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Note

Short and efficient synthesis of (2*S*,3*R*,4*R*,5*R*) and (2*S*,3*R*,4*R*,5*S*)-tetrahydroxyazepanes via the Henry reaction

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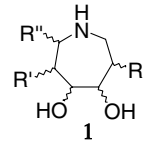
Abstract—The Henry reaction with the easily available α-D-*xylo*-pentodialdose afforded a diastereomeric mixture of nitroaldoses with the α-D-*gluco*- and β-L-*ido*-configuration, respectively, in good yield. When *n*-BuLi was used as the base, the reaction afforded the α-D-*gluco*-nitroaldose as the only product. The reduction of the nitro group in the α-D-*gluco*- and β-L-*ido*-nitroaldoses, removal of the protecting groups and intramolecular reductive cyclo-amination afforded the corresponding (2*S*,3*R*,4*R*,5*R*) and (2*S*,3*R*,4*R*,5*S*) tetrahydroxyazepanes.

Keywords: Carbohydrates; Henry reaction; Enzyme inhibitors; Azepanes

The Henry reaction is recognized as one of the classical name reactions in organic synthesis.[1] This coupling reaction between a carbonyl compound and a nitroalkane bearing an α-hydrogen enables the formation of a new carbon–carbon bond under mild basic conditions with the generation of a β-nitroalcohol, thus enabling access to either β-aminoalcohol or nitro-olefin compounds. The reaction has found use in both inter- and intramolecular sense, in the synthesis of natural products[1,2] and also in enantioselective synthesis.[3] In particular, the nitroaldoses[4] obtained on Henry reaction with sugar aldehydes represent versatile substrates as they provide a polyhydroxylated carbon framework with multiple stereogenic centres as well as the possibility for transformations of the nitro group, which has allowed the synthesis of nitrocyclitols,[5] myoinositols,[6] spirolactones,[7] branched chain sugars[8] (an important backbone of antibiotics) and six-membered azasugars.[9] Among azasugars,[10] the polyhydroxylated azepanes **1** (Fig. 1) are known to be potential glycosidase inhibitors[11] as well as DNA minor groove binding ligands (MGBL).[12] Due to the flexibility of the seven-membered ring, the hydroxyl groups in azepanes adopt different conformations, thereby increasing the probability of forming hydrogen bonds with the nitrogen bases thus improving their ability to point into the minor groove of DNA. An additional advantage of **1** is their high water solubility, which allows them to circumvent the problem of poor bioavailability seen with many other MGBL compounds. The design of azepane molecules is therefore mainly concerned with the different positional and stereochemical orientation of the hydroxyl functionality at C-2/C-3/C-4/C-5, which has resulted in the synthesis of a variety of di-, tri- and tetrahydroxyazepane analogues.[13] In this respect, we recently reported the synthesis of tri-, tetra- and pentahydroxyazepanes[14] and now



1

dihydroxyazepane: R = R' = R" = H
trihydroxyazepane: R = OH; R' = R" = H
tetrahydroxyazepane: R = R' = OH; R" = H
pentahydroxyazepane: R = R' = OH; R" = CH_2OH

Figure 1.

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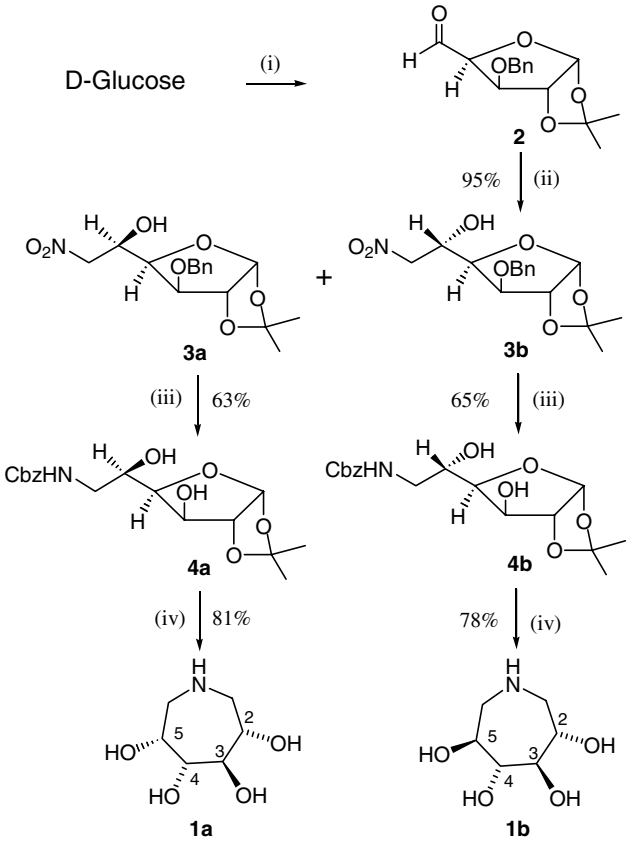

Scheme 1. Reagents and conditions: (i) Ref. 15; (ii) Et_3N, CH_3NO_2, rt, 10 h; (iii) (a) $HCOONH_4$, Pd/C, MeOH, reflux, 1 h; (b) ClCOOBn, MeOH–H_2O, 0–25 °C, 2 h; (iv) (a) TFA–H_2O, 25 °C, 2 h; (b) H_2, Pd/C, MeOH, 80 psi, 25 °C, 24 h.

describe a short synthetic route, utilizing the Henry approach with sugar aldehyde **2**, to (2*S*,3*R*,4*R*,5*R*) and (2*S*,3*R*,4*R*,5*S*) tetrahydroxyazepanes (Fig. 1).

The Henry reaction of 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*xylo*-pentodialdose **2** with nitromethane in the presence of sodium methoxide (0.85 equiv) afforded, in our hands, α-D-*gluco*- and β-L-*ido*-configurated nitroaldoses **3a** and **3b**, respectively, in a 67:33 ratio as reported earlier (Scheme 1).[†] To improve/alter the diasteroselectivity in favour of either diastereomer, we have carefully studied the reaction of **2** with nitromethane under various conditions by changing the solvent, temperature and stoichiometry of different bases. The results are shown in Table 1. Thus, the reaction in the presence of catalytic amount of sodium methoxide (0.10 equiv) at room temperature was found to be sluggish and at 70 °C led to a complex mixture of products. The use of sodium hydroxide or potassium carbonate (1.1 equiv) in methanol at 30 °C afforded **3a**/**3b** in a 75:25 ratio along with side products (entry 2).

An improvement in the formation of D-*gluco*-isomer was noticed when a homogeneous base like triethylamine was used in nitromethane at room temperature. Under these conditions, the reaction afforded **3a** and **3b** in a 88:12 ratio in 95% yield (entry 3). A similar result was obtained when THF was used as the solvent together with stoichiometric amounts of triethylamine and nitromethane (entry 4). The use of TBAF in THF gave lower selectivity (entry 5). However, the use of *n*-BuLi (1.5 equiv) and nitromethane (1.1 equiv) in THF at −78 °C for 3 h afforded the D-*gluco* isomer **3a** as the only isolable product in 95% yield (entry 6). Interestingly, a change in product selectivity was observed by using potassium *tert*-butoxide (1.1 equiv) in THF at 0 °C for 2 h, which afforded **3a** and **3b** in a 17:83 ratio (entry 7). The observed stereoselectivity in favour of **3a** for the reaction with *n*-BuLi in THF can be rationalized by considering the Cram-chelation model **I** (Fig. 2) in which the favourable *Si*-face attack led to the formation of **3a** as the exclusive product.

In the next step (Scheme 1), treatment of **3a** with ammonium formate and 10% Pd/C in methanol followed by selective *N*-Cbz protection with benzyl chloroformate afforded **4a**.[‡] Treatment of **4a** with TFA–water followed by hydrogenation using 10% Pd/C in methanol afforded (2*S*,3*R*,4*R*,5*R*)-tetrahydroxyazepane **1a** as a sticky white solid ($[\alpha]_D$ −18.2 (*c* 0.6, H_2O); lit.[13m,14a] $[\alpha]_D$ −15.0 (*c* 1.0, H_2O) and $[\alpha]_D$ −19.5 (*c* 0.6, H_2O)). A similar sequence of reactions was repeated with **3b**, which afforded (2*S*,3*R*,4*R*,5*S*)-tetrahydroxyazepane **1b** as a white sticky solid ($[\alpha]_D$ 18.8 (*c* 0.1, H_2O); lit.[13e,14a] $[\alpha]_D$ 19.9 (*c* 2.0, H_2O) and $[\alpha]_D$ 20.1 (*c* 0.2, H_2O)). The spectral and analytical data of **1a**, **1b** and **4b** were found to be in good agreement with those reported earlier by us.[14a]

In conclusion, we have demonstrated the utility of the Henry reaction in the synthesis of tetrahydroxyazepanes **1a** and **1b**. Thus, starting from D-glucose, the overall yield of **1a** was found to be 25% (based on *n*-BuLi mediated reaction) and that of **1b**, 20% (based on the *t*-BuOK mediated reaction). The use of readily available D-glucose as the starting material, the low number of steps and high yields make our synthetic route practical and efficient on a multigram scale.

[†] Saeki et al.[5a] first reported the addition of nitromethane to 3-*O*-benzyl-α-D-*xylo*-pentodialdose **2** using sodium methoxide as the base. In this work, they obtained the α-D-*gluco*-configurated nitroaldoses in 70% yield and studied the stereochemical outcome of the reaction with different substitutes at C-3. Subsequently, Yoshimura et al.,[8b] Kovar et al.[5b,c,d] and Tronchet et al.[4] have investigated the addition of nitromethane with 3-*O*-methyl-α-D-*xylo*-pentodialdose using sodium methoxide as the base. The configuration at C-5 was assigned on the basis of spectral and analytical data as reported by earlier wherein L-*ido*-isomer was obtained as a white solid.

[‡] Saeki and Iwashige have reported[5a] the amine hydrochloride salt of the amino alcohol formed by the reduction of **3a** and **3b**, however, its conversion to the corresponding azepane has not been described.

Table 1. The Henry reaction of **2** with nitromethane (1.1 equiv)

Entry	Base (equiv)	Solvent	Reaction condition, temp (°C)/time (h)	Yield[a] (%)	Ratio[b] **3a**:**3b**
1	MeONa (0.85)	Methanol	30/24	75	67:33
2	K_2CO_3 (1.1)	Methanol	30/0.5	80	75:25
3	Et_3N (1.2)	CH_3NO_2	30/09	95	88:12
4	Et_3N (1.2)	THF	30/07	95	88:12
5	TBAF (1.0)	THF	30/05	95	83:17
6	*n*-BuLi (1.5)	THF	−78/03	95	100:0
7	*t*-BuOK (1.1)	THF	0/02	90	17:83

[a] Yields refer to isolated yield after chromatography.
[b] Ratio determined by ^{1}H NMR of crude product and confirmed by isolation of products.

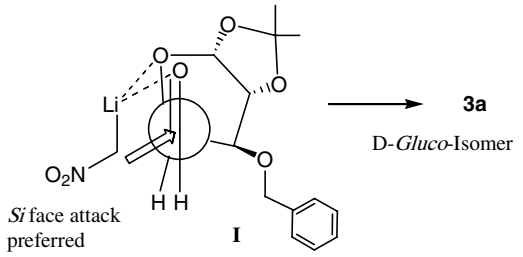

Figure 2. Chelation transition state **I** for **2**.

1. Experimental

1.1. General methods

Melting points were recorded with Thomas Hoover Capillary melting point apparatus and are uncorrected. IR spectra were recorded with Shimadzu FTIR-8400 as a thin film or in Nujol mull or using KBr pellets and are expressed in cm^{-1}. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with Varian Mercury 300 using $CDCl_3$ or D_2O as the solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard and J values are given in Hz. Elemental analyses were carried out with Thermo Flash Elemental Analyzer 1112. Optical rotations were measured using Bellingham Stanley-ADP 220 digital polarimeter with sodium light (589.3 nm) at 25 °C. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Visualization was made by absorption of UV light or by thermal development after spraying with 3.5% solution of 2,4-dinitrophenylhydrazine in ethanol–H_2SO_4 and with basic aqueous potassium permanganate solution. Column chromatography was carried out with silica gel (100–200 mesh). Reactions were carried out in oven-dried glassware under dry N_2 atmosphere. MeOH, acetone, THF, Et_3N and nitromethane were purified and dried before use. Distilled hexane and EtOAc were used for column chromatography. Nitromethane, benzyl chloroformate and 10% Pd–C were purchased from Aldrich and/or Fluka. After quenching of the reaction mixture with water, reaction workup involved washing of the combined organic layer with water, brine, drying over anhydrous Na_2SO_4 and evaporation of solvent at reduced pressure.

1.2. 3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*gluco*-furanose (3a) and 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-β-L-*ido*-furanose (3b) using Et_3N as the base

To a solution of **2** (1.9 g, 6.83 mmol) in nitromethane (10 mL), Et_3N (1.42 mL, 8.19 mmol) was added at room temperature. The reaction mixture was stirred for 9 h. Et_3N and nitromethane were evaporated under reduced pressure and the residue was purified by column chromatography. Elution first with EtOAc/hexanes (1:19) afforded **3a** and **3b** in a 7:1 ratio. **3a**: Pale yellow syrup (2.04 g, 88%); $[\alpha]_D$ −36.16 (*c* 0.9, $CHCl_3$); R_f 0.5 (1:4, EtOAc/hexanes); IR (neat) 3600–3200, 1554, 1379 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 3H, Me), 1.48 (s, 3H, Me), 1.95–2.45 (br s, 1H, exchanges with D_2O, OH), 4.08 (dd, 1H, $J_{4,5} = 11.1$, $J_{4,3} = 3.6$ Hz, H-4), 4.10 (d, 1H, $J_{3,4} = 3.6$ Hz, H-3), 4.47 (dd, 1H, $J_{6,6'} = 13.2$, $J_{5,6} = 9.1$ Hz, H-4), 4.53 (d, 1H, $J = 11.7$ Hz, OCH_2Ph), 4.64 (ddd, 1H, $J_{5,4} = 11.1$, $J_{5,6} = 9.1$, $J_{5,6'}$ 2.3 Hz, H-5), 4.65 (d, 1H, $J_{1,2} = 3.8$ Hz, H-2), 4.71 (dd, 1H, $J_{6,6'} = 13.2$, $J_{6',5} = 2.3$ Hz, H-6′), 4.76 (d, 1H, $J = 11.7$ Hz, OCH_2Ph), 5.93 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 7.30–7.50 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.1, 26.6, 66.2, 72.1, 78.6, 79.9, 80.9, 81.9, 105.2, 112.1, 127.8, 128.3, 128.7, 136.8. Anal. Calcd for $C_{16}H_{21}NO_7$: C, 56.63; H, 6.24. Found: C, 56.59; H, 6.15. Compound **3b**: White crystals (0.29 g, 7%); mp 77–78 °C (from 1:1, EtOAc/hexanes); $[\alpha]_D$ −44 (*c* 0.5, $CDCl_3$); R_f 0.36 (1:4 EtOAc/*n*-hexane); IR (Nujol) 3550–3200, 1554, 1357 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H, Me), 1.48 (s, 3H, Me), 2.40–3.20 (br s, 1H, exchanges with D_2O, OH), 4.12 (d, 1H, $J_{3,4} = 3.6$ Hz, H-3), 4.20 (t, 1H, $J_{4,5}$, $J_{4,3} = 3.6$ Hz, H-4), 4.37 (dd, 1H, $J_{6,6'} = 12.9$, $J_{5,6} = 3.3$ Hz, H-6), 4.53 (d, 1H, $J = 12.0$ Hz, OCH_2Ph), 4.55 (dd, 1H, $J_{6,6'} = 12.9$, $J_{6'5} = 8.5$ Hz, H-6′), 4.71 (d, 1H, $J_{1,2} = 3.9$ Hz, H-2), 4.74 (ddd, 1H, $J_{5,6'} = 8.5$, $J_{5,4} = 3.6$, $J_{5,6}$ 3.3 Hz, H-5), 4.79 (d, 1H, $J = 12.0$ Hz, OCH_2Ph) 6.05 (d, 1H, $J_{1,2} = 3.9$ Hz, H-1), 7.30–7.50 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 26.8, 67.7, 71.9, 77.5,

79.0, 82.1, 82.4, 104.9, 112.2, 127.9(s), 128.4, 128.7(s), 135.9. Anal. Calcd for $C_{16}H_{21}NO_7$: C, 56.63; H, 6.24. Found: C, 56.59; H, 6.15.

1.3. 3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*gluco*-furanose (3a) and 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-β-L-*ido*-furanose (3b) using *n*-BuLi as the base

A solution of **2** (0.10 g, 0.36 mmol) in dry THF was cooled to −78 °C under N_2 atmosphere and *n*-BuLi (0.34 mL, 0.54 mmol) in hexane was added dropwise. After 3 h, the reaction mixture was quenched by the addition of a saturated solution of ammonium chloride. The THF was evaporated under reduced pressure and the resulting mixture was extracted with EtOAc (3 × 5 mL). The organic layer was dried and concentrated to afford a residue that was purified by column chromatography (1:19, EtOAc/hexane) to give **3a** as the only product.

1.4. 3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*gluco*-furanose (3a) and 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-β-L-*ido*-furanose (3b) using potassium *tert*-butoxide as the base

A solution of **2** (0.05 g, 0.18 mmol) in dry THF (5 mL) was cooled to 0 °C and a solution of potassium *tert*-butoxide (2.0 mL, 0.19 mmol) in *t*-BuOH was added dropwise. The reaction mixture was stirred for 2 h and the THF was then evaporated under reduced pressure. The resulting mixture was extracted with EtOAc (3 × 5 mL). The organic layer was dried and concentrated to afford a residue that was purified by column chromatography (1:19, EtOAc/hexane) to give **3a** and **3b** in a 1:5 ratio.

1.5. 3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*gluco*-furanose (3a) and 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-β-L-*ido*-furanose (3b) using potassium carbonate as the base

A solution of **2** (0.05 g, 0.18 mmol) was dissolved in dry THF (5 mL) and K_2CO_3 (0.03 g, 0.19 mmol) was added at rt. After 30 min, the THF was evaporated under reduced pressure. The resulting mixture was extracted with EtOAc (3 × 5 mL). The organic layer was dried and concentrated to afford a residue that was purified by column chromatography (1:19, EtOAc/hexane) to give **3a** and **3b** in a 3:1 ratio.

1.6. 3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*gluco*-furanose (3a) and 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-β-L-*ido*-furanose (3b) using TBAF as the base

A solution of **2** (0.05 g, 0.18 mmol) was dissolved in dry THF (5 mL) and TBAF (0.03 g, 0.09 mmol) was added at rt. After 5 h, the THF was evaporated under reduced pressure. The resulting mixture was extracted with EtOAc (3 × 5 mL). The organic layer was dried and concentrated to afford a residue that was purified by column chromatography (1:19, EtOAc/hexane) to give **3a** and **3b** in a 5:1 ratio.

1.7. 6-Deoxy-6-*N*-benzyloxycarbonyl-1,2-*O*-isopropylidene-3-*O*-phenylmethyl-α-D-*gluco*-1,4-furanose (4a)

A solution of **3a** (1.0 g, 2.94 mmol), ammonium formate (0.92 g, 15.10 mmol) and 10% Pd/C (0.2 g) in CH_3OH (10 mL) was heated at reflux for 40 min. The catalyst was filtered through Celite and washed with CH_3OH (2 × 5 mL). To the filtrate, cooled to 0 °C, were added sodium bicarbonate (0.82 g, 9.82 mmol) and benzyloxycarbonyl chloride (0.47 g, 2.70 mmol) and the reaction mixture was stirred and warmed to rt. After 2 h, the CH_3OH was removed under reduced pressure and the residue was extracted with EtOAc (3 × 5 mL). The combined extract was washed with brine, dried and concentrated to afford a residue that was purified by column chromatography (4:6, EtOAc/hexane) to give **4a** (0.66 g, 63%) as a white solid. Compound **4a**: White crystals (0.20 g, 7%); mp 89–90 °C (from 1:1, EtOAc/hexane); $[\alpha]_D$ +18.0 (*c* 0.2, $CHCl_3$); R_f 0.37 (6:4, EtOAc/hexane); IR (Nujol) 3421, 1685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 3H, Me), 1.46 (s, 3H, Me), 2.10–2.25 (br s, 1H, exchanges with D_2O, OH/NH), 3.22–3.40 (m, 1H, CH_2NHCbz), 3.50–3.65 (m, 1H, CH_2NHCbz), 3.70–4.01 (br s, 1H, exchanges with D_2O, OH/NH), 4.02 (br s, 2H, H-3 and H-5), 4.33 (br s, 1H, H-4), 4.50 (d, 1H, $J_{1,2} = 3.6$ Hz, H-2), 5.09 (s, 2H, OCH_2Ph), 5.55 (br s, 1H, exchanges with D_2O, OH/NH), 5.92 (d, 1H, $J_{1,2} = 3.6$ Hz, H-1), 7.30–7.45 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 26.7, 44.5, 67.1, 69.6, 74.8, 80.4, 85.0, 104.9, 111.7, 127.8, 128.0, 128.1, 128.5(s), 136.0, 158.0. Anal. Calcd for $C_{17}H_{23}NO_7$: C, 57.79; H, 6.55. Found: C, 58.02; H, 6.67.

1.8. 6-Deoxy-6-*N*-benzyloxycarbonyl-1,2-*O*-isopropylidene-3-*O*-phenylmethyl-β-L-*ido*-1,4-furanose (4b)

A reaction of **3b** (1.5 g, 3.75 mmol), ammonium formate (1.25 g, 19.10 mmol) and 10% Pd/C (0.3 g) in CH_3OH (10 mL), followed by reaction with sodium bicarbonate (1.59 g, 18.9 mmol) and benzyloxycarbonyl chloride (1.01 g, 5.96 mmol), as described for **3a**, afforded **4b** (0.78 g, 78%) as a thick liquid; $[\alpha]_D$ −9.8 (*c* 0.2, $CHCl_3$); R_f 0.55 (6:4, EtOAc/hexane); IR (neat) 3350, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H, Me), 1.48 (s, 3H, Me), 1.60–1.85 (br s, 2H, exchanges with D_2O, OH/NH), 3.29 (dd, 1H, $J = 14.3$, 6.1 Hz, CH_2NHCbz), 3.48 (dd, 1H, $J = 14.3$, 3.3 Hz, CH_2NHCbz), 4.00–4.07 (m, 1H, H-4), 4.10–4.17 (m, 1H, H-5), 4.30 (d, 1H,

$J_{2,3} = 2.8$ Hz, H-3), 4.50 (d, 1H, $J_{1,2} = 3.3$ Hz, H-2), 5.10 (s, 2H, OCH_2Ph), 5.46–5.58 (br s, 1H exchanges with D_2O, OH/NH), 5.95 (d, 1H, $J_{1,2} = 3.3$ Hz, H-1), 7.30–7.42 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.8, 44.9, 67.1, 70.3, 76.3, 79.9, 85.3, 104.8, 111.8, 128.0, 128.1, 128.4, 135.9, 157.2. Anal. Calcd for $C_{17}H_{23}NO_7$: C, 57.79; H, 6.55. Found: C, 57.90; H, 6.77.

1.9. (2*S*,3*R*,4*R*,5*R*)-Tetrahydroxyazepane (1a)

A solution of **4a** (0.10 g, 0.28 mmol) in TFA-H_2O (3 mL, 2:1) was stirred at 25 °C for 2.5 h. The TFA was then co-evaporated with benzene to furnish a thick liquid. To a solution of the above product in CH_3OH/HCl (5 mL, 9:1) was added 10% Pd/C (0.05 g). The solution was hydrogenated at 80 psi for 24 h. The catalyst was filtered through Celite and washed with CH_3OH. The filtrate was concentrated to obtain a semi-solid. The sticky solid was washed with $CHCl_3$ and loaded on DOWEX–H^+ resin. Elution with 5% ammonia–CH_3OH and evaporation of the CH_3OH afforded **1a** (0.04 g, 81%) as a sticky solid. R_f 0.11 (2:8, CH_3OH/$CHCl_3$); IR (neat) 3555–3340, 1592, 1194 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 2.65–2.87 (m, 4H, H_2CNHCH_2), 3.40–3.52 (m, 1H), 3.53–3.65 (m, 2H), 3.78–3.88 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 49.3, 49.6, 71.2, 73.3, 74.7, 75.2. Anal. Calcd for $C_6H_{13}NO_4 \cdot 2H_2O$: C, 36.18; H, 8.59. Found: C, 36.47; H, 8.90. A solution of **1a** (0.1 g) in CH_3OH (5 mL) and two drops of concentrated HCl was stirred at rt for 24 h. The solution was concentrated and the residue was dissolved in water (10 mL) and extracted with ether (2×10 mL). The aqueous layer was concentrated and the residue washed with CH_3OH–Et_2O to give a white gummy solid (0.08 g, 70%); $[\alpha]_D$ −18.2 (*c* 0.6, H_2O); lit.[13m,14a] $[\alpha]_D$ −15.0 (*c* 1.0, H_2O) and $[\alpha]_D$ −19.5 (*c* 0.6, H_2O).

1.10. (2*S*,3*R*,4*R*,5*S*)-Tetrahydroxyazepane (1b)

Reaction of **4b** (0.2 g, 0.56 mmol) with TFA–H_2O as described for **4a**, followed by hydrogenation with 10% Pd/C in CH_3OH gave **1b** (0.06 g 65%) as a thick liquid. $[\alpha]_D$ 18.8 (*c* 0.1, H_2O); lit.[13e,14a] $[\alpha]_D$ 19.9 (*c* 2.0, H_2O) and $[\alpha]_D$ 20.1 (*c* 0.2, H_2O); R_f 0.15 (1:4, $CH_3OH/CHCl_3$); IR (neat) 3560–3367, 1577, 1179 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 2.95–3.07 (dd, 2H, $J = 8.2$, 13.8 Hz, H_2CNHCH_2), 3.12–3.24 (dd, 2H, $J = 1.9$, 13.8 Hz, H_2CNHCH_2), 3.46–3.55 (m, 2H, H-2 and H-5), 3.84–3.96 (m, 2H, H-3 and H-4); ^{13}C NMR (75 MHz, D_2O) δ 47.0, 67.8, 76.7. Anal. Calcd for $C_6H_{13}NO_4 \cdot 2H_2O$: C, 36.18; H, 8.59. Found: C, 36.43; H, 8.77.

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