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γ-Aminoalcohol rearrangement applied to pentahydroxylated azepanes provides pyrrolidines epimeric to homoDMDP†

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A series of pentahydroxylated pyrrolidines, displaying five contiguous stereogenic centres and epimeric to α-glucosidase inhibitor homoDMDP, have been synthesized. The key step involves a γ-aminoalcohol rearrangement applied to polyhydroxylated azepanes. These five-membered iminosugars demonstrate micromolar inhibition of glycosidases.

Introduction

A vast array of iminosugars based on a polyhydroxylated pyrrolidine[1] scaffold have been isolated from natural sources, including the potent glycosidase inhibitors 1,4-dideoxy-1,4-imino-D-arabinitol (DAB),[2] 1,4-dideoxy-1,4-imino-D-mannitol (DIM),[3] 2,5-dideoxy-2,5-imino-D-mannitol (DMDP)[4] and 2,5-dideoxy-2,5-imino-*glycero*-D-manno-heptitol (homoDMDP)[5] (Fig. 1). The structural basis for the glycosidase inhibition of five-membered iminosugars has been elucidated.[6]

The high inhibitory potential of this family of molecules has prompted the discovery of powerful approaches that exploit nitrone chemistry,[7] Petasis-type aminocyclization,[8] RCM,[9] green[10] as well as chemo-enzymatic[11] routes being among the most recent ones. In addition, many analogs have been synthesized, some of them demonstrating therapeutic potential.[12] Designing new routes to this type of iminosugar that allow access to both configurational and structural diversity is of current interest to increase the number of compounds available for biological testing. Amongst polyhydroxylated pyrrolidines, homoDMDP, found to strongly inhibit β-glucosidase and β-galactosidase, represents the most complex representative as it exhibits five contiguous stereogenic centres. Several synthetic strategies toward this molecule, as well as epimers and analogs have been reported.[13] Exploiting a γ-aminoalcohol rearrangement applied to pentasubstituted azepanes, we report herein a new synthetic route to homoDMDP epimers including the 2,5-di*epi*- **1**, the 2,6-di*epi*- **2**, the patented 6-*epi*- **3**[14] and the 5-*epi*- **4** derivatives that were further evaluated as glycosidase inhibitors (Fig. 2).

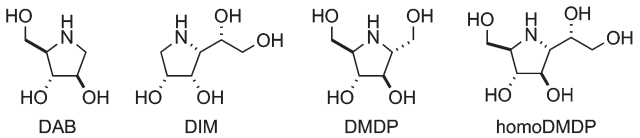

Fig. 1 Structures of DAB, DIM, DMDP, and homoDMDP.

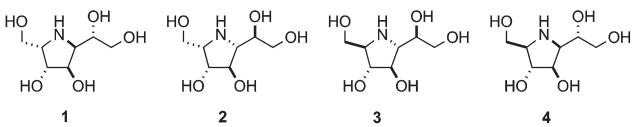

Fig. 2 Structure of homoDMDP epimers **1–4**.

In the last decade, our group[15] and colleagues[16] have disclosed a new class of glycosidase inhibitors, the pentasubstituted azepanes, which proved to be interesting molecules notably as hexosaminidase conformational probes[17] and/or inhibitors.[18] In addition to their biochemical usefulness, polyhydroxylated azepanes[19] also hold synthetic potential as their ring isomerisation can efficiently lead to highly substituted piperidines with complete stereocontrol. According to this methodology, Le Merrer[20] developed new access to deoxynojirimycin and Davies[21] reported a *de novo* preparation of piperidine iminosugars. Starting from pentahydroxylated azepanes, we have described a new route to iminosugar C-glycosides[22] and homoiminosugars,[23] some of them displaying potent glycosidase inhibition.[24] This transformation goes through a tran-

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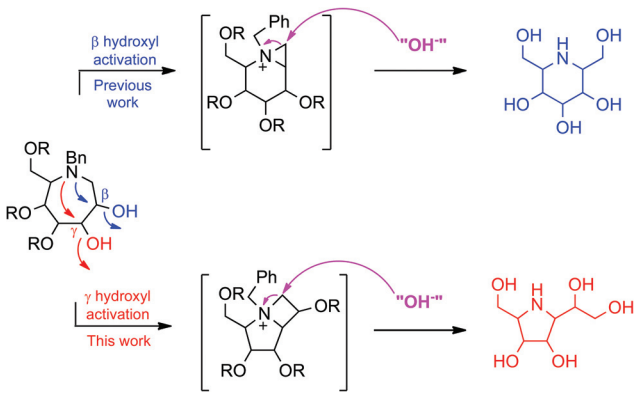
†This article is dedicated to Pr. Max Malacria on the occasion of his 65th birthday.



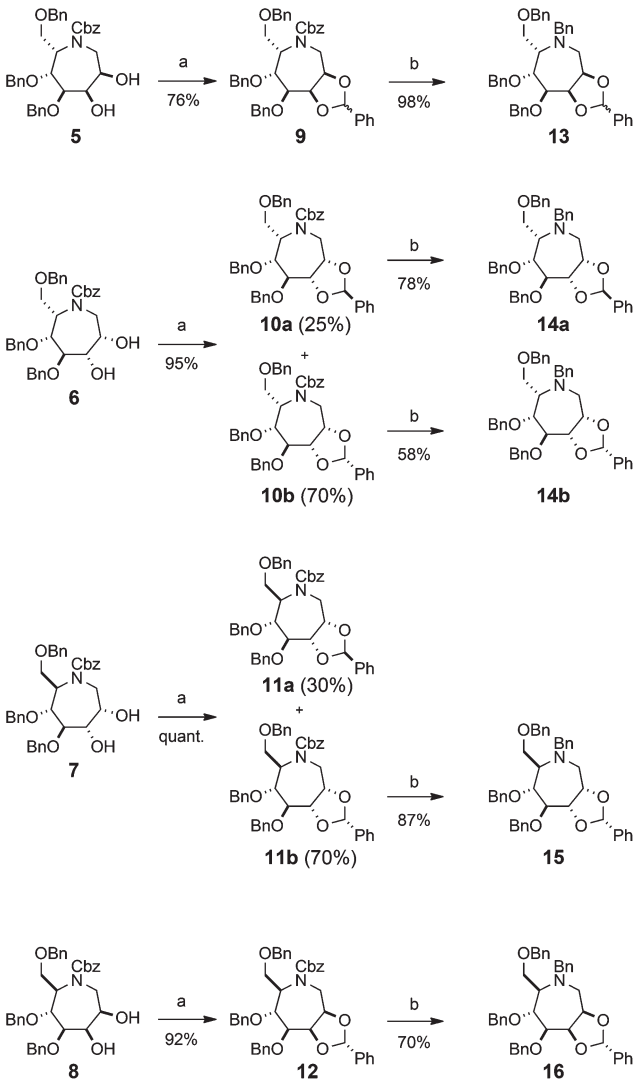
Scheme 1 Skeletal rearrangement strategy used to access homoDMDP congeners.

sient fused piperidine–aziridinium ion that is displaced at the methylene position by the released nucleophile to furnish the corresponding piperidine (Scheme 1). We would like now to apply this methodology to γ-aminoalcohols, starting from pentahydroxylated azepanes, which should provide the corresponding pyrrolidines. To the best of our knowledge there is only one example of such transformation applied to a tetrahydroxylated azepane[25] (Scheme 1).

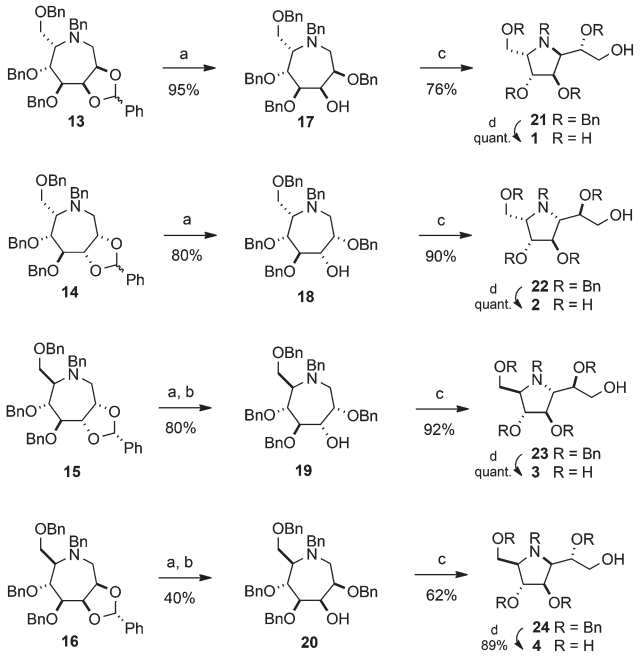
Results and discussion

To selectively obtain the target pyrrolidines from the corresponding azepanes, regioselective activation of the hydroxyl group γ to the nitrogen in the starting β,γ-dihydroxyazepane requires regioselective protection of the hydroxyl group β to the nitrogen. Silylation of this hydroxyl group proved unsatisfactory because of silyl group migration. Its protection as benzyl ether was investigated as hydrogenolysis in the final step could directly provide the target pyrrolidine. Regioselective benzylation of β,γ-dihydroxy azepanes **5–8** (easily available from D-arabinose)[15a] under various conditions (low temperature, stannylene activation, phase transfer conditions) failed to provide the γ-hydroxy derivatives in good yield. Alternatively, protection of the β,γ-diol as its benzylidene acetal followed by regioselective reductive ring opening was examined. Diols **5–8** were acetalized in good yield (76–100%) under standard conditions (benzylidene dimethyl acetal, CSA, acetonitrile) to furnish the corresponding azepanes **9–12** respectively as mixtures of epimeric acetals that were usually not separated and directly engaged in the next step. The γ-aminoalcohol rearrangement requires an electron-donating group on the endocyclic nitrogen. Removal of the benzyl carbamate (Lindlar catalyst, Et_3N, EtOH) followed by N-benzylation (BnBr, K_2CO_3, DMF) was achieved to yield the fully protected *N*-benzyl azepanes **13–16** in 58–98% yield over two steps (Scheme 2).

Regioselective reductive opening of the 1,2-*O*-benzylidene acetals was then studied. Benzylidene acetals are generally reduced at the less sterically hindered oxygen[26] but electronic effects of the adjacent substituents have also to be considered.[27] Several classical conditions ($NaBH_3CN$/TFA, $LiAlH_4$/$AlCl_3$, BH_3·THF/TMSOTf, Et_3SiH/TFA) were applied to azepanes **13–16** but failed to give the desired γ-hydroxyazepanes as the major product in good yield. Alternatively, DIBAL, known to achieve the reductive ring opening of 1,2-*O*-benzylidenes,[28] was used and afforded the desired alcohols **17–20** in moderate to excellent yield. Use of dichloromethane as the solvent is crucial to achieve a good regioselectivity, toluene giving a 1 : 1 mixture of the two secondary alcohols (Scheme 3). In the case of D-azepanes **15** and **16**, regioselectivity in the benzylidene ring opening with DIBAL was less pronounced and needed separation of the γ-hydroxyazepanes from the unwanted β-hydroxyazepanes. These regioisomers were not separable at this stage. Acetylation of the free OH group in these molecules followed by subsequent deacetylation afforded the pure γ-hydroxyazepanes **19** and **20**. With the azepane precursors in hand, several alcohol activation conditions were



Scheme 2 Synthesis of *N*-benzyl azepanes **13–16**. Reagents and conditions: (a) benzylidene dimethyl acetal, CSA, CH_3CN; (b) H_2, Pd Lindlar, Et_3N, EtOH then BnBr, K_2CO_3, DMF.



Scheme 3 Synthesis of homoDMDP epimers **1–4**. Reagents and conditions: (a) DIBAL, CH_2Cl_2, −78 °C to RT; (b) Ac_2O, pyridine then NaOH, MeOH; (c) TFAA, Et_3N, toluene then 10 % aq. NaOH; (d) H_2, 10% Pd/C, 1 M HCl, CH_3OH.

tested to efficiently generate the pyrrolidine ring. Mitsunobu conditions (PPh_3, DEAD, *p*-nitrobenzoic acid) produced the expected pyrrolidines albeit in low 22–44% yield. Use of less hindered phosphine ($PPhMe_2$) did not significantly improve the yield of this transformation. Finally, switching to the conditions developed by Cossy[29] using TFAA and Et_3N for the skeletal rearrangement of β-aminoalcohols provided the protected pyrrolidines **21–24** in good (62%) to excellent yield (92%) after trifluoroacetyl ester hydrolysis. HMBC NMR experiments were necessary to confirm the size of the azacycle. Final hydrogenolysis of pyrrolidines **21–24** under mild acidic conditions furnished the target pyrrolidines **1**, **2**, **3** and **4** as their hydrochloride salts (Scheme 3). The structure of iminosugar **2** was firmly established in comparison with its enantiomer, homo-D-galactitol,[30] a UDP-Gal mutase and mycobacterial galactan biosynthesis inhibitor. A good agreement between the spectroscopic data and an opposite value for the optical rotation was observed. Similarly, the structure of iminosugar **3** was confirmed by comparing its spectroscopic data with its L-enantiomer.[13a]

Glycosidase inhibition

The four pentahydroxylated pyrrolidines **1–4** were assayed as inhibitors of a collection of glycosidases, including glucosidases, galactosidases and mannosidases (Table 1). While 2,5- and 2,6-di*epi*-homoDMDP **1** and **2** showed weak glycosidase inhibition, 6-*epi*-homoDMDP **3** was a good but rather unselective α-glucosidase inhibitor (IC_{50} 14.4 μM for rice α-glucosidase). The 5-*epi*-homoDMDP **4** proved to be a weak (IC_{50} 167 μM) albeit selective α-glucosidase inhibitor.

Experimental

Materials and methods

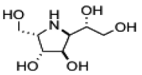
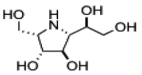
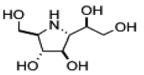
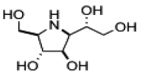
All commercial reagents were used as supplied. Solvents (DMF, THF) were distilled under anhydrous conditions. TLC plates (Macherey-Nagel, ALUGRAM® SIL G/UV_{254}, 0.2 mm silica gel 60 Å) were visualized under 254 nm UV light and/or by dipping the TLC plate into a solution of 3 g of phosphomolybdic acid in 100 mL of ethanol followed by heating with a heat gun. Flash column chromatography was performed using Macherey-Nagel silica gel 60 (15–40 μm). NMR experiments were recorded on a Bruker Avance 400 spectrometer at 400 MHz for ^{1}H nuclei and at 100 MHz for ^{13}C nuclei. The chemical shifts are expressed in parts 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 = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet. HRMS were obtained from the Mass Spectrometry Service, ICOA, at the University of Orléans, France, using a Bruker Maxis Q-TOF Maxis spectrometer.

(2*S*,3*R*,4*S*,5*R*,6*R*)-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)-methyl)-5,6-*O*-(benzylidene)azepane-1-carboxylate 9. A mixture of diol **5** (117 mg, 0.195 mmol), camphorsulfonic acid (cat., 10 mg) and benzaldehyde dimethyl acetal (88 μL, 0.588 mmol) in CH_3CN (10 mL) was stirred at 50 °C under an atmosphere of nitrogen overnight and quenched with triethylamine (0.2 mL). After concentration, the resulting residue was purified by flash column chromatography (Cy–EtOAc, 8 : 1) to give compound **9** as an oil (101 mg, 76%). Due to the mixture of rotational isomers, NMR was not resolved clearly and this compound was used directly in the next step. R_f 0.33, Cy–EtOAc, 4 : 1; ESI-HRMS calcd for $C_{43}H_{43}NO_7Na$ $[M + Na]^+$: 708.2931, found 708.2926.

(2*S*,3*R*,4*S*,5*R*,6*R*)-1-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)-methyl)-5,6-*O*-(benzylidene)azepane 13. Compound **9** (101 mg, 0.145 mmol) was dissolved in EtOH (20 mL) and a catalytic amount of Et_3N (15 μL) was introduced, followed by addition of Lindlar's catalyst (100 mg). The reaction flask was purged of air and filled with H_2. The suspension was stirred under H_2 for 4 h by the end of which TLC (Cy–EtOAc, 4 : 1) showed a complete reaction. The reaction mixture was filtered through a pad of Celite, eluted with MeOH and concentrated under reduced pressure to afford the crude N-deprotected azepane. This oil was dissolved in DMF (5 mL) and K_2CO_3 (61 mg, 0.435 mmol) was added, followed by benzyl bromide (35 μL, 0.292 mmol). The mixture was stirred at 50 °C under an atmosphere of nitrogen overnight. After concentration, the resulting residue was partitioned between water (20 mL) and DCM (20 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (Cy–EtOAc, 4 : 1) to give compound **13** as an oil (91 mg, 98%) and as an inseparable mixture of two epimers in a 3/7 ratio according to ^{1}H NMR. R_f 0.57, Cy–EtOAc, 4 : 1; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.56–7.25 (m, 40H, 8 × Ph), 6.31 (s, 1H, H-8′), 5.78 (s, 1H, H-8), 5.22 (d, 1H, J = 12.0 Hz, CHPh), 5.00 (dd, 1H, J = 7.4, 2.4 Hz,

Table 1 Glycosidase inhibition profile of pyrrolidines **1–4**

Concentration of iminosugars giving 50% inhibition of various glycosidases IC_{50} (μM)

Enzyme	 2,5-Di*epi*-homoDMDP **1**	 2,6-Di*epi*-homoDMDP **2**	 6-*epi*-homoDMDP **3**	 5-*epi*-homoDMDP **4**
α-Glucosidase				
Rice	465	NI[a] (26.2%)[b]	14.4	167
Yeast	254	NI (40.7%)	221	NI (45.4%)
Rat intestinal maltase	NI (26.4%)	NI (21.3%)	32.3	366
Aspergillus niger	NI (4.0%)	NI (1.9%)	817	NI (9.7%)
β-Glucosidase				
Almond	148	283	118	NI (34.1%)
Bovine liver	NI (40.4%)	318	765	NI (23.0%)
Aspergillus niger	NI (17.3%)	NI (8.7%)	NI (32.4%)	NI (14.2%)
α-Galactosidase				
Coffee beans	320	NI (28.4%)	660	NI (11.5%)
β-Galactosidase				
Bovine liver	NI (28.4%)	198	464	NI (32.2%)
α-Mannosidase				
Jack beans	287	NI (49.0%)	NI (41.0%)	NI (0.82%)
β-Mannosidase				
Snail	240	NI (32.2%)	705	NI (15.7%)
α-L-Rhamnosidase				
Penicillium decumbens	NI (17.8%)	NI (2.4%)	NI (8.5%)	NI (0%)
α-L-Fucosidase				
Bovine kidney	110	173	127	NI (16.1%)
β-Glucuronidase				
E.coli	79.6	424	255	NI (0%)
Bovine liver	198	780	389	NI (0%)
α,α-Trehalase				
Porcine kidney	NI (12.1%)	NI (4.17%)	NI (21.8%)	NI (14.7%)
Amyloglucosidase				
Aspergillus niger	NI (1.14%)	NI (0%)	NI (21.6%)	NI (0%)
Rhizopus Sp.	NI (0%)	NI (0%)	NI (23.4%)	NI (1.94%)

[a] NI: no inhibition (less than 50% inhibition at 1000 mM); ND: not determined. [b] ( ): inhibition % at 1000 mM.

H-5′), 4.87–4.83 (m, 2H, H-5, CHPh), 4.78–4.60 (dd, 2H, J = 11.8 Hz, H-6, H-6′), 4.65–4.40 (m, 12H, 12 × CHPh), 4.35 (dd, 1H, J = 6.5, 2.6 Hz, H-4′), 4.23 (dd, 1H, J = 6.5, 2.6 Hz, H-4), 4.04–3.96 (m, 4H, H-3, H-3′, 2NCHPh), 3.89–3.70 (m, 10H, H-2′, H-2, H-9′a, H-9a, H-9′b, H-9b, 2NCHPh, 2CHPh), 3.40–3.30 (m, 4H, H-7′a, H-7a, H-7′b, H-7b); ^{13}C NMR ($CDCl_3$, 100 MHz): 139.28, 139.24, 138.41, 137.68, 137.53, 137.46, 137.43, 137.37, 137.30, 136.14 (10 × C_{ipso}), 128.77–123.10 (50 aromatic C), 104.03 (C-8′), 103.57 (C-8), 79.66 (C-4′), 78.38 (C-4), 78.21 (C-3′), 78.10 (C-3), 77.93 (C-5′), 77.93 (C-5), 77.16 (C-6′), 76.85 (C-6), 74.45, 74.45, 74.27, 73.30, 73.19, 73.11, 73.07, 73.07 (8CHPh), 69.66 (C-9′), 69.60 (C-9), 61.42 (C-2′), 61.34 (C-2), 51.27 (NCH_2Ph), 51.27 (NCH_2Ph), 50.61 (C-7′), 50.61 (C-7); ESI-HRMS calcd for $C_{42}H_{44}NO_5$ $[M + H]^+$: 642.3214, found 642.3299.

(2*S*,3*R*,4*R*,5*R*,6*R*)-1-Benzyl-3,4,6-tris(benzyloxy)-2-((benzyloxy)-methyl) azepan-5-ol 17. To a solution of compound **13** (114 mg, 0.178 mmol) in dry DCM (3 mL) was added quickly DIBAL (1.77 mL, 1.5 M in toluene, 2.664 mmol) at −78 °C under an atmosphere of nitrogen with stirring. After 15 min at −78 °C, TLC (Cy–EtOAc, 4 : 1) showed that the starting material was consumed completely. Aqueous HCl (1.5 mL, 1 M solution) was added at −30 °C to quench the reaction. The resulting solution was warmed to r.t., then partitioned between water (20 mL) and DCM (20 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (Cy–EtOAc, 4 : 1) to give compound **17** as a clear oil (109 mg, 95%). R_f 0.26, Cy–EtOAc, 4 : 1; $[\alpha]_D$ −7 (c = 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.27–7.04 (m, 25H, 5 × Ph), 4.54–4.49 (t, 3H, J = 11.8, 10.0 Hz, 3 × CHPh), 4.36–4.20 (m, 5H, 5 × CHPh), 4.11 (s, 1H, H-5), 3.85 (d, 1H, J = 13.6, NCHPh), 3.70 (dd, 1H, J = 8.3, 5.4 Hz, H-3), 3.66–3.60 (m, 2H, H-8a, NCHPh), 3.52–3.46 (m, 2H, H-8b, H-6), 3.40 (m, 1H, H-2), 3.35 (dd, 1H, J = 8.5, 1.0 Hz, H-4), 3.08 (dd, 1H, J = 13.3, 6.8 Hz, H-7a), 2.70 (dd, 1H, J = 13.3, 8.7 Hz, H-7b); ^{13}C NMR ($CDCl_3$, 100 MHz): 139.34, 138.86, 138.57, 138.36, 138.14 (5 × C_{ipso}), 128.60–127.01 (25 aromatic C), 83.53 (C-4), 82.05 (C-3), 76.13 (C-6), 74.16, 73.22, 73.00, 71.13 (4 × CH_2Ph), 73.13 (C-5), 67.50 (C-8), 59.23 (C-2), 59.22 (N-CH_2Ph), 51.84 (C-7); ESI-HRMS calcd for $C_{42}H_{46}NO_5$ $[M + H]^+$: 644.3370, found 644.3354.

2-[(*S*)-1-Benzyloxy-2-hydroxyethyl]-(2*S*,3*R*,4*R*,5*S*)-1-benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidine 21. To a solution of **17** (50 mg, 0.078 mmol) in dry toluene (2 mL) were added trifluoroacetic anhydride (17 μL, 0.117 mmol) and Et_3N (17 μL, 0.156 mmol) at 0 °C. The reaction mixture was then refluxed for 5 hours before being cooled to room temperature. A solution of NaOH (10%, 2 mL) was added and the resulting mixture was stirred for 1 h. The reaction mixture was diluted with EtOAc and the organic and aqueous layers were separated. The aqueous layer was extracted twice with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then purified by column chromatography (P.E.–EtOAc, 8.5/1.5) to give **21** (38 mg, 76%) as colorless oil. R_f 0.28, Cy–EtOAc, 4 : 1; $[\alpha]_D$ −5.6 (c = 0.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz):7.39–7.15 (m, 25H, 5 × Ph), 4.78, 4.68 (2d, 2H, J = 11.4 Hz, CH_2Ph), 4.63–4.40 (m, 9H, 4 × CH_2Ph, H-4), 4.24 (t, 1H, J = 13.6 Hz, H-3), 3.98 (m, 2H, H-1′), 3.92–3.87 (m, 2H, NCH_2Ph), 3.69 (dd, 1H, J = 8.9, 4.4 Hz, H-2′), 3.67 (dd, 1H, J = 8.1, 4.8 Hz, H-5), 3.58 (dd, 1H, J = 10.2, 3.7 Hz, H-6a), 3.45 (dd, 1H, J = 10.2, 1.7 Hz, H-6b), 3.32 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): 139.43, 138.67, 138.51, 138.47, 138.41 (5 × C_{ipso}), 128.29–126.82 (25 aromatic C), 83.57 (C-4), 83.19 (C-3), 79.20 (C-2′), 73.68, 73.26, 72.64, 72.13 (4 × CH_2Ph), 66.03 (C-6), 63.89 (C-5), 61.28 (C-1′), 58.31 (C-2), 53.71 (NCH_2Ph); ESI-HRMS calcd for $C_{42}H_{46}NO_5$ $[M + H]^+$: 644.3370, found 644.3357.

(2*S*,3*R*,4*R*,5*S*)-2-((*S*)-1,2-Dihydroxyethyl)-5-(hydroxymethyl)-pyrrolidine-3,4-diol 1. To a solution of pyrrolidine **21** (20 mg, 0.031 mmol) in MeOH (3 mL) and 1 M aq. HCl (50 μL) was added 10% Pd/C (20 mg). The suspension was stirred under a H_2 atmosphere for 4 h at r.t., filtered through a Celite plug eluted with MeOH. The solvent was removed under reduced pressure to afford pyrrolidine **1** in quantitative yield as its hydrochloride salt. $[\alpha]_D$ + 54 (c = 0.1, CH_3OH); ^1H NMR (D_2O, 400 MHz): 4.37 (dd, 1H, J = 3.3, 1.5 Hz, H-3), 4.31 (dd, 1H, J = 3.6, 1.5 Hz, H-4), 4.12 (ddd, 1H, J = 8.7, 5.0, 3.3 Hz, H-2′), 4.04–3.86 (m, 4H, H-5, H-2, H-6), 3.78 (dd, 1H, J = 12.2, 3.3 Hz, H-1a′), 3.66 (dd, 1H, J = 12.2, 5.1 Hz, H-1b′); ^{13}C NMR (D_2O, 100 MHz): 77.96 (C-3), 75.33 (C-4), 68.16 (C-2′), 63.16 (C-5), 62.83 (C-1′), 62.52 (C-2), 57.37 (C-6); ESI-HRMS calcd for $C_7H_{16}O_5N$ $[M + H]^+$: 194.1023, found 194.1018.

(2*S*,3*R*,4*S*,5*S*,6*S*,8*R*)-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)-methyl)-5,6-*O*-(benzylidene)azepane-1-carboxylate 10a and (2*S*,3*R*,4*S*,5*S*,6*S*,8*S*)-benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)-methyl)-5,6-*O*-(benzylidene)azepane-1-carboxylate 10b. A mixture of diol **6** (340 mg, 0.57 mmol), camphorsulfonic acid (cat., 12 mg) and benzaldehyde dimethyl acetal (256 μL, 1.71 mmol) in CH_3CN (20 mL) was stirred at 50 °C under an atmosphere of nitrogen overnight. TLC (Cy–EtOAc, 4 : 1) showed a complete conversion. The reaction was quenched with triethylamine (0.6 mL). After concentration, the resulting residue was purified by flash column chromatography (Cy–EtOAc, 15 : 1) to give compound **10a** as an oil (98 mg, 25%) and further elution afforded compound **10b** as an oil (282 mg, 70%).

*Compound **10a**.* R_f 0.33, Cy–EtOAc, 4 : 1; $[\alpha]_D$ + 17 (c = 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.23–7.08 (m, 50H, 10 × Ph), 5.74 (s, 1H, H-8), 5.69 (s, 1H, H-8′), 5.11–5.01 (m, 3H, 3 × NCOOCHPh), 4.93 (d, 1H, J = 12.4 Hz, NCOOCHPh), 4.78–4.70 (m, 2H, H-2, CHPh), 4.66 (dd, 2H, J = 12.4, 1.7 Hz, 2 × CHPh), 4.58–4.30 (m, 16H, 9 × CHPh, H-6, H-6′, H-5, H-5′, H-4, H-4′, H-2′), 3.99 (t, 2H, J = 5.9, 5.4 Hz, H-3, H-3′), 3.85 (dd, 1H, J = 13.8, 5.4 Hz, H-7a), 3.77–3.48 (m, 7H, H-7a′, H-9a, H-9a′, H-9b, H-9b′, H-7b, H-7b′); ^{13}C NMR ($CDCl_3$, 100 MHz): 155.94, 155.67 (2 × C═O), 138.19, 138.08, 138.04, 138.04, 138.02, 138.02, 137.96, 137.96, 136.78, 136.66 (10 × C_{ipso}), 128.44–126.48 (50 aromatic C), 102.16 (C-8), 102.12 (C-8′), 79.74 (C-5), 79.12 (C-5′), 76.83 (C-3), 76.44 (C-3′), 75.04 (C-6), 74.89 (C-6′), 74.89 (C-4), 74.34 (C-4′), 73.99, 73.80, 73.76, 73.62, 73.25, 73.21, (6 × CH_2Ph), 67.51, 67.38 (2 × $NCOOCH_2Ph$), 67.28 (C-9), 67.10 (C-9′), 54.61 (C-2), 54.42 (C-2′), 42.99 (C-7), 42.74 (C-7′); ESI-HRMS calcd for $C_{43}H_{43}NO_7Na$ $[M + Na]^+$: 708.2931, found 708.2937.

*Compound **10b**.* R_f 0.31, Cy–EtOAc, 4 : 1; $[\alpha]_D$ + 43 (c = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.44–7.19 (m, 50H, 10 × Ph), 5.79 (s, 1H, H-8), 5.75 (s, 1H, H-8′), 5.22 (s, 2H, 2 × NCOOCHPh), 5.18 (dd, 2H, J = 12.4 Hz, 2 × NCOOCHPh), 4.90 (m, 1H, H-2), 4.82–4.69 (m, 7H, H-2′, 6 × CHPh), 4.60–4.39 (m, 12H, 6 × CHPh, H-6, H-6′, H-5, H-5′, H-4, H-4′), 4.05 (t, 2H, J = 6.3, 5.4 Hz, H-3, H-3′), 3.97 (dd, 1H, J = 13.4, 4.4 Hz, H-7a), 3.90–3.78 (m, 4H, H-7a′, H-9a, H-9a′, H-9b), 3.69–3.55 (m, 3H, H-9b′, H-7b, H-7b′); ^{13}C NMR ($CDCl_3$, 100 MHz): 155.77, 155.67 (2 × C═O), 138.31, 138.19, 138.12, 137.98, 137.98, 137.89, 136.90, 136.72, 136.72, 136.56 (10 × C_{ipso}), 129.44–126.90 (50 aromatic C), 103.36, 103.36 (C-8, C-8′), 81.16 (C-5), 80.66 (C-5′), 77.36 (C-3), 77.26 (C-3′), 75.30 (C-6), 75.11 (C-6′), 74.19, 74.02, 74.02, 73.84, 73.13, 73.09 (6 × CH_2Ph), 73.40 (C-4), 73.40 (C-4′), 67.40, 67.26 (2 × $NCOOCH_2Ph$), 67.26 (C-9), 66.97 (C-9′), 54.55 (C-2), 54.17 (C-2′), 43.90 (C-7), 43.66 (C-7′); ESI-HRMS calcd for $C_{43}H_{43}NO_7Na$ $[M + Na]^+$: 708.2931, found 708.2944.

(2*S*,3*R*,4*S*,5*S*,6*S*,8*R*)-1-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)-methyl)-5,6-*O*-(benzylidene)azepane 14a. Compound **10a** (400 mg, 0.58 mmol) was dissolved in EtOH (40 mL) and a catalytic amount of Et_3N (50 μL) was introduced, followed by addition of Lindlar's catalyst (400 mg). The reaction flask was purged of air and filled with H_2. The suspension was stirred under H_2 for 4 h by the end of which TLC (Cy–EtOAc, 4 : 1) showed a complete reaction. The reaction mixture was filtered through a pad of Celite, eluted with MeOH and concentrated under reduced pressure to afford the N-deprotected azepane as an oil. This oil was dissolved in DMF (15 mL), K_2CO_3 (244 mg, 1.74 mmol) was introduced, followed by addition of benzyl bromide (86 μL, 0.73 mmol). The mixture was stirred at 50 °C under an atmosphere of nitrogen overnight. After concentration, the resulting residue was partitioned between water (100 mL) and DCM (100 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (Cy–EtOAc, 4 : 1) to give compound **14a** as an oil (289 mg, 78%). R_f 0.58, Cy–EtOAc, 4 : 1; $[\alpha]_D$ −26 (c = 1.10,

$CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.31–7.18 (m, 25H, 5 × Ph), 5.89 (s, 1H, H-8), 4.80–4.70 (m, 3H, 3 × CHPh), 4.48–4.42 (m, 3H, 3 × CHPh), 4.34 (t, 1H, J = 7.4, 6.5 Hz, H-5), 4.26–4.24 (m, 1H, H-6), 3.98 (t, 1H, J = 7.9, 5.9 Hz, H-4), 3.93–3.64 (m, 5H, NCH_2Ph, H-9a, H-9b, H-3), 3.19 (s, 1H, H-2), 3.04 (t, 1H, J = 11.2 Hz, H-7a), 2.81 (t, 1H, J = 13.8 Hz, H-7b); ^{13}C NMR ($CDCl_3$, 100 MHz): 139.87, 138.65, 138.65, 138.40, 138.40 (5 × C_{ipso}), 128.50–126.10 (25 aromatic C), 101.96 (C-8), 80.88 (C-5), 80.26 (C-3), 79.37 (C-4), 74.57, 73.95, 73.22 (3 × CH_2Ph), 74.45 (C-6), 67.83 (C-9), 61.28 (C-2), 59.56 (N-CH_2Ph), 48.67 (C-7); ESI-HRMS calcd for $C_{42}H_{44}NO_5$ $[M + H]^+$: 642.3214, found 642.3214.

(2*S*,3*R*,4*S*,5*S*,6*S*,8*S*)-1-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)-methyl)-5,6-*O*-(benzylidene)azepane 14b. Compound **10b** (660 mg, 0.963 mmol) was dissolved in EtOH (60 mL) and a catalytic amount of Et_3N (60 μL) was introduced, followed by addition of Lindlar's catalyst (660 mg). The reaction flask was purged of air and filled with H_2. The suspension was stirred under H_2 for 4 h by the end of which TLC (Cy–EtOAc, 4 : 1) showed a complete reaction. The reaction mixture was filtered through a pad of Celite, eluted with MeOH and concentrated under reduced pressure to afford the *N*-deprotected azepane as an oil. This oil was dissolved in DMF (20 mL), K_2CO_3 (462 mg, 3.30 mmol) was introduced, followed by addition of benzyl bromide (164 μL, 1.38 mmol). The mixture was stirred at 50 °C under an atmosphere of nitrogen overnight. After concentration, the resulting residue was partitioned between water (100 mL) and DCM (100 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (Cy–EtOAc, 15 : 1) to give compound **14b** as an oil (450 mg, 87%). R_f 0.52, Cy–EtOAc, 4 : 1; $[\alpha]_D$ + 8 (c = 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.34–7.09 (m, 25H, 5 × Ph), 5.63 (s, 1H, H-8), 4.74–4.66 (m, 3H, 3 × CHPh), 4.49 (d, 1H, J = 11.6 Hz, CHPh), 4.41 (s, 2H, 2 × CHPh), 4.29 (t, 1H, J = 7.6 Hz, H-5), 4.23–4.20 (m, 1H, H-6), 3.95–3.89 (m, 2H, H-4, NCHPh), 3.81 (dd, 1H, J = 9.6, 6.8 Hz, H-9a), 3.76–3.66 (m, 3H, H-9b, NCHPh, H-3), 3.23 (b, 1H, H-2), 2.95 (dd, 1H, J = 13.8, 10.9 Hz, H-7a), 2.78 (dd, 1H, J = 13.8, 3.7 Hz, H-7b); ^{13}C NMR ($CDCl_3$, 100 MHz): 139.95, 138.74, 138.74, 138.46, 136.93 (5 × C_{ipso}), 129.41–126.80 (25 aromatic C), 103.00 (C-8), 81.86 (C-5), 80.47 (C-4), 80.26 (C-3), 74.98 (C-6), 74.83, 74.10, 73.30 (3 × CH_2Ph), 67.77 (C-9), 61.79 (C-2), 59.85 (N-CH_2Ph), 49.22 (C-7); ESI-HRMS calcd for $C_{42}H_{44}NO_5$ $[M + H]^+$: 642.3214, found 642.3219.

(2*S*,3*R*,4*R*,6*S*,5*S*)-1-Benzyl-3,4,6-tris(benzyloxy)-2-((benzyloxy)-methyl) azepan-5-ol 18. To a solution of dry compound **14b** (190 mg, 0.296 mmol) in dry DCM (7 mL) was added quickly DIBAL (2.96 mL, 1.5 M in toluene, 4.44 mmol) at −78 °C under an atmosphere of nitrogen with stirring. After 15 min at −78 °C, additional DIBAL (1 mL) was added. After another 1.5 h, TLC showed that the starting material was consumed completely. 1.5 mL of 1 M aq. HCl was added at −30 °C to quench the reaction. The resulting solution was warmed to r.t., then partitioned between water (50 mL) and DCM (50 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (Cy–EtOAc, 20 : 1) to give compound **18** as an oil (152 mg, 80%). R_f 0.35, Cy–EtOAc, 4 : 1; $[\alpha]_D$ + 6 (c = 1.07, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.38–7.28 (m, 25H, 5 × Ph), 4.82 (d, 1H, J = 11.2 Hz, CHPh), 4.69–4.48 (m, 7H, 7 × CHPh), 4.14 (d, 1H, J = 6.1 Hz, H-5), 4.04–3.88 (m, 6H, H-4, H-8a, H-6, NCH_2Ph, H-3), 3.82 (dd, 1H, J = 9.6, 5.9 Hz, H-8b), 3.57 (b, 1H, OH), 3.33 (dd, 1H, J = 10.5, 6.1 Hz, H-2), 3.24 (dd, 1H, J = 14.4, 4.8 Hz, H-7a), 2.88 (dd,1H, J = 14.4, 5.4 Hz, H-7b); ^{13}C NMR ($CDCl_3$, 100 MHz): 140.22, 138.79, 138.55, 138.25, 138.22 (5 × C_{ipso}), 128.52–127.00 (25 aromatic C), 82.56 (C-3), 79.83 (C-4), 76.96 (C-6), 74.34, 73.71, 73.71, 72.12 (4 × CH_2Ph), 72.62 (C-5), 68.34 (C-8), 60.24 (C-2), 59.44 (N-CH_2Ph), 50.97 (C-7); ESI-HRMS calcd for $C_{42}H_{46}NO_5$ $[M + H]^+$: 644.3370, found 644.3374.

2-[(*R*)-1-Benzyloxy-2-hydroxyethyl]-(2*R*,3*R*,4*R*,5S)-1-benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidine 22. To a solution of **18** (50 mg, 0.078 mmol) in dry toluene (2 mL) were added trifluoroacetic anhydride (17 μL, 0.117 mmol) and Et_3N (17 μL, 0.156 mmol) at 0 °C. Then the solution was refluxed for 5 hours before being cooled to room temperature. A solution of NaOH (10%, 2 mL) was added and the resulting mixture was stirred for another 1 h. EtOAc was added and the layers were separated. The aqueous layer was extracted twice with EtOAc and the combined organic layers were dried on $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then purified by column chromatography (P.E.–EtOAc, 8.5/1.5) to give **22** (45 mg, 90%) as colorless oil. R_f 0.33, Cy–EtOAc, 4 : 1; $[\alpha]_D$ + 20 (c = 1.12, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.38–7.18 (m, 25H, 5 × Ph), 4.62–4.39 (m, 8H, 4 × CH_2Ph), 4.13 (s, 1H, H-3), 3.95 (s, 1H, H-4), 3.94 (d, 1H, J = 13.6 Hz, NCHPh), 3.75 (d, 1H, J = 13.8 Hz, NCHPh), 3.71–3.68 (m, 2H, H-6a, H-1′b), 3.62 (dd, 1H, J = 8.5, 3.7 Hz, H-1′a), 3.52 (dd,1H, J = 9.2, 5.0 Hz, H-6b), 3.33–3.26 (m, 3H, H-2, H-5, H-2′); ^{13}C NMR ($CDCl_3$, 100 MHz): 136.68, 136.51, 136.51, 136.08, 135.95 (5 × C_{ipso}), 129.98–127.39 (25 aromatic C), 81.92 (C-4), 80.48 (C-3), 75.42 (C-2′), 72.86 (C-2), 73.39, 71.48, 71.77, 70.92 (4 × CH_2Ph), 69.08 (C-6), 66.07 (C-5), 62.34 (C-1′), 59.08 (NCH_2Ph); ESI-HRMS calcd for $C_{42}H_{46}NO_5$ $[M + H]^+$: 644.3370, found 644.3361.

(2*R*,3*R*,4*R*,5*S*)-2-((*R*)-1,2-Dihydroxyethyl)-5-(hydroxymethyl)-pyrrolidine-3,4-diol 2. To a solution of pyrrolidine **22** (41 mg, 0.064 mmol) in MeOH (3 mL) and conc. HCl (20 μL) was added 10% Pd/C (40 mg). The suspension was stirred under a H_2 atmosphere for 24 h at r.t., filtered through a Celite plug eluted with MeOH. The solvent was removed under reduced pressure to afford pyrrolidine **2** in quantitative yield as its hydrochloride salt. $[\alpha]_D$ +20 (c = 1.21, CH_3OH); ^1H NMR (CD_3OD, 400 MHz): 4.13 (dd, 2H, J = 5.9, 2.8 Hz, H-3, H-4), 3.98–3.91 (m, 3H, H-6a, H-6b, H-2′), 3.76 (dd, 2H, J = 11.7, 4.0 Hz, H-2, H-1′a), 3.68 (dd, 1H, J = 11.6, 4.6 Hz, H-1′b), 3.48 (dd, 1H, J = 7.7, 2.9 Hz, H-5); ^{13}C NMR (CD_3OD, 100 MHz): 78.30 (C-4), 76.52 (C-3), 70.96 (C-2′), 69.70 (C-5), 64.78 (C-1′), 64.68 (C-2), 58.37 (C-6); ESI-HRMS: Calcd for $C_7H_{16}O_5N$ $[M + H]^+$: 194.1023, found 194.1022.

(2*R*,3*R*,4*S*,5*S*,6*S*,8*R*)-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)-methyl)-5,6-*O*-(benzylidene)azepane-1-carboxylate 11a and

(2*R*,3*R*,4*S*,5*S*,6-S,8*S*)-benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)-methyl)-5,6-*O*-(benzylidene)azepane-1-carboxylate 11b. To a solution of diol **7** (50 mg, 0.083 mmol) in CH_3CN (2 mL) were added benzaldehyde dimethyl acetal (38 μL, 0.25 mmol) and camphorsulfonic acid (3 mg). The mixture was stirred for 1.5 h at 50 °C. The reaction mixture was then cooled to r.t., neutralized with Et_3N, and concentrated under reduced pressure. Purification by flash column chromatography (Cy–EtOAc, 10 : 1) afforded acetal **11a** as an oil (17 mg, 30%). Further elution (Cy–EtOAc, 5 : 1) afforded acetal **11b** as an oil (40 mg, 70%).

*Compound **11a**.* R_f 0.68, Cy–EtOAc, 2 : 1; $[\alpha]_D$ +33 (c = 1.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.59–7.15 (m, 50H, 10 × Ph), 5.89 (s, 1H, H-8), 5.83 (s, 1H, H-8′), 5.34 (d, 1H, J = 12.5 Hz, NCOOCHPh), 5.19 (dd, 2H, J = 12.4, 12.2 Hz 2 × NCOOCHPh), 5.09–4.95 (m, 5H, 4 × CHPh, NCOOCHPh), 4.84 (dd, 2H, J = 11.4, 9.2 Hz, 2 × CHPh), 4.63–4.29 (m, 13H, 6 × CHPh, H-7a, H-7′a, H-5, H-5′, H-3, H-3′, H-2), 4.15–4.10 (m, 3H, H-4, H-4′, H-2′), 3.91–3.50 (m, 8H, H-9a, H-9′a, H-9b, H-9′b, H-7b, H-7′b, H-6, H-6′); ^{13}C NMR ($CDCl_3$, 100 MHz): 156.74, 156.74 (2 × C═O), 139.28, 138.51, 138.51, 138.20, 138.20, 138.10, 137.93, 137.93, 136.84, 136.56 (10 × C_{ipso}), 128.82–126.09 (50 aromatic C), 102.25 (C-8), 102.06 (C-8′), 81.34 (C-3), 81.10 (C-3′), 79.39 (C-6), 79.39 (C-6′), 74.97 (C-4), 74.89 (C-4′), 74.80 (C-5), 74.78 (C-5′), 75.64, 75.43, 75.39, 73.36, 73.31, 73.31 (6 × CH_2Ph), 70.17 (C-9), 69.90 (C-9′), 67.66, 67.32 (2 × NCOOCH_2Ph), 58.27 (C-2), 57.92 (C-2′), 41.35 (C-7), 41.35 (C-7′); ESI-HRMS calcd for $C_{43}H_{43}NO_7Na$ $[M + Na]^+$: 708.2931, found 708.2929.

*Compound **11b**.* R_f 0.56, Cy–EtOAc, 2 : 1; $[\alpha]_D$ +26 (c = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.35–7.06 (m, 50H, 10 × Ph), 5.89 (s, 1H, H-8), 5.83 (s, 1H, H-8′), 5.16 (d, 1H, J = 12.2 Hz, NCOOCHPh), 5.08 (d, 1H, J = 12.2 Hz, NCOOCHPh), 5.00 (s, 2H, 2 × NCOOCHPh), 4.88 (d, 1H, J = 10.9 Hz, CHPh), 4.83 (d, 1H, J = 10.7 Hz, CHPh), 4.70 (d, 1H, J = 11.2 Hz, CHPh), 4.61 (dd, 1H, J = 13.8, 2.2 Hz, H-7a), 4.56 (d, 1H, J = 11.1 Hz, CHPh), 4.46–4.10 (m, 14H, H-7′a, 8 × CHPh, H-5, H-5′, H-4, H-4′, H-2), 3.95 (d, 1H, J = 9.6 Hz, H-2′), 3.78 (dd, 1H, J = 3.0 Hz, H-9a), 3.72 (dd, 1H, J = 3.0 Hz, H-9′a), 3.68–3.46 (m, 8H, H-9b, H-9′b, H-7b, H-7′b, H-6, H-6′, H-3, H-3′); ^{13}C NMR ($CDCl_3$, 100 MHz): 156.87, 156.64 (2 × C═O), 138.89, 138.89, 138.70, 138.38, 138.38, 138.22, 138.22, 138.08, 137.93, 136.58 (10 × C_{ipso}), 129.27–126.41 (50 aromatic C), 103.36 (C-8), 103.11 (C-8′), 83.51 (C-6), 83.20 (C-6′), 80.25 (C-5), 80.19 (C-5′), 77.37 (C-4), 77.29 (C-4′), 76.05, 75.87, 75.64, 75.44 (4 × CH_2Ph), 74.77 (C-3), 74.63 (C-3′), 73.56, 73.47 (2 × CH_2Ph), 70.46 (C-9), 70.08 (C-9′), 67.70, 67.70 (2 × NCOOCH_2Ph), 58.32 (C-2), 58.04 (C-2′), 41.43 (C-7), 41.36 (C-7′); ESI-HRMS calcd for $C_{43}H_{43}NO_7Na$ $[M + Na]^+$: 708.2931, found 708.2926.

(2*R*,3*R*,4*S*,5*S*,6*S*,8*S*)-1-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)-methyl)-5,6-*O*-(benzylidene)azepane 15. To a solution of acetal **11b** (538 mg, 0.790 mmol) in EtOH (60 mL) was added a catalytic amount of Et_3N (60 μL), followed by addition of Lindlar's catalyst (538 mg). The reaction flask was purged of air and filled with H_2. The suspension was stirred under a H_2 atmosphere for 4 h. TLC (Cy–EtOAc, 4 : 1) showed a complete reaction. The reaction mixture was filtered through a Celite plug eluted with MeOH and concentrated under reduced pressure to afford the *N*-deprotected azepane as an oil. This crude compound was dissolved in DMF (30 mL), then K_2CO_3 (403 mg, 2.88 mmol) and benzyl bromide (143 μL, 1.20 mmol) were added successively. The mixture was stirred at 50 °C under an atmosphere of nitrogen overnight. After concentration, the resulting residue was partitioned between water (100 mL) and DCM (100 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (Cy–EtOAc, 8 : 1) to give acetal **15** as a clear oil (360 mg, 58%). R_f 0.27, Cy–EtOAc, 4 : 1; $[\alpha]_D$ +94 (c = 1.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.43–7.03 (m, 25H, 5 × Ph), 5.77 (s, 1H, H-8), 4.86 (d, 1H, J = 10.7 Hz, CHPh), 4.72 (d, 1H, J = 11.3 Hz, CHPh), 4.61 (d, 1H, J = 11.3 Hz, CHPh), 4.40–4.31 (m, 3H, 3 × CHPh), 4.19 (dd, 1H, J = 8.4, 1.1 Hz, H-5), 4.05–4.02 (m, 1H, H-6), 3.98–3.94 (dd, 2H, J = 12.6, 8.6 Hz, H-4, NCHPh), 3.77 (d, 1H, J = 13.5 Hz, NCHPh), 3.71–3.67 (dd, 1H, J = 10.0, 9.9, 2.4 Hz, H-9a), 3.65–3.62 (dd, 1H, J = 10.0, 9.9, 3.5 Hz, H-9b), 3.52 (t, 1H, J = 9.4 Hz, H-3), 3.62–3.57 (dd, 1H, J = 15.9, 2.6 Hz, H-7a), 3.04–3.00 (dd, 1H, J = 15.9, 3.5 Hz, H-7b), 2.67–2.63 (dd, 1H, J = 9.4, 2.6 Hz, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): 138.51, 138.02, 137.44, 137.40, 136.25 (5 × C_{ipso}), 127.69–125.82 (25 aromatic C), 101.97 (C-8), 82.41 (C-4), 80.01 (C-5), 77.35 (C-6), 76.03 (C-3), 74.27, 74.27, 72.34 (3 × CH_2Ph), 66.91 (C-9), 61.26 (C-2), 58.19 (N-CH_2Ph), 47.98 (C-7); ESI-HRMS calcd for $C_{42}H_{44}NO_5$ $[M + H]^+$: 642.3214, found 642.3204.

(2*R*,3*R*,4*R*,5*S*,6*S*)-1-Benzyl-3,4,6-tris(benzyloxy)-2-((benzyloxy)-methyl) azepan-5-ol 19. To a solution of acetal **15** (300 mg, 0.47 mmol) in dry DCM (7 mL) was quickly added DIBAL (4.6 mL, 1.5 M in toluene, 7.01 mmol) at −78 °C under an atmosphere of nitrogen with stirring. After 1.5 h at −78 °C, TLC indicated a complete reaction. A solution of 1 M aq. HCl (1.5 mL) was added at −30 °C to quench the reaction. The resulting solution was then warmed to r.t., partitioned between DCM (50 mL) and water (50 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford a mixture of alcohols (R_f 0.24, Cy–EtOAc, 4 : 1), which were difficult to separate by flash column chromatography. The mixture of crude alcohols was dissolved in pyridine (4 mL), and Ac_2O (2 mL) was added. The reaction mixture was stirred under an atmosphere of nitrogen at r.t. overnight and concentrated under reduced pressure. Purification by flash column chromatography (Cy–EtOAc, 15 : 1) afforded a minor acetylated compound as an oil (58 mg, 18%). Further elution afforded major acetylated compound as an oil (258 mg, 80%).

Minor acetylated compound. R_f 0.39, Cy–EtOAc, 4 : 1; $[\alpha]_D$ +37 (c = 1.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.29–7.11 (m, 25H, 5 × Ph), 5.40 (d, 1H, J = 6.5 Hz, H-6), 4.62–4.49 (m, 5H, 5 × CHPh), 4.37 (s, 2H, 2 × CHPh), 4.32 (d, 1H, J = 11.3 Hz, CHPh), 4.02–3.93 (m, 3H, NCHPh, H-4, H-5), 3.79 (d, 1H, J = 14.6 Hz, NCHPh), 3.71 (dd, 1H, J = 8.5, 3.1 Hz, H-3), 3.65 (d, 2H, J = 4.5 Hz, H-8a, H-8b), 3.43 (dd, 1H, J = 9.1, 4.5 Hz, H-2), 2.99 (t, 1H, J = 13.2, 10.8 Hz, H-7a), 2.75 (dd, 1H, J = 13.2, 4.7

Hz, H-7b), 1.87 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.44 (C═O), 140.95, 138.73, 138.66, 138.66, 138.44 (5 × C_{ipso}), 128.62–126.75 (25 aromatic C), 81.78 (C-3), 80.36 (C-5), 79.86 (C-4), 73.41, 73.26, 73.16, 72.90 (4 × CH_2Ph), 70.84 (C-8), 69.36 (C-6), 63.96 (C-2), 53.39 (NCH_2Ph), 49.70 (C-7), 21.39 (CH_3); ESI-HRMS: calcd for $C_{44}H_{48}NO_6$ $[M + H]^+$: 686.3476, found 686.3481.

Major acetylated compound. R_f 0.33, Cy–EtOAc, 4 : 1; $[\alpha]_D$ +30 (c = 0.68, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.39–7.24 (m, 25H, 5 × Ph), 5.61 (dd, 1H, J = 5.2, 1.9 Hz, H-5), 4.75–4.67 (m, 3H, 3 × CHPh), 4.57 (d, 1H, J = 11.8 Hz, CHPh), 4.44 (d, 1H, J = 11.8 Hz, CHPh), 4.37–4.30 (m, 4H, 3 × CHPh, H-4), 4.05–40.1 (m, 1H, H-6), 3.96 (d, 1H, J = 14.2 Hz, NCHPh), 3.78–3.68 (m, 3H, NCHPh, H-3, H-8a), 3.59 (d, 1H, H-8b), 3.25–3.21 (m, 1H, H-2), 2.89 (dd, 1H, J = 12.4, 5.6 Hz, H-7a), 2.76 (t, 1H, J = 12.4, 10.0 Hz, H-7b), 1.95 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.69 (C═O), 140.31, 140.31, 138.28, 138.28, 138.11 (5 × C_{ipso}), 128.43–126.76 (25 aromatic C), 80.23 (C-4), 79.77 (C-3), 74.09 (C-5), 73.04 (C-6), 73.82, 73.31, 73.22, 71.26 (4 × CH_2Ph), 68.70 (C-8), 65.54 (C-2), 56.41 (N-CH_2Ph), 50.24 (C-7), 21.17 (CH_3); ESI-HRMS: calcd for $C_{44}H_{48}NO_6$ $[M + H]^+$: 686.3476, found 686.3472.

A mixture of major acetylated compound (100 mg, 0.140 mmol), NaOH (17 mg, 0.440 mmol) in MeOH (3 mL) and water (0.5 mL) was refluxed for 1 h. The reaction mixture was neutralized with 1 M HCl (0.15 mL) and concentrated under reduced pressure. The resulting residue was partitioned between DCM (20 mL) and water (20 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford compound **19** as an oil (98 mg, quant.). R_f 0.32, Cy–EtOAc, 4 : 1; $[\alpha]_D$ −5 (c = 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.34–7.17 (m, 25H, 5 × Ph), 4.65–4.51 (m, 4H, J = 3.0 Hz, J = 13.1 Hz, 4 × CHPh), 4.43–4.29 (m, 4H, 4 × CHPh), 4.13 (s, 1H, H-5), 3.95–3.91 (m, 2H, H-6, H-4), 3.87 (d, 1H, J = 12.9 Hz, NCHPh), 3.76 (d, 1H, J = 13.1 Hz, NCHPh), 3.66–3.61 (m, 3H, H-3, H-8a, H-8b), 3.19 (dd, 2H, J = 12.0, 6.8 Hz, H-2, H-7a), 2.81 (dd, 1H, J = 12.0, 8.5 Hz, H-7b); ^{13}C NMR ($CDCl_3$, 100 MHz): 139.14, 138.58, 138.53, 138.46, 138.33 (5 × C_{ipso}), 129.17–127.45 (25 aromatic C), 83.61 (C-4), 79.10 (C-3), 75.52 (C-6), 74.66 (C-5), 73.29, 73.29, 72.85, 71.43 (4 × CH_2Ph), 67.15 (C-8), 63.16 (C-2), 60.69 (NCH_2Ph), 51.34 (C-7); ESI-HRMS calcd for $C_{42}H_{46}NO_5$ $[M + H]^+$: 644.3370, found 644.3373.

2-[(*R*)-1-Benzyloxy-2-hydroxyethyl]-(2*R*,3*R*,4*R*,5*R*)-1-benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidine 23. To a solution of **19** (50 mg, 0.078 mmol) in dry toluene (2 mL) were added trifluoroacetic anhydride (17 μL, 0.117 mmol) and Et_3N (17 μL, 0.156 mmol) at 0 °C. Then the solution was refluxed for 5 hours before being cooled to room temperature. To this solution, NaOH (10%, 2 mL) was added and the resulting mixture was stirred for another 1 h. EtOAc was added and the layers were separated. The aqueous layer was extracted twice with EtOAc and the combined organic layers were dried on $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then purified by column chromatography (P.E.–EtOAc, 8.5/1.5) to give **23** (46 mg, 92%) as colorless oil. R_f 0.25, Cy–EtOAc, 4 : 1; $[\alpha]_D$ −20 (c = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.27–7.16 (m, 25H, 5 × Ph), 4.65–4.33 (m, 9H, 4 × CH_2Ph, H-4), 4.07 (s, 1H, H-3), 3.97 (d, 1H, J = 13.6 Hz, NCHPh), 3.88–3.71 (m, 5H, H-6a, H-1′a, H-6b, H-2′, NCHPh), 3.61 (m, 1H, H-1′b), 3.46 (m, 2H, H-5, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): 138.50, 138.50, 138.41, 138.41, 138.02 (5 × C_{ipso}), 128.59–127.25 (25 aromatic C), 84.07 (C-4), 83.18 (C-3), 76.35 (C-2′), 73.29, 71.87, 71.62, 71.29 (4 × CH_2Ph), 70.17 (C-2), 65.76 (C-1′), 63.16 (C-5), 62.10 (C-6), 52.82 (NCH_2Ph); ESI-HRMS calcd for $C_{42}H_{46}NO_5$ $[M + H]^+$: 644.3370, found 644.3379.

(2*R*,3*R*,4*R*,5*R*)-2-((*R*)-1,2-Dihydroxyethyl)-5-(hydroxymethyl)-pyrrolidine-3,4-diol 3. To a solution of pyrrolidine **23** (40 mg, 0.062 mmol) in MeOH (3 mL) and conc. HCl (20 μL) was added 10% Pd/C (40 mg). The suspension was stirred under a H_2 atmosphere for 24 h at r.t., filtered through a Celite plug eluted with MeOH. The solvent was removed under reduced pressure to afford pyrrolidine **3** in quantitative yield as its hydrochloride salt. $[\alpha]_D$ +29 (c = 0.31, CH_3OH); ^1H NMR (CD_3OD, 400 MHz): 4.07 (t, 1H, J = 7.5, 6.8 Hz, H-4), 3.99 (t, 1H, J = 7.9, 6.8 Hz, H-3), 3.92 (dd, 1H, J = 9.0, 4.9 Hz, H-2′), 3.88–3.75 (m, 2H, H-6), 3.66 (d, 2H, J = 5.0, H-1′), 3.44 (dd, 1H, J = 7.6, 4.0 Hz, H-2), 3.37 (m, 1H, H-5); ^{13}C NMR (CD_3OD, 100 MHz): 77.29 (C-4), 75.85 (C-3), 69.27 (C-2′), 65.14 (C-2), 65.07 (C-5), 64.90 (C-2′), 59.06 (C-6); ESI-HRMS calcd for $C_7H_{16}O_5N$ $[M + H]^+$: 194.1023, found 194.1025.

(2*R*,3*R*,4*S*,5*R*,6*R*)-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)-methyl)-5,6-*O*-(benzylidene)azepane-1-carboxylate 12. A mixture of diol **8** (115 mg, 0.193 mmol), camphorsulfonic acid (cat., 2 mg) and benzaldehyde dimethyl acetal (87 μL, 0.579 mmol) in CH_3CN (4 mL) was stirred at 50 °C under an atmosphere of nitrogen overnight and quenched with triethylamine (0.1 mL). After concentration, the resulting residue was purified by flash column chromatography (Cy–EtOAc, 5 : 1) to yield compound **12** as an oil (120 mg, 91%). Due to the mixture of rotational isomers, NMR was not resolved clearly and this compound was used directly in the next step. R_f 0.51, Cy–EtOAc, 4 : 1; ESI-HRMS calcd for $C_{43}H_{43}NO_7Na$ $[M + Na]^+$: 708.2931, found 708.2928.

(2*R*,3*R*,4*S*,5*R*,6*R*)-1-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)-methyl)-5,6-*O*-(benzylidene)azepane 16. Compound **12** (56 mg, 0.081 mmol) was dissolved in EtOH (5 mL) and a catalytic amount of Et_3N (5 μL) was introduced, followed by the addition of Lindlar's catalyst (56 mg). The reaction flask was purged of air and filled with H_2. The suspension was stirred under H_2 for 4 h by the end of which TLC (Cy–EtOAc, 4 : 1) showed a complete reaction. The reaction mixture was filtered through a pad of Celite, eluted with MeOH and concentrated under reduced pressure to afford the *N*-deprotected azepane as an oil. This oil was dissolved in DMF (3 mL), K_2CO_3 (34 mg, 0.243 mmol) was introduced, followed by addition of benzyl bromide (20 μL, 0.163 mmol). The mixture was stirred at 50 °C under an atmosphere of nitrogen overnight. After concentration, the resulting residue was partitioned between water (20 mL) and DCM (20 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The result-

ing residue was purified by flash column chromatography (Cy–EtOAc, 8 : 1) to give compound **16** as an oil (36 mg, 70%), which was an inseparable mixture of two epimers. R_f 0.55, Cy–EtOAc, 4 : 1; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.44–7.12 (m, 50H, 10 × Ph), 6.16 (s, 1H, H-8′), 5.74 (s, 1H, H-8), 4.90–4.25 (m, 14H, 6 × CHPh, H-5, H-5′), 4.25–4.11 (m, 3H, H-6, H-6′, H-4), 4.05–3.65 (m, 11H, H-4′, H-3, H-3′, NCH_2Ph, NCH_2Ph′, H-9, H-9′), 3.50–3.20, (m, 2H, H-7a, H-7a′), 3.25–2.99, (m, 2H, H-2, H-2′), 2.87–2.65 (m, 2H, H-7b, H-7b′; ^{13}C NMR ($CDCl_3$, 100 MHz): 140.18, 140.15, 139.50, 138.66, 136.61, 138.51, 138.45, 138.42, 138.38 (10 × C_{ipso}), 129.29–126.28 (50 aromatic C), 104.14, 103.73 (C-8, C-8′), 81.70, 80.93 (C-4, C-4′), 80.31, 79.45 (C-5, C-5′), 78.55, 76.34 (C-6, C-6′), 75.70, 75.17 (C-3, C-3′), 74.75, 74.44, 74.03, 73.29, 73.14, 72.62 (10 × CH_2Ph), 68.68, 66.59 (C-9, C-9′), 63.80, 63.27 (C-2, C-2′), 60.67, 60.40 (N-CH_2Ph, N-CH_2Ph′), 48.68, 48.05 (C-7, C-7′); ESI-HRMS calcd for $C_{42}H_{44}NO_5$ $[M + H]^+$: 642.3214, found 642.3206.

(2*R*,3*R*,4*R*,5*R*,6*R*)-1-Benzyl-3,4,6-tris(benzyloxy)-2-((benzyloxy)-methyl) azepan-5-ol 20. To a solution of compound **16** (349 mg, 0.544 mmol) in dry DCM (5 mL) was added quickly DIBAL (7.3 mL, 1.5 M in toluene, 2.664 mmol) at −78 °C under an atmosphere of nitrogen with stirring. After 30 min at −78 °C, TLC (Cy–EtOAc, 4 : 1) showed that the starting material was consumed completely. A solution of 1 M aq. HCl (3 mL) was added at −30 °C to quench the reaction. The resulting solution was warmed to r.t., and then extracted with DCM/water, dried over $MgSO_4$, concentrated under reduced pressure, to provide an inseparable mixture of diols. This mixture of crude diols was dissolved in pyridine (4 mL) and Ac_2O (2 mL), then stirred under an atmosphere of nitrogen at r.t. overnight. After evaporation, the resulting residue was purified by flash column chromatography (Cy–EtOAc, 15 : 1) to give minor acetylated compound as a clear oil (66 mg, 18%), and further elution afforded major acetylated compound as a clear oil (173 mg, 46%).

Minor acetylated compound. R_f 0.52, Cy–EtOAc, 4 : 1; $[\alpha]_D$ +7 (c = 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.43–7.20 (m, 25H, 5 × Ph), 4.90–4.69 (m, 5H, 4 × CHPh, H-6), 4.52–4.38 (m, 4H, 4 × CHPh), 4.25 (d, 1H, J = 2.6 Hz, H-5), 4.09–3.94 (m, 4H, NCH_2Ph, H-4, H-3), 3.79 (dd, 1H, J = 9.5, 6.0 Hz, H-8a), 3.70 (dd, 1H, J = 9.5, 5.8 Hz, H-8b), 3.31–3.22 (m, 2H, H-2, H-7a), 2.61 (dd, 1H, J = 14.0, 4.6 Hz, H-7b), 1.99 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.35 (C═O), 140.05, 138.97, 138.90, 138.86, 138.75 (5 × C_{ipso}), 128.68–127.11 (25 aromatic C), 82.97 (C-3), 79.56 (C-4), 78.81 (C-5), 74.23, 73.78, 73.39, 73.05 (4 × CH_2Ph), 72.30 (C-6), 69.25 (C-8), 64.26 (C-2), 61.23 (NCH_2Ph), 46.39 (C-7), 21.24 (CH_3); ESI-HRMS: calcd for $C_{44}H_{48}NO_6$ $[M + H]^+$: 686.3476, found 686.3482.

Major acetylated compound. R_f 0.47, Cy–EtOAc, 4 : 1; $[\alpha]_D$ +19 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.37–7.10 (m, 25H, 5 × Ph), 5.83 (s, 1H, H-5), 4.78–4.66 (ddd, 3H, J = 11.4, 11.2, 10.8 Hz, 3 × CHPh), 4.78–4.66 (4d, 4H, J = 12.3, 11.8, 10.9 Hz, 4 × CHPh), 4.19 (d, 1H, J = 12.0 Hz, CHPh), 4.01 (dd, 1H, J = 8.8, 1.1 Hz, H-6), 3.92–3.80 (m, 3H, NCH_2Ph, H-4), 3.75–3.65 (m, 2H, H-8a, H-8b), 3.13–3.11 (m, 3H, H-7a, H-3, H-2), 2.53 (d, 1H, J = 10.2 Hz, H-7b), 2.13 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.44 (C═O), 140.03, 138.75, 138.68, 138.52, 138.21 (5 × C_{ipso}), 128.98–127.24 (25 aromatic C), 80.32 (C-6), 77.94 (C-4), 76.57 (C-3), 74.28, 73.21, 73.21, 71.11 (4 × CH_2Ph), 71.02 (C-5), 69.02 (C-8), 65.17 (C-2), 61.06 (NCH_2Ph), 47.05 (C-7), 21.38 (CH_3); ESI-HRMS: calcd for $C_{44}H_{48}NO_6$ $[M + H]^+$: 686.3476, found 686.3481.

A mixture of major acetylated compound (150 mg, 0.218 mmol), NaOH (26 mg, 0.654 mmol) in MeOH (3 mL) and water (0.5 mL) was refluxed for 1 h. The reaction mixture was neutralized with 1 M HCl (0.3 mL) and concentrated under reduced pressure. The resulting residue was partitioned between DCM (20 mL) and water (20 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford compound **20** as a syrup (120 mg, 86%). R_f 0.28, Cy–EtOAc, 4 : 1; $[\alpha]_D$ +13 (c = 2.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.38–7.09 (m, 25H, 5 × Ph), 4.87 (dd, 2H, J = 11.8, 11.2 Hz, 2 × CHPh), 4.69 (d, 1H, J = 11.6 Hz, CHPh), 4.51–4.43 (m, 3H, 3 × CHPh), 4.24 (d, 1H, J = 12.0 Hz, CHPh), 4.22 (ddd, 1H, J = 2.9, 1.5, 1.3 Hz, H-6), 4.14 (d, 1H, J = 12.0 Hz, CHPh), 4.07 (t, 1H, J = 8.8, 7.6 Hz, H-4), 3.96 (dd, 1H, J = 8.8, 1.3 Hz, H-5), 3.90 (d, 1H, J = 13.2 Hz, NCHPh), 3.81 (d, 1H, J = 13.2 Hz, NCHPh), 3.75 (dd, 1H, J = 10.1, 5.6 Hz, H-8a), 3.65 (dd, 1H, J = 10.1, 3.5 Hz, H-8b), 3.13–3.06 (m, 2H, H-7a, H-3), 3.02 (tt, 1H, J = 10.8, 3.52 Hz, H-2), 2.48 (dd, 1H, J = 13.6, 3.5 Hz, H-7b); ^{13}C NMR ($CDCl_3$, 100 MHz): 140.25, 138.95, 138.87, 138.72, 138.18 (5 × C_{ipso}), 129.13–127.19 (25 aromatic C), 81.17 (C-5), 77.89 (C-3), 76.32 (C-4), 74.61, 74.02, 73.19, 71.06 (4 × CH_2Ph), 71.98 (C-6), 69.18 (C-8), 65.75 (C-2), 60.84 (N-CH_2Ph), 45.29 (C-7); ESI-HRMS calcd for $C_{42}H_{46}NO_5$ $[M + H]^+$: 644.3370, found 644.3364.

2-[(*S*)-1-Benzyloxy-2-hydroxyethyl]-(2*S*,3*R*,4*R*,5*R*)-1-benzyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidine 24. To a solution of **20** (70 mg, 0.109 mmol) in dry toluene (3 mL) were added trifluoroacetic anhydride (23 μL, 0.163 mmol) and Et_3N (30 μL, 0.218 mmol) at 0 °C. Then the solution was refluxed for 5 hours before being cooled to room temperature. A solution of NaOH (10%, 2 mL) was added and the resulting mixture was stirred for another 1 h. EtOAc was added and the layers were separated. The aqueous layer was extracted twice with EtOAc and the combined organic layers were dried on $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then purified by column chromatography (P.E.–EtOAc, 8.5/1.5) to give **24** (43 mg, 62%) as a colorless oil. R_f 0.25, Cy–EtOAc, 4 : 1; $[\alpha]_D$ +3 (c = 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.40–7.10 (m, 25H, 5 × Ph), 4.68–4.37 (m, 7H, CH_2Ph), 4.29 (d, 1H, J = 12.1 Hz, CH_2Ph), 4.15–4.04 (m, 4H, H-3, H-4, NCH_2Ph), 3.96 (dd, 1H, J = 11.4, 5.4 Hz, H-1′a), 3.78 (dd, 1H, J = 9.4, 5.5 Hz, H-2′), 3.70 (d, 1H, OH), 3.63 (dd, 1H, J = 11.3, 3.7 Hz, H-1′b), 3.46 (t, 1H, J = 5.8 Hz, H-5), 3.39 (t, 1H, J = 9.1 Hz, H-6′a) 3.14 (ddd, 1H, J = 7.5, 5.3, 1.8 Hz, H-2), 3.05 (dd, 1H, J = 9.1, 5.4 Hz, H-6′b); ^{13}C NMR ($CDCl_3$, 100 MHz): 138.97, 138.52, 138.52, 138.44, 137.81 (5 × C_{ipso}), 129.62–127.34 (25 aromatic C), 83.30 (C-4), 82.46 (C-3), 78.60 (C-2′), 72.84, 72.25, 72.16, 71.84 (4 × CH_2Ph), 71.21 (C-6), 68.17 (C-2), 66.87 (C-5), 62.40 (C-1′), 61.53 (NCH_2Ph); ESI-MS (m/z):

644 (M^+ + H). ESI-HRMS calcd for $C_{42}H_{46}NO_5$ $[M + H]^+$: 644.3370, found 644.3369.

(2*S*,3*R*,4*R*,5*R*)-2-((*S*)-1,2-Dihydroxyethyl)-5-(hydroxymethyl)-pyrrolidine-3,4-diol 4. To a solution of pyrrolidine **24** (21 mg, 0.033 mmol) in MeOH (2 mL) and 1 M aq. HCl (50 μL) was added 10% Pd/C (20 mg). The suspension was stirred under a H_2 atmosphere for 4 h at r.t., filtered through a Celite plug eluted with MeOH. The solvent was removed under reduced pressure to afford pyrrolidine **4** (3.1 mg, 89%) as its hydrochloride salt. $[\alpha]_D$ +104 (*c* = 0.1, CH_3OH); ^1H NMR (CD_3OD, 400 MHz): 4.09–4.13 (m, 2H), 4.04–3.99 (m, 1H), 3.91 (dd, 1H, *J* = 11.7, 5.5 Hz), 3.85 (dd, 2H, *J* = 11.4, 8.9 Hz), 3.78 (dd, 1H, *J* = 6.8, 3.2), 3.75 (dd, 1H, *J* = 9.8, 3.5 Hz), 3.67 (dd, 1H, *J* = 11.6, 4.2 Hz), 3.49 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz): 78.23, 76.24, 69.62, 69.20, 65.94, 64.69, 61.35; ESI-MS (*m*/*z*): 194 (M^+ + H). ESI-HRMS: calcd for $C_7H_{16}O_5N$ $[M + H]^+$: 194.1023, found 194.1024.

Conclusions

We have demonstrated that, starting from easily available dihydroxyazepane precursors, a regioselective protection of the hydroxyl group β to the nitrogen allows the orientation of the ring isomerization of the seven-membered azacycle towards highly substituted polyhydroxylated pyrrolidines developed as homoDMDP epimers. Amongst them, the 6-*epi*-homoDMDP proved to be a fairly good α-glucosidase inhibitor.

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