ARTICLE

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The first synthesis of substituted azepanes mimicking monosaccharides: a new class of potent glycosidase inhibitors

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The synthesis of the first examples of seven-membered ring iminoalditols, molecules displaying an extra hydroxymethyl substituent on their seven-membered ring compared to the previously reported polyhydroxylated azepanes, has been achieved from D-arabinose in 10 steps using RCM of a protected *N*-allyl-aminohexenitol as a key step. While the (2*R*,3*R*,4*R*)-2-hydroxymethyl-3,4-dihydroxy-azepane **10**, a seven-membered ring analogue of fagomine, is a weak inhibitor of glycosidases, the (2*R*,3*R*,4*R*,5*S*,6*S*)-2-hydroxymethyl-3,4,5,6-tetrahydroxy-azepane **9** selectively inhibits green coffee bean α-galactosidase in the low micromolar range (*K*i = 2.2 μM) despite a *D-gluco* relative configuration.

Introduction

Glycosidase inhibitors have been the subject of extensive interest in the past two decades due to their therapeutic potential.[1] Some of them have already been tested or approved in the treatment of diabetes,[2] Gaucher's disease,[3] HIV infection,[4] viral infections[5] or cancer.[6] They have also been used as chemical probes, in combination with protein crystallography and kinetics studies, to provide new insight into glycosidase mechanisms[7] and are now expected to find an increasing number of therapeutic applications.[8]

A common strategy for designing such inhibitors is based on the mimicry of the cyclic alkoxycarbenium-like transition state occurring during the glycosidic bond cleavage. For this purpose, a large number of aminated compounds, wherein a nitrogen atom has replaced the endocyclic oxygen or the anomeric carbon of the parent sugar, have been synthesized.[9] At physiological pH, these aminated compounds are protonated and thus develop a positive charge which provides stabilizing electrostatic interactions with active site carboxylate residues, and might serve to mimic the charge present in the oxycarbenium-like transition state in glycosidase-catalyzed hydrolysis reactions. Many synthetic efforts have been devoted to the design of substituted pyrrolidines and piperidines, which mimic the ring size and the substitution pattern of the parent sugar, but only a few syntheses of higher homologues, that is, substituted azepanes and azocanes, have been reported so far. A very recent paper by Martin and co-workers on the first synthesis of an eight-membered ring iminoalditol[10] prompted us to publish our results describing the first synthesis of seven-membered ring aminoalditols. This work is part of an ongoing project on new carbohydrate mimetics in order to find more potent/selective glycosidase inhibitors.[11]

Tri- and tetrahydroxylated azepanes were prepared for the first time by Paulsen and Todt in 1967[12] and extensively studied in the last decade.[13] A selection of these synthetic substituted azepanes is shown in Fig. 1.

Malto-oligosaccharides[14] and analogues of di- and trisaccharides[15] containing them have been also described. These compounds are glycosidase[13c,13d,13e,14,15] and/or HIV/FIV protease inhibitors.[13d] Some derivatives have exhibited anticancer activities in various cancer lines with GI_{50} values in the low micromolar range[13c] while others have been used as new motifs for DNA minor groove binding agents.[13f]

To our knowledge, 1,6-dideoxy-1,6-iminoheptitols (see Fig. 2) have not been described so far. Unlike all the polyhydroxylated azepanes reported to date displaying only secondary hydroxyl groups (see Fig. 1), the compounds described herein possess an extra hydroxymethyl group which may allow an additional favourable interaction of these molecules in the glycosidase active site. They constitute a novel family of polyhydroxylated azepanes and can be considered as higher homologues of nojirimycin and fagomine (Fig. 2). Insertion of a methylene group between the nitrogen atom and the pseudo-anomeric hydroxyl group ensures chemical stability of these compounds unlike nojirimycin. Such structures are more flexible than the corresponding pyrrolidines and piperidines and should adopt several puckered low-energy conformations.[13d] They should thus be able to adapt to the space filling and polar requirements of glycosidases. The subsequent unusual spatial distribution of the hydroxyl groups present in these compounds should hopefully generate a new inhibition profile for these molecules.

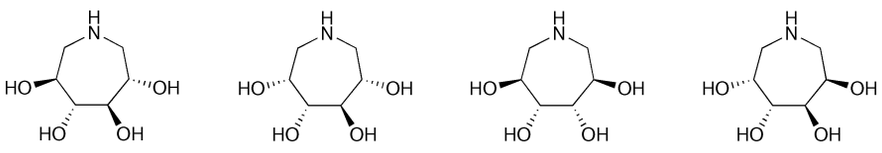

Fig. 1 Four examples of synthetic tetrahydroxylated azepanes.

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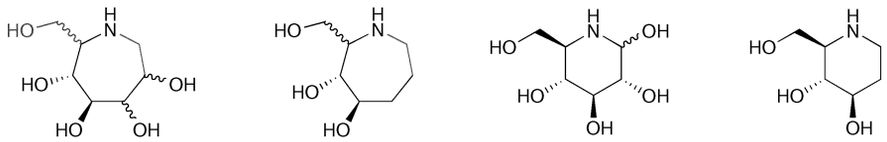
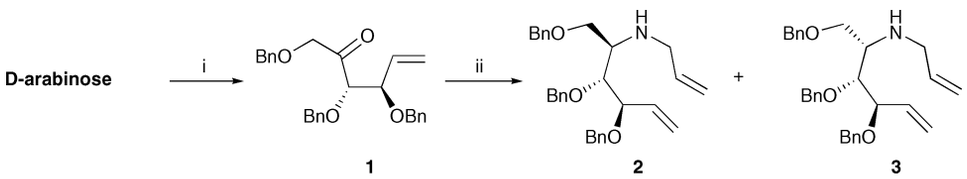
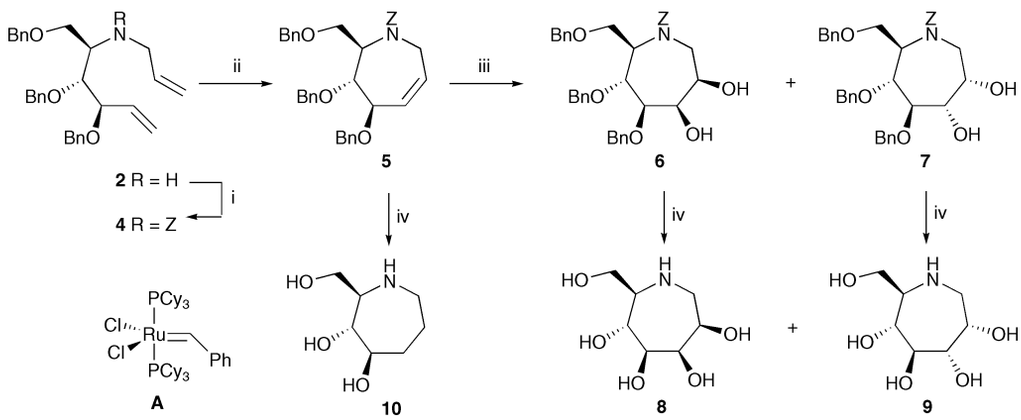


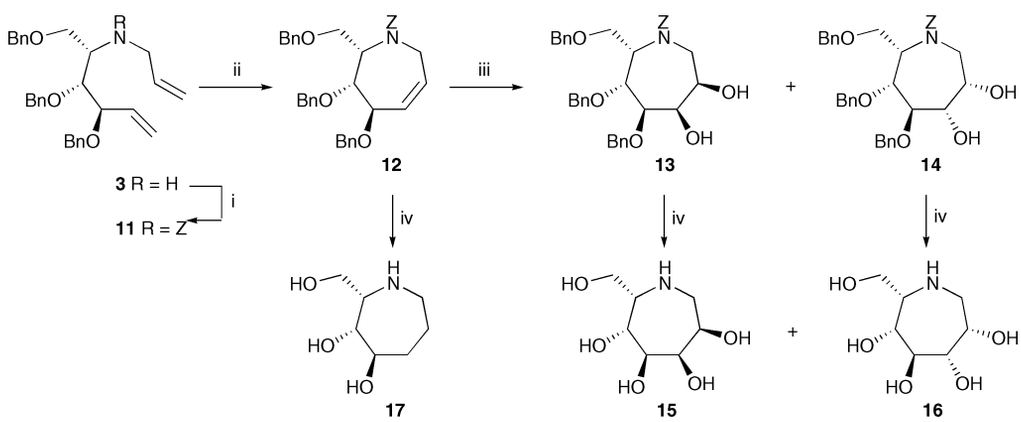
Fig. 2 General structure of substituted azepanes synthesized in this work and comparison with the well known inhibitors nojirimycin and fagomine.



Scheme 1 Synthesis of D-*arabino* and L-*xylo* aminohexenitols **2** and **3** from D-arabinose. *Conditions*: i) Ref. 18 ii) allylamine, AcOH, $NaBH_3CN$, CH_2Cl_2, 30 °C, 58% yield.



Scheme 2 Synthesis of seven-membered iminoalditols **8**–**10**. *Conditions*: i) ZCl, $KHCO_3$, 91% yield; ii) Grubbs' catalyst **A**, DCM, 45 °C, 3 days, 91% yield; iii) OsO_4, NMO, acetone/water, 96% yield; iv) H_2, 10% Pd/C, AcOH, quant. yield.



Scheme 3 Synthesis of seven-membered iminoalditols **15**–**17**. *Conditions*: i) ZCl, $KHCO_3$, 90% yield; ii) Grubbs' catalyst **A**, DCM, 45 °C, 3 days, 84% yield; iii) OsO_4, NMO, acetone/water, 89% yield; iv) H_2, 10% Pd/C, AcOH, quant. yield.

Results and discussion

Synthesis

Our synthetic strategy, relying on the powerful ring-closing alkene metathesis (RCM) methodology,[16] is similar to the one recently reported by Martin.[10] Several other iminosugar-based glycosidase inhibitors[17] have also been obtained through RCM.

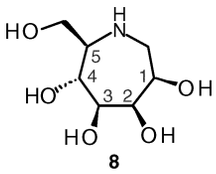
Reductive amination of the known ketone **1**,[18] easily available from D-arabinose, with allylamine and acetic acid in the presence of $NaBH_3CN$ gave the D-*arabino* and L-*xylo* *N*-allyl-aminohexenitols **2** and **3** in 58% yield (ratio 3 : 2) (Scheme 1).

In order to suppress the chelation of the ruthenium catalyst by the amine moiety in the forthcoming RCM step,[19] the secondary amine of the D-*arabino* aminodiene **2** was protected with a benzyloxycarbonyl group to afford carbamate **4** in 90% yield. Subsequent olefin metathesis of the diene **4** using Grubbs'catalyst proceeded in excellent yield to afford didehydroazepane **5** in 91% yield. Dihydroxylation of **5** (OsO_4, NMO) proceeded smoothly with modest facial diastereoselectivity to give *cis* diols **6** and **7** in 96% yield (3 : 7 ratio). Hydrogenolysis of the benzyl ethers in **5**–**7** afforded the target 1,6-dideoxy-1,6-iminoheptitols **8**–**10** in quantitative yield (Scheme 2).

The same sequence was uneventfully applied to the L-*xylo* *N*-allyl-aminohexenitol **3** to afford the 1,6-dideoxy-1,6-imino-heptitols **15**–**17** (Scheme 3).

The pseudo β-D-*manno*, α-D-*gluco*, α-L-*gulo* and β-L-*ido* configurations of compounds **8**, **9**, **15** and **16**, respectively, were

Table 1 Selected vicinal $^3J_{H,H}$ for compounds **8**, **9**, **15** and **16**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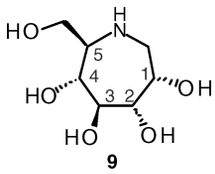
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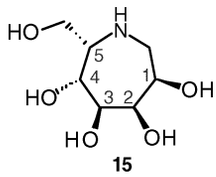
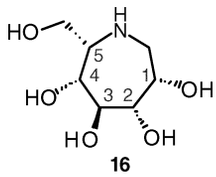
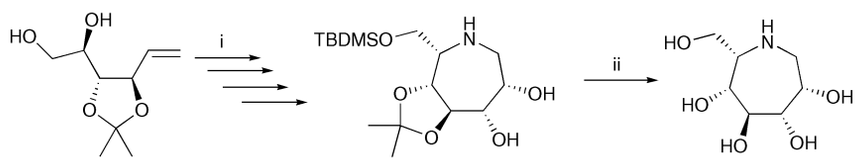

15


16

Relative configuration	β-D-Manno	α-D-Gluco	α-L-Gulo	β-L-Ido
$^3J_{H,H}$	$J_{1,2}$ = 1.4 Hz $J_{2,3}$ = 1.9 Hz $J_{3,4}$ = 8.8 Hz $J_{4,5}$ = 8.8 Hz	$J_{1,2}$ = 2.4 Hz $J_{2,3}$ = 8.4 Hz $J_{3,4}$ = 8.4 Hz $J_{4,5}$ = 9.4 Hz	$J_{1,2}$ = 2.0 Hz $J_{2,3}$ = 2.9 Hz $J_{3,4}$ = n.d. $J_{4,5}$ = 1.0 Hz	$J_{1,2}$ = 6.3 Hz $J_{2,3}$ = 6.3 Hz $J_{3,4}$ = 2.7 Hz $J_{4,5}$ ≈ 0 Hz


19 **18** **16**

Scheme 4 Synthesis of 1,6-dideoxy-1,6-iminoheptitol **16** *via* a different route. *Conditions*: i) Ref. 21; ii) 50% aq. TFA, quant. yield.

indicated by the vicinal $^3J_{H,H}$ coupling constants in their ^{1}H-NMR spectra (see Table 1).

Because of the relative conformational flexibility of seven-membered rings,[20] the $^3J_{H,H}$ coupling constants are not fully reliable to assess the configuration of the stereocentres in the seven-membered ring iminoalditols. Fortunately, compound **16** was obtained using a different route (Scheme 4).[21] The known diol **19**[22] was converted into **16** *via* the semi-protected precursor **18** from which the structure was unambiguously established by X-ray crystallography (Fig. 3).[23] Comparison of the NMR data of stereoisomers **8**, **9** and **15** with those of **16** confirmed our structural assignments (Table 1).

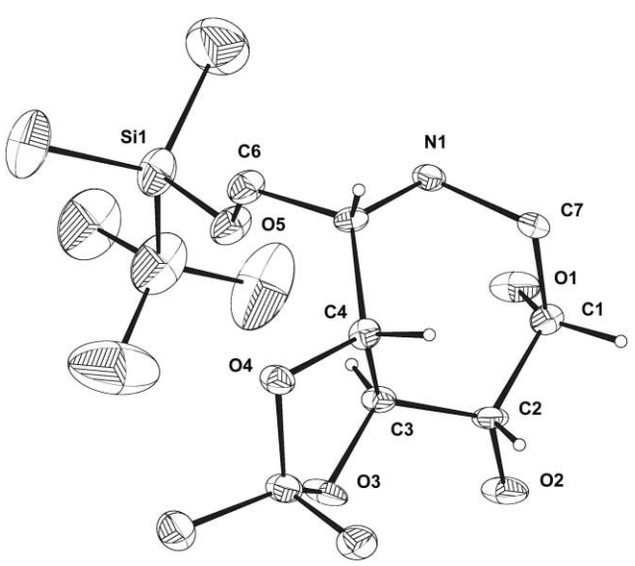


Fig. 3 X-ray structure of compound **18**.

Inhibitory activity

The new iminoheptitols **8**, **9**, **10**, **15** and **16** have been assayed for their inhibitory activity toward 24 commercially available glycosidases.[24] They did not inhibit the following enzymes at 1 mM concentration and optimal pH: α-L-fucosidase from bovine epididymis, α-galactosidases from *Aspergillus niger* and *E. coli*, α-mannosidases from Jack beans and from almonds, β-mannosidase from *Helix pomatia*, β-xylosidase from *A. niger*, β-*N*-acetylglucosaminidases from Jack beans and bovine epididymis A and B. For other enzymes the results are shown in Table 2.

Compound **9** shows the highest inhibitory activity toward α-galactosidase from coffee beans (*K*i = 2.2 μM, competitive) and ignores other α-galactosidases and many other glycosidases. Its 6-epimer **16** also inhibits α-galactosidase from coffee beans (*K*i = 16 μM, competitive). As both compounds **9** and **16** do not have the relative configuration of D-galactopyranose, it appears that they can adopt conformations imitating those of α-D-galactose in the active site of the enzyme or bind in a different way from their parent sugar in the binding pocket of the hydrolase. The same hypotheses can be retained to explain the good competitive inhibition (*K*i = 5.7 μM) of β-galactosidase from bovine liver by compound **8**. This compound, with the relative configuration of β-D-mannopyranose, is not recognized by β-mannosidase from *Helix pomatia*, but by all the glycosidases listed in Table 2. It is thus the least selective inhibitor amongst the five seven-membered ring iminoalditols assayed in this work. We can notice that these iminoheptitols are more potent than the iminooctitol reported by Martin.[10] This result can be explained by invoking the critical size of the eight-membered ring. We need also to consider the lower degree of hydroxylation and the different orientation of the OH groups imposed by the specific conformation of the 1,2,3,7-tetradeoxy-1,7-iminooctitol.

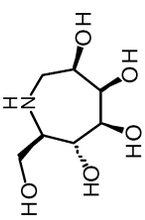
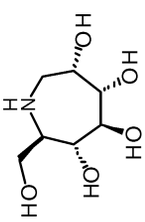
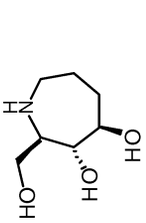
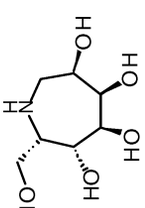
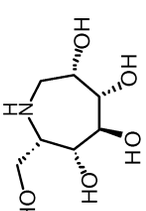
The lower degree of hydroxylation could also explain the disappointing biological results obtained for compound **10**, a seven-membered ring analogue of natural product fagomine[25](Fig. 1). Compound **10** was found to be a weak inhibitor of amyloglucosidases and bovine liver α-galactosidase and much less active than fagomine, reported to be a potent α-glucosidase inhibitor.[26]

Conclusion

We have achieved for the first time the efficient preparation of seven-membered ring iminoheptitols using RCM methodology as the key step to afford new polyhydroxylated azepanes. Our polyhydroxylated azepanes have an extra hydroxymethyl group compared to the previously reported analogues.

Three of the six iminoalditols synthesized show potent glycosidase inhibition in the low micromolar range, displaying a new inhibition profile compared to the previously reported polyhydroxylated azepanes. The best results are obtained with compound **9**, which is a selective and potent green coffee bean

Table 2 Inhibitory activity of compounds **8**, **9**,**10**,**15** and **16**. Percentage inhibition at 1 mM concentration, *Ki* (in brackets), optimal pH, 35 °C, NI = no inhibition at 1 mM concentration of the inhibitor

	 **8**	 **9**	 **10**	 **15**	 **16**
α-Galactosidase					
Coffee beans	52%	98% (**2.2 μM**)	NI	74%	88% (**16 μM**)
β-Galactosidase					
Escherichia coli	28%	NI	NI	36%	NI
Bovine liver	95% (**5.7 μM**)	54%	49%	63%	48%
Jack beans	27%	NI	NI	NI	NI
α-Glucosidase					
Yeast	39%	25%	NI	NI	NI
Rice	52%	53%	NI	34%	NI
Baker's yeast isomaltase	88% (**103 μM**)	74%	NI	54%	26%
Aspergillus niger amyloglucosidase	34%	NI	35%	45%	NI
Rhizopus mold amyloglucosidase	46%	NI	40%	53%	NI
β-Glucosidase					
Almonds	62%	NI	NI	39%	NI
Caldocellum saccharolyticum	36%	22%	NI	NI	NI

α-galactosidase inhibitor. The inhibition profile observed for each seven-membered ring iminoalditol, which can not be correlated to its relative configuration, could be explained by a) the relative flexibility of these iminoalditols adopting a specific conformation in the binding pocket that favorably orientates the hydroxyl groups in the enzyme active site and/or b) by the different positioning of these compounds in the enzyme active site compared to the corresponding parent sugar.

A conformational study of these molecules, as well as docking experiments with model glycosidases, are under way to determine their active conformation and hopefully better understand their inhibition profile.

Experimental section

General methods

Melting points (mp) were determined with a Büchi B-535 apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C with a Perkin Elmer Model 241 digital polarimeter, using a 10 cm, 1 mL cell. Chemical Ionisation Mass Spectra (CI-MS ammonia) and Fast Atom Bombardment Mass Spectra (FAB-MS) were recorded on a JMS-700 spectrometer. Elemental analyses were performed by the Service de Microanalyse de l'Université Pierre et Marie Curie, 4 Place Jussieu, 75005 Paris, France. ^{1}H NMR and ^{13}C NMR were performed on a Bruker DRX 400 spectrometer (400 MHz for ^{1}H, 100.6 MHz for ^{13}C). All chemical shifts (δ) are given in ppm relative to the residual deuterated solvent signals. Coupling constants (J) are reported in Hertz. Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F_{254} precoated plates and detection by charring with sulfuric acid. Flash column chromatography was performed on silica gel 60 Merck 60 (230–400 mesh).

Note: for the assignment of the NMR spectra, the numbering of all the cyclic compounds in this paper is based on the analogy with the corresponding parent sugar, as shown in Table 1, and not on the IUPAC rules for commodity reasons.

(3*R*,4*R*,5*R*)-5-Allylamino-3,4,6-tribenzyloxy-hex-1-ene 2 and (3*R*,4*R*,5*S*)-5-allylamino-3,4,6-tribenzyloxy-hex-1-ene 3. To a solution of ketone **1** (500 mg, 1.2 mmol) in dry CH_2Cl_2 (10 mL) was added AcOH (0.21 mL), $NaBH(OAc)_3$ (0.38 g, 1.79 mmol) and allylamine (0.30 mL, 4 mmol) at RT under argon. The reaction mixture was stirred for 36 hours at 40 °C and quenched by 1 M aq. NaOH (4 mL) at RT. The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were dried with $MgSO_4$, the solution was filtered and the solvent was evaporated. Purification by flash chromatography (AcOEt/cyclohexane, 1 : 6) afforded diene **3** (128 mg, 23% yield) as an oil.

$[\alpha]_D$ +14 (c = 1.01 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.38–7.30 (m, 15H, aromatic H), 5.94–5.82 (m, 2H, H-2, H-8), 5.41 (m, 1H, H-1a), 5.37 (m, 1H, H-1b), 5.16 (ddd, 1H, J = 1.6 Hz, J = 3.3 Hz, J = 17.1 Hz, H-9a), 5.06 (ddd, 1H, J = 1.4 Hz, J = 2.8 Hz, J = 10.0 Hz, H-9b), 4.93 (d, 1H, J = 11.2 Hz, CHPh), 4.66 (d, 1H, J = 11.6 Hz, CHPh), 4.60 (d, 1H, J = 11.2 Hz, CHPh), 4.47 (d, 1H, J = 12.0 Hz, CHPh), 4.43 (d, 1H, J = 12.0 Hz, CHPh), 4.42 (d, 1H, J = 11.6 Hz, CHPh), 4.25 (dd, 1H, J = 7.0 Hz, J = 7.5 Hz, H-3), 3.77 (dd, 1H, J = 3.3 Hz, J = 7.0 Hz, H-4), 3.53 (dd, 1H, J = 5.0 Hz, J = 9.2 Hz, H-6a), 3.48 (dd, 1H, J = 7.3 Hz, J = 9.2 Hz, H-6b), 3.37 (ddt, 1H, J = 1.4 Hz, J = 6.0 Hz, J = 12.6 Hz, H-7a), 3.20 (ddt, 1H, J = 1.4 Hz, J = 6.0 Hz, J = 13.7 Hz, H-7b), 2.98 (ddd, 1H, J = 3.3 Hz, J = 5.0 Hz, J = 7.3 Hz, H-5) ^{13}C NMR ($CDCl_3$, 100 MHz): 138.98, 138.63, 138.28 (3 × Cipso), 137.50 (C-8), 135.70 (C-2), 128.41–127.35 (15 aromatic C), 118.69 (C-1), 115.44 (C-9), 82.80 (C-3), 81.40 (C-4), 75.15, 73.02, 70.70 (3 × CH_2Ph), 69.53 (C-6), 56.83 (C-5), 50.53 (C-7); m/z (CI, NH_3): 458 (M + H$^+$, 100%); Anal. Calcd for $C_{30}H_{35}O_3N$: C, 78.74; H, 7.71; N, 3.06; Found C, 78.73; H, 7.77; N, 3.00%.

Further elution afforded diene **2** (192 mg, 35% yield) as an oil.

$[\alpha]_D$ −14 (c = 1.49 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.38–7.30 (m, 15H, aromatic H), 5.95 (ddd, 1H, J = 7.5 Hz, J = 10.5 Hz, J = 18.1 Hz, H-2), 5.83 (m, 1H, H-8), 5.35 (m, 1H, H-1a), 5.32 (m, 1H, H-1b), 5.14 (app. dq, 1H, J = 1.6 Hz, J = 17.1 Hz, H-9a), 5.06 (app. dq, 1H, J = 1.4 Hz, J = 10.2 Hz, H-9b), 4.81 (d, 1H, J = 11.4 Hz, CHPh), 4.68 (d, 1H, J = 11.4 Hz, CHPh), 4.67 (d, 1H, J = 11.8 Hz, CHPh), 4.57 (d, 1H, J = 12.0 Hz, CHPh), 4.49 (d, 1H, J = 12.0 Hz, CHPh), 4.42 (d, 1H, J = 11.8 Hz, CHPh), 4.22 (dd, 1H, J = 4.8 Hz, J = 7.5 Hz, H-3), 3.69 (dd, 1H, J = 4.1 Hz, J = 9.6 Hz, H-6a), 3.65 (m, 2H, H-4, H-6b), 3.23 (ddt, 1H, J = 1.4 Hz, J = 6.2 Hz, J = 15.1 Hz, H-7a), 3.13 (ddt, 1H, J = 1.4 Hz, J = 5.6 Hz, J = 13.9 Hz, H-7b), 3.03 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz): 138.76, 138.45, 138.38 (3 × Cipso), 137.29 (C-8), 136.02 (C-2), 128.27–127.38 (15 aromatic C), 118.27 (C-1), 115.43 (C-9), 81.37 (C-4), 81.10 (C-3), 74.73, 73.02, 70.51 (3 × CH_2Ph), 68.50 (C-6), 57.35 (C-5), 50.20 (C-7); m/z (CI, NH_3): 458 (M + H^+, 100%); Anal. Calcd for $C_{30}H_{35}O_3N$: C, 78.74; H, 7.71; N, 3.06; Found C, 78.79; H, 7.85; N, 2.89%.

(3*R*,4*R*,5*R*)-*N*-Benzyloxycarbonyl-5-allylamino-3,4,6-tribenzyloxy-hex-1-ene 4. Benzyl chloroformate (0.06 mL, 0.43 mmol) was added dropwise over a period of 30 min to an ice-cold solution of diene **2** (93 mg, 0.204 mmol) and $KHCO_3$ (0.38 g, 3.8 mmol) in a H_2O/AcOEt mixture (10 mL, 1 : 1, v/v). The reaction mixture was stirred for 6 hours at RT, the organic layer was separated, washed with 1 M aq. HCl (5 mL) and brine (5 mL), dried with $MgSO_4$, filtered and the solvent was evaporated. Purification by flash chromatography (AcOEt/cyclohexane, 1 : 8) afforded carbamate **4** (110 mg, 91% yield) as an oil.

$[\alpha]_D$ + 4 (c = 1.31 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, 2 rotamers): 7.41–7.30 (m, 40H, aromatic H), 6.02–5.78 (m, 4H, H-2, H-2′, H-8, H-8′), 5.40–5.01 (m, 8H, H-1, H-1′, H-9, H-9′, H-6a, H-6b, H-6′a, H-6′b), 4.85 (m, 2H, 2 × CHPh), 4.65–4.33 (m, 8H, 4 × CH_2Ph), 4.09–3.68 (m, 8H, H-3, H-4, H-5, H-7a, H-7b, H-7′a, H-7′b); ^{13}C NMR ($CDCl_3$, 100 MHz): 156.08 (C=O), 138.33, 138.25, 138.11, 136.81 (4 × Cipso), 135.81, 135.41 (C-2, C-8), 128.31–127.35 (20 aromatic C), 119.13, 119.01 (C-1, C-1′), 115.68, 115.42 (C-9, C-9′), 81.91, 81.59, 81.20 (C-3, C-4, C-5), 74.71, 72.68, 70.43 (4 × CH_2Ph), 68.20, 67.93, 67.18, 66.87 (C-6, C-6′, C-7, C-7′); m/z (CI, NH_3): 592 (M + H^+, 82%), 609 (M + NH_4^+, 100%); Anal. Calcd for $C_{38}H_{41}O_5N$: C, 77.13; H, 6.98; N, 2.37; Found C, 77.25; H, 7.04; N, 2.20%.

(2*R*,3*R*,4*R*)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-3,4-dibenzyloxy-5,6-didehydro-azepane 5. Compound **4** (106 mg, 0.179 mmol) was dissolved in dry CH_2Cl_2 (50 mL) and the solution was degassed for 30 min by bubbling argon through the solution. Grubbs' catalyst (16 mg, 0.019 mmol, 10%mol) was added and the solution was stirred for 76 hours at 45 °C under argon. The reaction was quenched by stirring the reaction mixture with $Pb(OAc)_4$ (16 mg, 0.036 mmol) for 5 hours. The solvent was evaporated and the residue purified by flash chromatography (AcOEt/cyclohexane, 1 : 8) to afford compound **5** (92 mg, 91% yield) as an oil.

$[\alpha]_D$ −67 (c = 0.9 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, 2 rotamers): 7.37–7.25 (m, 40H, aromatic H), 6.06 (ddd, 1H, J = 2.1 Hz, J = 6.1 Hz, J = 11.5 Hz, H-1), 5.92 (ddd, 1H, J = 2.2 Hz, J = 6.1 Hz, J = 11.7 Hz, H-1′), 5.77 (m, 2H, H-2, H-2′), 5.18 (s, 2H, CH_2Ph), 5.14 (d, 1H, J = 12.4 Hz, CHPh), 5.02 (d, 1H, J = 12.4 Hz, CHPh), 5.01 (m, 1H, H-5′), 4.86 (m, 1H, H-5), 4.65–4.50 (m, 12H, 6 × CH_2Ph), 4.40 (m, 1H, H-7a), 4.30 (m, 1H, H-7′a), 4.27 (m, 1H, H-3), 4.23 (m, 1H, H-3′), 4.08 (dd, 1H, J = 4.3 Hz, J = 6.9 Hz, H-4′), 4.05 (dd, 1H, J = 4.4 Hz, J = 6.8 Hz, H-4), 3.90–3.80 (m, 2H, H-7b, H-7′b), 3.87 (dd, 1H, J = 7.0 Hz, J = 9.6 Hz, H-6′a), 3.83 (dd, 1H, J = 7.3 Hz, J = 9.4 Hz, H-6a), 3.74 (dd, 1H, J = 8.2 Hz, J = 9.6 Hz, H-6′b), 3.67 (dd, 1H, J = 7.6 Hz, J = 9.4 Hz, H-6b); ^{13}C NMR ($CDCl_3$, 100 MHz): 155.85, 155.46 (2 × C=O), 138.47, 138.43, 138.38, 138.29, 138.21, 138.10 (6 × Cipso), 136.89, 136.73 (2 × Cipso), 133.49, 132.14 (C-1, C-1′), 128.40–127.43 (20 aromatic C), 127.21, 126.31 (C-2, C-2′), 78.99, 78.86 (C-4, C-4′), 75.93, 75.69 (C-3, C-3′), 73.09, 73.01, 72.91, 71.80, 71.63, 67.27, 67.10 (8 × CH_2Ph), 66.52, 65.97 (C-6, C-6′), 54.59, 54.24 (C-5, C-5′), 42.67, 42.15 (C-7, C-7′); m/z (CI, NH_3): 564 (M + H^+, 100%), 581 (M + NH_4^+, 55%); Anal. Calcd for $C_{36}H_{37}O_5N$: C, 76.71; H, 6.62; N, 2.48; Found C, 76.74; H, 6.59; N, 2.48%.

(2*R*,3*R*,4*R*,5*R*,6*R*)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-3,4-dibenzyloxy-5,6-dihydroxy-azepane 6 and (2*R*,3*R*,4*R*,5*S*,6*S*)-*N*-benzyloxycarbonyl-2-benzyloxymethyl-3,4-dibenzyloxy-5,6-dihydroxy-azepane 7. Compound **5** (130 mg, 0.231 mmol) was dissolved in acetone/water (8 : 1, 1 mL). NMO (110 mg, 0.94 mmol) was added, followed by OsO_4 (0.05 mL, 2.5% wt in t-BuOH). The reaction mixture was stirred for 24 hours at 30 °C and then quenched by addition of $Na_2S_2O_3.5H_2O$ (28 mg, 0.112 mmol). The reaction mixture was then saturated with NaCl, extracted thoroughly with CH_2Cl_2 (2 × 20 mL). The organic layer was dried with $MgSO_4$ and concentrated to give a residue that was purified by flash chromatography (AcOEt/cyclohexane, 2 : 3) to afford diol **6** (40 mg, 0.067 mmol, 28% yield).

$[\alpha]_D$ −10 (c = 1.08 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.39–7.23 (m, 40H, aromatic H), 5.17 (s, 2H, CH_2Ph), 5.16 (d, 1H, J = 12.3 Hz, CHPh), 5.10 (d, 1H, J = 12.3 Hz, CHPh), 4.89 (d, 1H, J = 10.9 Hz, CHPh), 4.88 (d, 1H, J = 11.2 Hz, CHPh), 4.83 (d, 2H, J = 11.3 Hz, 2 × CHPh), 4.65 (d, 1H, J = 11.6 Hz, CHPh), 4.60 (d, 1H, J = 11.3 Hz, CHPh), 4.52 (d, 1H, J = 11.2 Hz, CHPh), 4.52 (d, 1H, J = 10.9 Hz, CHPh), 4.47 (d, 1H, J = 12.2 Hz, CHPh), 4.46 (d, 1H, J = 10.9 Hz, CHPh), 4.40 (d, 1H, J = 12.1 Hz, CHPh), 4.38 (d, 1H, J = 12.2 Hz, CHPh), 4.28–4.23 (m, 3H, H-4, H-4′, H-5′), 4.23–4.20 (m, 3H, H-2, H-2′, H-3′), 4.15 (m, 1H, H-5), 3.83–3.66 (m, 6H, H-1, H-3, H-6a, H-6′a, H-7a, H-7′a), 3.65 (dd, 1H, H-6′b), 3.61 (m, 1H, H-1), 3.55 (dd, 1H, H-6b), 3.37 (dd, 1H, H-7′b), 3.29 (dd, 1H, H-7b); ^{13}C NMR ($CDCl_3$, 100 MHz): 156.07, 155.90 (2 × C=O), 138.14, 138.02, 137.98, 137.93, 137.85 (6 × Cipso), 136.40, 136.23 (2 × Cipso), 128.51–127.47 (20 aromatic C), 82.51, 81.81, 72.76, 72.67, 71.92, 71.78, 69.70, 68.58 (C-1, C-2, C-3, C-4, C-1′, C-2′, C-3′, C-4′), 74.74, 74.36, 74.05, 72.92, 72.89, 67.56, 67.32 (8 × CH_2Ph), 69.42, 69.19 (C-6, C-6′), 58.67, 58.59 (C-5, C-5′), 45.07, 44.48 (C-7, C-7′); m/z (CI, NH_3): 598 (M + H^+, 55%), 615 (M + NH_4^+, 100%); HRMS (CI, NH_3): Calcd for $C_{36}H_{40}O_7N$ (M + H^+): 598.2805, Found 598.2800.

Further elution afforded diol **7** (94 mg, 0.157 mmol, 68% yield).

$[\alpha]_D$ + 4 (c = 1.02 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, 2 rotamers): 7.39–7.26 (m, 40H, aromatic H), 5.24 (d, 1H, J = 12.3 Hz, CHPh), 5.22 (d, 1H, J = 12.5 Hz, CHPh), 5.18 (d, 1H, J = 12.5 Hz, CHPh), 5.16 (d, 1H, J = 12.3 Hz, CHPh), 5.06 (d, 1H, J = 11.1 Hz, CHPh), 5.04 (d, 1H, J = 11.1 Hz, CHPh), 4.98 (d, 1H, J = 10.9 Hz, CHPh), 4.96 (d, 1H, J = 11.2 Hz, CHPh), 4.64 (d, 1H, J = 11.1 Hz, CHPh), 4.58 (d, 1H, J = 11.2 Hz, CHPh), 4.53 (d, 1H, J = 11.2 Hz, CHPh), 4.48 (d, 1H, J = 12.0 Hz, CHPh), 4.47 (d, 1H, J = 10.9 Hz, CHPh), 4.43 (d, 1H, J = 11.7 Hz, CHPh), 4.38 (dd, 1H, J = 4.8 Hz, J = 15.9 Hz, H-7a), 4.36 (d, 1H, J = 10.7 Hz, CHPh), 4.35 (m, 1H, H-5′), 4.33 (d, 1H, J = 12.0 Hz, CHPh), 4.25 (dd, 1H, J = 5.1 Hz, J = 15.7 Hz, H-7′a), 4.13 (app. t, 1H, J = 4.1 Hz, H-1), 4.09 (dt, 1H, J = 2.1 Hz, J = 2.4 Hz, J = 9.2 Hz, H-5), 4.01 (app. t, 1H, J = 4.0 Hz, H-1′), 3.83 (dd, 1H, J = 2.9 Hz, J = 9.8 Hz, H-6a), 3.86–3.73 (m, 5H, H-3, H-3′, H-4, H-4′, H-6′a), 3.68 (dd, 1H, J = 2.6 Hz, J = 9.8 Hz, H-6b), 3.62–3.55 (m, 3H, H-2, H-2′, H-6′b), 3.31 (d, 1H, J = 16.4 Hz, H-7b), 3.27 (dd, 1H, J = 15.7 Hz, H-7′b); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.91, 156.78 (2 × C=O), 138.10, 137.94, 137.91, 137.89, 137.84, 137.73

(6 × Cipso), 136.69, 136.22 (2 × Cipso), 128.49–127.57 (20 aromatic C), 80.59, 80.17, 78.06, 77.84 (C-3, C-3′, C-4, C-4′), 76.06, 75.76, 75.60, 74.24, 73.20, 73.09, 67.90, 67.41 (8 × CH_2Ph), 75.55, 75.01 (C-2, C-2′), 69.92, 69.57 (C-6, C-6′), 67.97, 67.39 (C-1, C-1′), 58.09, 57.94 (C-5, C-5′), 44.70, 44.41 (C-7, C-7′); *m/z* (CI, NH_3): 490 (100%), 507 (50%), 598 (M + H^+, 4%), 615 (M + NH_4^+, 2%); HRMS (CI, NH_3): Calcd for $C_{36}H_{40}O_7N$ (M + H^+): 598.2805, Found 598.2814.

(2*R*,3*R*,4*R*,5*R*,6*R*)-2-Hydroxymethyl-3,4,5,6-tetrahydroxy-azepane 8. Diol **6** (87 mg, 0.145 mmol) was dissolved in AcOH (6.5 mL) and 10% Pd/C (10 mg) was added. The suspension was stirred under H_2 for 4 hours at 30 °C, filtered through Celite and eluted with MeOH. The solvent was removed under reduced pressure to afford compound **8** as a colorless oil (28 mg, 0.145 mmol, quant. yield).

$[a]_D$ −9 (*c* = 1.07 in CH_3OH); ^1H NMR (D_2O, 400 MHz): 4.22 (ddd, 1H, *J* = 1.4 Hz, *J* = 5.9 Hz, *J* = 8.7 Hz, H-1), 4.15 (dd, 1H, *J* = 1.4 Hz, *J* = 1.9 Hz, H-2), 3.96 (dd, 1H, *J* = 3.8 Hz, *J* = 12.3 Hz, H-6a), 3.85 (app. t, 1H, *J* = 8.8 Hz, H-4), 3.76 (dd, 1H, *J* = 7.2 Hz, *J* = 12.3 Hz, H-6b), 3.74 (dd, 1H, *J* = 1.9 Hz, *J* = 8.8 Hz, H-3), 3.41 (dd, 1H, *J* = 5.8 Hz, *J* = 13.5 Hz, H-7a), 3.27 (dd, 1H, *J* = 7.5 Hz, *J* = 13.5 Hz, H-7b), 3.24 (ddd, 1H, *J* = 3.8 Hz, *J* = 7.2 Hz, *J* = 8.8 Hz, H-5); ^{13}C NMR (D_2O, 100 MHz): 75.25 (C-3), 74.78 (C-2), 68.67 (C-4), 66.18 (C-1), 60.84 (C-5), 59.67 (C-6), 47.06 (C-7); *m/z* (CI, NH_3): 194 (M + H^+, 100%); HRMS (CI, NH_3): Calcd for $C_7H_{16}O_5N$ (M + H^+): 194.1028, Found 194.1031.

(2*R*,3*R*,4*R*,5*S*,6*S*)-2-Hydroxymethyl-3,4,5,6-tetrahydroxy-azepane 9. Diol **7** (280 mg, 0.469 mmol) was deprotected as described for compound **8** to afford compound **9** (90 mg, quant. yield) as a colorless oil.

$[a]_D$ +32 (*c* = 1.13 in CH_3OH); ^1H NMR (D_2O, 400 MHz): 4.23 (ddd, 1H, *J* = 2.3 Hz, *J* = 2.4 Hz, *J* = 6.3 Hz, H-1), 3.94 (dd, 1H, *J* = 3.6 Hz, *J* = 12.5 Hz, H-6a), 3.85 (dd, 1H, *J* = 6.6 Hz, *J* = 12.5 Hz, H-6b), 3.73 (app. t, 1H, *J* = 8.4 Hz, H-3), 3.65 (dd, 1H, *J* = 2.4 Hz, *J* = 8.4 Hz, H-2), 3.63 (dd, 1H, *J* = 8.4 Hz, *J* = 9.4 Hz, H-4), 3.48 (ddd, 1H, *J* = 3.6 Hz, *J* = 6.6 Hz, *J* = 9.4 Hz, H-5), 3.36 (dd, 1H, *J* = 6.3 Hz, *J* = 14.2 Hz, H-7a), 3.28 (dd, 1H, *J* = 2.3 Hz, *J* = 14.2 Hz, H-7b); ^{13}C NMR (D_2O, 100 MHz): 74.38 (C-2), 73.47 (C-3), 68.62 (C-4), 66.33 (C-1), 59.19 (C-6), 59.17 (C-5), 44.45 (C-7); *m/z* (CI, NH_3): 194 (M + H^+, 100%); HRMS (CI, NH_3): Calcd for $C_7H_{16}O_5N$ (M + H^+): 194.1028, Found 194.1031.

(2*R*,3*R*,4*R*)-2-Hydroxymethyl-3,4-dihydroxy-azepane 10. Didehydro-azepane **5** (57 mg, 0.101 mmol) was deprotected as described for compound **8** to afford compound **10** (16 mg, quant. yield) as a colorless oil.

$[a]_D$ +6.5 (*c* = 1.05 in CH_3OH); ^1H NMR (D_2O, 400 MHz): 3.97 (dd, 1H, *J* = 3.6 Hz, *J* = 12.3 Hz, H-6a), 3.86 (dd, 1H, *J* = 6.7 Hz, *J* = 12.3 Hz, H-6b), 3.78 (dt, 1H, *J* = 2.8 Hz, *J* = 8.4 Hz, H-3), 3.67 (app. t, 1H, *J* = 8.3 Hz, H-4), 3.28–3.40 (m, 2H, H-7a, H-5), 3.18 (m, 1H, H-7b), 1.66–2.12 (m, 4H, H-1a, H-1b, H-2a, H-2b); ^{13}C NMR (D_2O, 100 MHz): 73.95 (C-3), 72.18 (C-4), 60.52 (C-5), 59.75 (C-6), 46.13 (C-7), 28.53 (C-2), 19.16 (C-1); *m/z* (CI, NH_3): 162 (M + H^+, 100%); HRMS (CI, NH_3): Calcd for $C_7H_{16}O_3N$ (M + H^+): 162.1130, Found 162.1125.

(3*R*,4*R*,5*S*)-*N*-Benzyloxycarbonyl-5-allylamino-3,4,6-tri-benzyloxy-hex-1-ene 11. This product was synthesized as previously described for compound **4**.

Diene **3** (100 mg, 0.219 mmol) afforded compound **11** (118 mg, 0.199 mmol, 90% yield) as an oil.

$[a]_D$ −23 (*c* = 1.06 in $CHCl_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): 156.31 (C=O), 138.72, 138.31, 138.23, 136.82 (4 × Cipso), 135.79, 135.48, 134.93, 134.67 (C-2, C-2′, C-8, C-8′), 128.33–127.45 (20 aromatic C), 118.85, 118.70 (C-1, C-1′), 116.00 (C-9, C-9′), 81.38, 80.86 (C-3, C-4, C-5), 75.25, 72.79, 70.56 (4 × CH_2Ph), 68.52, 68.26, 66.99 (C-6, C-6′, C-7, C-7′); *m/z* (CI, NH_3): 592 (M + H^+, 72%), 609 (M + NH_4^+, 100%); Anal. Calcd for $C_{38}H_{41}O_5N$: C, 77.13; H, 6.98; N, 2.37; Found C, 77.11; H, 7.17; N, 2.23%.

(2*S*,3*R*,4*R*)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-3,4-dibenzyloxy-5,6-didehydro-azepane 12. This product was synthesized as previously described for compound **5**.

Carbamate **11** (90 mg, 0.152 mmol) afforded compound **12** (72 mg, 84% yield) as an oil.

$[a]_D$ −14 (*c* = 0.79 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.38–7.25 (m, 40H, aromatic H), 5.79–5.68 (m, 4H, H-1, H-1′, H-2, H-2′), 5.17 (m, 4H, 2 × CH_2Ph), 4.98 (d, 1H, *J* = 11.3 Hz, CHPh), 4.95 (d, 1H, *J* = 11.1 Hz, CHPh), 4.82 (d, 1H, *J* = 11.6 Hz, CHPh), 4.75 (d, 1H, *J* = 11.7 Hz, CHPh), 4.70 (d, 1H, *J* = 11.6 Hz, CHPh), 4.68 (d, 1H, *J* = 11.7 Hz, CHPh), 4.60 (m, 1H, H-5), 4.54 (d, 1H, *J* = 11.3 Hz, CHPh), 4.51 (d, 1H, *J* = 11.1 Hz, CHPh), 4.50 (d, 1H, *J* = 12.0 Hz, CHPh), 4.49 (d, 1H, *J* = 12.0 Hz, CHPh), 4.47 (m, 1H, H-5′), 4.34–4.26 (m, 4H, H-3, H-3′, H-7a, H-7′a), 3.92–3.73 (m, 6H, H-4, H-4′, H-6a, H-6′a, H-7b, H-7′b), 3.65 (dd, 1H, *J* = 2.9 Hz, *J* = 10.2 Hz, H-6′b), 3.58 (dd, 1H, *J* = 3.2 Hz, *J* = 10.2 Hz, H-6b); ^{13}C NMR ($CDCl_3$, 100 MHz): 156.13, 156.03 (2 × C=O), 138.54, 138.44, 138.41, 138.24, 138.10, 137.95 (6 × Cipso), 136.69, 136.55 (2 × Cipso), 131.82, 131.26 (C-1, C-1′ or C-2, C-2′), 128.77–127.53 (20 aromatic C), 128.40, 128.33 (C-1, C-1′ or C-2, C-2′), 80.39, 80.10, 79.92 (C-3, C-4, C-5), 74.83, 74.66, 73.74, 73.40, 72.88, 72.80, 67.47, 67.28 (8 × CH_2Ph), 69.31 (C-6, C-6′), 57.96, 57.55 (C-5, C-5′), 42.91 (C-7, C-7′); *m/z* (CI, NH_3): 564 (M + H^+, 100%), 581 (M + NH_4^+, 55%); Anal. Calcd for $C_{36}H_{37}O_5N$: C, 76.71; H, 6.62; N, 2.48; Found C, 76.73; H, 6.61; N, 2.40%.

(2*S*,3*R*,4*R*,5*R*,6*R*)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-3,4-dibenzyloxy-5,6-dihydroxy-azepane 13 and (2*S*,3*R*,4*R*,-5*S*,6*S*)-*N*-benzyloxycarbonyl-2-benzyloxymethyl-3,4-dibenzyl-oxy-5,6-dihydroxy-azepane 14. These products were synthesized as previously described for compounds **6** and **7**.

Compound **12** (69 mg, 0.122 mmol) afforded compounds **13** and **14** (64 mg, 0.107 mmol, 87% yield) in a 4 : 1 ratio and as oils.

Diol **13**: $[a]_D$ +12 (*c* = 1.1 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.37–7.24 (m, 40H, aromatic H), 5.22 (d, 1H, *J* = 12.4 Hz, CHPh), 5.17 (d, 1H, *J* = 12.4 Hz, CHPh), 5.16 (d, 1H, *J* = 12.3 Hz, CHPh), 5.08 (d, 1H, *J* = 12.3 Hz, CHPh), 4.75 (m, 1H, *J* = 4.6 Hz, H-5), 4.66–4.50 (m, 9H, 4 × CH_2Ph, H-5′), 4.46 (d, 1H, *J* = 12.0 Hz, CHPh), 4.41 (d, 1H, *J* = 12.0 Hz, CHPh), 4.27 (m, 1H, H-7a), 4.19 (m, 1H, H-7′a), 4.18 (dd, 1H, *J* = 5.2 Hz, *J* = 7.4 Hz, H-4), 4.14 (m, 2H, H-3, H-3′), 4.11 (dd, 1H, *J* = 5.1 Hz, *J* = 7.4 Hz, H-4′), 4.03 (m, 3H, H-1, H-2, H-2′), 3.93 (m, 1H, H-1′), 3.79 (dd, 1H, *J* = 8.7 Hz, *J* = 9.7 Hz, H-6′a), 3.73 (dd, 1H, *J* = 8.9 Hz, *J* = 9.5 Hz, H-6a), 3.64 (dd, 1H, *J* = 5.0 Hz, *J* = 8.7 Hz, H-6′b), 3.50 (dd, 1H, *J* = 5.3 Hz, *J* = 8.9 Hz, H-6b), 3.35–3.28 (m, 3H, H-7b, H-7′b, OH), 2.81 (d, 1H, *J* = 11.4 Hz, OH); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.53, 156.31 (2 × C=0), 138.21, 137.97, 137.60, 137.45, 137.15, 136.66, 136.35 (8 × Cipso), 128.61–127.47 (40 aromatic C), 82.62, 82.52 (C-3, C-3′), 74.89, 74.75, 74.21, 74.07 (4 × CH_2Ph), 74.18, 73.89 (C-4, C-4′), 73.08, 73.05 (2 × CH_2Ph), 72.44, 72.41 (C-1, C-1′), 69.86, 69.63 (C-2, C-2′), 67.71, 67.29 (2 × CH_2Ph), 67.27, 66.67 (C-6, C-6′), 55.41 (C-5, C-5′), 44.17, 44.09 (C-7, C-7′); *m/z* (CI, NH_3): 598 (M + H^+, 100%), 615 (M + NH_4^+, 30%); HRMS (CI, NH_3): Calcd for $C_{36}H_{40}O_7N$ (M + H^+): 598.2805, Found 598.2797.

Diol **14**: $[a]_D$ +4 (*c* = 1.05 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.40–7.27 (m, 40H, aromatic H), 5.27 (d, 1H, *J* = 12.5 Hz, CHPh), 5.21 (d, 1H, *J* = 12.5 Hz, CHPh), 5.17 (d, 1H, *J* = 12.4 Hz, CHPh), 5.13 (d, 1H, *J* = 12.4 Hz, CHPh), 4.74 (m, 1H, H-5), 4.74 (d, 2H, *J* = 10.5 Hz, 2 × CHPh), 4.69 (d, 1H, *J* = 8.6 Hz, CHPh), 4.66–4.48 (m, 7H, 3 × CH_2Ph, H-5′), 4.38 (app. t, 1H, *J* = 6.2 Hz, H-4), 4.30 (app. t, 1H, *J* = 6.1 Hz, H-4′), 4.18 (d, 1H, *J* = 8.8 Hz, H-2), 4.09–4.01 (m, 4H, H-1′, H-2′,

H-3, H-3′), 3.93 (m, 2H, H-1, H-7′a), 3.88–3.78 (m, 3H, H-6a, H-6′a, H-7a), 3.71 (dd, 1H, J = 5.5 Hz, J = 9.0 Hz, H-6b), 3.62 (dd, 1H, J = 5.6 Hz, J = 9.1 Hz, H-6′b), 3.32–3.22 (m, 2H, H-7b, H-7′b), 2.98 (d, 1H, J = 8.8 Hz, OH), 2.96 (d, 1H, J = 8.8 Hz, OH); ^{13}C NMR ($CDCl_3$, 100 MHz): 155.62, 155.51 (2 × C=0), 137.85, 137.68, 137.46, 137.42, 136.59, 136.53, 136.26, 136.24 (8 × Cipso), 128.67–127.38 (40 aromatic C), 78.61, 78.54 (C-4, C-4′), 75.40, 75.32 (2 × CH_2Ph), 74.56, 73.94 (C-3, C-3′), 73.19, 73.10, 72.80, 72.73 (4 × CH_2Ph), 72.62, 72.57 (C-2, C-2′), 69.52, 68.86 (C-1, C-1′), 67.25, 67.14 (2 × CH_2Ph), 67.03, 66.74 (C-6, C-6′), 53.92, 53.79 (C-5, C-5′), 44.66, 44.38 (C-7, C-7′); *m/z* (CI, NH_3): 598 (M + H^+, 100%), 615 (M + NH_4^+, 65%); HRMS (CI, NH_3): Calcd for $C_{36}H_{40}O_7N$ (M + H^+): 598.2805, Found 598.2800.

(2*S*,3*R*,4*R*,5*R*,6*R*)-2-Hydroxymethyl-3,4,5,6-tetrahydroxy-azepane 15. Diol **13** (30 mg, 0.05 mmol) was deprotected as described for compound **8** to afford compound **15** (10 mg, 0.05 mmol) as a colorless oil.

$[\alpha]_D$ −5 (c = 0.95 in CH_3OH); ^{1}H NMR (D_2O, 400 MHz): 4.28 (ddd, 1H, J = 2.0 Hz, J = 4.3 Hz, J = 8.7 Hz, H-1), 4.06 (dd, 1H, J = 2.0 Hz, J = 2.9 Hz, H-2), 4.02 (m, 2H, H-3, H-4), 3.91 (ddd, 1H, J = 1.0 Hz, J = 4.8 Hz, J = 9.1 Hz, H-5), 3.82 (dd, 1H, J = 4.8 Hz, J = 11.9 Hz, H-6a), 3.74 (dd, 1H, J = 9.1 Hz, J = 11.9 Hz, H-6b), 3.36 (m, 2H, H-7a, H-7b); ^{13}C NMR (D_2O, 100 MHz): 73.60 (C-3), 72.52 (C-2), 69.45 (C-4), 68.88 (C-1), 60.78 (C-6), 57.84 (C-5), 45.92 (C-7); *m/z* (CI, NH_3): 194 (M + H^+, 100%); HRMS (CI, NH_3): Calcd for $C_7H_{16}O_5N$ (M + H^+): 194.1028, Found 194.1033.

(2*S*,3*R*,4*R*,5*S*,6*S*)-2-Hydroxymethyl-3,4,5,6-tetrahydroxy-azepane 16. Diol **14** (120 mg, 0.20 mmol) was deprotected as described for compound **8** to afford compound **16** (39 mg, 0.20 mmol) as a colorless oil.

$[\alpha]_D$ +8 (c = 1.07 in CH_3OH); ^{1}H NMR (D_2O, 400 MHz): 4.22 (br d, 1H, J = 6.5 Hz, H-1), 3.92 (dd, 1H, J = 2.7 Hz, J = 6.3 Hz, H-3), 3.87 (app. d, 1H, J = 6.3 Hz, H-2), 3.84 (d, 1H, J = 2.7 Hz, H-4), 3.74 (dd, 1H, J = 5.6 Hz, J = 11.9 Hz, H-6a), 3.67 (dd, 1H, J = 8.9 Hz, J = 11.9 Hz, H-6b), 3.48 (dd, 1H, J = 5.6 Hz, J = 8.9 Hz, H-5), 3.46 (dd, 1H, J = 6.5 Hz, J = 13.8 Hz, H-7a), 3.25 (dd, 1H, J = 2.5 Hz, J = 13.8 Hz, H-7b); ^{13}C NMR (D_2O, 100 MHz): 76.84 (C-2), 74.49 (C-3), 70.05 (C-4), 68.25 (C-1), 60.68 (C-6), 58.31 (C-5), 47.97 (C-7); *m/z* (CI, NH_3) : 194 (M + H^+, 100%); HRMS (CI, NH_3): Calcd for $C_7H_{16}O_5N$ (M + H^+): 194.1028, Found 194.1032.

(2*S*,3*R*,4*R*)-2-Hydroxymethyl-3,4-dihydroxy-azepane 17. Didehydro-azepane **12** (49 mg, 0.087 mmol) was deprotected as described for compound **8** to afford compound **17** (14 mg, quant. yield) as a colorless oil.

$[\alpha]_D$ −3.5 (c = 1.05 in CH_3OH); ^{1}H NMR (D_2O, 400 MHz): 4.00 (m, 1H, H-3), 3.89 (d, 1H, J = 4.0 Hz, H-4), 3.81 (dd, 1H, J = 5.4 Hz, J = 11.7 Hz, H-6a), 3.75 (dd, 1H, J = 8.7 Hz, J = 11.7 Hz, H-6b), 3.64 (m, 1H, H-5), 3.31–3.26 (m, 2H, H-7a, H-7b), 2.25–1.76 (m, 4H, H-1a, H-1b, H-2a, H-2b); ^{13}C NMR (D_2O, 100 MHz): 70.15 (C-3), 70.02 (C-4), 60.96 (C-6), 55.95 (C-5), 46.75 (C-7), 29.10 (C-2), 17.57 (C-1); *m/z* (CI, NH_3): 162 (M + H^+, 100%); HRMS (CI, NH_3): Calcd for $C_7H_{16}O_3N$ (M + H^+): 162.1130, Found 162.1133.

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