluted with DMF (3 mL) then K_2CO_3 (120 mg, 0.86 mmol) and benzyl bromide (0.1 mL, 0.86 mmol) were added at 0 °C. The mixture was stirred at room temperature for 14 h, quenched with H_2O, and extracted with EtOAc/toluene (2:1). The organic layers were washed with H_2O and brine, dried with $MgSO_4$ and concentrated in vacuo after filtration. The residue was purified by flash chromatography (EtOAc/PE 10:90) to afford the corresponding *N*-benzyl amine as a colorless syrup (110 mg, 66 % over 2 steps); $[\alpha]_D$ = 49 (c 1.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.32-7.23 (m, 20H, ArH), 4.88 (d, J = 11.2 Hz, 1H, OCHPh), 4.79 (d, J = 11.0 Hz, 1H, OCHPh), 4.72 (d, J = 11.0 Hz, 1H, OCHPh), 4.67 (d, J = 11.5 Hz, 1H, OCHPh), 4.55 (d, J = 11.2 Hz, 1H, OCHPh), 4.44 (d, J = 11.5 Hz, 1H, OCHPh), 3.99 (d, J = 14.1 Hz, 1H, NCHPh), 3.92 (td, J = 8.2 Hz, J = 3.8 Hz, 1H, H-6), 3.80-3.63 (m, 4H, H-4, H-5, H-3, NCHPh), 3.20 (dd, J = 13.7 Hz, J = 3.7 Hz, 1H, H-7), 2.96 (m, 2H, H-2, OH), 2.60 (dd, J = 13.7 Hz, J = 8.3 Hz, 1H, H-7), 1.70-1.28 (m, 6H, 3 x CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 138.7, 138.6, 138.2 (aromatic Cipso), 128.6-126.9 (aromatic CH), 85.1, 84.8, 84.4 (C-3, C-4, C-5), 74.55, 74.47, 73.7, (3 x OCH_2Ph), 68.7 (C-6), 60.6 (C-2), 57.5

(NCH_2Ph), 52.7 (C-7), 30.4 (CH_2), 27.8 (CH_2), 22.9 (CH_2), 14.1 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{38}H_{46}NO_4$: 580.3427; found: 580.3421. To a solution of amine (95 mg, 0.164 mmol) in CH_3OH (8 mL) was added 10% Pd/C (45 mg), Pd black (45 mg) and a 1 M HCl aqueous solution (0.33 mL, 0.33 mmol). The solution was purged with H_2. After stirring overnight at room temperature, the reaction mixture was purged with N_2, filtered on Celite, washed with CH_3OH. The solution was concentrated under reduced pressure, to give **7a** as its hydrochloride salt (41.9 mg, quantitative yield). $[\alpha]_D$ = 1 (c 0.6, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.13 (ddd, J = 9.6 Hz, J = 8.2 Hz, J = 2.0 Hz, 1H, H-6), 3.96 (d, J = 4.7 Hz, 1H, H-3), 3.92 (app. t, J = 4.7 Hz, J = 4.0 Hz, 1H, H-4), 3.62 (dd, J = 8.2 Hz, J = 4.0 Hz, 1H, H-5), 3.47 (dd, J = 9.0 Hz, J = 4.7 Hz, 1H, H-2), 3.30 (dd, J = 13.3 Hz, J = 2.0 Hz, 1H, H-7), 3.10 (dd, J = 13.3 Hz, J = 9.6 Hz, 1H, H-7), 1.78-1.69 (m, 2H, CH_2), 1.42 (m, 4H, 2 x CH_2), 0.97 (t, J = 7.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ 80.9 (C-5), 76.8 (C-4), 71.6 (C-3), 69.4 (C-6), 57.5 (C-2), 49.4 (C-7), 31.8 (CH_2), 28.8 (CH_2), 23.4 (CH_2), 14.2 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{10}H_{22}NO_4$: 220.1549; found: 220.1547.

(2R,3S,4R,5R,6S)-2-hexylazepane-3,4,5,6-tetraol (7b). The same procedure as for compound **7a** was applied to compound **6b** to give the corresponding *N*-benzyl amine as a colorless syrup (208 mg, 68 %, 2 steps); $[\alpha]_D$ = 51 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.23 (m, 20H, ArH), 4.87 (d, J = 11.2 Hz, 1H, OCHPh), 4.79 (d, J = 11.0 Hz, 1H, OCHPh), 4.72 (d, J = 11.0 Hz, 1H, OCHPh), 4.67 (d, J = 11.5 Hz, 1H, OCHPh), 4.55 (d, J = 11.2 Hz, 1H, OCHPh), 4.44 (d, J = 11.5 Hz, 1H, OCHPh), 3.99 (d, J = 14.1 Hz, 1H, NCHPh), 3.92 (td, J = 8.2 Hz, J = 3.8 Hz, 1H, H-6), 3.80-3.73 (m, 2H, H-4, NCHPh), 3.69 (dd, J = 8.2 Hz, J = 3.4 Hz, 1H, H-3), 3.65 (dd, J = 8 Hz, J = 6.7 Hz, 1H, H-5), 3.19 (dd, J = 13.8 Hz, J = 3.8 Hz, 1H, H-7), 2.96 (m, 1H, H-2), 2.60 (dd, J = 13.8 Hz, J = 8.2 Hz, 1H, H-7), 1.71-1.26 (m, 10H, 5 x CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 138.9, 138.7, 138.3 (aromatic Cipso), 128.6-127.0 (aromatic CH), 85.0, 84.8, 84.7 (C-3, C-4, C-5), 74.7, 74.6, 73.9, (3 x OCH_2Ph), 68.8 (C-6), 60.7 (C-2), 57.7 (NCH_2Ph), 52.9 (C-7), 31.9 (CH_2), 29.6 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 22.7 (CH_2), 14.2 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{40}H_{50}NO_4$: 608.3740; found: 608.3735. The same hydrogenolysis procedure as described for compound **7a** afforded compound **7b** as its hydrochloride salt (41 mg, quantitative yield); $[\alpha]_D$ = -2 (c 0.7, CH_3OH); 1H NMR (400 MHz, CD_3OD): δ 4.12 (ddd, J = 9.6 Hz, J = 8.2 Hz, J = 2.2 Hz, 1H, H-6), 3.96 (d, J = 4.8 Hz, 1H, H-3), 3.91 (app. t, J = 4.8 Hz, J = 3.9 Hz, 1H, H-4), 3.62 (dd, J = 8.2 Hz, J = 3.9 Hz, 1H, H-5), 3.47 (dd, J = 9.1 Hz, J = 4.8 Hz, 1H, H-2), 3.30 (dd, J = 13.3 Hz, J = 2.2 Hz, 1H, H-7), 3.10 (dd, J = 13.3 Hz, J = 9.6 Hz, 1H, H-7), 1.81-1.64 (m, 2H, CH_2), 1.45-1.36 (m, 8H, 4 x CH_2), 0.93 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): 80.9 (C-5), 76.8 (C-4), 71.5 (C-3), 69.4 (C-6), 57.4 (C-2), 49.4 (C-7), 31.7 (CH_2), 32.1 (CH_2), 30.0 (CH_2), 26.6 (CH_2), 23.6 (CH_2), 14.4 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{12}H_{26}NO_4$: 248.1862; found: 248.1856.

(2R,3S,4R,5R,6S)-2-nonylazepane-3,4,5,6-tetraol (7c). The same procedure as for compound **7a** was applied to **6c** to give the corresponding *N*-benzyl amine as a colorless syrup (107 mg, 70 %, 2 steps); $[\alpha]_D$ = 44 (c 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.23 (m, 20H, ArH), 4.87 (d, J = 11.2 Hz, 1H, OCHPh), 4.78 (d, J = 11.0 Hz, 1H, OCHPh), 4.71 (d, J = 11.0 Hz, 1H, OCHPh), 4.68 (d, J = 11.5 Hz, 1H, OCHPh), 4.55 (d, J = 11.2 Hz, 1H, OCHPh), 4.44 (d, J = 11.5 Hz, 1H, OCHPh), 3.99 (d, J = 14.0 Hz, 1H, NCHPh), 3.93 (m, 1H, H-6), 3.80-3.73 (m, 2H, H-4, NCHPh), 3.71-3.64 (m, 2H, H-5, H-3), 3.19 (dd, J = 13.8 Hz, J = 3.8 Hz, 1H, H-7), 2.96 (m, 1H, H-2), 2.61 (m , 1H, H-7), 1.76-1.26 (m, 16H, 8 x CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2, 138.7, 138.6, 138.2 (aromatic Cipso), 128.6-127.4 (aromatic CH), 84.8 (br. s, C-3, C-4, C-5), 74.6, 74.5, 73.7, (3 x OCH_2Ph), 68.7 (C-6), 60.6 (C-2), 57.5 (NCH_2Ph), 52.7 (C-7), 31.9 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 28.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{43}H_{56}NO_4$: 650.4209; found: 650.4204. The same hydrogenolysis procedure as described for compound **7a** afforded compound **7c** as its hydrochloride salt (46 mg, quantitative yield); $[\alpha]_D$ = -3 (c 0.5, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.12 (ddd, J = 9.6 Hz, J = 8.2 Hz, J = 2.1 Hz, 1H, H-6), 3.96 (d, J = 4.9 Hz, 1H, H-3), 3.91 (app. t, J = 4.9 Hz, J = 3.9 Hz, 1H, H-4), 3.62 (dd, J = 8.2 Hz, J = 3.9 Hz, 1H, H-5), 3.47 (dd, J = 9.0 Hz, J = 4.8 Hz, 1H, H-2), 3.30 (dd, J = 13.3 Hz, J = 2.1 Hz, 1H, H-7), 3.10 (dd, J = 13.3 Hz, J = 9.6 Hz, 1H, H-7), 1.79-1.64 (m, 2H, CH_2), 1.32 (m, 14H, 7 x CH_2), 0.93 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): 80.9 (C-5), 76.8 (C-4), 71.6 (C-3), 69.4 (C-6), 57.4 (C-2), 49.3 (C-7), 33.0 (CH_2), 32.1 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 26.6 (CH_2), 23.7 (CH_2), 14.4 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{15}H_{32}NO_4$: 290.2331; found: 290.2326.

(2R,3S,4R,5R,6S)-2-dodecylazepane-3,4,5,6-tetraol (7d). The same procedure as for compound **7a** was applied to compound **6d** to give the corresponding *N*-benzyl amine as a colorless syrup (69.5 mg, 74 %, 2 steps); $[\alpha]_D$ = 44 (c 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.22 (m, 20H, ArH), 4.87-4.42 (m, 6H, 3 x OCH_2Ph), 4.03-3.95 (m, 2H, NCHPh, H-6), 3.80-3.64 (m, 4H, NCHPh, H-4, H-5, H-3), 3.19 (dd, J = 13.8 Hz, J = 3.5 Hz, 1H, H-7), 2.99 (m, 1H, H-2), 2.64 (m, 1H, H-7), 1.70-1.60 (m, CH_2), 1.42-1.25 (m, 20H, 10 x CH_2), 0.88 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 138.7, 138.6, 138.2 (aromatic Cipso), 128.5-127.4 (aromatic CH), 84.9 (br. s, C-3, C-4, C-5), 74.5, 73.8, (3 x OCH_2Ph), 68.7 (C-6), 60.6 (C-2), 57.6 (NCH_2Ph), 52.8 (C-7), 31.9 (CH_2), 29.8 (CH_2), 29.72 (CH_2), 29.67 (CH_2), 29.61 (CH_2), 29.4 (CH_2), 28.13 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{46}H_{62}NO_4$: 692.4673; found: 692.4679. The same hydrogenolysis procedure as described for compound **7a** afforded compound **7d** as its hydrochloride salt (35.5 mg, quantitative yield); $[\alpha]_D$ = -3.8 (c 0.7, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.12 (ddd, J = 9.6 Hz, J = 8.2 Hz, J = 2.2 Hz, 1H, H-6), 3.96 (d, J = 4.8 Hz, 1H, H-3), 3.91 (app. t, J = 4.8 Hz, J = 3.9 Hz, 1H, H-4), 3.62 (dd, J = 8.2 Hz, J = 3.9 Hz, 1H, H-5), 3.47 (dd, J = 9.1 Hz, J = 4.8 Hz, 1H, H-2), 3.31 (dd, J = 13.3 Hz, 2.2 Hz, 1H, H-7), 3.10 (dd, J = 13.3 Hz, J = 9.6 Hz, 1H, H-7), 1.82-1.61 (m, 2H, CH_2), 1.31 (m, 20H, 10 x CH_2), 0.91 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): 80.9 (C-5), 76.8 (C-4), 71.6 (C-3), 69.4 (C-6), 57.4 (C-2), 49.3 (C-7), 33.0 (CH_2), 32.1 (CH_2), 30.8 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 30.50 (CH_2), 30.48 (CH_2), 30.36 (CH_2), 26.7 (CH_2), 23.7 (CH_2), 14.5 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{18}H_{38}NO_4$: 332.2801; found: 322.2795.

***C*-alkyl azepanes 10b-d and 13b-d**. General procedure for cross metathesis reactions and subsequent deprotection reactions: To a solution of azepane **8** or **11** (0.20 mmol) in dry dichloromethane (6 mL) under Ar were added first (0.06 to 0.12 equiv.) or second generation Hoveyda-Grubbs catalyst (0.3 to

0.4 equiv.) and alkene (4.0 equiv. for 1-octene and 1-undecene, 13.0 equiv. for 1-pentene). The reaction mixture was stirred for 24 to 48h at 40 °C under Ar. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (PE/EtOAc 9:1 to 8:2) to afford compounds **9b-d** (42-67% yield) and **12b-d** (60-83% yield). Trifluoroacetic acid (0.4 mL) was added to a solution of azepane **9b-d** or **12b-d** (0.150 mmol) in anhydrous dichloromethane (4.0 mL) at 0 °C. The mixture was stirred at room temperature for 3 h and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc/MeOH 100:0 to 90:10). To a solution of the obtained amine in a mixture EtOH/EtOAc (1:1, 6 mL) were added 10% Pd/C (45 mg) and a 1 M HCl aqueous solution (0.50 mL). The mixture was stirred under H_2 atmosphere for 24 h, filtered on Celite and washed with CH_3OH. The solution was concentrated under reduced pressure, diluted with water and freeze-dried to give **10b-d** and **13b-d** (quantitative yields, 2 steps) as hydrochloride salts.

(2S,3S,4R,5R,6R)-2-hexylazepane-3,4,5,6-tetraol (10b).
According to the general procedure described above, cross metathesis between **8** (135 mg, 0.235 mmol) and 1-pentene (0.350 mL, 3.05 mmol) in the presence of Hoveyda-Grubbs I catalyst (9.1 mg, 0.06 eq, 15.2 µmol) gave **9b** (61 mg, 42%). TFA hydrolysis (0.30 mL) followed by hydrogenolysis gave **10b** (28 mg, quant.) as a white foam. $[\alpha]_D$ = -13 (c 0.4, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.23 (m, 1H, H-6), 3.86 (app. t, J = 7.3 Hz, 1H, H-4), 3.81 (dd, J = 2.2 Hz, J = 7.5 Hz, 1H, H-5), 3.66 (t, J = 7.5 Hz, 1H, H-3), 3.41 (m, 1H, H-2), 3.29 (m, 2H, H-7), 1.95 (m, 1H, CH), 1.78 (m, 1H, CH), 1.56 (m, 1H, CH), 1.37 (m, 7H, CH, 3 x CH_2), 0.93 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): 76.5 (C-5), 74.4 (C-4), 73.2 (C-3), 67.5 (C-6), 61.5 (C-2), 46.1 (C-7), 32.6 (CH_2), 31.6 (CH_2), 30.2 (CH_2), 26.0 (CH_2), 23.6 (CH_2), 14.3 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{12}H_{26}NO_4$: 248.1856; found: 248.1851.

(2S,3S,4R,5R,6R)-2-nonylazepane-3,4,5,6-tetraol (10c).
According to the general procedure described above, cross metathesis between **8** (129 mg, 0.226 mmol) and 1-octene (0.150 mL, 0.904 mmol) in the presence of Hoveyda-Grubbs II catalyst (49.5 mg, 0.35 eq, 79.1 µmol) gave **9c** (68 mg, 46%). TFA hydrolysis (0.30 mL) followed by hydrogenolysis gave **10c** (32 mg, quant.) as a white foam. $[\alpha]_D$ = +11 (c 0.4, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.22 (m, 1H, H-6), 3.85 (m, 1H, H-4), 3.80 (m, 1H, H-5), 3.65 (m, 1H, H-3), 3.40 (m, 1H, H-2), 3.28 (m, 2H, H-7), 1.95 (m, 1H, CH), 1.77 (m, 1H, CH), 1.56 (m, 1H, CH), 1.50-1.30 (m, 13H, 1 x CH, 6 x CH_2), 0.93 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): 76.5 (C-5), 74.5 (C-4), 73.3 (C-3), 67.4 (C-6), 61.6 (C-2), 46.1 (C-7), 33.1 (CH_2), 31.6 (CH_2), 30.7 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 26.1 (CH_2), 23.7 (CH_2), 14.4 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{15}H_{32}NO_4$: 290.2326; found: 290.2328.

(2S,3S,4R,5R,6R)-2-dodecylazepane-3,4,5,6-tetraol (10d).
According to the general procedure described above, cross metathesis between **8** (130 mg, 0.226 mmol) and 1-undecene (0.186 mL, 0.906 mmol) in the presence of Hoveyda-Grubbs II catalyst (42.5 mg, 0.3 eq, 67.9 µmol) gave **9d** (106 mg, 67%). TFA hydrolysis (0.40 mL) followed by hydrogenolysis gave **10d** (56 mg, quant.) as a white foam. $[\alpha]_D$ = -8 (c 1.2, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.25 (m, 1H, H-6), 3.88 (app. t, J = 7.5 Hz, 1H, H-4), 3.83 (dd, J = 2.1 Hz, J = 7.6 Hz, 1H, H-5), 3.69 (t, J = 7.5 Hz, 1H, H-3), 3.42 (m, 1H, H-2), 3.31 (m, 2H, H-7), 1.95 (m, 1H, CH), 1.79 (m, 1H, CH), 1.57 (m, 1H, CH), 1.50-1.28 (m, 19H, 1 x CH, 9 x CH_2), 0.91 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): 76.4 (C-5), 74.2 (C-4), 73.0 (C-3), 67.4 (C-6), 61.4 (C-2), 46.0 (C-7), 33.0 (CH_2), 31.6 (CH_2), 30.7 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 26.1 (CH_2), 23.7 (CH_2), 14.4 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{18}H_{38}NO_4$: 332.2795; found: 332.2798.

(2S,3S,4R,5R,6S)-2-hexylazepane-3,4,5,6-tetraol (13b).
According to the general procedure described above, cross metathesis between **11** (133 mg, 0.231 mmol) and 1-pentene (0.330 mL, 3.01 mmol) in the presence of Hoveyda-Grubbs I catalyst (17.2 mg, 0.12 eq, 28.6 µmol) gave **12b** (86 mg, 60%). TFA hydrolysis (0.35 mL) followed by hydrogenolysis gave **13b** (40 mg, quant.) as a white foam. $[\alpha]_D$ = -2 (c 1.0, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.04 (ddd, J = 2.0 Hz, J = 6.6 Hz, J = 8.4 Hz, 1H, H-6), 3.83 (t, J = 7.5 Hz, 1H, H-3), 3.77 (t, J = 6.5 Hz, 1H, H-5), 3.72 (app. t, J = 7.0 Hz, J = 6.7 Hz, 1H, H-4), 3.37 (m, 1H, H-7), 3.26 (m, 2H, H-2, H-7), 1.98 (m, 1H, CH), 1.76 (m, 1H, CH), 1.53 (m, 2H, CH_2), 1.36 (m, 6H, 3 x CH_2), 0.93 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): 77.8 (C-4), 77.6 (C-5), 72.2 (C-3), 69.1 (C-6), 62.4 (C-2), 47.6 (C-7), 32.6 (CH_2), 31.2 (CH_2), 30.3 (CH_2), 26.3 (CH_2), 23.6 (CH_2), 14.3 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{12}H_{26}NO_4$: 248.1856; found: 248.1860.

(2S,3S,4R,5R,6S)-2-nonylazepane-3,4,5,6-tetraol (13c).
According to the general procedure described above, cross metathesis between **11** (130 mg, 0.226 mmol) and 1-octene (0.142 mL, 0.901 mmol) in the presence of Hoveyda-Grubbs II catalyst (56.6 mg, 0.40 eq, 90.4 µmol) gave **12c** (102 mg, 69%). TFA hydrolysis (0.40 mL) followed by hydrogenolysis gave **13c** (50 mg, quant.) as a yellowish foam. $[\alpha]_D$ = -6 (c 0.5, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.00 (ddd, J = 2.1 Hz, J = 6.4 Hz, J = 8.4 Hz, 1H, H-6), 3.80 (t, J = 7.5 Hz 1H, H-3), 3.75 (t, J = 6.2 Hz 1H, H-5), 3.67 (app. t, J = 6.4 Hz, J = 7.1 Hz, 1H, H-4), 3.57 (m, 1H, H-7), 3.20 (m, 2H, H-2, H-7), 1.98 (m, 1H, CH), 1.71 (m, 1H, CH), 1.51 (m, 2H, CH_2), 1.48 (m, 12H, 6 x CH_2), 0.93 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): 78.1 (C-4), 77.6 (C-5), 72.4 (C-3), 69.1 (C-6), 62.5 (C-2), 47.6 (C-7), 33.0 (CH_2), 31.2 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 26.3 (CH_2), 23.7 (CH_2), 14.4 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{15}H_{32}NO_4$: 290.2326; found: 290.2322.

(2S,3S,4R,5R,6S)-2-dodecylazepane-3,4,5,6-tetraol (13d).
According to the general procedure described above, cross metathesis between **11** (44 mg, 0.08 mmol) and 1-octene (0.070 mL, 0.310 mmol) in the presence of Hoveyda-Grubbs II catalyst (14.4 mg, 0.30 eq, 23.0 µmol) gave **12d** (45 mg, 83%). TFA hydrolysis (0.15 mL) followed by hydrogenolysis gave **13d** (25 mg, quant.) as a yellowish foam. $[\alpha]_D$ = -9 (c 0.5, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.04 (ddd, J = 1.9 Hz, J = 6.5 Hz, J = 8.2 Hz, 1H, H-6), 3.83 (t, J = 7.5 Hz, 1H, H-3), 3.76 (t, J = 6.3 Hz, 1H, H-5), 3.70 (app. t, J = 7.0 Hz, J = 7.3 Hz, 1H, H-4), 3.38 (m, 1H, H-7), 3.26 (m, 2H, H-2, H-7), 1.98 (m, 1H, CH), 1.75 (m, 1H, CH), 1.52 (m, 2H, CH_2), 1.33 (m, 18H, 9 x CH_2), 0.91 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): 78.0 (C-4), 77.6 (C-5), 72.3 (C-3), 69.1 (C-6), 62.5 (C-2), 47.6 (C-7), 33.0 (CH_2), 31.2 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 30.6 (CH_2), 30.4 (CH_2), 26.3 (CH_2), 23.7 (CH_2), 14.4 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{18}H_{38}NO_4$: 332.2795; found: 332.2797.

(3R,4R,5R,6S)-4,5,6-tris(benzyloxy)azepan-3-ol (14). $NaBH_3CN$ (190 mg, 3.01 mmol) was added to a solution of **2** (520 mg, 1.20 mmol) in CH_3COOH (4 mL). The reaction was stirred at room temperature for 14 h, quenched with a 1N NaOH aqueous solution and extracted with CH_2Cl_2. The organic layer was washed sequentially with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure after filtration to afford compound **14** as a colorless oil (386 mg, 74%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, 15H, ArH), 4.69-4.52 (m, 6H, 3 x OCH_2Ph), 4.00 (dt, J = 5.6 Hz, J = 1.6 Hz, 1H, H-3), 3.93 (ddd, J = 6.1 Hz, J = 2.5 Hz, J = 0.8 Hz, 1H, H-5), 3.70 (dd, J = 6.0 Hz, J = 1.6 Hz, 1H, H-4), 3.54 (ddd, J = 6.0 Hz, J = 2.5Hz, J = 0.8 Hz, 1H, H-6), 3.15 (dd, J = 15.2 Hz, J = 6.0 Hz, 1H, H-7a), 3.09 (dd, J = 14.4 Hz, J = 5.6 Hz, 1H, H-2a), 2.83 (dd, J = 15.2 Hz, J = 0.8 Hz, 1H, H-7b), 2.75 (dd, J = 14.4 Hz, J = 1.6 Hz, 1H, H-2b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 138.0, 137.0 (aromatic Cipso), 128.6-127.6 (aromatic CH), 86.3 (C-4), 82.7 (C-5), 78.0 (C-6), 73.1 (OCH_2Ph), 72.4 (OCH_2Ph), 71.7 (C-3), 71.6 (OCH_2Ph), 52.0 (C-2), 46.7 (C-7).

(3R,4R,5R,6S)-4,5,6-tris(benzyloxy)-1-butylazepan-3-ol (15a). Potassium carbonate (128 mg, 0.927 mmol) was added to a stirred solution of azepane **14** (80 mg, 0.184 mmol) and n-butyl bromide (40 µL, 0.37 mmol) in a 8:1 mixture of EtOAc/H_2O (12:2 mL) under nitrogen. The reaction mixture was stirred at 85° C for 18h, by which time TLC revealed no trace of starting material. The reaction mixture was extracted with EtOAc, the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC chromatography (EA/PE, 50:50) afforded the corresponding azepane **15a** (51 mg, 56%); $[\alpha]_D$ = 12 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.23 (m, 15H, ArH), 4.70-4.52 (m, 6H, 3 x OCH_2Ph), 4.01 (br. d, J = 6.5 Hz, 1H, H-3), 3.92 (dd, J = 6.3 Hz, J = 3.9 Hz, 1H, H-5), 3.64 (dd, J = 6.3Hz, J = 1.4 Hz, 1H, H-4), 3.65-3.60 (m, 1H, H-6), 2.96-2.90 (m, 2H, H-7a, H-2a), 2.60 (dd, J = 14.0 Hz, J = 1.1 Hz, 1H, H-7b), 2.54-2.49 (m, 3H, NCH_2, H-2b), 1.46-1.40 (m, 2H, CH_2), 1.33-1.25 (m, 2H, CH_2), 0.89 (t, J = 7.3 Hz, 1H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.4, 138.03 (aromatic Cipso), 128.4-127.5 (aromatic CH), 85.09 (C-4), 83.7 (C-5), 79.2 (C-6), 73.3, 72.5, 71.2 (3 x CH_2Ph), 70.0 (C-3), 58.9 (NCH_2Ph), 58.8 (C-2), 53.9 (C-7), 29.3 (CH_2), 20.4 (CH_2), 14.0 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{31}H_{40}NO_4$: 490.2957; found: 490.2957.

(3R,4R,5R,6S)-4,5,6-tris(benzyloxy)-1-hexylazepan-3-ol (15b). Compound **15b** was obtained by alkylation of **14** (77 mg, 0.177 mmol), with hexyl bromide, as described above to afford a colourless syrup (50 mg, 54%); $[\alpha]_D$ = 11.5 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.23 (m, 15H, ArH), 4,70-4,51 (m, 6H, 3 x OCH_2Ph), 4.01 (br. d, J = 6.1 Hz, 1H, H-3), 3.92 (dd, J = 6.3 Hz, J = 3.9 Hz, 1H, H-5), 3.65 (dd, J = 6.3 Hz, J = 1.2 Hz, 1H, H-4), 3.65-3.60 (m, 1H, H-6), 2.96-2.90 (m, 2H, H-7a, H-2a), 2.60 (d, J = 13.9 Hz, 1H, H-7b), 2.54-2.50 (m, 3H, NCH_2Ph, H-2b), 1.46-1.41 (m, 2H, CH_2), 1.26 (m, 6H, 3 x CH_2), 0.87 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.4, 138.0 (aromatic C), 128.4-127.5 (aromatic CH), 85.1 (C-4), 83.7 (C-5), 79.2 (C-6), 73.3, 72.5, 71.2 (3 x CH_2Ph), 70.0 (C-3), 59.3 (NCH_2Ph), 58.9 (C-2), 53.9 (C-7), 31.8 (CH_2), 27.2 (CH_2), 27.0 (CH_2), 22.6 (CH_2), 14.0 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{33}H_{44}NO_4$: 518.3270; found: 518.3270.

(3R,4R,5R,6S)-4,5,6-tris(benzyloxy)-1-nonylazepan-3-ol (15c). Compound **15c** was obtained by alkylation of **14** (82.5 mg, 0.190 mmol), with nonyl bromide, as described above to afford a colourless syrup (61 mg, 57 %); $[\alpha]_D$ = 9 (c 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.23 (m, 15H, ArH), 4.69-4.52 (m, 6H, 3 x OCH_2Ph), 4.03 (br. d, J = 6.4 Hz, 1H, H-3), 3.91 (dd, J = 6.3 Hz, J = 4.0 Hz, 1H, H-5), 3.65 (dd, J = 6.3 Hz, J = 1.3 Hz, 1H, H-4), 3.65-3.61 (m, 1H, H-6), 2.97-2.90 (m, 2H, H-2a, H-7a), 2.61 (dd, J = 13.9 Hz, J = 0.9 Hz, 1H, H-7b), 2.54-2.50 (m, 3H, NCH_2Ph, H-2b), 1.46 (m, 2H, CH_2), 1.25 (m, 12H, 6 x CH_2), 0.87 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.4, 138.0 (aromatic Cipso), 128.4-127.5 (aromatic CH), 85.1 (C-4), 83.7 (C-5), 79.2 (C-6), 73.3, 72.4, 71.2 (3 CH_2Ph), 70.0 (C-3), 59.3 (NCH_2Ph), 58.8 (C-2), 53.9 (C-7), 31.9 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{36}H_{50}NO_4$: 560.3739; found: 560.3735.

(3R,4R,5R,6S)-4,5,6-tris(benzyloxy)-1-dodecylazepan-3-ol (15d). Compound **15d** was obtained by alkylation of **14** (78 mg, 0.180 mmol), with dodecyl bromide, as described above as a colourless syrup (58 mg, 53 %); $[\alpha]_D$ = 9.4 (c 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.24 (m, 15H, ArH), 4.69-4.51 (m, 6H, 3 x OCH_2Ph), 4.02 (br. d, J = 6.3 Hz, 1H, H-3), 3.91 (dd, J = 6.3 Hz, J = 4.0 Hz, 1H, H-5), 3,65 (dd, J = 6.3 Hz, J = 1.4 Hz, 1H, H-4), 3.65-3.58 (m, 1H, H-6), 2.97-2.90 (m, 2H, H-2a, H-7a), 2.60 (dd, J = 13.9 Hz, J = 0.9 Hz, 1H, H-7b), 2.54-2.50 (m, 3H, NCH_2Ph, H-2b), 1.45 (m, 2H, CH_2), 1.25 (m, 20H, 10 x CH_2), 0.87 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.4, 138.0 (aromatic Cipso), 128.4-127.5 (aromatic CH), 85.1 (C-4), 83.7 (C-5), 79.2 (C-6), 73.4, 72.5, 71.2 (3 x CH_2Ph), 70.0 (C-3), 59.3 (NCH_2Ph), 58.9 (C-2), 53.9 (C-7), 31.9 (CH_2), 29.71 (CH_2), 29.68 (CH_2), 29.64 (CH_2), 29.48 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 25.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{39}H_{56}NO_4$: 602.4209; found: 602.4209.

(3R,4R,5R,6S)-1-butylazepane-3,4,5,6-tetraol (16a). To a solution of protected compound **15a** (48 mg, 0.098 mmol) in CH_3OH (6 mL) was added 10% Pd/C (25 mg), Pd black (25 mg) and a 1 M HCl aqueous solution (0.20 mL, 0.2 mmol). The solution was purged with N_2 then with H_2. After stirring overnight at room temperature under H_2 atmospher, the reaction mixture was filtered on Celite, washed with CH_3OH. To the solution, was added a 7N ammonia solution in methanol (0.2 mL), then the mixture was concentrated under reduced pressure, to give **16a** (21.4 mg, quantitative yield); $[\alpha]_D$ = -5.8 (c 0.4, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.17 (dd, J = 6.5 Hz, J = 3.8 Hz, 1H), 3.79 (m, 3H), 3.23-3.10 (m, 4H, H-2a, H-2b, H-7a, H-7b), 2.95 (t, J = 7.8 Hz, 2H, NCH_2), 1.70-1.63 (m, 2H, CH_2), 1.45-1.38 (m, 2H, CH_2), 0.99 (t, J = 7.3 Hz, 1H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ 77.4, 75.8, 72.4, 68.9 (C-3, C-4, C-5, C-6), 60.1 (NCH_2), 57.6, 57.2 (C-2, C-7), 28.6 (CH_2), 21.1 (CH_2), 14.1 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{10}H_{22}NO_4$: 220.1548; found: 220.1548.

(3R,4R,5R,6S)-1-hexylazepane-3,4,5,6-tetraol (16b). The same hydrogenolysis procedure was applied to compound **15b** (48 mg, 0.0928 mmol) to give **16b** (22.8 mg, quantitative yield); $[\alpha]_D$ = -10 (c 0.4, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.12 (m, 1H), 3.73 (m, 3H), 3.18-3.05 (m, 4H, H-2a, H-2b, H-7a, H-7b), 2.90 (t, J = 7.7 Hz, 2H, NCH_2), 1.62 (m, 2H, CH_2), 1.30 (m, 6H, 3 x CH_2), 0.87 (t, J = 6.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ 77.4, 75.7, 72.2, 68.8 (C-3, C-

4, C-5, C-6), 60.3 (NCH_2), 57.4, 57.1 (C-2, C-7), 32.6 (CH_2), 27.6 (CH_2), 26.4 (CH_2), 23.6 (CH_2), 14.3 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{12}H_{26}NO_4$: 248.1861; found: 248.1861.

(3R,4R,5R,6S)-1-nonylazepane-3,4,5,6-tetraol (16c). The same hydrogenolysis procedure was applied to compound **15c** (59 mg, 0.105 mmol) to give **16c** (30.5 mg, quantitative yield); $[\alpha]_D$ = -14 (c 0.6, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 4.18, 3.80 (2 x m, 1H, 3H, H-3, H-4, H-5, H-6), 3.13 (m, 4H, H-2a, H-2b, H-7a, H-7b), 2.92 (t, J = 6.4 Hz, 2H, NCH_2), 1.67 (m, 2H, CH_2), 1.34 (m, 12H, 6 x CH_2), 0.92 (t, J = 6.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ 77.2, 75.8, 72.4, 69.1 (C-3, C-4, C-5, C-6), 60.3 (NCH_2), 57.7, 57.3 (C-2, C-7), 33.0 (CH_2), 30.6 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 27.9 (CH_2), 26.7 (CH_2), 23.7 (CH_2), 14.5 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{15}H_{32}NO_4$: 290.2331; found: 290.2328.

(3R,4R,5R,6S)-1-dodecylazepane-3,4,5,6-tetraol (16d). The same hydrogenolysis procedure was applied to compound **15d** (58 mg, 0.0965 mmol) to give **16d** (32 mg, quantitative yield); $[\alpha]_D$ = -5.8 (c 0.6, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 4.00, 3.70 (3 x m, 1H, 2H, 1H, H-3, H-4, H-5, H-6), 2.77-2.71 (m, 4H, H-2a, H-2b, H-7a, H-7b), 2.51 (t, J = 7.5 Hz, 2H, NCH_2), 1.51 (m, 2H, CH_2), 1.31 (m, 18H, 9 x CH_2), 0.92 (t, J = 6.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ 77.1, 76.7, 74.7, 71.4 (C-3, C-4, C-5, C-6), 60.3, 59.6, 58.7 (C-2, C-7, NCH_2), 33.1 (CH_2), 30.7, 30.6, 30.4, 28.4, 28.2, 23.7 (6 x CH_2), 14.5 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{18}H_{38}NO_4$: 332.2800; found: 332.2803.

(3S,4R,5R,6R)-benzyl-3,4,5-tris(benzyloxy)-6-hydroxyazepane-1-carboxylate (17). Triphenylphosphine polymer bound (1 g, 3.2 mmol.g-1, 3.2 mmol) was added to a solution of azidolactol **1** (1 g, 2.10 mmol) in anhydrous THF (30 mL). The reaction mixture was stirred at 40 °C overnight, then filtered onto Celite and the solvent removed under reduced pressure to give the crude bicyclic *N,O*-acetal **2** as a colorless oil (990 mg) that was dissolved in CH_3COOH (8 mL). $NaBH_3CN$ (173 mg, 2.74 mmol) was added and the mixture was stirred at room temperature for 14 h, quenched with a 1N NaOH aqueous solution and extracted with CH_2Cl_2. The organic layer was washed sequentially with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure after filtration, to afford azepane **14** as a colorless oil (822 mg, 1.90 mmol). To a cooled biphasic solution of the crude azepane **14** (822 mg, 1.90 mmol) in ethyl acetate/water (50 mL:50 mL) at 0°C were added potassium bicarbonate (1.9 g, 19 mmol) and benzyl chloroformate (0.8 mL, 5.64 mmol). The reaction mixture was stirred at room temperature for 18h, then extracted with ethyl acetate. The combined organic layers were successively washed with a 1N HCl solution, water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (EA/PE, 5% to 20%) afforded the corresponding azepane **17** (536 mg, 45% over 3 steps); ^1H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 7.30 (m, 20H, ArH), 5.11-5.02 (m, 2H, $NCOOCH_2Ph$, $NCOOCH_2$'Ph), 4.77-4.40 (m, 6H, 3 x OCH_2Ph, 3 x OCH_2'Ph), 4.18-4.05 (m, 1H, H-6, H-6'), 4.01-3.26 (m, 7H, H-2a, H-2b, H-3, H-4, H-5, H-7a, H-7b, H-2'a, H-2'b, H-3', H-4', H-5', H-7'a, H-7'b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 155.7 (2 x C=O), 140.9, 138.0, 137.9, 136.6, 136.4 (aromatic C), 128.6-126.9 (aromatic CH), 82.9, 82.3 (C-5, C-5'), 80.2, 80.0, 79.8 and 77.9 (C-3, C-3', C-4, C-4'), 73.0, 72.9, 72.7, 72.6, 72.1, 71.9 (3 x OCH_2Ph, 3 x OCH_2'Ph), 68.7, 68.6 (C-6, C-6'), 67.5, 67.2 ($NCOOCH_2Ph$, $NCOOCH_2$'Ph,), 49.5, 49.3, 47.0, 46.4 (C-2, C-2', C-7, C-7').

(3S,4R,5R,6S)-benzyl 3,4,5-tris(benzyloxy)-6-hydroxyazepane-1-carboxylate (18). Diethyl azodicarboxylate (DEAD) 40% in toluene (2 ml, 4.30 mmol) was added to a solution of azepane **17** (1.22 g, 2.15 mmol), triphenylphosphine (1.12g, 4.30 mmol) and *p*-nitrobenzoic acid (562 mg, 3.3 mmol) in anhydrous THF (30 mL) at 0 °C. The mixture was stirred at room temperature for 3 h and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/PE 5:95) to afford the corresponding inverted *p*-nitrobenzoic ester as a pale yellow oil (1.0 g, 65 %); ^1H NMR (400 MHz, $CDCl_3$): δ 8.01, 7.96, 7.87, 7.73 (4 x m, 4H, ArH), 7.41-7.01 (m, 20H, ArH), 5.35-3.37 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 163.6 (2 x C=O), 156.2, 156.1 (2 x C=O), 150.1, 138.1, 138.0, 137.8, 137.7, 137.3, 136.4, 136.2, 135.0 (aromatic Cipso), 130.7, 130.6, 128.7, 128.6, 128.43, 128.41, 128.34, 128.29, 128.14, 128.12, 128.19, 127.96, 127.80, 127.77, 127.72, 127.61, 127.57, 127.27, 123.27 (aromatic CH), 84.0, 83.6, 82.8, 81.7 (C-4, C-5), 76.1, 75.6 (C-3), 73.2, 73.0, 72.7, 72.6, 72.5 (OCH_2Ph), 71.4, 71.2 (C-6), 67.7, 67.3 ($COOCH_2Ph$), 45.5, 45.3, 44.5, 44.3 (C-2, C-7); HRMS (ESI) m/z: [M+H]+ calcd for $C_{42}H_{41}N_2O_9$: 717.2812; found: 717.2812. Potassium carbonate (1.8 g, 12.7 mmol) was added to a solution of inverted ester (916 mg, 1.27 mmol) in MeOH/THF (40 mL:10 mL). The mixture was stirred at room temperature for 5 h, concentrated in vacuo and diluted with CH_2Cl_2. The solution was washed with H_2O, dried over $MgSO_4$ and concentrated in vacuo after filtration. The residue was purified by flash chromatography (EtOAc/PE 15:85) to afford azepane **18** as a colorless oil (600 mg, 83 %, 54% over two steps); $[\alpha]_D$ = 20 (c 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ (presence of 2 rotamers) 7.30 (m, 20H, ArH), 5.16–5.05 (m, 2H, $NCOOCH_2Ph$, $NCOOCH_2$'Ph), 4.78-4.38 (m, 6H, 3 OCH_2Ph, 3 OCH_2'Ph), 4.03-3.38 (m, 8H, H-2a, H-2b, H-3, H-4, H-5, H-6, H-7a, H-7b, H-2'a, H-2'b, H-3', H-4', H-5', H-6', H-7'a, H-7'b), 3.10 (br. s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 156.3 (2x C=O), 138.2, 138.1, 137.84, 137.77, 137.7, 136.7, 136.4 (aromatic Cipso), 128.5-127.4 (aromatic CH), 83.2, 83.1, 81.4, 81.1, 80.6, 79.5 (C-5, C-5', C-3, C-3', C-4, C-4'), 73.5, 73.3, 71.8, 71.7 (3 x OCH_2Ph, 3 OCH_2'Ph), 71.1, 71.0 (C-6, C-6'), 67.6, 67.2 ($NCOOCH_2Ph$, $NCOOCH_2$'Ph), 49.0, 48.9, 45.84, 45.81 (C-2, C-2', C-7, C-7'). HRMS (ESI) m/z: [M+H]+ calcd for $C_{35}H_{38}NO_6$: 568.2699; found: 568.2698.

(3S,4R,5R,6S)-4,5,6-tris(benzyloxy)-1-butylazepan-3-ol (19a). To a solution of azepane **18** (600 mg, 1.058 mmol) and triethylamine (74 µL, 0.529 mmol) in CH_3OH (40 mL) was added 5% $Pd/CaCO_3$ (600 mg). The solution was degassed three times and air was replaced by H_2. After stirring for 4 h at RT, the reaction mixture was filtered, eluted with CH_3OH, and concentrated to afford the corresponding amine as a colorless oil (437 mg, 95.4%) used crude in the next step; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.26 (m, 15H, ArH), 4.79 (d, J = 11.3 Hz, 1H, OCH_2Ph), 4,65-4,57 (m, 4H, 2 x OCH_2Ph), 4.54 (d, J = 11.3 Hz, 1H, OCH_2Ph), 3.86-3.82 (m, 2H, H-3, H-5), 3.66 (m, 1H, H-6), 3,60 (dd, J = 8.1 Hz, J = 5.5 Hz, 1H, H-4), 3.21 (dd, J = 13.9 Hz, J = 2.4 Hz, 1H, H-2a), 3.09 (dd, J = 14.4 Hz, J = 6.3 Hz, 1H, H-7a), 2.93 (d, J = 14.4 Hz, 1H, H-7b), 2.74 (dd, J = 13.9 Hz, J = 8.3 Hz, 1H, H-2b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 138.22, 138.18 (aromatic Cipso), 128.6-127.8 (aromatic CH), 85.4 (C-4), 83.0 (C-5), 79.8 (C-6), 74.0 (OCH_2Ph), 73.3 (OCH_2Ph), 71.8 (OCH_2Ph), 71.5 (C-3), 51.7 (C-2), 47.7 (C-7);

HRMS (ESI) m/z: [M+H]+ calcd for $C_{27}H_{32}NO_4$: 434.2331; found: 434.2330. Potassium carbonate (160 mg, 1.16 mmol) was added to a stirred solution of crude amine (100 mg, 0.23 mmol) and n-butyl bromide (50 µL, 0.46 mmol) in a 8:1 mixture of EtOAc/H_2O (12:2 mL) under nitrogen. The reaction mixture was stirred at 85° C for 24h and then extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC chromatography (EtOAc/PE, 30:70) afforded the corresponding azepane **19a** (78 mg, 69%); $[\alpha]_D$ = 14 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 15H, ArH), 4.79-4.54 (m, 6H, 3 x OCH_2Ph), 3.85 (m, 1H, H-3), 3.71-3.66 (m, 3H, H-4, H-5, H-6), 2.89 (d, J = 12.4 Hz, 1H, H-2a), 2.79 (d, J = 13.6 Hz, 1H, H-7a), 2.65 (m, 2H, H-7b, H-2b), 2.53 (t, J = 7.3 Hz, 1H, NCH_2), 1.42 (m, 2H, CH_2), 1.29 (m, 2H, CH_2), 0.89 (t, J = 7.3 Hz, 1H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 138.5, 138.2 (aromatic Cipso), 128.4-127.5 (aromatic CH), 86.1, 84.1, 80.5 (C-4, C-5, C-6), 74.8, 73.9, 72.8 (3 x CH_2Ph), 69.2 (C-3), 59.0 (NCH_2), 57.5 (C-2), 56.4 (C-7), 29.2 (CH_2), 20.4 (CH_2), 14.0 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{31}H_{40}NO_4$: 490.2957; found: 490.2959.

(3S,4R,5R,6S)-4,5,6-tris(benzyloxy)-1-hexylazepan-3-ol (19b). Compound **19b** was obtained by alkylation of amine (77 mg, 0.177 mmol), with hexyl bromide, as described above to afford a colourless syrup (50 mg, 54%); $[\alpha]_D$ = 15 (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 15H, ArH), 4.79-4.53 (m, 6H, 3 x OCH_2Ph), 3.85 (m, 1H, H-3), 3.74-3.65 (m, 3H, H-4, H-5, H-6), 2.91 (dd, J = 12.4 Hz, J = 2.0 Hz, 1H, H-2a), 2.81 (d, J = 12.7 Hz, 1H, H-7a), 2.69-2.64 (m, 2H, H-7b, H-2b), 2.54 (t, J = 7.4 Hz, 1H, NCH_2), 1.45 (m, 2H, CH_2), 1.26 (m, 6H, 3 x CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 138.5, 138.2 (aromatic Cipso), 128.4-127.5 (aromatic CH), 86.2, 84.3, 80.6 (C-4, C-5, C-6), 74.8, 74.0, 72.7 (3 x OCH_2Ph), 69.2 (C-3), 59.3 (NCH_2), 57.6 (C-2), 56.5 (C-7), 31.7 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{33}H_{44}NO_4$: 518.3270; found: 518.3271.

(3S,4R,5R,6S)-4,5,6-tris(benzyloxy)-1-nonylazepan-3-ol (19c). Compound **19c** was obtained by alkylation of amine (82.5 mg, 0.190 mmol), with nonyl bromide, as described above to afford a colourless syrup (61 mg, 57 %); $[\alpha]_D$ = 7 (c 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 15H, ArH), 4.80-4.54 (m, 6H, 3 x OCH_2Ph), 3.85 (m, 1H, H-3), 3.71-3.64 (m, 3H, H-4, H-5, H-6), 2.89 (dd, J = 12.4 Hz, J = 2.7 Hz, 1H, H-2a), 2.78 (d, J = 13.4 Hz, 1H, H-7a), 2.66-2.61 (m, 2H, H-7b, H-2b), 2.51 (t, J = 7.4 Hz, 1H, NCH_2), 1.43 (m, 2H, CH_2), 1.26 (m, 12H, 6 x CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 138.5, 138.2 (aromatic Cipso), 128.4-127.5 (aromatic CH), 86.2, 84.3, 80.5 (C-4, C-5, C-6), 74.8, 74.0, 72.8 (3 x OCH_2Ph), 69.2 (C-3), 59.4 (NCH_2), 57.5 (C-2), 56.5 (C-7), 31.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{36}H_{50}NO_4$: 560.3740; found: 560.3740.

(3S,4R,5R,6S)-4,5,6-tris(benzyloxy)-1-dodecylazepan-3-ol (19d). Compound **19d** was obtained by alkylation of amine (78 mg, 0.180 mmol), with dodecyl bromide, as described above to afford a colourless syrup (58 mg, 54 %); $[\alpha]_D$ = 9 (c 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.25 (m, 15H, ArH), 4.79-4.53 (m, 6H, 3 x OCH_2Ph), 3.85 (m, 1H, H-3), 3.71-3.61 (m, 3H, H-4, H-5, H-6), 2.90 (dd, J = 12.4 Hz, J = 2.5 Hz, 1H, H-2a), 2.80 (d, J = 13.4 Hz, 1H, H-7a), 2.68-2.63 (m, 2H, H-7b, H-2b), 2.53 (t, J = 7.4 Hz, 1H, NCH_2), 1.45 (m, 2H, CH_2), 1.25 (m, 18H, 9 x CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 138.5, 138.2 (aromatic Cipso), 128.4-127.5 (aromatic CH), 86.2, 84.3, 80.6 (C-4, C-5, C-6), 74.8, 74.0, 72.7 (3 x CH_2Ph), 69.3 (C-3), 59.3 (NCH_2), 57.6 (C-2), 56.5 (C-7), 31.9 (CH_2), 29.67 (CH_2), 29.64 (CH_2), 29.62 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{39}H_{56}NO_4$: 602.4209; found: 602.4209.

(3S,4R,5R,6S)-1-butylazepane-3,4,5,6-tetraol (20a). To a solution of protected compound **19a** (71 mg, 0.145 mmol) in CH_3OH (8 mL) was added 10% Pd/C (36 mg), Pd black (36 mg) and a 1 N HCl aqueous solution (0.3 mL, 0.3 mmol). The solution was purged with N_2 then with H_2. After stirring overnight at room temperature, the reaction mixture was purged with N_2, filtered on Celite, washed with CH_3OH. The solution was concentrated under reduced pressure to give **20a** as its hydrochloride salt (36 mg, quantitative yield); $[\alpha]_D$ = 12.5 (c 0.8, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.16 (td, J = 9.0 Hz, J = 2.0 Hz, 1H, H-3), 4.10 (m, 1H, H-6), 3.85 (t, J = 4.5 Hz, 1H, H-5), 3.60 (dd, J = 9.0 Hz, J = 4.5 Hz, 1H, H-4), 3.44 (br. s, 2H, H-7a, H-7b), 3.38-3.20 (m, 4H, H-2a, H-2b, NCH_2), 1.82-1.72 (m, 2H, CH_2), 1.48-1.39 (m, 2H, CH_2), 1.02 (t, J = 7.2 Hz, 1H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ 80.1 (C-4), 76.6 (C-5), 69.2 (C-6), 68.9 (C-3), 59.7 (NCH_2), 58.7 (C-2), 54.3 (C-7), 27.0 (CH_2), 20.9 (CH_2), 13.9 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{10}H_{22}NO_4$: 220.1549; found: 220.1546.

(3S,4R,5R,6S)-1-hexylazepane-3,4,5,6-tetraol (20b). Azepane **19b** (75 mg, 0.145 mmol) was deprotected as described above to afford compound **20b** as its hydrochloride salt, an amorphous white solid (40.9 mg, quantitative yield); $[\alpha]_D$ = 11 (c 0.7, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): 4.06 (td, J = 9.0 Hz, J = 1.9 Hz, 1H, H-3), 4.00 (m, 1H, H-6), 3.74 (t, J = 4.5 Hz, 1H, H-5), 3.49 (dd, J = 9.0 Hz, J = 4.5 Hz, 1H, H-4), 3.32 (br. s, 2H, H-7a, H-7b), 3.27-3.11 (m, 4H, H-2a, H-2b, NCH_2), 1.66 (m, 2H, CH_2), 1.28 (m, 6H, 3 x CH_2), 0.83 (t, J = 6.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ 80.2 (C-4), 76.7 (C-5), 69.4 (C-6), 69.0 (C-3), 60.0 (NCH_2), 58.7 (C-2), 54.4 (C-7), 32.4 (CH_2), 27.3 (CH_2), 25.2 (CH_2), 23.5 (CH_2), 14.3 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{12}H_{26}NO_4$: 248.1861; found: 248.1857.

(3S,4R,5R,6S)-1-nonylazepane-3,4,5,6-tetraol (20c). Azepane **19c** (66 mg, 0.118 mmol) was deprotected as described above to afford compound **20c** as its hydrochloride salt, an amorphous white solid (38.4 mg, quantitative yield); $[\alpha]_D$ = 12 (c 0.3, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): 4.16 (td, J = 8.9 Hz, 1.9 Hz, 1H, H-3), 4.10 (m, 1H, H-6), 3.85 (t, J = 4.5 Hz, 1H, H-5), 3.60 (dd, J = 8.9 Hz, J = 4.5 Hz, 1H, H-4), 3.43 (br. s, 2H, H-7a, H-7b), 3.38-3.20 (m, 4H, H-2a, H-2b, NCH_2), 1.78 (m, 2H, CH_2), 1.34 (m, 12H, 6 x CH_2), 0.92 (t, J = 6.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ 80.2 (C-4), 76.7 (C-5), 69.4 (C-6), 69.0 (C-3), 60.0 (NCH_2), 58.8 (C-2), 54.3 (C-7), 33.0 (CH_2), 30.5 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 27.6 (CH_2), 25.2 (CH_2), 23.7 (CH_2), 14.4 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{15}H_{32}NO_4$: 290.2331; found: 290.2330.

(3S,4R,5R,6S)-1-dodecyl-azepane-3,4,5,6-tetraol (20d). Azepane **19d** (66 mg, 0.118 mmol) was deprotected as described above to afford compound **19d** as its hydrochloride salt, as an amorphous white solid (38.4 mg, quantitative yield);

$[\alpha]_D$ = 14 (c 0.3, CH_3OH); ^1H NMR (400 MHz, CD_3OD): 4.16 (td, J = 9.0 Hz, J = 2.2 Hz, 1H, H-3), 4.10 (m, 1H, H-6), 3.85 (t, J = 4.5 Hz, 1H, H-5), 3.60 (dd, J = 9.0 Hz, J = 4.5 Hz, 1H, H-4), 3.43 (br. s, 2H, H-7a, H-7b), 3.37 (m, 1H, H-2a), 3.28-3.15 (m, 3H, H-2b, NCH_2), 1.83-1.74 (m, 2H, CH_2), 1.40-1.30 (m, 18H, 9 x CH_2), 0.91 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz; CD_3OD): δ 80.1, 76.7, 69.4, 69.0 (C-3, C-4, C-5, C-6), 60.0 (NCH_2), 58.7 (C-2), 54.4 (C-7), 33.1 (CH_2), 30.8 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 27.7 (CH_2), 25.2 (CH_2), 23.7 (CH_2), 14.5 (CH_3); HRMS (ESI) m/z: [M+H]+ calcd for $C_{18}H_{38}NO_4$: 332.2800; found: 332.2801.

(3S,4R,5R,6R)-azepane-3,4,5,6-tetraol (A). To a solution of protected compound **14** (51 mg, 0.0899 mmol) in CH_3OH (10 mL) was added 10% Pd/C (25 mg), Pd black (25 mg) and a 1 M HCl aqueous solution (0.092 mL, 0.092 mmol). The solution was purged with N_2 then with H_2. After stirring overnight at room temperature, the reaction mixture was purged with N_2, filtered on Celite, washed with CH_3OH. The solution was concentrated under reduced pressure to give **A** as its hydrochloride salt (16.5 mg, quantitative yield);^1H NMR (400 MHz, CD_3OD): δ 4.25 (dd, J = 7.9 Hz, J = 3.0 Hz, 1H, H-3 or H-6), 3.90 (m, 1H, H-6 or H-3), 3.83 (m, 2H, H-4, H-5), 3.41-3.21 (m, 4H, H-2a, H-2b, H-7a, H-7b); ^{13}C NMR (100 MHz, CD_3OD): δ 78.0, 75.1 (C-4, C-5), 70.9, 67.6 (C-3, C-6), 47.54, 47.46 (C-2, C-7).

(3S,4R,5R,6S)-azepane-3,4,5,6-tetraol (B). Azepane **18** (52.6 mg, 0.0927) was deprotected as described for azepane **A**, to afford compound **B** as its hydrochloride salt and as an amorphous white solid (17 mg, quantitative yield); ^1H NMR (400 MHz, CD_3OD): δ 4.10 (app. t, J = 6.5 Hz, J = 6.3 Hz, 2H, H-3, H-6), 3.75 (m, 2H, H-4, H-5), 3.33 (m, 2H, H-2a, H-2b), 3.17 (dd, J = 13.2 Hz, J = 7.8 Hz, 2H, H-7a, H-7b); ^{13}C NMR (100 MHz, CD_3OD): δ 78.7 (C-4, C-5), 69.7 (C-3, C-6), 48.3 (C-2, C-7).

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Notes and references

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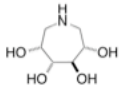
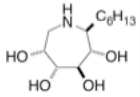
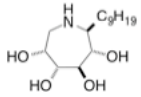
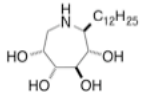
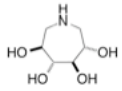
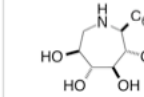
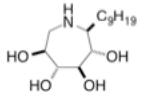
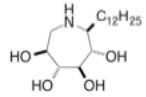
Enzyme	A	4a	4b	4c	4d	B	7a	7b	7c	7d
α-Glucosidase										
Rice	[a]NI [b](8.6%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](6.6%)	[a]NI [b](0%)	[a]NI [b](14.6%)	[a]NI [b](8.0%)	[a]NI [b](25.6%)	[a]NI [b](44.7%)	[a]NI [b](27.0%)
Yeast	[a]NI [b](36.4%)	[a]NI [b](21.9%)	[a]NI [b](3.1%)	[a]NI [b](15.8%)	[a]NI [b](9.4%)	772	[a]NI [b](2.3%)	[a]NI [b](33.6%)	[a]NI [b](33.3%)	[a]NI [b](19.1%)
Rat intestinal maltase	[a]NI [b](31.0%)	[a]NI [b](6.9%)	[a]NI [b](9.7%)	[a]NI [b](13.7%)	[a]NI [b](7.2%)	[a]NI [b](32.3%)	[a]NI [b](7.3%)	[a]NI [b](31.2%)	[a]NI [b](37.5%)	[a]NI [b](18.0%)
Aspergillus niger	[a]NI [b](3.8%)	[a]NI [b](7.1%)	[a]NI [b](0.2%)	[a]NI [b](1.9%)	[a]NI [b](3.1%)	[a]NI [b](29.4%)	[a]NI [b](7.1%)	[a]NI [b](9.6%)	[a]NI [b](0%)	[a]NI [b](2.4%)
β-Glucosidase										
Almond	[a]NI [b](25.6%)	295	[a]NI [b](24.4%)	[a]NI [b](16.0%)	[a]NI [b](16.5%)	38	[a]NI [b](41.0%)	179	515	[a]NI [b](27.5%)
Bovine liver	[a]NI [b](27.1%)	[a]NI [b](45.8%)	765	50	14	[a]NI [b](43.4%)	[a]NI [b](21.6%)	478	33	7,7
Aspergillus niger	[a]NI [b](13.6%)	[a]NI [b](16.6%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](2.5%)	59	[a]NI [b](0%)	[a]NI [b](13.4%)	[a]NI [b](12.8%)	[a]NI [b](3.3%)
Human lysosome	[a]NI [b](20.1%)	116	653	34	17	287	[a]NI [b](23.3%)	326	13	2,6
α-Galactosidase										
Coffee beans	[a]NI [b](6.9%)	[a]NI [b](26.1%)	[a]NI [b](8.3%)	[a]NI [b](12.8%)	[a]NI [b](3.0%)	[a]NI [b](36.9%)	[a]NI [b](5.5%)	[a]NI [b](37.7%)	578	[a]NI [b](14.3%)
β-Galactosidase										
Bovine liver	[a]NI [b](30.1%)	396	227	14	4.5	[a]NI [b](48.3%)	[a]NI [b](16.3%)	152	13	4.1
α-Mannosidase										
Jack beans	[a]NI [b](6.7%)	[a]NI [b](4.8%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](46.7%)	[a]NI [b](2.0%)	[a]NI [b](7.2%)	[a]NI [b](6.6%)	[a]NI [b](7.7%)
β-Mannosidase										
Snail	[a]NI [b](7.8%)	[a]NI [b](0%)	[a]NI [b](1.5%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](2.0%)	[a]NI [b](0%)	[a]NI [b](3.0%)	[a]NI [b](0%)	[a]NI [b](0%)
α-L-Rhamnosidase										
Penicillium decumbens	[a]NI [b](1.1%)	[a]NI [b](4.8%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](48.0%)	[a]NI [b](0%)	[a]NI [b](4.5%)	[a]NI [b](3.2%)	[a]NI [b](3.0%)
α-L-Fucosidase										
Bovine kidney	62	[a]NI [b](45.9%)	[a]NI [b](0%)	[a]NI [b](18.2%)	[a]NI [b](12.9%)	[a]NI [b](33.8%)	[a]NI [b](0.2%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](0%)
β-Glucuronidase										
E.coli	[a]NI [b](5.5%)	261	[a]NI [b](8.1%)	[a]NI [b](39.1%)	[a]NI [b](8.0%)	866	[a]NI b[b](5.5%)	[a]NI [b](42.3%)	405	[a]NI [b](47.3%)
Bovine liver	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](23.2%)	[a]NI [b](0%)	[a]NI [b](4.9%)	[a]NI [b](0%)	[a]NI [b](0%)
α,α-Trehalase										
Porcine kidney	[a]NI [b](6.5%)	[a]NI [b](2.4%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](27.3%)	[a]NI [b](10.1%)	[a]NI [b](19.5%)	[a]NI [b](24.2%)	[a]NI [b](3.3%)
Amyloglucosidase										
Aspergillus niger	[a]NI [b](0%)	[a]NI [b](4.3%)	[a]NI [b](0%)	[a]NI [b](5.3%)	[a]NI [b](12.6%)	[a]NI [b](2.6%)	[a]NI [b](2.8%)	[a]NI [b](1.2%)	[a]NI [b](9.8%)	[a]NI [b](12.8%)
Rhizopus sp	[a]NI [b](2.8%)	[a]NI [b](2.3%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](3.2%)	[a]NI [b](5.9%)	[a]NI [b](3.2%)	[a]NI [b](3.4%)	[a]NI [b](2.2%)	[a]NI [b](3.3%)

[a]NI : No inhibition (less than 50% inhibition at 1000 μM). [b]( ) : inhibition % at 1000 μM

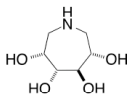
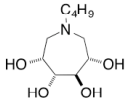
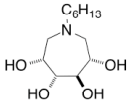
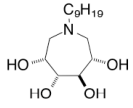
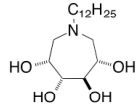
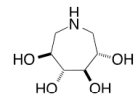
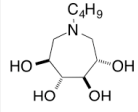
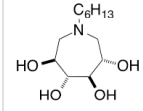
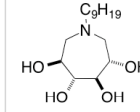
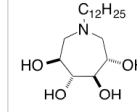
[a]NI : No inhibition (less than 50% inhibition at 100 μM). [b]( ) : inhibition % at 100 μM

Table 2. Concentration of alkaloid azepanes giving 50% inhibition of various glycosidases

		IC50 (μM)							
									
enzyme		**A**	**10b**	**10c**	**10d**	**B**	**13b**	**13c**	**13d**
α-Glucosidase									
	Yeast	[a]NI [b](8.6%)	[a]NI [b](2.4%)	[c]NI [d](45.8%)	[c]NI [d](7.7%)	[a]NI [b](14.6%)	536	288	[c]NI [d](10.1%)
	Aspergillus niger	[a]NI [b](36.4%)	[a]NI [b](3.4%)	[c]NI [d](11.2%)	[c]NI [d](13.8%)	772	[a]NI [b](6.0%)	[a]NI [b](13.1%)	[c]NI [d](11.2%)
	Rice	[a]NI [b](31.0%)	[a]NI [b](13.5%)	[c]NI [d](19.1%)	[c]NI [d](16.3%)	[a]NI [b](32.3%)	[a]NI [b](38.4%)	[a]NI [b](23.9%)	[c]NI [d](1.0%)
	Rat intestinal maltase	[a]NI [b](3.8%)	[a]NI [b](14.5%)	[c]NI [d](6.1%)	[c]NI [d](7.5%)	[a]NI [b](29.4%)	[a]NI [b]19.6%)	[a]NI [b](34.7%)	[c]NI [d](0%)
β-Glucosidase									
	Almond	[a]NI [b](25.6%)	[a]NI [b](38.5%)	[c]NI [d](37.4%)	[c]NI [d](15.0%)	38	185	431	[c]NI [d](32.7%)
	Bovine liver	[a]NI [b](27.1%)	[a]NI [b](46.4%)	62	10	[a]NI [b](43.4%)	[a]NI [b](12.7%)	807	57
	Aspergillus niger	[a]NI [b](13.6%)	[a]NI [b](3.2%)	[c]NI [d](5.9%)	[c]NI [d](0.5%)	59	[a]NI [b](24.8%)	[a]NI [b](18.1%)	[c]NI [d](16.8%)
	Human lysosome	[a]NI [b](20.1%)	[a]NI [b](42.5%)	5,5	7,2	287	159	9,7	3,5
α-Galactosidase									
	Coffee beans	[a]NI [b](6.9%)	[a]NI [b](0%)	[c]NI [d](34.0%)	[c]NI [d](0%)	[a]NI [b](36.9%)	[a]NI [b](0%)	[a]NI [b](0%)	[c]NI [d](0.8%)
β-Galactosidase									
	Bovine liver	[a]NI [b](30.1%)	177	26	4,8	[a]NI [b](48.3%)	763	135	27
α-Mannosidase									
	Jack bean	[a]NI [b](6.7%)	[a]NI [b](1.9%)	[c]NI [d](13.8%)	[c]NI [d](1.3%)	[a]NI [b](46.7%)	[a]NI [b](1.4%)	[a]NI [b](0.8%)	[c]NI [d](0.8%)
β-Mannosidase									
	Snail	[a]NI [b](7.8%)	[a]NI [b](4.6%)	[c]NI [d](6.9%)	[c]NI [d](0%)	[a]NI [b](2.0%)	[a]NI [b](6.7%)	[a]NI [b](0%)	[c]NI [d](5.4%)
α-L-Fucosidase									
	Bovine kidney	62	[a]NI [b](0%)	[c]NI [d](31.8%)	[c]NI [d](0%)	[a]NI [b](48.0%)	[a]NI [b](0%)	[a]NI [b](4.5%)	[c]NI [d](0%)
β-Glucuronidase									
	E.coli	[a]NI [b](5.5%)	[a]NI [b](6.4%)	27	[c]NI [d](24.9%)	866	[a]NI [b](0%)	[a]NI [b](21.3%)	[c]NI [d](21.8%)
	Bovine liver	[a]NI [b](0%)	[a]NI [b](0%)	93	[c]NI [d](0%)	[a]NI [b](23.2%)	[a]NI [b](0%)	[a]NI [b](0%)	[c]NI [d](0%)
α,α-Trehalase									
	Porcine kidney	[a]NI [b](6.5%)	[a]NI [b](5.9%)	[c]NI [d](9.3%)	[c]NI [d](0%)	[a]NI [b](27.3%)	[a]NI [b](23.2%)	[a]NI [b](11.9%)	[c]NI [d](0%)
	Rat intestinal trehalase	[a]NI [b](0%)	[a]NI [b](4.2%)	[c]NI [d](8.1%)	[c]NI [d](2.6%)	[a]NI [b](0%)	[a]NI [b](13.5%)	[a]NI [b](16.5%)	[c]NI [d](2.3%)
Amyloglucosidase									
	Aspergillus niger	[a]NI [b](0%)	[a]NI [b](4.0%)	[c]NI [d](11.7%)	[c]NI [d](15.7%)	[a]NI [b](2.6%)	[a]NI [b](3.3%)	[a]NI [b](6.7%)	[c]NI [d](7.7%)
	Rhizopus sp	[a]NI [b](2.8%)	[a]NI [b](5.4%)	[c]NI [d](5.1%)	[c]NI [d](1.1%)	[a]NI [b](5.9%)	[a]NI [b](1.6%)	[a]NI [b](2.0%)	[c]NI [d](0.4%)
α-L-Rhamnosidase									
	Penicillium decumbens	[a]NI [b](1.1%)	[a]NI [b](0%)	[c]NI [d](0%)	[c]NI [d](0%)	[a]NI [b](48.0%)	[a]NI [b](0.6%)	[a]NI [b](14.7%)	[c]NI [d](10.3%)

[a]NI : No inhibition (less than 50% inhibition at 1000 μM).
[b]( ) : inhibition % at 1000 μM
[c] NI : No inhibition (less than 50% inhibition at 100 μM).
[d]( ) : inhibition % at 100 μM

Table 3. Concentration of azepanes A and B and their N-alkyl derivatives giving 50 % inhibition of various glycosidases

	IC_{50} (μM)									
										
Enzyme	**A**	**10a**	**10b**	**10c**	**10d**	**B**	**14a**	**14b**	**14c**	**14d**
α-Glucosidase										
Rice	[a]NI [c](8.6%)	[a]NI [c](7.2%)	[a]NI [c](17.5%)	[a]NI [c](19.8%)	[a]NI [c](3.3%)	[a]NI [c](14.6%)	1000	[a]NI [b](21.0%)	[a]NI [b](39.2%)	[a]NI [d](39.5%)
Yeast	[a]NI [b](36.4%)	[a]NI [b](5.2%)	[a]NI [b](9.5%)	[a]NI [b](8.0%)	[a]NI [b](3.8%)	772	[a]NI [b](14.0%)	[a]NI [b](46.2%)	[a]NI [b](39.1%)	[c]NI [d](0.5%)
Rat intestinal maltase	[a]NI [b](31.0%)	[a]NI [b](14.1%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](3.4%)	[a]NI [b](32.3%)	[a]NI [b](22.3%)	[a]NI [b](8.7%)	[a]NI [b](16.7%)	[c]NI [d](9.8%)
Aspergillus niger	[a]NI [b](3.8%)	[a]NI [b](0.9%)	[a]NI [b](5.5%)	[a]NI [b](2.4%)	[a]NI [b](13.8%)	[a]NI [b](29.4%)	[a]NI [b](15.1%)	[a]NI [b](25.9%)	[a]NI [b](33.5%)	[c]NI [d](17.3%)
β-Glucosidase										
Almond	[a]NI [b](25.6%)	538	1000	[a]NI [b](26.3%)	[a]NI [b](17.8%)	38	60	4,1	9,8	2,5
Bovine liver	[a]NI [b](27.1%)	[a]NI [b](46.2%)	[a]NI [b](34.3%)	453	21	[a]NI [b](43.4%)	[a]NI [b](46.1%)	540	75	9,2
Aspergillus niger	[a]NI [b](13.6%)	[a]NI [b](0%)	[a]NI [b](9.7%)	[a]NI [b](8.0%)	[a]NI [b](14.6%)	59	302	158	60	52
Human lysosome	[a]NI [b](20.1%)	[a]NI [b](17.8%)	[a]NI [b](37.9%)	83	13	287	826	176	17	1,1
α-Galactosidase										
Coffee beans	[a]NI [b](6.9%)	[a]NI [b](28.9%)	[a]NI [b](24.1%)	[a]NI [b](28.1%)	[a]NI [b](2.4%)	[a]NI [b](36.9%)	[a]NI [b](45.2%)	[a]NI [b](29.9%)	[a]NI [b](27.8%)	[c]NI [d](0%)
β-Galactosidase										
Bovine liver	[a]NI [b](30.1%)	[a]NI [b](27.3%)	614	55	6,2	[a]NI [b](48.3%)	171	123	14	2,4
α-Mannosidase										
Jack beans	[a]NI [b](6.7%)	[a]NI [b](21.5%)	[a]NI [b](27.3%)	[a]NI [b](47.9%)	[a]NI [b](19.9%)	[a]NI [b](46.7%)	638	334	149	[c]NI [d](45.5%)
β-Mannosidase										
Snail	[a]NI [b](7.8%)	[a]NI [b](1.9%)	[a]NI [b](4.9%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](2.0%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](0%)	[c]NI [d](0%)
α-L-Rhamnosidase										
Penicillium decumbens	[a]NI [b](1.1%)	[a]NI [b](7.4%)	[a]NI [b](6.2%)	[a]NI [b](11.7%)	[a]NI [b](9.9%)	[a]NI [b](48.0%)	506	278	53	19
α-L-Fucosidase										
Bovine kidney	62	20	311	81	[a]NI [b](27.3%)	[a]NI [b](33.8%)	[a]NI [b](8.5%)	[a]NI [b](24.4%)	[a]NI [b](0%)	[c]NI [d](0%)
β-Glucuronidase										
E.coli	[a]NI [b](5.5%)	[a]NI [b](18.1%)	[a]NI [b](19.9%)	811	[a]NI [b](30.0%)	866	662	163	10	3,3
Bovine liver	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](4.5%)	[a]NI [b](1.7%)	[a]NI [b](0%)	[a]NI [b](23.2%)	[a]NI [b](1.2%)	[a]NI [b](21.9%)	[a]NI [b](3.2%)	[c]NI [d](0%)
α,α-Trehalase										
Porcine kidney	[a]NI [b](6.5%)	[a]NI [b](0%)	[a]NI [b](0.7%)	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](27.3%)	[a]NI [b](3.4%)	[a]NI [b](13.2%)	[a]NI [b](27.2%)	[c]NI [d](2.4%)
Amyloglucosidase										
Aspergillus niger	[a]NI [b](0%)	[a]NI [b](0%)	[a]NI [b](2.4%)	[a]NI [b](2.9%)	[a]NI [b](4.1%)	[a]NI [b](2.6%)	[a]NI [b](0%)	[a]NI [b](2.5%)	[a]NI [b](10.3%)	[c]NI [d](17.7%)
Rhizopus sp	[a]NI [b](2.8%)	[a]NI [b](0%)	[a]NI [b](1.4%)	[a]NI [b](4.0%)	NI (0%)	[a]NI [b](5.9%)	[a]NI [b](4.0%)	[a]NI [b](4.6%)	[a]NI [b](12.6%)	[c]NI [d](18.4%)

[a] NI : No inhibition (less than 50% inhibition at 1000 μM).
[b] ( ) : inhibition % at 1000 μM
[c] NI : No inhibition (less than 50% inhibition at 100 μM).
[d] ( ) : inhibition % at 100 μM

Figure 3: F508del-CFTR correction by azepanes