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Intra-molecular nitrone–olefin cycloaddition of D-glucose derived allylic alcohol: synthesis of new aminocyclohexitols

Chaitali Chakraborty, Vinod P. Vyavahare and Dilip D. Dhavale*

Department of Chemistry, Garware Research Centre, University of Pune, Pune 411007, Maharashtra, India

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Abstract—Diastereo- and regioselelective intra-molecular nitrone–olefin cycloaddition reaction of in situ generated *N*-benzylnitrones, obtained from D-glucose derived precursors **5a/5b** furnished dihydroxy functionalized isoxazolidines. The *N*–*O* bond reductive cleavage and removal of *N*/*O*-benzyl groups led to the formation of stereochemically well defined aminocyclohexitols.

1. Introduction

Amongst polyhydroxylated carbocycles,[1] the amino substituted polyhydroxylated carbocycles, commonly known as aminocyclitols, constitute the key structural fragments for amino-glycoside antibiotics and are potential glycosidase inhibitors as well as antiviral agents.[2] Advances in the elucidation of biological processes have proved the importance of the six membered aminocyclitols owing to their sugar-mimetic structure. For example, validamine **1** (Fig. 1), a natural aminocyclohexitol, and its unnatural derivatives are at the forefront of the bio-organic research field because of their ability to serve as potent glycosidase inhibitors. This has consequently made them valuable therapeutic agents.[3] These compounds, however, receive limited synthetic attention as compared to the five membered aminocyclopentitols. In general, carbohydrates have been exploited as substrates for the synthesis of the aminocyclitols utilizing ring closing metathesis, metal catalyzed reactions and free radical cyclizations[1d,4] as the key steps. Apart from these methodologies, an intra-molecular nitrone–olefin cycloaddition (INOC) reaction, especially with the nitrones derived from sugars, has received more attention.[5,6] The sugar substituted isoxazolidines thus obtained are amenable to the construction of five/six/seven membered aminocyclitols, depending on the formation of bicyclic fused/bridged isoxazolidine ring systems wherein the regio/stereo-chemical outcome of the reaction is controlled by the geometric constraints, steric and electronic factors.[5h,7] We have recently reported the INOC reaction of an in situ generated D-glucose derived nitrone for the synthesis of aminocyclopentitol.[8] As a part of our continuing interest in the area of nitrones,[9] we have now investigated the INOC reaction of an in situ generated nitrone, obtained from the cleavage of the 1,2-acetonide functionality in 3,5-di-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-hept-6-ene-furanose **5** followed by treatment with *N*-benzylhydroxylamine hydrochloride. The reaction resulted in the formation of a fused bicyclic isoxazolidine ring skeleton, which on *N*–*O* bond reductive cleavage afforded three new aminocyclohexitols **2a**–**c**. Our results in this direction are presented herein.

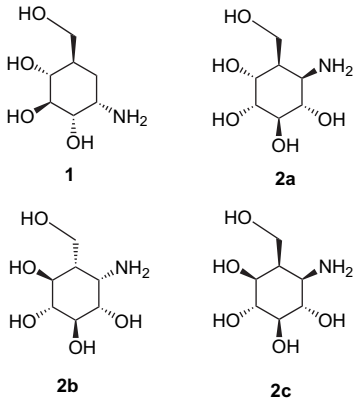

Figure 1. Validamine and its analogues.

2. Results and discussion

As shown in Scheme 1, the Grignard reaction of vinylmagnesium bromide with 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdose **3**,[10] in THF at 0 °C gave D-*gluco*- and L-*ido*-configurated allylic alcohols **4a** and **4b**, respectively, in the ratio of 2:3 as reported earlier by us and others.[11]

Keywords: Cyclitols; Nitrones; Isoxazolidines; Carbohydrates.
* Corresponding author. E-mail: ddd@chem.unipune.ernet.in

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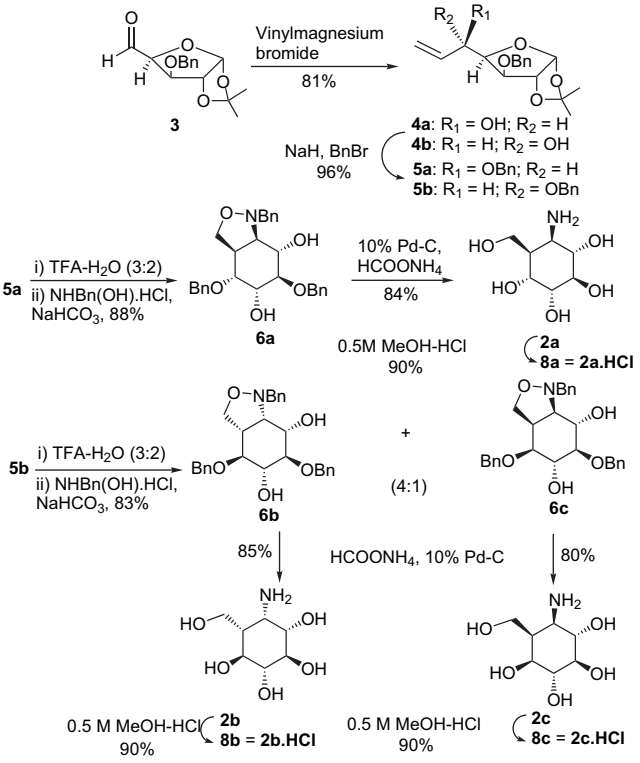
Treatment of **4a** and **4b** individually with benzyl bromide and NaH in THF afforded the corresponding benzyl protected compounds **5a** and **5b**. Removal of the 1,2-acetonide group in **5a** with TFA/H_2O afforded a hemiacetal[†] that was directly reacted with *N*-benzylhydroxylamine hydrochloride and $NaHCO_3$ in ethanol/water (8:2) under reflux to give fused bicyclic isoxazolidine **6a** as a single diastereomer in 88% yield. The formation of the isoxazolidine **6a** plausibly involves in situ formation of *N*-benzyl nitrone at the C-1 that concomitantly undergoes regio- and stereoselective INOC reaction to give **6a**.[12] In the next step, treatment of **6a** with 10% Pd/C and ammonium formate in refluxing methanol afforded aminocyclohexitol **2a** as a semisolid wherein reductive cleavage of the *N–O* bond and removal of the *N*- and *O*-benzyl protections were achieved in one pot. Reaction of **2a** with methanolic-HCl (0.5 M) at room temperature afforded corresponding hydrochloride salt **8a**. Similarly, treatment of **5b** with TFA/H_2O followed by treatment with *N*-benzylhydroxylamine hydrochloride and $NaHCO_3$ in ethanol/water under reflux afforded a diastereomeric mixture of fused bicyclic isoxazolidines **6b** and **6c** in the ratio 4:1.[12] The individual reaction of **6b** and **6c** with 10% Pd/C and ammonium formate in refluxing methanol afforded corresponding aminocyclohexitols **2b** and **2c** that on treatment with methanolic-HCl gave hydrochloride salts **8b** and **8c**, respectively.



Scheme 1. Syntheses of aminocyclohexitols.

2.1. Conformational assignment

It is known that the stereochemical outcome of INOC of sugar-derived nitrones is dictated by the orientation of the hydroxyl (or protected hydroxyl) substituents in the sugar ring skeleton.[13] We observed that the relative stereochemistry at C1 and C6 in aminocyclitols **2a–c** is determined by the configuration of the C5–OBn group found in compound **5**. For the stereochemical elucidation, isoxazolidines **6a–c** were individually acetylated with acetic anhydride in pyridine/DMAP to afford corresponding diacetylated derivatives **7a–c**. The conformational and configurational assignments were made on the basis of coupling constant data (Table 1), obtained by decoupling experiments, and 1D NOESY studies.

In the ^{1}H NMR spectrum of isoxazolidine **7a**, H1 showed a triplet with large coupling constant (J=9.0 Hz). This indicated the trans boat-diaxial relationship of H1 and H2 and an eclipsed conformational arrangement between H1 and H6. In the precursor **5a**, the relative stereochemistry at H2–H3 and H3–H4 is trans while that at H4–H5 is cis and the same stereochemistry is retained in the isoxazolidine **6a** and its diacetylated derivative **7a** as evident from the coupling constant values. This observation was attributed to the *cis*-fused isoxazolidine **7a** with a boat conformation in which the C2 acetyl and C5–OBn groups are projecting outwards. This fact was supported by 1D NOESY experiments in which irradiation at H1 showed NOE at H6 and H3 while irradiation at H5 showed NOE at H2 and H7. Further evidence for the *cis*-fused isoxazolidine **7a** was derived from the coupling constant values in the corresponding aminocyclitol **2a** in which $J_{4,5}$ was found to be 10.8 Hz indicating a trans diaxial orientation, while $J_{5,6}$ was found to be 5.4 Hz and $J_{1,6}$ to be 2.4 Hz. This indicated the 5*R* and 6*R* absolute configurations with the axial orientation of $-CH_2OH$ functionality at C6 and equatorial position of the amino functionality.

In case of isoxazolidine **7b**, H1 appeared as a doublet of doublet (δ 3.5) with small coupling constants ($J_{1,2}$=4.5; $J_{1,6}$= 6.3 Hz), while H5 appeared as a triplet with J=8.0 Hz. This showed an axial–axial relationship between H5 and H6. This observation was attributed to the *cis*-fused isoxazolidine **7b** with the chair conformation as shown in Figure 2. This fact was further supported by the ^{1}H NMR data of **2b** in which H1 appeared as a triplet with J=3.6 Hz, and H5 as a triplet with J=10.8 Hz accounting to equatorial and axial orientation of the hydroxy methyl group at C6 and the amino group at C5, respectively, with the 5*S* and 6*S* absolute configuration. In the case of isoxazolidine **7c**, an analogous observation as in the case of **7a** was noticed except for the orientation of C5–OBn. Therefore, the *cis*-fused isoxazolidine

Table 1. Coupling constant values in hertz for compounds **2a–c**, **7a–c** and **8a–c**

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{1,6}$
7a[a]	9.0	8.4	2.8	3.0	8.4	9.0
2a	2.4	—	7.2	10.8	5.4	2.4
8a	3.3	9.9	—	—	—	3.0
7b[a]	4.5	9.0	9.0	8.0	8.0	6.3
2b	10.8	9.3	9.3	3.6	3.6	10.8
8b	9.3	9.3	9.3	—	—	11.4
7c[a]	9.3	9.3	8.7	8.7	6.0	8.0
2c	10.0	9.1	9.1	11.1	4.5	5.5
8c	9.9	9.0	9.0	11.7	4.5	5.1

[a] For **7a–c**, the proton numberings are as in Figure 2.

[†] The INOC of the hemiacetals did not go to completion even after prolonged reflux for 20 h.

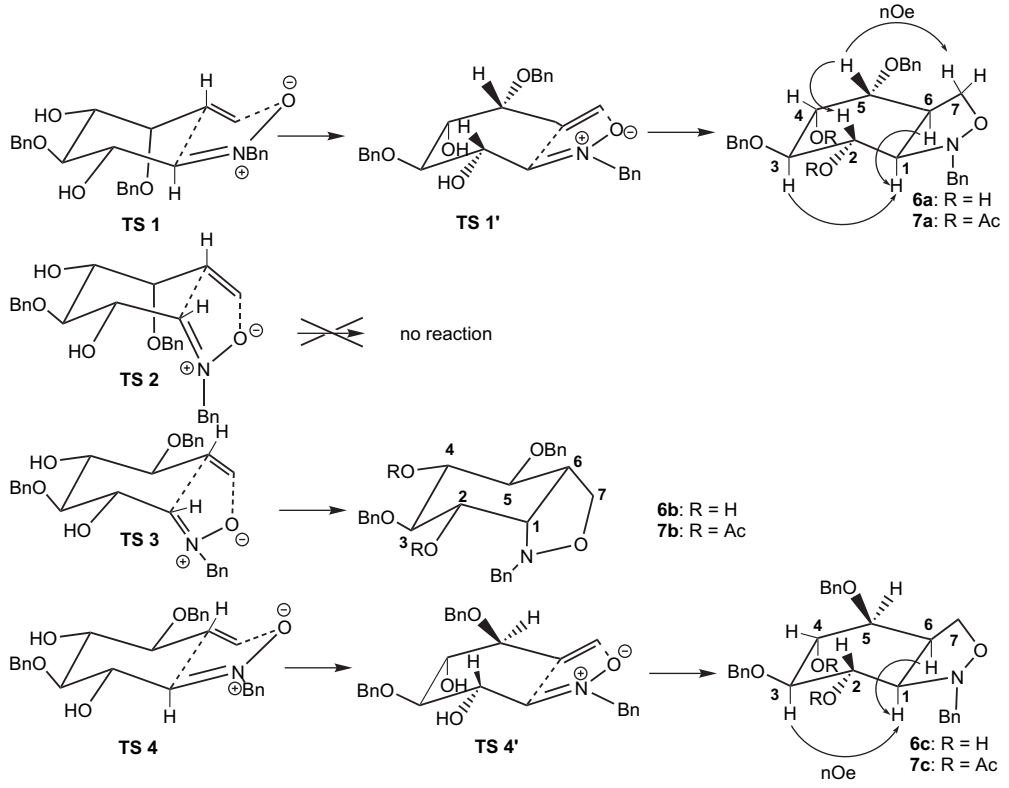


Figure 2. Transition states for INOC.

with the boat conformation having a 1*S* and 6*R* configuration was assigned to **7c** based on coupling constant and 1D NOESY data. Formation of isoxazolidines **6a–c** could be explained based on the six membered transition states (TS) 1–4 in which we propose that the orientation of the C5–OBn functionality dictates the geometry of the in situ generated nitrone (*Z* or *E*) and in turn decides the stereochemical outcome of the INOC. Thus, in case of the D-*gluco*-configured nitrone substrate derived from **5a**, we believe that TS1 with a *Z*-nitrone prevails over TS2 having an *E*-nitrone geometry[13] due to the 1,3-diaxial interactions between C5–OBn and the C1–C=N. In the chair-like TS1, the olefin C=C and C=N of the nitrone are orthogonal, therefore the TS1 changes to the boat conformation (TS1′) wherein the parallel orientation of olefin and nitrone achieves the maximum orbital overlap (with the relief of the 1,3-diaxial interaction) leading to exclusive formation of the isoxazolidine **6a**.

In case of the L-*ido*-configurated nitrone (derived from **5b**), the TS3 with the *E*-nitrone geometry having the pseudo-axial orientation of C=N is preferred over the *Z*-nitrone, which on subsequent INOC reaction led to the preferred chair conformation of the major isomer **6b**, while the INOC of the *Z*-nitrone via the TS4 gave the minor isomer **6c** with preferable boat conformation. In both cases we presume that the stability of the product conformation dictates the preferential formation of the TS.

In conclusion, we have demonstrated that the in situ generated nitrones from D-*gluco*- and L-*ido*-configured 3,5-di-*O*-benzyl-6,7-dideoxy-1,2-*O*-isoropylidene-heptulo-6-en-1,4-furanoses **5a** and **5b**, respectively, undergo INOC reaction to give isoxazolidines **6** in which the stereochemical outcome is dictated by the orientation of the C5–OBn functionality. The isoxazolidines thus obtained were elaborated to the new analogues of aminohexitols, **2a–c**.

3. Experimental

3.1. General methods

Melting points were recorded with Thomas Hoover Capillary melting point apparatus and are uncorrected. IR spectra were recorded with a FTIR as a thin film or in Nujol mull or using KBr pellets and are expressed in cm^{-1}. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded using $CDCl_3$ or D_2O as a solvent. Chemical shifts were reported in δ units (ppm) with reference to TMS as an internal standard, and *J* values are given in hertz. Elemental analyses were carried out with a C, H-analyzer. Optical rotations were measured using a Jasco P-1020 polarimeter at 25 °C. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography was carried out with silica gel (100–200 mesh). The reactions were carried out in oven-dried glassware under dry N_2. Methanol and THF were purified and dried before use. Distilled *n*-hexane and ethyl acetate were used for column chromatography. Pd/C (10%) was purchased from Aldrich and/or Fluka and ammonium formate from Merck. After quenching of the reaction with water, the work-up involves washing of combined organic layers with water, brine, drying over anhydrous sodium sulfate and evaporation of the solvent at reduced pressure.

3.1.1. 3,5-Di-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-hepta-6-en-1,4-furanose (5a). Sodium

hydride (0.67 g, 16.81 mmol) was washed with dry hexane (10 mL). Compound **4a** (3.43 g, 11.21 mmol) was dissolved in dry THF (30 mL) and added dropwise to the reaction mixture at 0 °C. After stirring the reaction mixture for 30 min, benzyl bromide (1.47 mL, 12.33 mmol) was added dropwise followed by the addition of tetrabutylammonium iodide (0.2 g, 0.56 mmol). The whole mixture was stirred at room temperature for 6 h. The mixture was then poured into ice water (10 mL) and the THF was evaporated under reduced pressure. The residual aqueous layer was extracted with ether (25 mL×3) and purified by column chromatography (*n*-hexane/ethyl acetate=98:2) to give **5a** as a white crystalline solid (1.24 g, 96%). Mp=54–56 °C; R_f=0.6 (*n*-hexane/ethyl acetate=4:1); $[\alpha]_D^{25}$ −37.3 (*c* 0.75, $CHCl_3$); IR (Nujol)=1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 4.18 (dd, *J*=13.8, 3.0 Hz, 1H, H-4), 4.21 (d, *J*=11.2 Hz, 1H, *O*–CH_2Ph), 4.23 (dd, *J*=13.8, 9.0 Hz, 1H, H-5), 4.34 (d, *J*=11.2 Hz, 1H, *O*–CH_2Ph), 4.55 (d, *J*=3.0 Hz, 1H, H-3), 4.57 (d, *J*=11.7 Hz, 1H, *O*–CH_2Ph), 4.63 (d, *J*=3.6 Hz, 1H, H-2), 4.68 (d, *J*=11.7 Hz, 1H, *O*–CH_2Ph), 5.43 (dt, *J*=10.2, 1.8 Hz, 1H, H-7a), 5.47 (dt, *J*=14.7, 1.8 Hz, 1H, H-7b), 5.95 (ddd, *J*=13.8, 10.2, 7.2 Hz, 1H, H-6), 5.98 (d, *J*=3.6 Hz, 1H, H-1), 7.21–7.45 (10H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.7, 70.3, 72.2, 81.5, 81.7, 82.0, 105.0, 111.7, 119.1, 127.5, 127.7, 127.8, 128.3, 128.4, 128.8, 129.0, 137.6, 138.2, 136.1. Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.2; H, 7.12. Found: C, 72.12; H, 7.21.

3.2. General procedure for nitrone–olefin cycloaddition

Compound **5** (1.0 g, 2.52 mmol) was dissolved in TFA/water (6:4, 10 mL) and stirred at 0 °C for 20 min and allowed to attain room temperature. The solution was stirred for 2 h and concentrated under reduced pressure. Column chromatography on silica gel (hexane/ethyl acetate=4:1) afforded the hemiacetal as a thick oil (0.73 g, 82%). The ^1H NMR spectrum suggested a mixture of two anomers (α/β=7:3). To a well-stirred solution of the hemiacetal (0.57 g, 1.60 mmol) in ethanol/water (3:1, 10 mL) was added *N*-benzylhydroxylamine hydrochloride (0.49 g, 3.07 mmol) followed by sodium bicarbonate (0.35 g, 4.1 mmol) and the solution was heated at reflux for 4 h. Ethanol was removed under reduced pressure and the residue was extracted with $CHCl_3$ (10 mL×3). Usual work-up and column chromatography purification afforded isoxazolidine **6**.

3.2.1. (3a*R*,4*R*,5*R*,6*R*,7*S*,7a*R*)-1-Benzyl-4,6-bis(benzyloxy)-octahydrobenzo[*c*]isoxazole-5,7-diol (6a). Chromatography on silica gel (*n*-hexane/ethyl acetate=9:1) yielded compound **6a** (0.9 g, 88%) as a pale yellow oil. R_f=0.31 (hexane/ethyl acetate=7:3); $[\alpha]_D^{25}$ +40.6 (*c* 0.69, $CHCl_3$); IR (neat)=3433 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+D_2O) δ 3.04–3.14 (m, 1H, H-3a), 3.25 (t, *J*=9.0 Hz, 1H, H-7a), 3.63 (dd, *J*=9.0, 4.2 Hz, 1H, H-6), 3.68 (t, *J*=8.5 Hz, 1H, H-3), 3.75 (t, *J*=9.0 Hz, 1H, H-7), 3.86 (dd, *J*=7.8, 3.0 Hz, 1H, H-4), 3.99 (ABq, *J*=13.5 Hz, 2H, *N*–CH_2Ph), 4.07 (dd, *J*=4.2, 3.0 Hz, 1H, H-5), 4.27 (t, *J*=8.5 Hz, 1H, H-3′), 4.63 (ABq, *J*=11.5 Hz, 2H, *O*–CH_2Ph), 4.80 (br s, 2H, *O*–CH_2Ph), 7.21–7.45 (m, 15H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.7, 60.4, 68.0, 69.0, 70.7, 71.1, 71.9, 72.7, 77.0, 82.0, 127.3, 127.5, 127.5, 127.6, 127.8, 128.0, 128.1, 128.2, 128.3, 128.8, 136.5, 137.3, 138.0. Anal. Calcd for $C_{28}H_{31}NO_5$: C, 72.86; H, 6.77. Found: C, 73.05; H, 6.94.

3.2.2. (3a*S*,4*S*,5*R*,6*R*,7*S*,7a*S*)-1-Benzyl-4,6-bis(benzyloxy)-octahydrobenzo[*c*]isoxazole-5,7-diol (6b). Chromatography on silica gel (hexane/ethyl acetate=9:1) yielded compound **6b** (0.3 g, 66%) as a colourlss oil. R_f=0.37 (hexane/ethyl acetate=7:3); $[\alpha]_D^{25}$ −22.2 (*c* 0.45, $CHCl_3$); IR (neat)=3411.8, 1074.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+D_2O) δ 2.71–2.73 (m, 1H, H-3a), 3.39 (dd, *J*=5.1, 2.7 Hz, 1H, H-7a), 3.77–3.85 (m, 5H), 4.03–4.10 (m, 3H), 4.62 (dd, *J*=11.7, 4.2 Hz, 1H, H-3), 4.79 (ABq, *J*=12.0 Hz, 2H, *O*–CH_2Ph), 7.23–7.31 (m, 15H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.0, 62.3, 65.4, 69.4, 69.5, 69.6, 73.1, 73.7, 76.2, 80.8, 81.8, 127.5, 127.7, 128.4, 128.9, 136.7, 138.1. Anal. Calcd for $C_{28}H_{31}NO_5$: C, 72.86; H, 6.77. Found: C, 72.74; H, 6.62.

3.2.3. (3a*R*,4*S*,5*R*,6*R*,7*S*,7a*R*)-1-Benzyl-4,6-bis(benzyloxy)-octahydrobenzo[*c*]isoxazole-5,7-diol (6c). Chromatography on silica gel (hexane/ethyl acetate=9:1) yielded **6c** (0.1 g, 17%) as a colourless oil. R_f=0.25 (hexane/ethyl acetate=7:3); $[\alpha]_D^{25}$ +14.8 (*c* 0.27, $CHCl_3$); IR (neat)=3435, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+D_2O) δ 3.04 (dd, *J*=9.3 Hz, 1H, H-7a), 3.18 (t, *J*=9.3 Hz, 1H, H-3), 3.32–3.38 (m, 1H, H-3a), 3.68 (t, *J*=9.3 Hz, 1H, H-7), 3.71 (dd, *J*=10.8, 4.8 Hz, 1H, H-4), 3.75 (d, *J*=13.5 Hz, 2H, *N*–CH_2Ph), 3.78 (t, *J*=9.3 Hz, 1H, H-5), 3.84 (t, *J*=8.7 Hz, 1H, H-3′), 4.07 (d, *J*=12.6 Hz, 1H, *O*–CH_2Ph), 4.63 (m, 3H, *O*–CH_2Ph), 4.91 (d, *J*=11.2 Hz, 1H, *O*–CH_2Ph), 7.21–7.41 (m, 15H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.7, 60.6, 67.4, 67.8, 72.0, 72.2, 72.6, 74.7, 78.0 81.3, 127.6, 127.7, 128.0, 128.1, 128.2, 128.4, 128.4, 128.5, 129.0, 137.9, 138.3. Anal. Calcd for $C_{28}H_{31}NO_5$: C, 72.86; H, 6.77. Found: C, 73.09; H, 7.07.

3.3. General procedure for the conversion of 6 to 7

To an ice cold solution of **6** (0.1 g, 0.20 mmol) in dry pyridine (0.3 mL, 3.82 mmol) were added acetic anhydride (0.6 mL, 6.43 mmol) and DMAP (0.0019 g, 0.015 mmol) and the mixture was stirred for 12 h at room temperature. The reaction mixture was treated with cold water (2 mL) and extracted with chloroform (3×5 mL).

3.3.1. (3a*R*,4*R*,5*R*,6*R*,7*S*,7a*R*)-1-Benzyl-4,6-bis(benzyloxy)-octahydrobenzo[*c*]isoxazole-5,7-diyl diacetate (7a). By column chromatography (*n*-hexane/ethyl acetate=9:1), compound **7a** was obtained as a yellow liquid (0.1 g, 88%). R_f=0.40 (hexane/ethyl acetate=7:3); $[\alpha]_D^{25}$ +19.6 (*c* 0.61, $CHCl_3$); IR (neat)=1100, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.84 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.14–3.16 (m, 1H, H-3a), 3.32 (t, *J*=9.0 Hz, 1H, H-7a), 3.57 (dd, *J*=8.4, 2.8 Hz, 1H, H-6), 3.80 (dd, *J*=8.7, 5.1 Hz, 1H, H-3), 3.86 (d, *J*=12.9 Hz, 1H, *N*–CH_2Ph), 3.92 (dd, *J*=8.4, 2.8 Hz, 1H, H-4), 4.07 (d, *J*=12.9 Hz, 1H, *N*–CH_2Ph), 4.29 (t, *J*=8.7 Hz, 1H, H-3′), 4.48 (d, *J*=11.7 Hz, 1H, *O*–CH_2Ph), 4.58 (d, *J*=12.0 Hz, 1H, *O*–CH_2Ph), 4.68 (d, *J*=11.7 Hz, 1H, *O*–CH_2Ph), 4.74 (d, *J*=12.0 Hz, 1H, *O*–CH_2Ph), 5.18 (dd, *J*=9.9, 8.4 Hz, 1H, H-7), 5.39 (t, *J*=2.8 Hz, 1H, H-5), 7.21–7.45 (m, 15H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 21.1, 43.5, 60.3, 64.7, 69.5, 71.2, 71.9, 71.9, 74.9, 78.6, 127.5, 127.7,

127.9, 128.0, 128.1, 128.3, 128.6, 129.0, 136.7, 137.4, 137.7, 169.5, 170.0. Anal. Calcd for $C_{32}H_{35}NO_7$: C, 70.44; H, 6.47. Found: C, 70.27; H, 6.62.

3.3.2. (3a*S*,4*S*,5*R*,6*R*,7*S*,7a*S*)-1-Benzyl-4,6-bis(benzyloxy)-octahydrobenzo[*c*]isoxazole-5,7-diyl diacetate (7b). After column chromatography (*n*-hexane/ethyl acetate=4:1), compound **7b** was obtained as a white crystalline solid (0.09 g, 77%). Mp=136–137 °C; R_f=0.38 (hexane/ethyl acetate=7:3); $[\alpha]_D^{25}$ −35.4 (*c* 0.62, $CHCl_3$); IR (Nujol)=1074, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.73 (m, 1H, H-3a), 3.51 (dd, *J*=6.3, 4.5 Hz, 1H, H-7a), 3.75 (dd, *J*=8.4, 1.8 Hz, 1H, H-3), 3.87 (d, *J*=13.8 Hz, 1H, *N*–CH_2Ph), 3.91 (t, *J*=9.3 Hz, 1H, H-6), 3.94 (dd, *J*=8.4, 3.4 Hz, 1H, H-3′), 3.99 (d, *J*=13.8 Hz, 1H, *N*–CH_2Ph), 4.02 (t, *J*=8.0 Hz, 1H, H-4), 4.55 (d, *J*=11.4 Hz, 1H, *O*–CH_2Ph), 4.67 (br s, 3H, *O*–CH_2Ph), 5.23 (dd, *J*=9.0, 8.0 Hz, 1H, H-5), 5.24 (dd, *J*=9.0, 4.5 Hz, 1H, H-7), 7.22–7.36 (m, 15H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6 (s), 45.4, 61.0, 61.6, 66.1, 66.9, 71.8, 72.2, 74.1, 74.3, 75.1, 124.8, 125.3, 125.7, 126.0, 126.6, 134.9, 135.6, 167.4 (s). Anal. Calcd for $C_{32}H_{35}NO_7$: C, 70.44; H, 6.47. Found: C, 70.59; H, 6.25.

3.3.3. (3a*R*,4*S*,5*R*,6*R*,7*S*,7a*R*)-1-Benzyl-4,6-bis(benzyloxy)-octahydrobenzo[*c*]isoxazole-5,7-diyl diacetate (7c). After column chromatography (*n*-hexane/ethyl acetate=4:1), compound **7c** was obtained as a white crystalline solid (0.09 g, 78%). Mp=131–133 °C; R_f=0.25 (hexane/ethyl acetate=7:3); $[\alpha]_D^{25}$ +10.6 (*c* 0.75, $CHCl_3$); IR (Nujol)=1070, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 3.12 (br dd, *J*=9.3, 8.0 Hz, 1H, H-7a), 3.29–3.38 (m, 1H, H-3a), 3.43 (t, *J*=9.3 Hz, 1H, H-6), 3.73 (d, *J*=14.1 Hz, 1H, *N*–CH_2Ph), 3.75 (dd, *J*=8.7, 6.0 Hz, 1H, H-4), 4.08 (t, *J*=8.7 Hz, 1H, H-3), 4.14 (d, *J*=14.1 Hz, 1H, *N*–CH_2Ph), 4.22 (t, *J*=8.7 Hz, 1H, H-3′), 4.58 (ABq, *J*=11.7 Hz, 2H, *O*–CH_2Ph), 4.65 (br s, 2H, *O*–CH_2Ph), 5.30 (t, *J*=9.3 Hz, 1H, H-7), 5.40 (t, *J*=8.7 Hz, 1H, H-5), 7.22–7.43 (m, 15H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (s), 41.7, 60.5, 64.2, 67.4, 72.2 (s), 72.4, 73.5, 75.2, 78.8, 127.5, 127.7, 127.8, 128.2, 128.3, 128.8, 136.5, 137.6, 137.8, 169.2, 169.5. Anal. Calcd for $C_{32}H_{35}NO_7$: C, 70.44; H, 6.47. Found: C, 70.28; 6.33.

3.4. General procedure for the conversion of 6 to 2

To a well-stirred solution of compound **6** (0.1 g, 0.20 mmol) in dry methanol (5 mL) were added 10% Pd/C (0.1 g) and ammonium formate (0.9 g, 1.41 mmol). The reaction was heated at reflux for 45 min. The reaction mixture was filtered through Celite and solvent was evaporated to give a sticky solid. The residue was washed with dry ether and ethyl acetate.

3.4.1. (1*R*,2*R*,3*R*,4*S*,5*R*,6*R*)-5-Amino-6-(hydroxymethyl)-cyclohexane-1,2,3,4-tetraol (2a). Column chromatography (chloroform/methanol=1:9) afforded **2a** as a semisolid (0.03 g, 84%). $[\alpha]_D^{25}$ −114.2 (*c* 0.04, MeOH); IR (neat)=3433, 1417 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 2.32–2.36 (m, 1H, H-6), 3.26 (dd, *J*=10.8, 5.4 Hz, 1H, H-5), 3.48 (dd, *J*=10.8, 7.2 Hz, 1H, H-4), 3.55–3.62 (m, 3H, H-3, H-2, H-7a), 3.82 (dd, *J*=11.4, 6.0 Hz, 1H, H-7b), 4.14 (t, *J*=2.4 Hz, 1H, H-1); ^{13}C NMR (75 MHz, D_2O) δ 45.6, 50.8, 58.2, 70.0, 71.1, 73.4, 73.8. Anal. Calcd for $C_7H_{15}NO_5$: C, 43.52; H, 7.83. Found: C, 43.80; H, 8.10.

3.4.2. (1*S*,2*R*,3*R*,4*S*,5*S*,6*S*)-5-Amino-6-(hydroxymethyl)-cyclohexane-1,2,3,4-tetraol (2b). Column chromatography (chloroform/methanol=1:9) afforded compound **2b** as a semisolid (0.03 g, 85%). $[\alpha]_D^{25}$ −86.9 (*c* 0.07, MeOH); IR (neat)=3350, 1417–1454 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.78–1.90 (m, 1H, H-6), 3.31 (t, *J*=9.3 Hz, 1H, H-3), 3.51 (t, *J*=3.6 Hz, 1H, H-5), 3.52–3.62 (m, 2H, H-2, H-1) 3.64 (dd, *J*=9.3, 3.6 Hz, 1H, H-4), 3.78 (dd, *J*=10.8, 7.5 Hz, 1H, H-7a), 3.90 (dd, *J*=11.4, 4.2 Hz, 1H, H-7b); ^{13}C NMR (75 MHz, D_2O) δ 43.2, 51.4, 59.8, 69.2, 72.2, 72.5, 77.32. Anal. Calcd for $C_7H_{15}NO_5$: C, 43.52; H, 7.83. Found: C, 43.86; H, 8.03.

3.4.3. (1*S*,2*S*,3*R*,4*S*,5*R*,6*R*)-5-Amino-6-(hydroxymethyl)-cyclohexane-1,2,3,4-tetraol (2c). Column chromatography (chloroform/methanol=1:9) afforded compound **2c** as a semisolid (0.03 g, 80%). $[\alpha]_D^{25}$ −30.7 (*c* 0.13, MeOH); IR (neat)=3352, 1421–1452 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 2.49–2.56 (m, 1H, H-6), 3.20 (dd, *J*=11.1 Hz, 4.5 Hz, 1H, H-5), 3.29 (t, *J*=9.1 Hz, 1H, H-3), 3.52 (dd, *J*=10.0, 9.1 Hz, 1H, H-2), 3.74 (dd, *J*=10.0, 5.5 Hz, 1H, H-1), 3.77 (dd, *J*=11.1, 9.1 Hz, 1H, H-4), 3.86 (dd, *J*=11.8, 7.8 Hz, 1H, H-7a), 3.96 (dd, *J*=11.8, 4.2 Hz, 1H, H-7b); ^{13}C NMR (75 MHz, D_2O) δ 46.8, 54.8, 59.1, 73.9, 75.7, 75.9, 78.3. Anal. Calcd for $C_7H_{15}NO_5$: C, 43.52; H, 7.83. Found: C, 43.75; H, 7.95.

3.5. General procedure for the conversion of 2 to 8

A solution of compound **2** (0.02 g, 0.09 mmol) in 0.5 M HCl (1 mL) in methanol was stirred at room temperature for 20 h. The solvent was evaporated under reduced pressure and residue was dried in vacuo. The residue was washed with dry ether and ethyl acetate.

3.5.1. (1*R*,2*R*,3*R*,4*S*,5*R*,6*R*)-5-Amino-6-(hydroxymethyl)-cyclohexane-1,2,3,4-tetraol hydrochloride (8a). Compound was dried in vacuo to afford the hydrochloride salt **8a** (0.02 g, 0.09 mmol) as a semisolid. $[\alpha]_D^{25}$ −100.0 (*c* 0.12, MeOH); IR (neat)=3440, 1454 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 2.53–2.57 (m, 1H, H-6), 3.58 (dd, *J*=9.9, 3.3 Hz, 1H, H-2), 3.61–3.85 (m, 5H, H-5, H-4, H-3, H-7a, H-7b), 4.12 (t, *J*=3.0 Hz, 1H, H-1); ^{13}C NMR (75 MHz, D_2O) δ 43.7, 51.9, 58.7, 69.8, 70.4, 71.0, 73.7. Anal. Calcd for $C_7H_{16}ClNO_5$: C, 36.61; H, 7.02. Found: C, 36.52; H, 7.19.

3.5.2. (1*S*,2*R*,3*R*,4*S*,5*S*,6*S*)-5-Amino-6-(hydroxymethyl)-cyclohexane-1,2,3,4-tetraol hydrochloride (8b). Compound was dried in vacuo to afford the hydrochloride salt **8b** (0.02 g, 0.09 mmol) as a semisolid. $[\alpha]_D^{25}$ −42.8 (*c* 0.07, MeOH); IR (neat)=3330, 1456 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.96–2.21 (m, 1H, H-6), 3.38 (t, *J*=9.3 Hz, 1H, H-2), 3.49 (t, *J*=9.3 Hz, 1H, H-3), 3.69 (dd, *J*=11.4, 9.3 Hz, 1H, H-1), 3.81–3.86 (m, H-1, 2H, H-4), 3.89 (dd, *J*=11.7, 3.0 Hz, 1H, H-7a), 3.98 (dd, *J*=11.7, 5.4 Hz, 1H, H-7b); ^{13}C NMR (75 MHz, D_2O) δ 40.6, 54.0, 58.9, 67.4, 69.6, 72.0, 76.4. Anal. Calcd for $C_7H_{16}ClNO_5$: C, 36.61; H, 7.02. Found: C, 36.45; H, 6.91.

3.5.3. (1*S*,2*S*,3*R*,4*S*,5*R*,6*R*)-5-Amino-6-(hydroxymethyl)-cyclohexane-1,2,3,4-tetraol hydrochloride (8c). Compound was dried in vacuo to afford the hydrochloride salt **8c** (0.02 g, 0.09 mmol) as a semisolid. $[\alpha]_D^{25}$ −10.5 (*c* 0.19, MeOH); IR (neat)=3346, 1417–1450 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 2.58–2.68 (m, 1H, H-6), 3.31 (t, *J*=9.0 Hz, 1H, H-3), 3.36 (dd, *J*=11.7, 4.5 Hz, 1H, H-5), 3.49 (t, *J*=9.9 Hz, 1H, H-2), 3.74 (dd, *J*=9.9, 5.1 Hz, 1H, H-1), 3.82–3.93 (m, H-4, 2H, H-7a), 4.01 (dd, *J*=11.4, 3.3 Hz, 1H, H-7b); ^{13}C NMR (75 MHz, D_2O) δ 44.3, 55.3, 58.9, 72.1, 72.6, 75.2, 77.9. Anal. Calcd for $C_7H_{16}ClNO_5$: C, 36.61; H, 7.02. Found: C, 36.79; H, 7.13.

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