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Synthesis of branched seven-membered 1-*N*-iminosugars and their evaluation as glycosidase inhibitors

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ABSTRACT

Four branched tetra- and pentahydroxylated azepanes have been synthesized from a common azepane precursor through dihydroxylation followed by deoxygenation. They have been assayed as glycosidase inhibitors on a panel of 22 glycosidases and one methylated azepane displayed selective, competitive, and moderate inhibition toward bovine kidney α-L-fucosidase.

1. Introduction

Interest continues to mount in new applications of natural and synthetic glycosidase inhibitors to basic research and medicine as iminosugar-based inhibitors[1] have been shown to exhibit potent activity on diabetes,[2] HIV infection,[3] viral infections[4] or cancer[5] leading sometimes to therapeutics.[6] In the last two decades, 1-*N*-iminosugars have emerged as a major new class of very potent glycosidase inhibitors by virtue of their resemblance with the carbocationic form of glycosidase transition state. The most famous molecule of this family, coined isofagomine **1**, was reported by Bols[7] and proved to be a strong β-glucosidase inhibitor. As expected, the potency of isofagomine was further improved by introducing a hydroxyl group at the C-2 position to afford noeuromycin **2**, a nanomolar β-glucosidase inhibitor.[8] Meanwhile, many other sugar analogs with nitrogen at the pseudoanomeric position have been prepared[9] including branched derivatives such as compounds **3–6** (Fig. 1).[10] The introduction of an extra tertiary hydroxyl group was justified in order to hold the sugar hydroxyl groups in the correct topological orientation and hopefully generate more selective and potent glycosidase inhibitors. This modification was also applied to polyhydroxylated pyrrolidine generating compounds such as **7**[11] and **8** (Fig. 1), this latter displaying promising activity as corrector of del508-CFTR involved in cystic fibrosis.[12]

2. Synthesis

In an ongoing program on the design of new glycosidase inhibitors, our group has recently reported the synthesis[13] and biological evaluation[14] of ring homologs of noeuromycin. We would like to report herein our results on branched derivatives of these compounds. We used a similar strategy as the one developed by Pandey[15] based on the dihydroxylation of the exoalkene present on the available azacycle **9**. Dihydroxylation of **9** using OsO_4 and NMO afforded the separable diols **10** and **11** (93% yield) which were hydrogenolyzed under mild acidic conditions to afford the corresponding pentahydroxylated azepanes **12** and **13** as their hydrochloride salts (Scheme 1).

As tetrahydroxylated azepanes have been proved to be potent glycosidase inhibitors,[16] we were also interested in synthesizing branched analogs of these compounds and introducing some conformational bias with an extra methyl group. Tosylation of the neopentylic alcohol in diol **10** furnished the crude tosylate in good yield which was directly reduced with Superhydride® to yield the corresponding deoxy derivative **14** (68% yield over two steps). Final hydrogenolysis furnished the branched tetrahydroxyazepane **15** as its hydrochloride salt (Scheme 2). The same sequence was applied to diol **11** to furnish the intermediate **16** (65% yield) and the branched tetrahydroxyazepane **17**.

3. Structure determination

The configuration of compounds **15** and **17** was confirmed by NOESY experiments. While the CH_3 group in compound **15** showed

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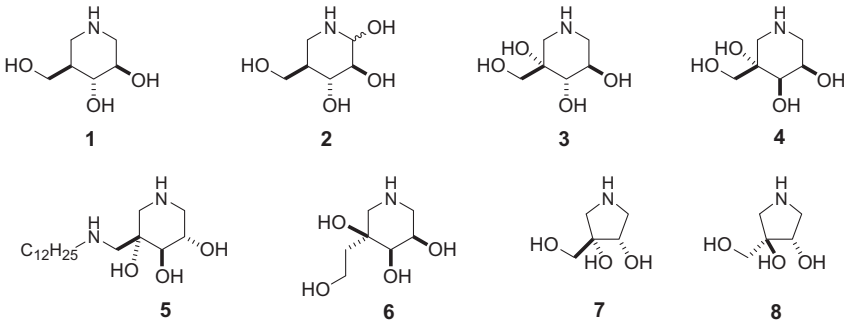
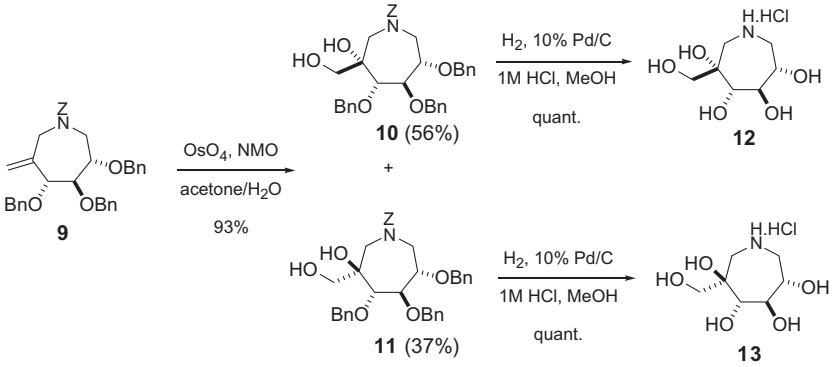
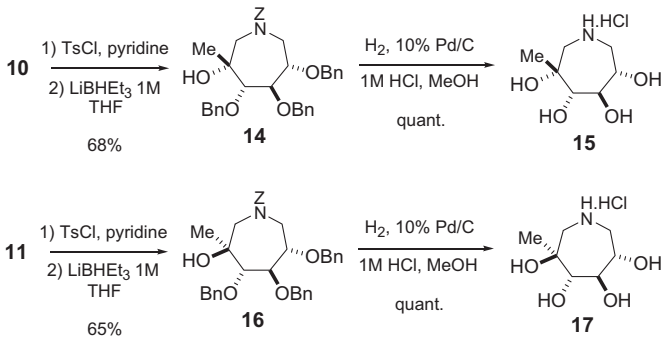


Figure 1. Structure of isofagomine **1**, noeuromycin **2** and branched derivatives **3**–**8**.



Scheme 1. Synthesis of pentahydroxylated azepanes **12** and **13**.



Scheme 2. Synthesis of tetrahydroxylated azepanes **15** and **17**.

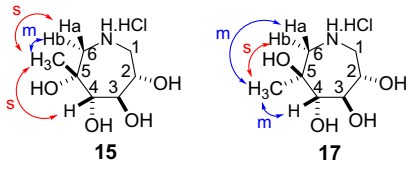


Figure 2. Main NOE data for tetrahydroxylated azepanes **15** and **17**.

a strong NOE effect with H-4 and H-6a and a medium NOE effect with H-6b, the CH_3 group in compound **17** showed a strong NOE effect with H-6b and a medium NOE effect with H-4 and H-6a demonstrating a *cis* relationship for H-4 and the methyl group in compound **15** and a *trans* relationship for H-4 and the methyl group in compound **17** (Fig. 2) and enabling the unambiguous deduction of the configuration of related compounds **12** and **13**.

4. Glycosidase inhibition assay

Azepanes **12**, **13**, **15,** and **17** were assayed for their inhibitory activity toward 22 commercially available glycosidases.[17] They did not inhibit the following enzymes at 1 mM concentration and optimal pH: coffee bean α-galactosidase, β-galactosidases from *Aspergillus oryzae* and *Escherichia coli*, rice α-glucosidase, amyloglucosidase from *Aspergillus niger*, snail β-mannosidase, β-*N*-acetylglucosaminidases from jack bean and bovine kidney. For other enzymes the results are shown in Table 1.

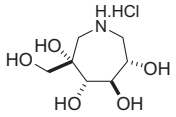
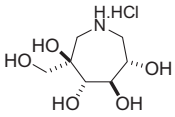
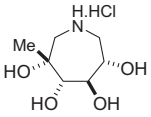
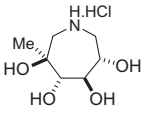
All the branched azepanes were found to be weak glycosidase inhibitors except for azepane **17** which displayed selective and moderate competitive L-fucosidase inhibition. This last result can tentatively be explained by the presence of the methyl group and the adjacent hydroxyl group which partially display the configuration of L-fucose. Compared to the noeuromycin ring homologs, introduction of an extra hydroxyl group on the carbon that bears the hydroxymethyl group appears detrimental to the inhibition potency of this family of compounds. Compared to tetrahydroxylated azepanes, introduction of an additional hydroxymethyl group on the tetrahydroxyazepane scaffold also strongly affects the glycosidase inhibition of these compounds. Such observation has already been made in the case of polyhydroxylated azepanes mimicking glyconojirimycins.[18] In conclusion, increasing the size and lowering the conformational flexibility of seven-membered iminosugars by introducing an extra CH_3 or CH_2OH group mainly abolishes inhibitory potency and therefore draws the size limits for a glycosidase iminosugar-based inhibitor.

5. Experimental section

5.1. General methods

Melting points (mp) were determined with a Büchi B-535 apparatus and are uncorrected. Optical rotations were measured at

Table 1
Glycosidase inhibitory activity of compounds **12**, **13**, **15** and **17**

Compound/enzyme	 **12**	 **13**	 **15**	 **17**
α-L-Fucosidase				
Bovine kidney	NI	NI	NI	87% (118 μM)
β-Galactosidase				
Bovine liver	NI	NI	20%	29%
α-Glucosidase				
yeast	NI	NI	21%	NI
β-Glucosidase				
Sweet almonds	39%	NI	60%	NI
α-Mannosidase				
Jack bean	NI	30%	79%	NI
β-Xylosidase				
Aspergillus niger	NI	NI	56%	NI

% of inhibition at 1 mM concentration, optimal pH, 35 °C, IC_{50} in brackets, NI = no inhibition at 1 mM concentration of the inhibitor.

20 ± 2 °C with a Perkin Elmer Model 241 digital polarimeter, using a 10 cm, 1 mL cell. Chemical Ionisation Mass Spectra (CI-MS ammonia) and Fast Atom Bombardment Mass Spectra (FAB-MS) were recorded on a JMS-700 spectrometer. ^{1}H NMR and ^{13}C NMR were performed on a Bruker DRX 400 spectrometer (400 MHz for ^{1}H, 100.6 MHz for ^{13}C). All chemical shifts (δ) are given in ppm relative to the residual deuterated solvent signals. Coupling constants (J) are reported in Hertz. Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F_{254} precoated plates and detection by charring with sulfuric acid. Flash column chromatography was performed on silica gel Merck 60 (230–400 mesh).

Note: For compounds **10**, **11**, **14**, and **16** bearing a benzyloxycarbonyl group on the nitrogen, they appear as a mixture of rotamers by NMR.

5.1.1. (3*S*,4*S*,5*R*,6*S*)-*N*-Benzyloxycarbonyl-3-hydroxy-3-hydroxymethyl-4,5,6-tribenzyloxyazepane 10 and (3*R*,4*S*,5*R*,6*S*)-*N*-benzyloxycarbonyl-3-hydroxy-3-hydroxymethyl-4,5,6-tribenzyloxyazepane 11

Exoalkene **9** (91 mg, 0.162 mmol) was dissolved in acetone/water 8:1 (0.7 mL). *N*-Morpholine oxyde (75 mg, 0.641 mmol) was added, followed by OsO_4 (0.03 mL, 2.5% wt in *t*-BuOH). The reaction mixture was stirred at room temperature for 24 h and then quenched by addition of $Na_2S_2O_3{\cdot}5H_2O$ (6 mg). The reaction mixture was stirred for 15 min and then diluted with EtOAc, dried with $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (Cy/EtOAc, 2:1) afforded diol **11** as an oil (36 mg, 37%, R_f 0.25, Cy/EtOAc, 2:1). Further elution (Cy/EtOAc, 3:2) gave diol **10** as an oil (54 mg, 56% yield, R_f 0.13, Cy/EtOAc, 6:1).

5.1.1.1. Compound 10. $[\alpha]_D$ −14 (c = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.43–7.18 (m, 40H, 8 × Ph), 5.29–5.16 (m, 4H, 4 × NCOOCHPh), 4.89–4.40 (m, 12H, 6 × CH_2Ph), 4.24 (dd, 1H, $J_{1'a,2'}$ = 3.4 Hz, $J_{1'a,1'b}$ = 13.6 Hz, H-1′a), 4.17 (dt, 1H, $J_{2',3'}$ = 3.9 Hz, $J_{1'b,2'}$ = 10.0 Hz, H-2′), 4.11 (t, 1H, $J_{3',4'}$ = 3.9 Hz, H-3′), 4.05–3.96 (m, 6H, H-1a, H-2, H-3, H-6a, H-6′a, OH), 3.94 (d, 1H, H-4′), 3.75 (d, 1H, $J_{3,4}$ = 3.7 Hz, H-4), 3.55–3.40 (m, 5H, H-1b, H-7a, H-7′a, H-7b, H-7′b), 3.39 (dd, 1H, H-1′b), 3.25 (d, 2H, $J_{6a,6b}$ = $J_{6'a,6'b}$ = 14.1 Hz, H-6b, H-6′b), 2.94 (t, 1H, OH), 2.45 (dd, 1H, OH′), 2.04 (br, 1H, OH′); ^{13}C NMR ($CDCl_3$, 100 MHz): 156.76 and 156.44 (2 × C═O), 138.21, 138.02, 137.43, 137.38, 137.27, 137.07, 136.82 and 136.24 (8 × Cipso), 128.48–127.45 (40 × aromatic C), 82.33 (C-3), 82.25 (C-2), 81.80 (C-3′), 81.21 (C-2′), 78.34 (C-4), 77.53 (C-5), 77.39 (C-4′), 77.34 (C-5′), 72.92, 72.77, 72.72, 71.62 and 71.51 (6 × CH_2Ph), 67.75 and 66.99 (2 × $NCOOCH_2$Ph), 65.98 and 65.88 (C-7′ and C-7), 49.58 and 49.19 (C-6′ and C-6), 46.68 and 46.08 (C-1′ and C-1); m/z (CI, CH_4): 598 ($M+H^+$, 100%); HRMS (CI, CH_4): Calcd for $C_{36}H_{40}O_7N$ ($M+H^+$): 598.2805. Found 598.2799.

5.1.1.2. Compound 11. $[\alpha]_D$ −23 (c = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.42–7.18 (m, 40H, 8 × Ph), 5.26–5.14 (m, 4H, 4 × NCOOCHPh), 4.90–4.38 (m, 12H, 6 × CH_2Ph), 4.06 (dd, 1H, $J_{1'a,2'}$ = 2.7 Hz, $J_{1'a,1'b}$ = 13.9 Hz, H-1′a), 4.02 (dd, 1H, $J_{3',4'}$ = 3.9 Hz, $J_{2',3'}$ = 5.6 Hz, H-3′), 3.97–3.93 (m, 2H, H-1a, H-6a), 3.91 (dd, 1H, $J_{3,4}$ = 4.2 Hz, $J_{2,3}$ = 5.8 Hz, H-3), 3.82 (ddd, 1H, $J_{2',3'}$ = 5.6 Hz, $J_{1'b,2'}$ = 10.1 Hz, H-2′), 3.78 (d, 1H, $J_{6'a,6'b}$ = 14.2 Hz, H-6′a), 3.75 (d, 1H, $J_{3,4}$ = 4.2 Hz, H-4), 3.74 (d, 1H, H-4′), 3.69 (d, 1H, $J_{7'a,7'b}$ = 12.2 Hz, H-7′a), 3.62 (d, 1H, $J_{7a,7b}$ = 12.7 Hz, H-7a), 3.58 (ddd, 1H, $J_{1a,2}$ = 3.2 Hz, $J_{2,3}$ = 5.8 Hz, $J_{1b,2}$ = 10.7 Hz, H-2), 3.53 (d, 1H, H-7b), 3.50 (dd, 1H, H-1′b), 3.48 (app. d, 1H, H-7′b), 3.43 (d, 1H, H-6′b), 3.37 (dd, 1H, $J_{1a,1b}$ = 14.1 Hz, H-1b), 3.36 (br, 1H, OH), 3.34 (d, 1H, $J_{6a,6b}$ = 14.1 Hz, H-6b), 3.00 (br, 2H, OH, OH′), 2.48 (br, 1H, OH′); ^{13}C NMR ($CDCl_3$, 100 MHz): 156.67 and 155.59 (2 × C═O), 137.98, 137.93, 137.85, 137.76, 137.51, 137.37, 136.09 and 135.93 (8 × Cipso), 128.62–127.43 (40 × aromatic C), 83.30 (C-4′), 83.22 (C-3), 82.88 (C-2), 82.12 (C-3′), 82.09 (C-4), 81.69 (C-2′), 77.21 and 76.51 (C-5 and C-5′), 74.34, 73.94, 73.51, 73.32, 71.81 and 71.63 (6 × CH_2Ph), 68.10 and 67.67 (2 × $NCOOCH_2$Ph), 65.28 and 64.37 (C-7′ and C-7), 49.12 and 48.82 (C-6′ and C-6), 45.66 and 45.03 (C-1 and C-1′); m/z (CI, CH_4): 598 ($M+H^+$, 100%); HRMS (CI, CH_4): Calcd for $C_{36}H_{40}O_7N$ ($M+H^+$): 598.2805. Found 598.2798.

5.1.2. (3*S*,4*S*,5*R*,6*S*)-3-Hydroxymethyl-3,4,5,6-tetrahydroxyazepane 12

Hydrogenolysis of diol **10** (53 mg, 0.089 mmol) with 10% Pd/C in MeOH and in the presence of 1 M HCl solution furnished quantitatively compound **12** (21 mg) as an oil. $[\alpha]_D$ +9.2 (c = 1.1 in CH_3OH); ^{1}H NMR (D_2O, 400 MHz): 4.27 (ddd, 1H, $J_{1a,2}$ = 2.3 Hz, $J_{2,3}$ = 7.8 Hz, $J_{1b,2}$ = 10.1 Hz, H-2), 3.89 (d, 1H, $J_{3,4}$ = 2.8 Hz, H-4), 3.77 (dd, 1H, H-3), 3.64 (dq, 1H, $J_{7a,7b}$ = 12.0 Hz, H-7a), 3.58 (dq, 1H, H-7b), 3.40 (dd, 1H, $J_{1a,1b}$ = 13.5 Hz, H-1a), 3.35 (d, 1H, $J_{6a,6b}$ = 13.7 Hz, H-6a), 3.29 (dd, 1H, H-1b), 3.17 (d, 1H, H-6b); ^{13}C NMR (D_2O, 100 MHz): 80.02 (C-3), 74.55 (C-4), 74.33 (C-5), 70.21 (C-2), 65.87 (C-7), 47.75 (C-1), 46.37 (C-6); m/z (CI, C_4H_{10}): 194 ($M+H^+$, 100%); HRMS (CI, C_4H_{10}): Calcd for $C_7H_{16}O_5N$ ($M+H^+$): 194.1028. Found 194.1028.

5.1.3. (3*R*,4*S*,5*R*,6*S*)-3-Hydroxymethyl-3,4,5,6-tetrahydroxyazepane 13

Hydrogenolysis of diol **11** (35 mg, 0.059 mmol) with 10% Pd/C in MeOH and in the presence of 1 M HCl solution furnished quantitatively compound **13** (14 mg) as an oil. $[\alpha]_D$ – 2.5 (c = 1.0 in CH_3OH); ^1H NMR (D_2O, 400 MHz): 3.58 (ddd, 1H, $J_{1a,2}$ = 3.7 Hz, $J_{1b,2}$ = $J_{2,3}$ = 8.3 Hz, H-2), 3.79 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 8.3 Hz, H-3), 3.69 (d, 1H, $J_{7a,7b}$ = 11.5 Hz, H-7a), 3.66 (d, 1H, H-7b), 3.59 (d, 1H, H-4), 3.43 (dd, 1H, $J_{1a,1b}$ = 13.6 Hz, H-1a), 3.41 (d, 1H, $J_{6a,6b}$ = 14.3 Hz, H-6a), 3.33 (dd, 1H, H-1b), 3.24 (d, 1H, H-6b), 1.36 (dd, 1H, J = 4.7 Hz, 6.6 Hz, OH); ^{13}C NMR (D_2O, 100 MHz): 74.98 (C-3), 74.13 (C-4), 72.62 (C-5), 66.93 (C-2), 65.00 (C-7), 48.09 (C-6), 47.14 (C-1); m/z (CI, C_4H_{10}): 194 ($M+H^+$, 100%); HRMS (CI, C_4H_{10}): Calcd for $C_7H_{16}O_5N$ ($M+H^+$): 194.1028. Found 194.1031.

5.1.4. (3*R*,4*S*,5*R*,6*S*)-*N*-Benzyloxycarbonyl-3-hydroxy-3-methyl-4,5,6-tribenzyloxyazepane 14

To a stirred solution of compound **10** (78 mg, 0.131 mmol) in dry pyridine (0.5 mL) under argon was added *p*-toluenesulfonyl chloride (30 mg, 0.187 mmol) at 0 °C. The reaction mixture was kept at room temperature under argon for 24 h by which time TLC (Cy/EtOAc, 3:2) showed a complete reaction. The mixture was then diluted with EtOAc, washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford a crude product. To a stirred solution of this crude product in dry THF (0.5 mL) was added Super-hydride® (0.12 mL, 1 M solution in THF) at 0 °C. The reaction mixture was kept at 0 °C under argon for 2 h and then diluted with EtOAc at 0 °C. The organic layer was washed with 1 M HCl solution, water and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (Cy/EtOAc, 5:1) afforded alcohol **14** as an oil (52 mg, 68%, R_f 0.42, Cy/EtOAc, 2:1).

$[\alpha]_D$ −14 (c = 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.43–7.30 (m, 40H, 8 × Ph), 5.29–5.16 (m, 4H, 4 × NCOOCHPh), 4.86–4.36 (m, 12H, 6 × CH_2Ph), 4.17–4.12 (m, 2H, H-1′a, H-2′), 4.05 (t, 1H, $J_{2',3'}$ = $J_{3',4'}$ = 4.2 Hz, H-3′), 4.02–3.92 (m, 4H, H-1a, H-2, H-3, H-6′a), 3.89 (d, 1H, $J_{6a,6b}$ = 14.4 Hz, H-6a), 3.60 (d, 1H, H-4′), 3.59 (s, 1H, OH), 3.58 (d, 1H, $J_{3,4}$ = 3.7 Hz, H-4), 3.42 (dd, 1H, $J_{1'b,2'}$ = 10.7 Hz, $J_{1'a,1'b}$ = 14.5 Hz, H-1′b), 3.37 (dd, 1H, $J_{1b,2}$ = 10.6 Hz, $J_{1a,1b}$ = 14.9 Hz, H-1b), 3.33 (d, 1H, $J_{6a,6b}$ = 14.4 Hz, H-6b), 3.28 (d, 1H, $J_{6'a,6'b}$ = 14.3 Hz, H-6′b), 3.19 (s, 1H, OH′), 1.32 and 1.26 (2s, 6H, 2 × Me); ^{13}C NMR ($CDCl_3$, 100 MHz): 156.66 and 156.43 (2 × C═O), 138.29, 138.18, 137.63, 137.53, 137.49, 137.35, 136.94 and 136.45 (8 × Cipso), 128.49–127.49 (40 × aromatic C), 83.94 and 83.45 (C-4 and C-4′), 82.52 and 81.21 (C-2 and C-2′), 82.35 and 82.03 (C-3 and C-3′), 75.29 and 75.19 (C-5 and C-5′), 73.11, 73.04, 72.96, 72.82, 71.58 and 71.46 (6 × CH_2Ph), 67.61 and 67.00 (2 × $NCOOCH_2$Ph), 53.64 and 53.15 (C-6 and C-6′), 46.81 and 46.14 (C-1′ and C-1), 26.86 and 25.46 (2 × Me); m/z (CI, CH_4): 582 ($M+H^+$, 100%); HRMS (CI, CH_4): Calcd for $C_{36}H_{40}O_6N$ ($M+H^+$): 582.2856. Found 582.2859.

5.1.5. (3*R*,4*S*,5*R*,6*S*)-3-Methyl-3,4,5,6-tetrahydroxyazepane 15

Hydrogenolysis of diol **14** (46 mg, 0.079 mmol) with 10% Pd/C in MeOH and in the presence of 1 M HCl solution furnished quantitatively compound **15** (18 mg) as an oil. $[\alpha]_D$ +5.2 (c = 1.0 in CH_3OH); ^1H NMR (D_2O, 400 MHz): 4.22 (ddd, 1H, $J_{1a,2}$ = 2.3 Hz, $J_{2,3}$ = 7.5 Hz, $J_{1b,2}$ = 9.9 Hz, H-2), 3.75 (d, 1H, $J_{3,4}$ = 3.3 Hz, H-4), 3.70 (dd, 1H, H-3), 3.35 (d, 1H, $J_{6a,6b}$ = 13.7 Hz, H-6a), 3.34 (dd, 1H, $J_{1a,1b}$ = 13.6 Hz, H-1a), 3.23 (dd, 1H, H-1b), 3.05 (d, 1H, H-6b), 1.37 (s, 3H, Me); ^{13}C NMR (D_2O, 100 MHz): 79.71 (C-3), 78.58 (C-4), 71.98 (C-5), 70.23 (C-2), 50.41 (C-6), 47.55 (C-1), 26.23 (Me); m/z (CI, CH_4): 178 ($M+H^+$, 100%); HRMS (CI, CH_4): Calcd for $C_7H_{16}O_4N$ ($M+H^+$): 178.1079. Found 178.1081.

5.1.6. (3*S*,4*S*,5*R*,6*S*)-*N*-Benzyloxycarbonyl-3-hydroxy-3-methyl-4,5,6-tribenzyloxyazepane 16

Regioselective deoxygenation of **11** (55 mg, 0.092 mmol) as described above for the preparation of **14** furnished compound **16** as an oil (35 mg, 65%, R_f 0.41, Cy/EtOAc, 2:1).

$[\alpha]_D$ +4 (c = 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.43–7.31 (m, 40H, 8 × Ph), 5.24–5.15 (m, 4H, 4 × NCOOCHPh), 4.92–4.37 (m, 12H, 6 × CH_2Ph), 4.03 (dd, 1H, $J_{1a,2}$ = 2.2 Hz, $J_{1a,1b}$ = 14.0 Hz, H-1a), 3.96 (dd, 1H, $J_{3,4}$ = 3.2 Hz, $J_{2,3}$ = 6.0 Hz, H-3), 3.94 (dd, 1H, $J_{3',4'}$ = 3.6 Hz, $J_{2',3'}$ = 6.2 Hz, H-3′), 3.89 (m, 2H, H-1′a, H-6′a), 3.83 (ddd, 1H, $J_{1b,2}$ = 9.8 Hz, H-2), 3.74 (d, 1H, $J_{6a,6b}$ = 13.8 Hz, H-6a), 3.63 (ddd, 1H, $J_{1'a,2'}$ = 2.3 Hz, $J_{1'b,2'}$ = 9.6 Hz, H-2′), 3.59 (d, 1H, H-4′), 3.57 (d, 1H, H-4), 3.41 (dd, 1H, $J_{1a,1b}$ = 14.0 Hz, H-1b), 3.40 (dd, 1H, $J_{1'a,1'b}$ = 14.0 Hz, H-1′b), 3.37 (d, 1H, H-6b), 3.31 (d, 1H, $J_{6'a,6'b}$ = 13.6 Hz, H-6′b), 2.68 and 2.58 (2s, 1H, 2 × OH), 1.36 and 1.28 (2s, 6H, 2 × Me); ^{13}C NMR ($CDCl_3$, 100 MHz): 155.85 and 155.82 (2 × C═O), 138.12, 138.09, 138.01, 137.60, 137.55, 136.39 and 136.29 (8 × Cipso), 128.55–127.47 (40 × aromatic C), 86.46 and 85.99 (C-4 and C-4′), 82.69 and 81.84 (C-2′ and C-2), 82.25 and 81.94 (C-3′ and C-3), 74.48 and 74.14 (C-5′ and C-5), 73.21, 73.02, 72.96, 72.92, 71.77 and 71.75 (6 × CH_2Ph), 67.74 and 67.42 (2 × $NCOOCH_2$Ph), 53.04 and 52.79 (C-6′ and C-6), 45.43 and 45.32 (C-1 and C-1′), 22.63 and 22.23 (2 × Me); m/z (CI, CH_4): 582 ($M+H^+$, 100%); HRMS (CI, CH_4): Calcd for $C_{36}H_{40}O_6N$ ($M+H^+$): 582.2856. Found 582.2850.

5.1.7. (3*S*,4*S*,5*R*,6*S*)-3-Methyl-3,4,5,6-tetrahydroxyazepane 17

Hydrogenolysis of alcohol **16** (35 mg, 0.060 mmol) with 10% Pd/C in MeOH and in the presence of 1 M HCl solution furnished quantitatively compound **17** (14 mg) as an oil.

$[\alpha]_D$ −8.8 (c = 0.83 in CH_3OH); ^1H NMR (D_2O, 400 MHz): 3.98 (ddd, 1H, $J_{1a,2}$ = 3.8 Hz, $J_{1b,2}$ = $J_{2,3}$ = 8.1 Hz, H-2), 3.72 (t, 1H, H-3), 3.40 (d, 1H, $J_{3,4}$ = 8.4 Hz, H-4), 3.39 (dd, 1H, $J_{1a,1b}$ = 13.6 Hz, H-1a), 3.32 (dd, 1H, H-1b), 3.27 (d, 1H, $J_{6a,6b}$ = 14.3 Hz, H-6a), 3.21 (d, 1H, H-6b), 1.36 (s, 3H, Me); ^{13}C NMR (D_2O, 100 MHz): 77.64 (C-4), 75.32 (C-3), 70.74 (C-5), 67.07 (C-2), 51.57 (C-6), 47.01 (C-1), 24.93 (Me); m/z (CI, CH_4): 178 ($M+H^+$, 100%); HRMS (CI, CH_4): Calcd for $C_7H_{16}O_4N$ ($M+H^+$): 178.1079. Found 178.1078.

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