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Towards a stable noeuromycin analog with a D-manno configuration: Synthesis and glycosidase inhibition of D-manno-like tri- and tetrahydroxylated azepanes

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ABSTRACT

Noeuromycin is a highly potent albeit unstable glycosidase inhibitor due to its hemiaminal function. While stable D-gluco-like analogs have been reported, no data are available for D-manno-like structures. A series of tri- and tetrahydroxylated seven-membered iminosugars displaying either a D-*manno*-or a L-*gulo*-like configuration, were synthesized from methyl α-D-mannopyranoside using a reductive amination-mediated ring expansion as the key step. Screening towards a range of commercial glycosidases demonstrated their potency as competitive glycosidase inhibitors while cellular assay showed selective albeit weak glycoprotein processing mannosidase inactivation.

1. Introduction

The quest for strong and selective glycosidase inhibitors is the subject of intensive research from many synthetic and biochemical groups as glycosidases are involved in an increasing number of pathologies[1] which require innovative structures able to selectively and strongly inhibit these therapeutically relevant enzymes. The most studied and promising structures to date are iminosugars,[2] sugar analogs in which a nitrogen atom is replacing the endocyclic oxygen. They have been devised to act as stable mimics of the glycosidase transient oxacarbenium-like transition state. These molecules can modulate cellular functions and promising results have been obtained in the field of diabetes,[3] HIV,[4] viral infections,[5] cancer[6] and lysosomal storage diseases[7] leading in some cases to therapeutics.[8]

Our group[9] and others[10] have focused on the design of unusual seven-membered iminosugars also named polyhydroxylated azepanes (Fig. 1). Seven-membered analogs of lead six-membered iminosugars including 1-deoxynojirimycin **1**,[11] 1-deoxymannojirimycin **2**,[12] 2-acetamido-1,2-dideoxynojirimycin **3**,[13] nojirimycin **4**[14] and noeuromycin **5**[15] have been reported and proved to be potent glycosyl hydrolase inhibitors. Their conformational flexibility has been also exploited to have insight into the glycosidase-mediated substrate ring distorsion performed by *O*-GlcNAcase,[16] a cytoplasmic β-*N*-acetylglucosaminidase.[17] Interestingly, a *N*-butylated azepane **6**[18] proved to be a potent inactivator of ceramide glucosyl transferase, an enzyme targeted in Gaucher disease,[19] the most prominent lysosomal storage disorder. More recently it has been shown that compound **6** and congeners, albeit

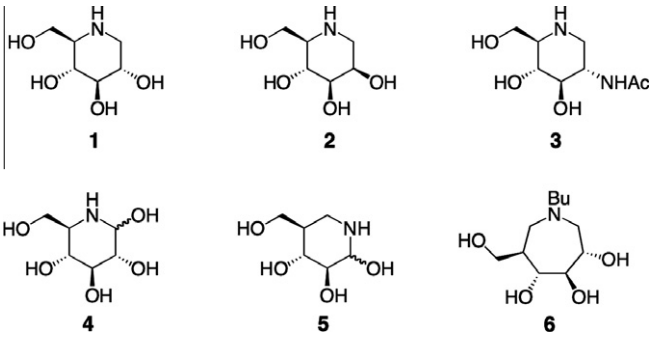

Figure 1. Structure of iminosugars **1**–**6**.

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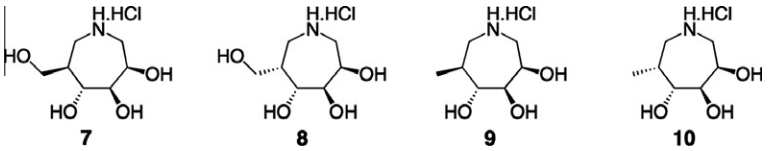


Figure 2. Structure of target iminosugars **7**–**10**.

displaying a D-*gluco*- or L-*ido*-like configuration, were selective and potent cytosolic mannosidase inhibitors, thus allowing to probe glycoprotein degradation pathways in cells.[20]

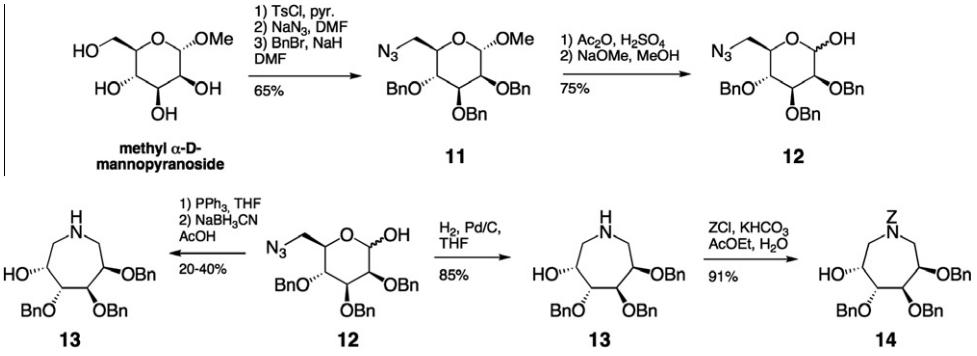
The configurational mismatch observed for compound **6** prompted us to explore the synthesis and determine the glycosidase inhibition profile of a series of D-*manno*-like tri- and C-6 epimeric tetrahydroxylated azepanes **7–10** (Fig. 2). Furthermore compounds **7** and **9** can be seen as D-*manno* configured noeuromycin ring homologs. Noeuromycin has been designed to mimic the carbocationic form of the glycosidase transition state and is a very potent and promising glycosidase inhibitor. Unfortunately its hemiaminal makes it unstable at neutral pH which has precluded its therapeutic development so far.[15] It is stable for a month as its hydrochloride salt, existing as a 1:2 mixture of D-*gluco* and D-*manno* configured species, but undergoes Amadori rearrangement at neutral pH. While chemically stable analogs of D-gluco-configured noeuromycin analogs have reported through 2-hydroxyl group homologation,[21] no derivative with a strict D-manno-like configuration has been described to the best of our knowledge. Regarding the crucial role of mannosidases in biochemical pathways and the potency of 1-*N*-iminosugars, there is a need for noeuromycin analogs displaying a D-manno configuration.

2. Synthesis

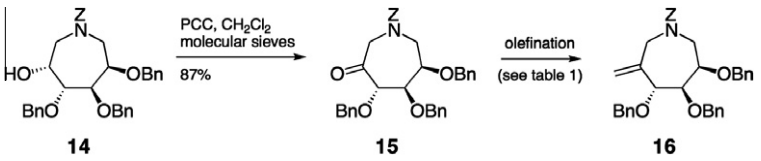
Our strategy towards target azepanes **7–10** is based on the ring expansion of an azidolactol derived from D-mannose via a tandem Staudinger/aza Wittig reaction[22] and requires the 6-azido-6-deoxy-D-mannopyranose which was synthesized as follows. Commercially available methyl α-D-mannopyranoside was regioselectively tosylated at C-6, displaced with sodium azide and perbenzylated to furnish the azide **11** in 65% yield over three steps. Acetolysis of the anomeric methoxy group in **11** followed by Zemplen deacetylation yielded the azidolactol **12**[23] in 75% yield as a mixture of anomers. Ring expansion was examined next. We have previously reported the ring isomerisation of 6-azido-6-deoxy-D-glucopyranose to generate D-*gluco*-configured noeuromycin homologs. In this latter work, hydrogenation of the D-gluco-configured azidolactol in the presence of triethylamine to avoid hydrogenolysis of the benzyl ethers failed to furnish the expected β-hydroxyazepane in satisfactory and reproductible yield while the alternative Staudinger-azaWittig methodology was more successful. Unfortunately, when applying the latter conditions to the D-*manno*-configured azidolactol **12**, the corresponding hydroxyazepane **13** was obtained in low yield. Surprisingly, hydrogenation-mediated ring expansion applied to the 6-azido-6-deoxy-mannopyranose **12** yielded the desired hydroxyazepane **13** in good yield (85%) emphasizing the opposite behavior of these azidolactols during ring expansion which can be related to the distinct stereochemistry of the hydroxyl groups present on the azepane ring eventually yielding to more or less stable hemiaminal bicyclic intermediates as previously observed.[24] Chemoselective protection of the amine in **13** as its benzyl carbamate yielded the azepane **14** (91%) ready for homologation of the free hydroxyl group (Scheme 1).

Oxidation with PCC furnished the corresponding ketone **15** (87%). Unlike the D-*gluco* isomer, olefination of **15** under standard Wittig conditions proved to be problematic and yielded the desired exoalkene **16** only in low yield (Scheme 2).

Optimization of the olefination step was thus necessary (Table 1). While temperature and amount of ylide introduced had no noticeable effect on the yield (entries 1–6), ylide concentration proved to influence the reaction outcome (entries 8 and 9). Most importantly, reverse addition greatly improved the yield (entries 6 and 7) and the best conditions (entry 9) furnished the expected exoalkene **16** in 50% yield. Use of other olefination reagents such



Scheme 1. Synthesis of hydroxyazepane **14**.



Scheme 2. Synthesis of exoalkene **16**.

Table 1
Optimization of the olefination conditions

Entry	Order of addition	Temperature	Equiv of PPh_3CH_2Br[a]	Yield (%)
1	Normal	−78 °C	10	Traces
2	Normal	0 °C	10	Traces
3	Normal	−20 °C	10	Traces
4	Normal	−10 °C then rt	10	Traces
5	Normal	−10 °C then rt	2	Traces
6	Normal	−10 °C then rt	30	Traces
7	Reverse	−10 °C then rt	10	20%
8	Reverse	−10 °C then rt	15[b]	30%
9	Reverse	−10 °C then rt	15	50%
10	Reverse	−10 °C then 60 °C	15	15%
11	—	Tebbe reagent, $PhCH_3$, 0 °C to rt		10%
12	—	Petasis reagent, $PhCH_3$, 80 °C		<10%

[a] 0.007 M solution in THF.
[b] 0.02 M solution in THF.

as Tebbe reagent[25] or Petasis reagent[26] (entries 11 and 12) was unsuccessful.

Since the 3,4,5-trihydroxy-6-methyl derivatives in the D-gluco series were found to be as potent glycosidase inactivators as the 3,4,5-trihydroxy-6-hydroxymethyl derivatives,[18] functionalization of the C=C bond by hydroboration and hydrogenation was performed. Hydroboration of **16** with 9-BBN was found sluggish and replaced by BH_3·THF which, after oxidation, furnished the separable hydroxymethyl derivatives **17a** and **17b** as the main products (50%) along with tertiary alcohols. Final hydrogenolysis quantitatively afforded the target azepanes **7** and **8** (Scheme 3).

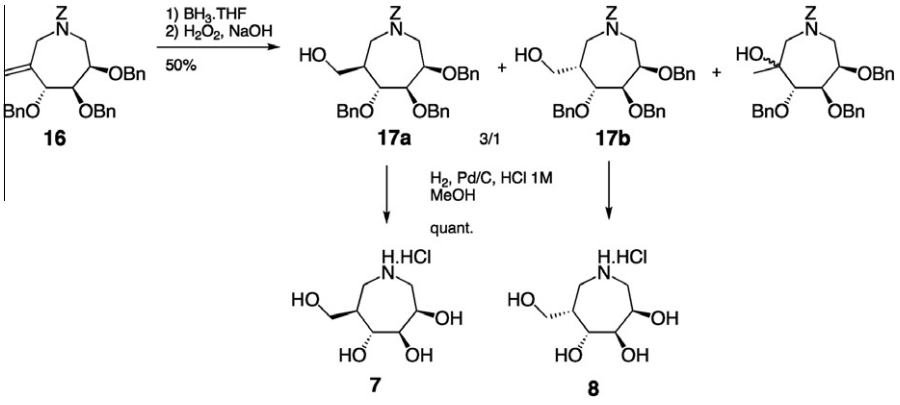
In parallel, treatment of exoalkene **16** with Wilkinson's catalyst yielded the two separable 6-methyl azepanes **18a** and **18b** (70% yield, 2:1 ratio) which were quantitatively deprotected to afford the trihydroxylated azepanes **9** and **10** (Scheme 4).

2.1. Inhibition of glycosidases from various sources

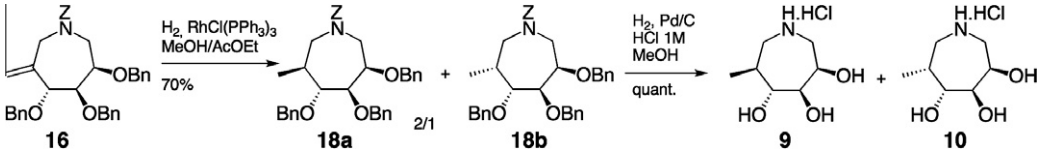
Polyhydroxylated azepanes **7–10** were assayed on a panel of commercially available glycosidases. The following glycosidases were not inhibited at 1 mM: β-mannosidase from snail, α-L-rhamnosidase from *Penicillium decumbens*, trehalase from porcine kidney, amyloglucosidase from *Aspergillus niger*. The four azepanes **7–10** display competitive inhibition, and, unlike the D-*gluco*- and L-*ido*-like azepanes which showed a marked selectivity towards glucosidases, the D-*manno* and L-*gulo* derivatives inhibit a broad range of glycosidases. Unfortunately, no trend toward a specific mannosidase inactivation was observed. The presence of a methyl or hydroxymethyl group at position 6 with a *R* configuration appears to be detrimental as azepanes **7** and **9** were less potent than azepanes **8** and **10** towards the range of glycosidases assayed except α-L-fucosidase. The trihydroxylated azepane **10** is more potent than the tetrahydroxylated azepane **8** indicating that the methyl group at C-6 is better accommodated by the glycosidase active site. Azepane **10** is the most potent inhibitor in this series and exhibits IC_{50} in the low micromolar range for three glycosidases (rice α-glucosidase, almond β-glucosidase and coffee beans α-galactosidase). This poor selectivity can be related to the pseudosymmetry of this azepane as broad range glycosidase inhibition has been previously observed in the case of *C*-2 symmetrical tetrahydroxylated azepanes. [10d]

2.2. Inhibition of glycosidases involved in glycoprotein degradation pathways

Multiple isoforms of mammalian α-mannosidases are active in the pathways of N-linked glycoprotein synthesis and catabolism.



Scheme 3. Synthesis of target azepanes **7** and **8**.



Scheme 4. Synthesis of target azepanes **9** and **10**.

They differ in specificity, function and location within the cell and can be selectively inhibited by iminosugar monosaccharide mimics. In a previous study, a series of structurally related novel seven-membered iminocyclitols were found to be potent and selective cytosolic α-mannosidase inhibitors while displaying configurations that did not match the stereochemical preference of the glycosidase. In this work, we aimed at detecting inhibition of mammalian mannosidase by azepanes **7–10** displaying either a D-manno or L-gulo like configuration through analysis of the free oligosaccharides (FOS)[27] as markers of endoplasmic reticulum (ER), Golgi, lysosomal and cytosolic α-mannosidase activities (Table 2). The four azepanes are weak α-mannosidase inhibitors in cells and effects are seen only at 1 mM (Figure 3). Interestingly and unlike assays above, only the azepanes **7** and **9** displaying a D-*manno*-like configuration significantly inhibit α-mannosidase and have similar potency at 1 mM. Azepanes **8** and **10** with a L-gulo like configuration do not inhibit these enzymes at the concentrations tested. We have used a lysosomal inhibitor, swainsonine, as control and azepanes **7** and **9** appear to act in a similar manner, increasing the amount of core $Man_3GlcNAc_2$(Manα1,3 (Manα1,6)Manß1,4GlcNAcß1,4GlcNAc) as a product of lysosomal mannosidase inhibition. The generation of additional species in treated cells including $Man_{5-8}GlcNAc_2FOS$ confirm lysosomal inhibition, but the significant increase in $Man_5GlcNAc_1$also supports inhibition of the cytosolic mannosidase (Figs. 3 and 4), similar to the effects seen using the seven-membered iminocyclitols published previously.[20]

3. Conclusion

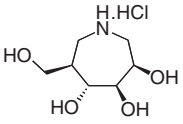
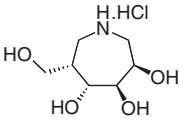
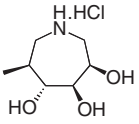
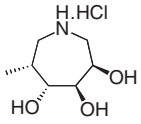
A series of new tri- and tetrahydroxylated seven-membered iminosugars displaying either a D-*manno*- or a L-*gulo*-like configuration have been synthesized with the aim to generate stable D-*manno* configured noeuromycin analogs. They have been assayed towards a range of commercial glycosidases and demonstrated competitive, potent but non selective glycosidase inhibition. No significant jack bean α-mannosidase inhibitory activity was observed. When shifting to cellular assay, weak glycoprotein processing mannosidase inactivation was observed with azepanes **7** and **9** displaying a D-manno-like configuration, these two compounds acting in a similar manner as swainsonine. The low degree of inhibition recorded might be due to the absence of *N*-alkyl chain known to facilitate cell penetration. Work is in progress to put this hypothesis on firmer ground.

4. Experimental section

4.1. General

NMR spectra were recorded on Bruker spectrometers (400 MHz for ^1H, 100 MHz for ^{13}C). Chemical shifts are reported in δ ppm from tetramethylsilane with the solvent resonance as the internal standard for ^1H NMR and chloroform-*d* (δ 77.0 ppm) for ^{13}C NMR. Coupling constants (*J*) are given in hertz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet,

Table 2
Inhibition profile of polyhydroxylated azepanes **7**–**10**

Enzyme	IC_{50} μm			
				
	7	**8**	**9**	**10**
α-Glucosidase				
Rice	NI (0%)	NI (14.7%)	226	12
Yeast	NI (18.7%)	71	NI (0%)	NI (37.8%)
β-Glucosidase				
Almond	NI (41.4%)	157	NI (29.4%)	14
Bovine liver	447	432	NI (49.2%)	244
α-Galactosidase				
Coffee beans	NI (16.8%)	65	NI (37.6%)	14
β-Galactosidase				
Bovine liver	442	420	876	198
α-Mannosidase				
Jack beans	NI (23.0%)	812	335	101
β-Mannosidase				
Snail	NI (0%)	NI (0%)	NI (4.3%)	NI (0.4%)
α-L-Rhamnosidase				
P. decumbens	NI (0.9%)	NI (1.5%)	NI (6.8%)	NI (20.6%)
α-L-Fucosidase				
Bovine kidney	NI (15.8%)	NI (25.0%)	181	64
β-Glucuronidase				
Bovine liver	NI (0%)	594	NI (0%)	139
Trehalase				
Porcine kidney	NI (16.6%)	NI (17.2%)	NI (22.2%)	NI (39.9%)
Amyloglucosidase				
Aspergillus niger	NI (14.2%)	NI (0.3%)	NI (0%)	NI (6.9%)

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

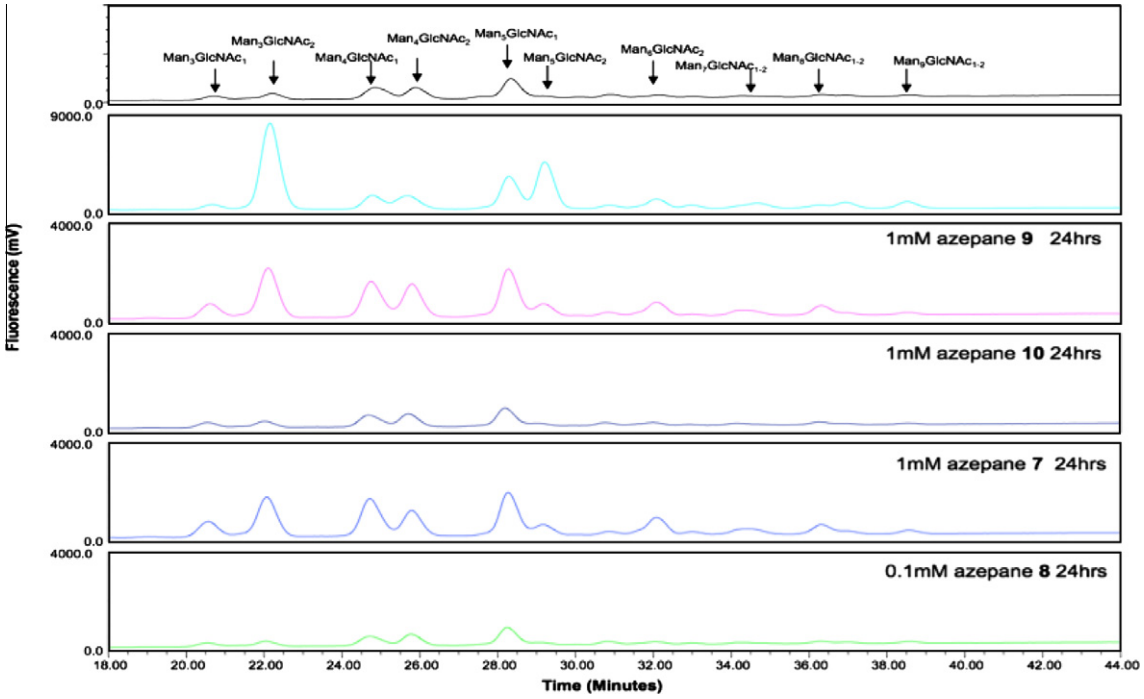


Figure 3. HPLC analysis of 2-AA fluorescently labeled FOS after treatment with azepanes **7**–**10**. The top two panels shows levels of mannosylated free glycans in untreated MDBK cells and swainsonine (1 mM for 24 h) treated cells, respectively.

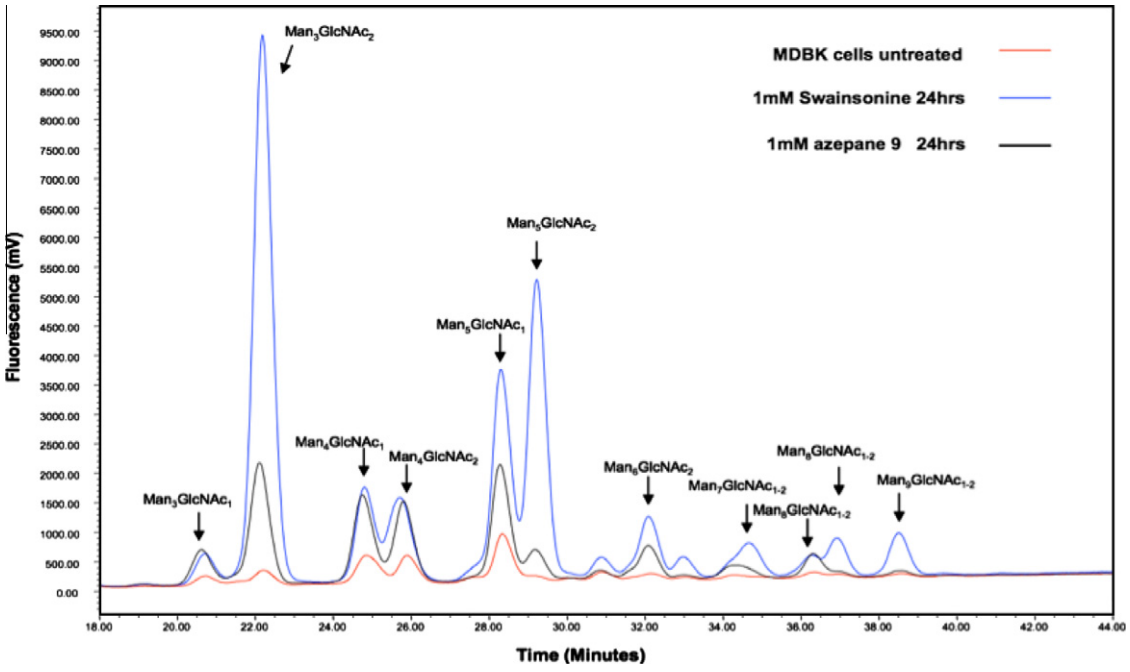


Figure 4. An overlay comparison ofthe HPLC analysis of 2-AA fluorescently labeled FOS from MDBK cells, untreated or following treatment with swainsonine and azepane **9**, shown in Figure 3.

q = quartet, m = mutiplet, br = broad signal. All assignments were confirmed by the aid of two-dimensional experiments (^{1}H, ^{1}H and ^{1}H, ^{13}C). The high-resolution mass spectra (HRMS) were obtained by the electrospray ionization method (Bruker Daltonics microTOF). $[\alpha]_D^{20}$ values were measured on a Perkin–Elmer 241 MC Polarimeter (concentration *c* are given in g/100 mL). Tetrahydrofuran, toluene and dichloromethane were distilled respectively under argon over sodium/benzophenone, sodium and calcium hydride.

4.1.1. 1-Methyl-6-azido-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-mannopyranoside (11)

This compound **11** was synthesized according to the reported procedure.[22] (65% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.28 (m, 15H, CH-Ar); 4.99 (d, ^2J = 11.0 Hz, 1H, CH_2-Bn); 4.80 (d, ^2J = 12.5 Hz, 1H, CH_2-Bn); 4.74 (d, ^2J = 12.4 Hz, 1H, CH_2-Bn); 4.73 (m, 1H, H_1); 4.64 (m, 2H, CH_2-Bn); 4.62 (d, ^2J = 11.1 Hz, 1H, CH_2-Bn); 3.91–3.39 (m, 2H, H_3 and H_4); 3.82 (m, 1H, H_2); 3.79–3.77 (m, 1H, H_5); 3.49–3.42 (m, 2H, H_6); 3.37 (s, 3H, OCH_3). ^{13}C NMR

(100 MHz, $CDCl_3$): δ 138.3, 138.2, 138.1 (C_{quat}-Ar); 129.7, 129.0, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6 (CH-Ar); 98.9 (C_1); 75.2 and 80.0 (C_3 and C_4); 51.5 (C_6); 75.0 (CH_2-Bn); 74.3 (C_2); 72.7 (CH_2-Bn); 72.0 (CH_2-Bn); 71.5 (C_5); 54.9 (OCH_3).

4.1.2. 6-Azido-2,3,4-tri-*O*-benzyl-6-deoxy-D-mannopyranoside (12)

To a cooled solution of methyl-6-azido-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-mannopyranoside **11** (2 g, 4.1 mmol) in dichloromethane (40 mL) at −10 °C were added dropwise acetic anhydride (3.0 mL, 20.5 mmol, 5 equiv) and sulfuric acid (240 μL, 4.1 mmol, 1 equiv). The reaction mixture was stirred at −10 °C for 5 min (the completion of the reaction was monitored by TLC). The reaction mixture was diluted with ethyl acetate, and then was quenched with ice. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were successively washed with water, sodium bicarbonate (twice), water and brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate: 5:1) to afford the acetate anomer as a colorless oil (1.8 g, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.18 (m, 15H, CH-Ar); 6.10 (d, ^3J = 2.0 Hz, 1H, H_1); 4.89 (d, ^2J = 10.9 Hz, 1H, CH_2-Bn); 4.70 (d, ^2J = 12.6 Hz, 1H, CH_2-Bn); 4.64 (d, ^2J = 12.6 Hz, 1H, CH_2-Bn); 4.53 (d, ^2J = 10.9 Hz, 1H, CH_2-Bn); 4.51 (s, 2H, CH_2-Bn); 3.93 (dd → t, ^3J = 9.6 Hz and 9.5 Hz, 1H, H_4); 3.75 (dd, ^3J = 9.4 Hz and 3.1 Hz, 1H, H_3); 3.72 (m, 1H, H_5); 3.66 (dd, ^3J = 3.0 Hz and 2.2 Hz, 1H, H_2); 3.45 (dd, ^2J = 9.9 Hz and ^3J = 1.7 Hz, 1H, H_{6b}); 3.30 (dd, ^2J = 9.9 Hz and ^3J = 4.1 Hz, 1H, H_{6a}); 1.95 (s, 3H, Ac). ^{13}C NMR (100 M Hz, $CDCl_3$) δ168.8 (C═O ester); 138.1, 138.0, 137.1 (C_{quat}-Ar); 128.5, 128.4, 128.1, 128.0, 127.9$_5$, 127.9, 127.8, 127.7 (CH-Ar); 91.5 (C_1); 79.0 (C_3); 75.4 (CH_2-Bn); 74.6 (C_4); 73.6 (C_5); 73.3 (C_2); 72.5 (CH_2-Bn); 72.0 (CH_2-Bn); 51.1 (C_6); 20.9 (CH_3).

To a solution of 1-acetyl-6-azido-2,3,4-tri-*O*-benzyl-6-deoxy-D-mannopyranoside (1.8 g, 3.5 mmol) in methanol (40 mL) was added sodium (160 mg, 7.0 mmol, 2 equiv) by portions. The reaction mixture was stirred at room temperature for 1 h. The completion of the reaction was monitored by TLC (cyclohexane/acetone; 30:1). The reaction mixture was neutralized with amberlyst 15 resin, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate: 5:1 then 4:1) to afford azidolactol **12** as a pale yellow oil (1.45 g, 87% yield); ^{1}H NMR (400 M Hz, $CDCl_3$): δ 7.42–7.28 (m, 15H, CH-Ar); 5.26–5.24 (m, 1H, H_1); 5.00–4.60 (m, 6H, 3 × CH_2-Bn); 4.00–3.88 (m, 3H, H_3, H_4 and H_5); 3.84 (m, 1H, H_2); 3.56–3.52 (m, 1H, H_{6b}); 3.47–3.37 (m, 1H, H_{6a}); 2.95 (br, OH). ^{13}C NMR (100 M Hz, $CDCl_3$): δ 138.2, 137.8137.6 (C_{quat}-Ar); 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6 (CH-Ar); 92.7 (C_1); 75.1, 72.8, 72.1 (3 × CH_2-Bn); 79.4, 75.4, 74.6, 71.4 (C_2, C_3, C_4, and C_5); 51.7 (C_6).

4.1.3. (3*R*,4*R*,5*R*,6*R*)-3-Hydroxy-4,5,6-tribenzyloxyazepane (13)

To a solution of 6-azido-2,3,4-tri-*O*-benzyl-6-deoxy-D-mannopyranoside **12** (570 mg, 1.2 mmol) in tetrahydrofuran (40 mL) was added palladium on charcoal (350 mg) under nitrogen. The system was then purged by hydrogen. The reaction mixture was stirred under hydrogen for 4 h. The completion of the reaction was monitored by TLC (CH_2Cl_2/CH_3OH; 15:1). The reaction mixture was filtered over Celite® and evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/CH_3OH; 30:1 then 15:1) to afford azepane **13** as a colorless oil (400 mg, 85% yield); ^{1}H NMR (400 M Hz, $CDCl_3$): δ 7.38–7.28 (m, 15H, CH-Ar); 4.74 (d, ^2J = 11.9 Hz, 1H, H_a of CH_2-Bn); 4.73 (d, ^2J = 11.6 Hz, 1H, H_a of CH_2-Bn); 4.69 (d, ^2J = 11.9 Hz, 1H, H_b of CH_2-Bn); 4.64 (d, ^2J = 12.1 Hz, 1H, H_b of CH_2-Bn); 4.62 (d, ^2J = 11.6 Hz, 1H, H_b of CH_2-Bn); 4.60 (d, ^2J = 12.1 Hz, 1H, H_b of CH_2-Bn); 3.99–3.95 (m, 3H, H_3, H_4, and H_6); 3.91 (dd, ^3J = 6.6 Hz and 4.2 Hz, 1H, H_5); 3.14 (dd, ^2J = 13.9 Hz and ^3J = 6.3 Hz, 1H, H_a of CH_2); 3.00 (dd, ^2J = 13.9 Hz and ^3J = 6.3 Hz, 1H, H_b of CH_2); 3.00 (dd, ^2J = 14.2 Hz and ^3J = 7.3 Hz, 1H, H_a of CH_2); 2.90 (dd, ^2J = 14.2 Hz and ^3J = 7.3 Hz, 1H, H_b of CH_2); 2.46 (s, 2H, OH + NH).13C NMR (100 MHz, $CDCl_3$): δ 138.5$_5$, 138.5, 138.0 (C_{quat}-Ar); 128.5, 128.3, 128.0, 127.9, 127.7, 127.6, 127.5 (CH-Ar); 80.4, 79.8, 78.0 (C_3, C_5, andC_6); 73.7 (CH_2-Bn); 73.3 (CH_2-Bn); 72.0 (CH_2-Bn); 69.9 (C_4); 48.7, 48.5 (C_2 and C_7).$[\alpha]_D^{20}$ = −26.0 (*c* 0.75 $CHCl_3$). HRMS (+ESI): calcd for $C_{27}H_{32}O_4N$: 434.2326; found: 434.2328.

4.1.4. (3*R*,4*R*,5*R*,6*R*)-*N*-Benzyloxycarbonyl-3-hydroxy-4,5,6-tribenzyloxyazepane (14)

To a cooled biphasic solution of (3*R*,4*R*,5*R*,6*R*)-3-hydroxy-4,5,6-tribenzyloxyazepane **13** (443 mg, 1.02 mmol) in ethyl acetate/water (15 mL/15 mL) at 0 °C were dropwise added potassium bicarbonate (185 mg, 1.83 mmol, 1.8 equiv) and benzyl chloroformate (330 μL, 2.76 mmol, 2.7 equiv). The completion of the reaction was monitored by TLC (CH_2Cl_2/CH_3OH; 20:1). After 3 h, the reaction mixture was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were successively washed with water, a HCl solution (1 M), water and brine, dried over magnesium sulfate, filtered and evaporated over reduced pressure. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate; 4:1 then 2:1) to afford azepane **14** as a colorless oil (558 mg, 97% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (presence of two rotamers) 7.35–7.18 (m, 40H, CH-Ar); 5.01 (d, ^2J = 12.4 Hz, 1H, H_a of CH_2-Bn); 4.96 (d, ^2J = 12.4 Hz, 1H, H_b of CH_2-Bn); 4.90 (d, ^2J = 12.4 Hz, 1H, H'_a of CH_2-Bn); 4.85 (d, ^2J = 12.4 Hz, 1H, H'_b of CH_2-Bn); 4.73–4.30 (m, 12H, 3 × CH_2-Bn + 3 × CH'_2-Bn); 4.14 (s, 1H, OH); 4.14–3.73 (m, 8H, H_3, H_4, H_5, H_6, and H'_3, H'_4, H'_5, H'_6); 3.70–3.47 (m, 8H, H_2, H_7 + H'_2, H'_7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (presence of two rotamers) 157.0, 156.0 (2 × C═O); 138.5, 138.4, 138.3, 138.2, 138.0, 137.7, 136.7, 136.6 (C_{quat}-Ar); 128.5, 128.4$_5$, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6$_5$, 127.6, 127.5 (CH-Ar); 79.2, 78.6 (CH and CH′); 77.8, 77.7 (CH and CH′); 75.5, 75.4 (CH and CH′); 73.9, 73.7 (CH_2-Bn and C′H_2-Bn); 71.8, 71.7 (CH_2-Bn and C′H_2-Bn); 70.3 (CH_2-Bn); 69.2 (CH); 67.3, 67.1 (CH_2-Bn and C′H_2-Bn); 50.6, 49.0, 46.7, 46.3 (C_2, C_7, and C'_2, C'_7); $[\alpha]_D^{20}$ = −29.4 (*c* 0.75 $CHCl_3$). HRMS (+ESI): calcd for $C_{35}H_{37}O_6NNa$: 590.2513; found: 590.2504.

4.1.5. (3*R*,4*R*,5*R*,6*R*)-*N*-Benzyloxycarbonyl-3-oxo-4,5,6-tribenzyloxyazepane (15)

To a solution of (3*R*,4*R*,5*R*,6*R*)-*N*-benzyloxycarbonyl-3-hydroxy-4,5,6-tribenzyloxyazepane **14** (558 mg, 0.98 mmol) in dichloromethane (40 mL) were added under nitrogen at room temperature molecular sieves 4 Å (480 mg) and pyridinium chlorochromate (636 mg, 2.95 mmol, 3 equiv). The completion of the reaction was monitored by TLC (cyclohexane/ethyl acetate; 4:1). After 3 h, the reaction mixture was filtered over Celite®. The filtrate was then evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate; 4:1) to afford ketone **15** as a pale yellow oil (480 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_{3)}$: $_\delta$ (presence of two rotamers) 7.28–7.00 (m, 40H, CH-Ar); 4.95 (d, ^2J = 12.3 Hz, 1H, H_a of CH_2-Bn); 4.85 (d, ^2J = 12.1 Hz, 1H, H'_a of CH_2-Bn); 4.80 (d, ^2J = 12.1 Hz, 1H, H_b of CH_2-Bn); 4.68–4.52 (m, 9H, H_{7a} and H'_{7a}, H'_b of CH_2-Bn, 3 × CH_2-Bn); 4.90–4.10 (m, 8H, 3 × CH_2-Bn, H_3 and H_{2a}); 4.06–4.00 (m, 1H, H'_3); 3.93–3.86 (m, 5H, H_4 and H'_4, H_5 and H'_5, H'_{2a}); 3.60–3.50 (2d, ^2J = 18.8 Hz, 2H, H_{7b} and H'_{7b}); 3.12–3.23 (m, 2H, H_{2b}, H'_{2b}). ^{13}C NMR (100 MHz, $CDCl_3$): δ (presence of two rotamers) 207.4, 206.5 (2 × C═O ketone); 155.9, 155.4 (2 × C═O carbamate); 138.3, 138.2, 137.8, 137.7, 136.8, 136.7, 136.3, 136.0 (C_{quat}-Ar); 128.4, 128.3$_5$, 128.3, 128.2$_5$, 128.0, 127.9$_5$, 127.9, 127.7, 127.6$_5$,

127.6, 127.4, 127.0 (CH-Ar); 83.6, 83.3 (C_5 and C'_5); 75.7, 75.4, 75.0, (C_3 and C'_3, C_4, and C'_4); 73.3, 73.1, 73.0, 72.5, 72.1, 71.8 ($3 \times CH_2$-Bn + $3 \times C'H_2$-Bn); 67.5, 67.4 (CH_2-Bn and $C'H_2$-Bn); 57.0, 56.8 (C_7 and C'_7); 46.3, 45.7 (C_2 and C'_2). $[\alpha]_D^{20} = -1.4$ (*c* 0.12 $CHCl_3$). HRMS (+ESI): calcd for $C_{35}H_{35}O_6NNa$: 588.2357; found: 588.2353.

4.1.6. (3*R*,4*R*,5*R*)-*N*-Benzyloxycarbonyl-3-methylene-4,5,6-tribenzyloxyazepane (16)

To a cooled solution of methyltriphenylphosphonium bromide (560 mg, 1.6 mmol, 10 equiv) in THF (5 mL) at −10 °C was dropwise added *n*-BuLi (570 μL, 1.4 mmol, 9 equiv) and the reaction mixture was stirred at −10 °C for 30 min. Then the ylide solution was added to a cooled solution of (3*R*,4*R*,5*R*,6*R*)-*N*-benzyloxycarbonyl-3-oxo-4,5,6-tribenzyloxyazepane **15** (90 mg, 0.16 mmol) in THF (2.5 mL). The reaction mixture was stirred at room temperature for 16 h, quenched with water and diluted with diethyl ether. The aqueous layer was extracted with diethyl ether and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography to afford exoalkene **16** as a colorless oil (45 mg, 50% yield).^{1}H NMR (400 MHz, $CDCl_3$): δ (presence of two rotamers) 7.28–6.66 (m, 40H, CH-Ar); 5.23 (m, 1H, H-alkene); 5.15 (m, 1H, H-alkene); 5.01–5.04 (d and m, ^2J = 12.4 Hz, 3H, 2H′-alkene and H_a of CH_2-Bn); 4.91 (s, 2H, CH_2-Bn); 4.79–4.63 (4d, ^2J = 12.4 Hz, 4H, $2 \times CH_2$-Bn); 4.50–4.47 (m, 5H, H_{7a} and $2 \times CH_2$-Bn); 4.45–4.37 (2d, ^2J = 12.2 Hz and 10.2 Hz, 4H, H_{7b}, H'_{7a} and CH_2-Bn); 4.28 (d, ^2J = 12.2 Hz, 1H, H_b of CH_2-Bn); 3.93–3.85 (m, 5H, H_3 and H'_3, H_4 and H'_4, H_{2a}); 3.79–3.70 (m, 3H, H'_{2a}, H_{2b}, H'_{7b}); 3.30–3.23 (m, 1H, H'_{2b}). ^{13}C NMR (100 MHz, $CDCl_3$): δ (presence of two rotamers) 141.2, 141.1 ($2 \times$ C=O carbamate); 138.9, 138.8, 138.7, 138.6, 138.1, 138.0, 136.8 (C_{quat}-Ar); 130.0 (C_{quat}); 128.9, 128.8, 128.4, 128.3$_5$, 128.3, 128.2, 128.0, 127.7$_5$, 127.7, 127.6$_5$, 127.6, 127.5, 127.4$_5$, 127.4, 127.3, 126.9 (CH-Ar); 118.9118.6 (=CH_2–alkene); 80.8 (C_5 and C'_5); 78.2, 77.8 (C_3 and C'_3); 76.7, 76.5 (C_4 and C'_4); 73.2, 73.1 (CH_2-Bn); 71.7, 71.5 (CH_2-Bn); 70.6, 70.3 (CH_2-Bn); 67.2, 67.0 (CH_2-Bn and $C'H_2$-Bn); 50.3, 50.1 (C_7 and C'_7); 44.9 (C_2 and C'_2). $[\alpha]_D^{20} = -3.0$ (*c* 0.09 $CHCl_3$). HRMS (+ESI): calcd for $C_{36}H_{37}O_5NNa$: 586.2563; found: 586.2555.

4.2. General procedure for the hydroboration of (16)

To a cooled solution of (3*R*,4*R*,5*R*)-*N*-benzyloxycarbonyl-3-methylene-4,5,6-tribenzyloxyazepane **16** (42 mg, 0.075 mmol) in THF (1.5 mL) at 0 °C was added the borane–THF complex (4×340 μL, 1.36 mmol) by portions. The reaction mixture was stirred at room temperature for 4 h. The colorless solution was oxidized and hydrolyzed by addition of ethanol (150 μL), an aqueous solution of hydroxide sodium (2 M, 200 μL) and hydrogen peroxide (200 μL). The reaction mixture was diluted in diethyl ether. The organic layer was successively washed with HCl (1 M), water and brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (cyclohexane/ethyl acetate; 8:1) to afford the twohydroxymethyl derivatives **17a** and **17b** (major isomer: 14 mg; minor isomer 7 mg; 50% yield).

4.2.1. (3*R*,4*R*,5*R*,6*R*)-*N*-Benzyloxycarbonyl-3-hydroxymethyl-4,5,5-tribenzyloxyazepane (17a)

^{1}H NMR (400 MHz, $CDCl_3$): δ (presence of two rotamers) 7.28–7.15 (m, 40H, CH-Ar); 4.92–4.39 (m, 16H, $8 \times CH_2$-Bn); 4.03–3.92 (m, 4H, H_3, H'_3, H_5 and H'_5); 3.86–3.74 (m, 4H, H_{2a}, H'_{2a}, H_6 and H_{7a}); 3.72–3.69 (m, 2H, H_3 and H_a of CH_2OH); 3.62–3.50 (m, 4H, H'_3, H'_{7a}, 2H′ of CH_2OH); 3.46–3.36 (m, 1H, H_b of CH_2OH); 3.35–3.32 (m, 3H, H_{2b}, H'_{2b}, H'_6); 2.31–2.16 (m, 2H, H_{7b} and H'_{7b}); 1.50 (s, 2H, $2 \times$ OH).13C NMR (100 MHz, $CDCl_3$): δ (presence of two rotamers) 157.4 ($2 \times$ C=O carbamate); 138.1, 138.0, 137.9, 137.8 (C_{quat}-Ar); 136.5 (C_{quat}); 128.6, 128.5, 128.4$_5$, 128.4, 128.2, 128.0, 127.8, 127.7$_5$, 127.7, 127.6, 127.5 (CH-Ar); 80.8, 80.7 (C'_4 and C_4); 78.5, 76.8 (C_5 and C'_5); 76.2, 75.1 (C_3 and C'_3); 73.1, 72.8 (CH_2-Bn and $C'H_2$-Bn); 72.2, 72.0, 71.8, 71.7 ($2 \times CH_2$-Bn and $2 \times C'H_2$-Bn); 67.5, 67.2 (CH_2-Bn and $C'H_2$-Bn); 63.9, 61.6 (CH_2OH and $C'H_2OH$); 46.9, 46.1 (C_7 and C'_7); 45.6, 45.5 (C_6 and C'_6); 45.5, 42.6 (C_2 and C'_2). $[\alpha]_D^{20} = -27.0$ (*c* 0.6 $CHCl_3$). HRMS (+ESI): calcd for $C_{36}H_{39}O_6NNa$: 604.2670; found: 604.22662.

4.2.2. (3*S*,4*R*,5*R*,6*R*)-*N*-Benzyloxycarbonyl-3-hydroxymethyl-4,5,5-tribenzyloxyazepane (17b)

^{1}H NMR (400 MHz, $CDCl_3$): δ (presence of two rotamers) 7.28–7.15 (m, 40H, CH-Ar); 5.15–4.25 (m, 16H, $8 \times CH_2$-Bn); 4.10–4.05 (m, 4H, H_4, (H'_4, H_5 and (H'_5); 4.00–3.95 (m, 4H, H_{2a}, (H'_{2a}, H_6 and H_{7a}); 3.84–3.73 (m, 2H, H_3 and H_a of CH_2OH); 3.70–3.65 (m, 4H, H'_3, H'_{7a}, 2H′ of CH_2OH); 3.47–3.41 (m, 1H, H_b of CH_2OH); 3.40–3.22 (m, 3H, H_{2b}, H'_{2b}, H'_6); 2.36–2.28 (m, 2H, H_{7b} and H'_{7b}); 1.50 (s, 2H, $2 \times$ OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (presence of two rotamers) 157.4 ($2 \times$ C=O carbamate); 138.1, 138.0, 137.9, 137.8 (C_{quat}-Ar); 136.6 (C_{quat}); 128.6, 128.5, 128.4$_5$, 128.4, 128.0, 127.8, 127.7$_5$, 127.7, 127.6, 127.5 (CH-Ar); 81.8, 81.7 (C_4 and C'_4); 76.5, 75.8 (C_5 and C'_5); 75.2, 74.1 (C_3 and C'_3); 72.1, 71.8 (CH_2-Bn and $C'H_2$-Bn); 71.2, 71.0, 70.8, 70.7 ($2 \times CH_2$-Bn and $2 \times C'H_2$-Bn); 66.5, 65.2 (CH_2-Bn and $C'H_2$-Bn); 62.9, 60.6 (CH_2OH and $C'H_2OH$); 48.9, 47.1 (C_7 and C'_7); 46.6, 44.5 (C_5 and C'_6); 42.5, 40.6 (C_2 and C'_2).$[\alpha]_D^{20} = -23.0$ (*c* 0.3 $CHCl_3$). HRMS (+ESI): calcd for $C_{36}H_{39}O_6NNa$: 604.2670; found: 604.2661.

4.3. General procedure for the selective reduction of (16)

Tris(triphenylphosphine)-rhodium (I) chloride (50 mg, 0.05 mmol) was added to a solution of (3*R*,4*R*,5*R*)-*N*-benzyloxycarbonyl-3-methylene-4,5,6-tribenzyloxyazepane **16** (60 mg, 0.11 mmol) in methanol (2 mL)/ethyl acetate (1 mL). The reaction mixture was purged from air and stirred under hydrogen atmosphere for 5 h. The completion of the reaction was monitored by TLC. The solvents were evaporated and the residue was purified by flash chromatography (toluene/ethyl acetate; 20:1) to afford the two methyl derivatives (**18a**: 30 mg; **18b**: 15 mg; 75% yield).

4.3.1. (3*S*,4*R*,5*R*,6*R*)-*N*-Benzyloxycarbonyl-3-methyl-4,5,6-tribenzyloxyazepane (18a)

^{1}H NMR (400 MHz, $CDCl_3$): δ (presence of two rotamers) (m, 40H, CH-Ar); 5.18–5.08 (m, 4H, $2 \times CH_2$-Bn); 4.81–4.42 (m, 12H, $3 \times CH_2$-Bn); 4.22–4.18 (dd, *J* = 13.5 Hz and 4.5 Hz, H_{2a}); 4.07–4.03 (dd, *J* = 7.8 Hz and 5.0 Hz, 1H, H'_{2a}); 4.01–3.96 (m, 4H, H_3, H'_3, H_4, H'_4); 3.78–3.74 (dd, *J* = 14.0 Hz and 4.1 Hz, 1H, H'_{7a}); 3.68–3.64 (dd, *J* = 14.6 Hz and 3.6 Hz, 1H, H'_{7a}); 3.55–3.50 (2dd, *J* = 8.7 Hz and 6.3 Hz, 2H, H_5 and H'_5); 3.45–3.34 (2dd, *J* = 13.6 Hz and 8.0 Hz, 2H, H_{2b} and H'_{2b}); 3.17–3.09 (2dd, *J* = 10.8 Hz and 8.0 Hz, 2H, H_{7b} and H'_{7b}); 2.25–2.20 (m, 1H, H_6); 2.06–2.02 (m, 1H, H'_6); 1.06 (d, ^3J = 7.1 Hz, 3H, CH_3); 1.01 (d, ^3J = 7.1 Hz, 3H, CH'_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (presence of two rotamers) 155.9, 155.6 ($2 \times$ C=O carbamate); 138.7, 138.5$_5$, 138.5, 138.4$_5$, 138.4 (C_{quat}-Ar); 137.0, 136.9 ($2 \times C_{quat}$); 128.3, 128.2, 127.8$_5$, 127.8, 127.7, 127.6$_5$, 127.6, 127.5, 127.4 (CH-Ar); 82.6, 82.4 (C_5 and C'_5); 82.1, 82.0 (C_3 and C'_3); 76.7, 76.5 (C_4 and C'_4); 73.6, 73.5, 72.3, 72.0, 71.8, 72.9 ($6 \times CH_2$-Bn); 67.0, 66.9 ($2 \times CH_2$-Bn); 49.9, 49.2 (C_7 and C'_7); 46.8 and 46.6 (C_2 and C'_2); 37.3, 38.8 (C_6 and C'_6); 18.5 (CH_3 and CH'_3).$[\alpha]_D^{20} = -17.3$ (*c* 0.6 $CHCl_3$). HRMS (+ESI): calcd for $C_{36}H_{39}O_5NNa$: 588.2720; found: 588.2707.

4.3.2. (3*R*,4*R*,5*R*,6*R*)-*N*-Benzyloxycarbonyl-3-methyl-4,5,6-tribenzyloxyazepane (18b)

^{1}H NMR (400 MHz, $CDCl_3$): δ presence of two rotamers) 7.50–7.21 (m, 40H, CH-Ar); 5.18–4.22 (m, 16H, $8 \times CH_2$-Bn); 4.04–3.86

(m, 4H, H_3, H_4, H'_3 and H'_4); 3.80–3.72 (m, 2H, H_{2a} and H_{2b}); 3.70–3.64 (m, 1H, H'_{2a}); 3.60–3.55 (m, 1H, H'_{2b}); 3.47–3.42 (2dd, J = 5.3 Hz and 1.9 Hz, 2H, H_5 and H'_5); 3.36–3.30 (m, 2H, H_{7a} and H'_{7a}); 3.22–3.16 (m, 2H, H_{7b} and H'_{7b}); 2.43–2.39 (m, 2H, H_6 and H'_6); 0.98 (d, ^3J = 7.1 Hz, 3H, CH_3); 0.91 (d, ^3J = 7.1 Hz, 3H, CH'_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (presence of two rotamers) 155.9, 155.6 (2 × C=O carbamate); 138.7, 138.5$_5$, 138.5, 138.4$_5$, 138.4 (C_{quat}-Ar); 137.0, 136.9 (2 × C_{quat}); 128.3, 128.1, 128.0, 127.8$_5$, 127.8, 127.7, 127.6$_5$, 127.6, 127.5, 127.4 (CH-Ar); 80.4, 79.9 (C_5 and C'_5); 77.8, 77.6 (C_3 and C'_3); 76.9, 76.6 (C_4 and C'_4); 73.7, 73.5, 73.4, 73.3, 73.0, 71.2 (6 × CH_2-Bn); 67.0, 66.8 (2 × CH_2-Bn); 46.8 (C_7 and C'_7); 44.1, 43.7 (C_2 and C'_2); 32.6, 31.8 (C_6 and C'_6); 17.4, 16.9 (CH_3 and CH'_3). $[\alpha]_D^{20}$ = −12.4 (c 0.25 $CHCl_3$). HRMS (+ESI): calcd for $C_{36}H_{39}O_5NNa$: 588.2720; found: 588.2705.

4.4. General procedure for the deprotection of (17) and (18)

To a solution of substrate in methanol in presence of HCl was added palladium on charcoal (10%). The mixture was purged from air and stirred under hydrogen atmosphere overnight. The reaction mixture was filtered through a Celite pad and the solvent was evaporated under vacuum to afford the hydrochloride salt.

4.4.1. (3*R*,4*R*,5*R*,6*R*)-3-Hydroxymethyl-4,5,6-trihydroxyazepane (7)

^{1}H NMR (400 MHz, D_2O): δ *4.35–4.32 (dt,* ^3J = 7.1 Hz, 1.8 Hz, 1H, H_6); 3.89–3.85 (dd, ^3J = 11.4 Hz and 3.8 Hz, 1H, H_5); 3.77–3.70 (m, 3H, H_4 and CH_2OH); 3.50–3.43 (m, 2H, H_7); 3.29–3.38 (m, 2H, H_1); 2.05–1.95 (m, 1H, H_2). ^{13}C NMR (100 MHz, D_2O): δ 40.5 (C_2); 44.1 (C_2); 44.6 (C_7); 61.2 (CH_2OH); 66.7 (C_6); 70.9 (C_4); 77.2 (C 5).$[\alpha]_D^{20}$ = +18.0 (c 0.4 CH_3OH). HRMS (+ESI): calcd for $C_7H_{16}O_4N$: 178.1079; found: 178.1083.

4.4.2. (3*S*,4*R*,5*R*,6*R*)-3-Hydroxymethyl-4,5,6-trihydroxyazepane (8)

^{1}H NMR (400 MHz, D_2O): δ 4.16–4.12 (ddd, ^3J = 9.2, 2.8 and 2.0 Hz, 1H, H_6); 3.90–3.86 (m, 1H, H_5); 3.75–3.67 (m, 3H, H_{7a} and CH_2OH); 3.61–3.57 (dd, ^3J = 11.2 and 7.6 Hz, 1H, H_4); 3.51–3.46 (m, 1H, H_{7b}); 3.27–3.22 (m, 2H, H_2); 2.55–2.45 (m, 1H, H_3). ^{13}C NMR (100 MHz, D_2O): δ 37.1 (C_5); 41.5 (C_6); 44.4 (C_1); 61.4 (CH_2OH); 65.9 (C_2); 69.6 (C_4); 74.3 (C_3).$[\alpha]_D^{20}$ = −26.0 (c 0.2 CH_3OH). HRMS (+ESI): calcd for $C_7H_{16}O_4N$: 178.1079; found: 178.1075.

4.4.3. (3*S*,4*R*,5*R*,6*R*)-4,5,6-Trihydroxy-3-methylazepane (9)

^{1}H NMR (400 MHz, D_2O): δ *4.33–4.31 (dt,* ^3J = 6.8 Hz and 2.0 Hz, 1H, H_6); 3.66–3.63 (dd, ^3J = *8.2* Hz and 2.4 Hz, 1H, H_5); 4.50–4.47 (m, 1H, H_{7a}); 3.43 (dd, ^3J = 6.8 and 6.0 Hz, 1H, H_4); 3.33–3.29 (m, 1H, H_{7b}); 3.29–3.26 (m, 2H, H_2); 2.01–1.95 (m, 1H, H_3); 1.06 (d, ^3J = 7.2 Hz, 3H, CH_3).^{13}C NMR (100 MHz, D_2O): δ 77.2 (C_5); 75.0 (C_4); 66.6 (C_6); 47.3 (C_7); 44.1 (C_3); 32.9 (C_2); 16.1 (CH_3). $[\alpha]_D^{20}$ = −18.8 (c 0.9 CH_3OH). HRMS (+ESI): calcd for $C_7H_{16}O_3N$: 162.1125; found: 162.1128.

4.4.4. (3*R*, 4*R*, 5*R*, 6*R*)-4,5,6-Trihydroxy-3-methylazepane (10)

^{1}H NMR (400 MHz, D_2O): δ *4.22–4.18 (ddd,* ^3J = 8.2 Hz, 2.9 Hz and 2.0 Hz, 1H, H_6); 3.94 (dd, ^3J = 5.1 Hz and 2.0 Hz, 1H, H_5); 3.76 (dd, ^3J = 5.2 Hz and 2.0 Hz, 1H, H_4); 3.40–2.99 (m, 4H, H_2 and H_7); 2.40–2.35 (m, 1H, H_3); 0.98 (d, ^3J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, D_2O): δ 74.7 (C_5); 73.1 (C_4); 65.9 (C_6); 44.5 and 45.3 (C_2 and C_7); 29.9 (C_3); 16.0 (CH_3).$[\alpha]_D^{20}$ = 20.8 (c0.4 CH_3OH). HRMS (+ESI): calcd for $C_7H_{16}O_3N$: 162.1125; found: 162.1124.

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