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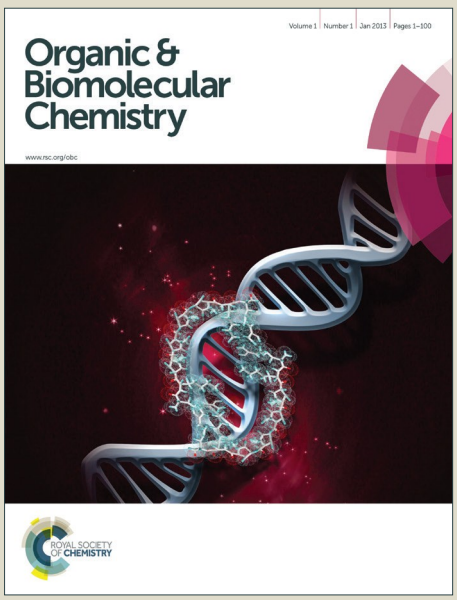

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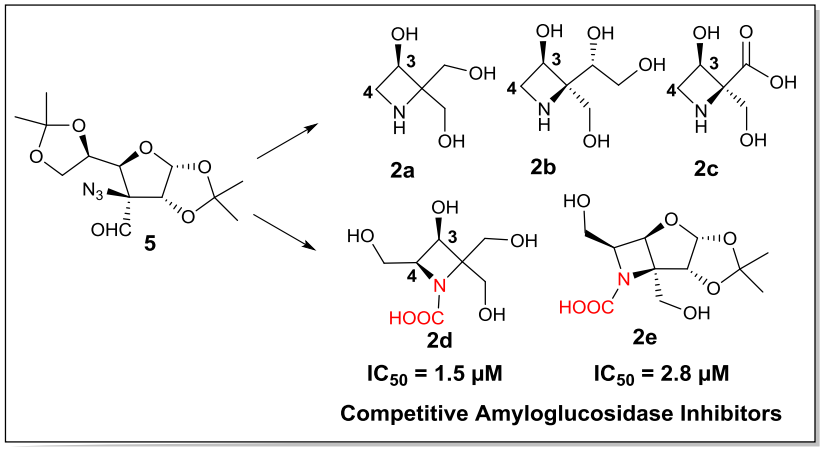
Azetidine- and *N*-Carboxylic Azetidine- Iminosugars as Amyloglucosidase Inhibitors: Synthesis, Glycosidase Inhibitory Activity and Molecular Docking Studies

Kishor S. Gavale[a], Shrawan R. Chavan[a], Ayesha Khan[a], Rakesh Joshi[b], Dilip D. Dhavale*[a]

[a] Department of Chemistry, Garware Research Centre, Savitribai Phule Pune University (formerly University of Pune), Pune, 411 007, India

[b] Institute of Bioinformatics and Biotechnology, Savitribai Phule Pune University, Pune 411007, India



ABSTRACT

A simple strategy for the synthesis of hitherto unknown azetidine iminosugars **2a-2c** and *N*-carboxylic azetidine iminosugar **2d** has been reported. The methodology involves conversion of 1,2:5,6-di-*O*-isopropylidene-3-oxo-α-D-glucofuranose **3** to 3-azido-3-deoxy-3-*C*-(formyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **5** using the Jocic-Reeve and Corey-Link approach. Compound **5** was transformed to 5-*O*Ts **10**/5-*O*Ms **19** derivatives that on intramolecular nucleophilic displacement with *in situ* generated 3-amino functionality afforded the key azetidine ring skeletons **11** and **20,** respectively. Hydrolysis of the 1,2-acetonide group and manipulation of the anomeric carbon in **12** provided azetidine iminosugars **2a-2c**. In an attempt to synthesize azetidine iminosugars with an additional 4-hydroxymethyl group from **20**, we encountered an interesting observation wherein *N*-Cbz group in **20** hydrolyzed to the *N*-COOH functionality under TFA:H_2O condition that gave an access for the synthesis of *N*-

carboxylic azetidine iminosugar **2d**. Glycosidase inhibitory activity of **2a-2d** and intermediates **2e-f** was studied with various glycosidases and compared with Miglitol and 1-deoxynojirimycin (DNJ). Azetidine iminosugars **2** were found to inhibit amyloglucosidase with competitive type of inhibition amongst which **2d** was found to be relatively more active than Miglitol and DNJ. These results were substantiated by *in silico* molecular docking studies.

INTRODUCTION

Amongst monocyclic iminosugars, the five-, six- and seven-membered analogues are widely studied to understand the carbohydrate mediated processes in glycobiology.[1,2] However, the four membered polyhydroxylated azetidine iminosugars are less exploited in the literature.[3,4] In 1997, Jager and co-workers first synthesized 1,3-dideoxy-1,3-imino-L-xylitol **1a** (Figure 1) which was found to be a specific inhibitor of amyloglucosidases.[5] Recently, Fleet and co-workers synthesized a variety of hydroxyalkyl substituted azetidine iminosugars **1a-1c** amongst which, **1b** showed a specific inhibition for non-mammalian glycosidases.[6] Moreover, azetidine iminosugars were found to be components of dopamine antagonists[7] and their carboxylic acid substituted (α- to the ring nitrogen) analogues are constituents of non-proteinogenic amino acids[8] and also recognized as components of peptidomimetics.[9] Apart from this, azetidin-3-ol[10] is a basic structural motif present in naturally occurring alkaloids such as Penaresidines A and B (**1d** and **1e**) which are known for their actomyosine-ATPase activating properties.[11] Furthermore azetidines are widely used in bioactive compounds.[12]

While designing iminosugars, the type of substituent on the heterocyclic ring with its position and stereochemistry are being considered. In general, substituents such as alkyl /hydroxyalkyl/halogen/acid are introduced either by replacing or retaining the pre-existing hydroxyl group. The structure activity relationship (SAR) data indicated that such modifications

play a key role in deciding glycosidase inhibitory activity.[13] In this direction, a variety of α-geminal di-hydroxyalkyl substituted five- and six-membered iminosugars are reported from our and other groups.[14] It has been demonstrated that the presence of an additional hydroxymethyl substituent at α-position of the ring nitrogen, leads to a selective and potential glycosidase inhibitory activity than the parent counterpart. Inspired by this observation and in order to know how the introduction of an additional hydroxymethyl group in azetidine ring position can alter its inhibitory activity, we are now reporting the synthesis, glycosidase inhibitory and molecular docking studies of α-geminal hydroxyalkyl **2a, 2b -** (α-to the ring nitrogen), 2-carboxylic acid **2c -** as well as *N*-carboxylic-α,γ-trihydroxymethyl **2d-** azetidine iminosugars. (Figure 1)

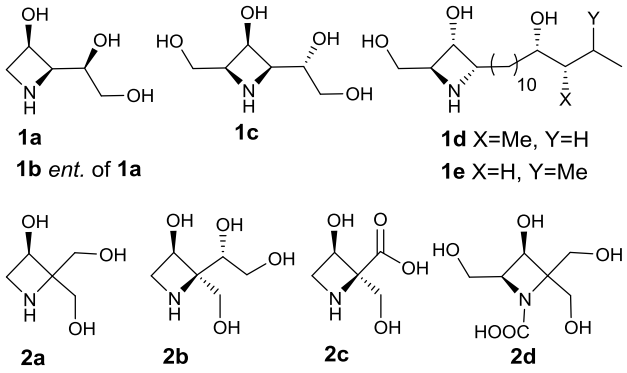
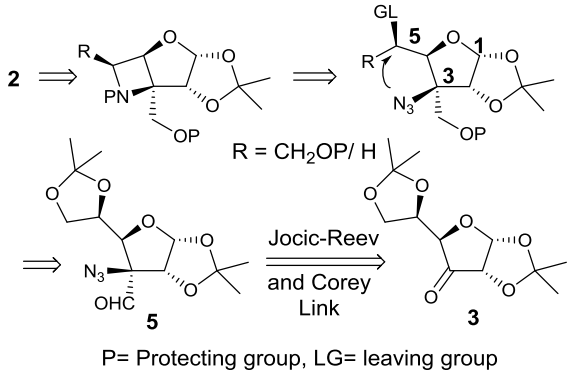


Figure 1. Azetidine iminosugars and natural alkaloids

For the formation of azetidine iminosugars, Jager and co-workers utilized [2+2] cycloaddition of imines with the α-alkoxyketenes[5] and Fleet and co-workers constructed azetidine core by double displacement of 3,5-di-*O*-triflate derivatives of α-furanosides or 2,4-di-*O*-triflate derivatives of β-pyranosides with alkyl amines.[6] In our approach (Scheme 1), we envisioned to construct azetidine ring of target molecules (**2a**-**2d**) by the S_N2 displacement of the C5-*O*Ts/5-*O*Ms group with C3-amino (formed *in situ* from C3-azido) functionality of D-glucofuranose. The azido and aldehyde functionalities at the C-3 position of D-glucose could be

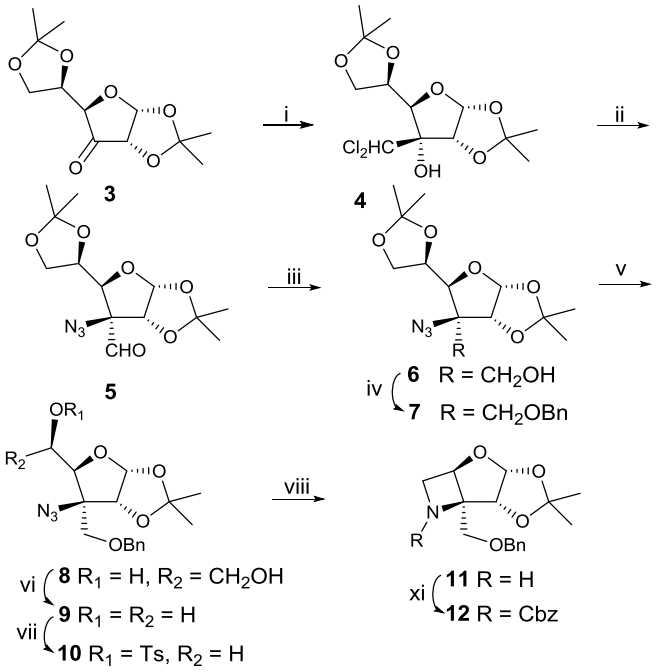
obtained simultaneously in one pot using the Corey-Link[15] and Jocic-Reeve type of approach with suitably protected 3-keto-D-glucohexose (Scheme 1).



Scheme 1. Retrosynthetic analysis for **2**

RESULTS AND DISCUSSION

Our synthesis starts from the 1,2:5,6-di-*O*-isopropylidene-3-oxo-α-D-glucofuranose **3** that was prepared from the diacetonide D-glucose as reported earlier[16] (Scheme 2). Treatment of **3** with dichloromethyl lithium, generated using dichloromethane and LDA in THF at -78 °C, afforded 3-dichloromethyl-D-allose **4** as the only diastereomer wherein attack of dichloromethyl anion took place exclusively from the β-face as the α-face is hindered due to the presence of 1,2-acetonide group. Treatment of **4** with NaN_3 and TBAI (1.5 eq) in DMF afforded 3-azido-3-formyl compound **5**, via *in situ* formation of α-oriented chlorooxirane intermediate followed by the S_N2 attack of the azide ion from the β-face.[13a,15] Reduction of **5** using $NaBH_4$ in MeOH:H_2O gave 3-azido-3-hydroxymethyl compound **6** that on reaction with benzyl bromide in the presence of NaH in THF gave benzyl ether derivative **7**. In the next step, removal of the 5,6-acetonide group in **7** using AcOH:H_2O (3:2) at 60 °C furnished diol **8** which was further exploited to synthesize azetidine iminosugars.

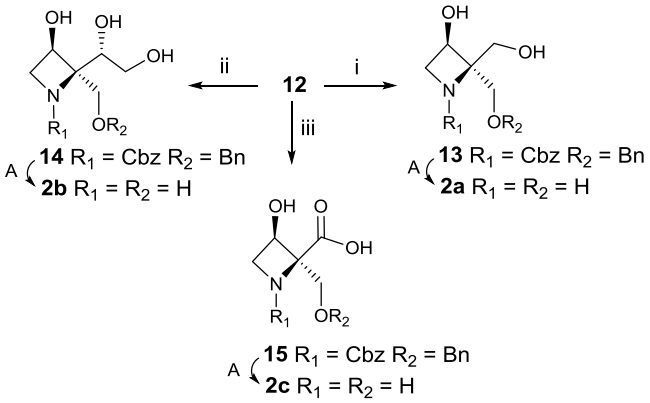


Reaction Conditions: i) LDA, CH_2Cl_2, THF. -78 °C, 60% ii) NaN_3, TBAI, DMF, 110 °C, 82% iii) $NaBH_4$, MeOH:water(9:1), 0 °C, 93% iv) BnBr, NaH, TBAI, 0 °C to rt, 92% v) AcOH:water(3:2), 55 °C, 91% vi) a) $NaIO_4$, acetone:water(9:1), 0 °C b) $NaBH_4$, MeOH:water(9:1), 0 °C, 85% (over 2 steps) vii) TsCl, Py, 60 °C, 88% viii) H_2, 10% Pd/C, MeOH, 79% ix) CbzCl, $NaHCO_3$, MeOH:water(9:1), 89%

Scheme 2. Synthesis of azetidine scaffold **12**

Diol **8** on treatment with $NaIO_4$ in acetone: water (9:1) followed by reduction using $NaBH_4$ gave primary alcohol **9** that was protected with TsCl in pyridine to afford 5-*O*Ts derivative **10**. Hydrogenation of **10** using 10% Pd/C in methanol at 100 psi afforded furanose fused azetidine ring skeleton **11**. This reaction involves reduction of the 3-azido group to 3-amino functionality followed by an intramolecular S_N2 displacement of 5-*O*Ts to give azetidine ring skeleton in one pot. In the next step, protection of the ring nitrogen atom in **11** using CbzCl gave carbamate derivative **12**. Hydrolysis of the 1,2-acetonide group in **12** using TFA: H_2O (3:1) afforded an anomeric mixture of hemiacetals (as evident from the ^{1}H-NMR of the crude product) that on oxidation using $NaIO_4$ followed by $NaBH_4$ reduction gave diol **13.** Hydrogenolysis of **13** with 20% $Pd(OH)_2/C$ in methanol furnished α-geminal dihydroxymethyl azetidine iminosugar **2a** as a sticky solid. Targeting towards the synthesis of α–geminal dihydroxyalkyl azetidine

iminosugar **2b**, treatment of **12** with TFA:H_2O (3:1) followed by reduction of the resulting hemiacetal with $NaBH_4$ gave benzyl protected azetidine triol **14**. Hydrogenolysis of **14** using 20% $Pd(OH)_2/C$ in methanol furnished the azetidine iminosugar **2b** as a sticky solid.



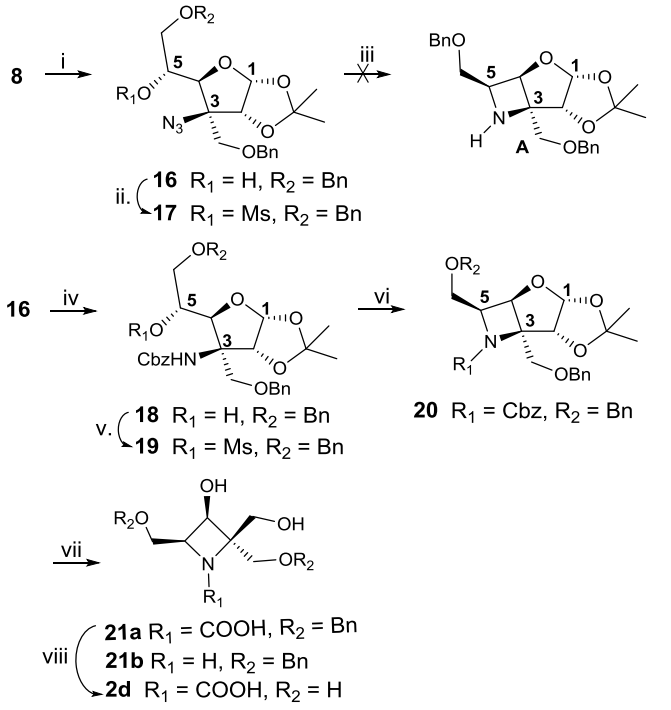
Reaction conditions: i. a) TFA:H_2O, b) $NaBH_4$, MeOH:H_2O (9:1), 0 °C, 72% (over 2 steps) ii) a) TFA:H_2O b) $NaIO_4$, acetone:H_2O (9:1), 0 °C c) $NaBH_4$, MeOH:H_2O (9:1), 0 °C, 78% (over 3 steps) iii. a) TFA:H_2O, b) $NaIO_4$, acetone:water (9:1), 0 °C c) $NaClO_2$, 30% H_2O_2, Aetonitrile:H_2O (1:1), 0 °C, 69% (over 3 steps) A) H_2, 20% $Pd(OH)_2/C$, MeOH, **2a** - 95%, **2b**-93%, **2c**-92%.

Scheme 3: Synthesis of iminosugars **2a**-**2c**

To obtain azetidine iminosugar **2c**, hydrolysis of the 1,2-acetonide group in **12** using TFA: water (3:1) and treatment with $NaIO_4$ followed by the Pinnick oxidation[17] using $NaClO_2$/30% H_2O_2 in the presence of buffer NaH_2PO_4 gave an acid **15** that on hydrogenolysis using 20% $Pd(OH)_2/C$ in MeOH provided the 3-hydroxy-2-hydroxymethyl-azetidine-2-carboxylic acid **2c** (Scheme 3).

Next, *N*-carboxylic azetidine iminosugar **2d** was obtained coincidently from the same diol **8** (Scheme 4). Thus, diol **8** on reaction with Bu_2SnO and benzyl bromide in the presence of TBAB[18] selectively afforded 6-*O*Bn protected derivative **16** that on reaction with MsCl and Et_3N gave 5-*O*Ms derivative **17**. In order to get the bicyclic furanose fused azetidine skeleton, compound **17** was subjected to hydrogenation conditions using 10% Pd/C in methanol (as described for azetidine iminosugars **2a**-**2c**), however, the reaction failed to give the desired bicyclic azetidine ring skeleton **A**. Our attempts under different reaction conditions such as mole

ratio of catalyst (5 to 20 mol %), temperature (room temperature to 60 °C) and pressure (80 psi to 200 psi) led to the complex mixture of products. Alternatively, the 3-azido functionality in **16** was reduced using 1,3-dithiane and Et_3N in methanol to afford a 3-amino compound (as evident from the IR spectrum that showed an absence of peak at 2118 cm^{-1}due to azide group) that was protected as its carbamate derivative using CbzCl and $NaHCO_3$ to get *N*-Cbz protected compound **18**. The 5-hydroxyl group in **18** was reacted with MsCl and Et_3N to get 5-*O*Ms derivative **19**. In the next step, reaction of **19** with K_2CO_3/methanol under reflux afforded the required bicyclic fused azetidine scaffold **20** in overall 64% yield from **16**.



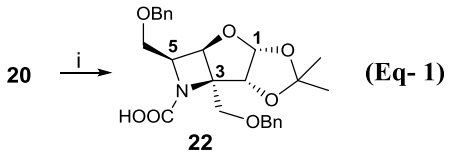
Reaction condtions: i. BnBr, TBAB, DIPEA, Bu_2SnO, 70 °C, 95% ii. MsCl, Et_3N, CH_2Cl_2, 0 °C, 97% iii. H_2,10% Pd/C, MeOH iv. a) 1,3-Dithiane, Et_3N, MeOH b) CbzCl, $NaHCO_3$, MeOH:H_2O, 92% (over 2 steps) v. MsCl, Et_3N, CH_2Cl_2, 0 °C, 91% vi.K_2CO_3, MeOH, Reflux, 95% vii. a) TFA:H_2O, 0 °C b) $NaIO_4$, (acetone:water), 0 °C c) $NaBH_4$, MeOH:water, 0 °C 88% (over 3 steps) viii) H_2, 20%, $Pd(OH)_2$/C, MeOH, 93%

Scheme 4. Synthesis of iminosugar **2d**

When compound **20** was treated with TFA:H_2O (3:1) and then with $NaIO_4$ followed by reduction with $NaBH_4$ (by the same sequence as was successfully employed in the synthesis of **2a** and **2b**), coincidently we got *N*-carboxylic azetidine iminosugar **21a** and not the expected

azetidine iminosugar **21b** (as it was evident from the ^{1}H NMR spectrum, the peak corresponding to benzylic *N*-Cbz protons in 5.00-5.25 δ (ppm) region was absent, see experimental section for other data). Hydrogenolysis of **21a** using 20% $Pd(OH)_2/C$ in MeOH at room temperature afforded *N*-carboxylic acid azetidine iminosugar **2d** (Scheme 4).[19]

The formation of **21a** from the *N*-Cbz protected compound **20** is intriguing. In order to know the fact that at which stage ($TFA:H_2O/NaIO_4/NaBH_4$ conditions) the *N*-Cbz moiety in **20** is converted to the *N*-carboxylic acid functionality; we investigated each step of the reaction sequence in detail. Thus compound **20** was treated with $TFA:H_2O$ (3:1) at 0 °C and the reaction was monitored cautiously by TLC analysis. After 30 minutes at 0 °C, we noticed complete disappearance of starting material **20** (R_f = 0.6; hexane/EtOAc: 4/1) and a new spot appeared at lower R_f (R_f = 0.2; hexane/EtOAc: 4/1) which on work up (see experimental detail) and column chromatography purification afforded *N*-carboxylic bicyclic azetidine skeleton **22** in 94% yield (Eq. 1). This experiment established the fact that *N*-Cbz functionality in **20** is getting hydrolysed to *N*-COOH group prior to the 1,2-acetonide cleavage under acidic conditions.[20] To the best of our knowledge, this is the first report of hydrolysis of *N*-Cbz moiety to *N*-COOH functionality under acidic conditions although, deprotection of *N*-Cbz group to amine is known under strong acidic/basic conditions.[21]



(Eq- 1)

Reaction conditions: i. $TFA:H_2O$, 0 °C, 30min, 96%

Comparing the structural features of **12** and **20**, it is observed that such type of conversion occurs only when an additional 5-CH_2OBn group is present α- to the azetidine ring nitrogen since under similar reaction conditions ($TFA:H_2O$, $NaIO_4$ and $NaBH_4$), **12** afforded *N*-

Cbz protected azetidine iminosugar **13**, while **20** afforded *N*-carboxylic acid azetidine iminosugar **21a**. We believe that α-orientation of the 1,2-acetonide and 3–CH_2*O*Bn functionalities in **20** forces *N*-Cbz group to remain in close proximity with 5-CH_2*O*Bn group. Under TFA:H_2O condition protonation of the *N*-Cbz carbonyl oxygen is stabilized by an intramolecular hydrogen bonding with the CH_2*O*Bn group. The protonated transition state **Y** is further stabilised by benzyloxy oxygen atom (as well as the ring nitrogen atom) which makes benzylic C-O bond weaker as shown in Figure 2. Attack of the water on benzylic carbon and cleavage of the C-O bond leads to the formation of *N*-carboxylic azetidine derivative which is in turn further stabilised by an intramolecular hydrogen bonding with 5-CH_2*O*Bn group.[22]

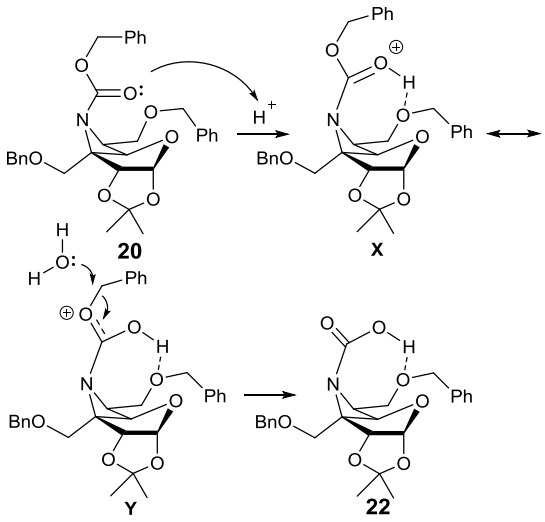
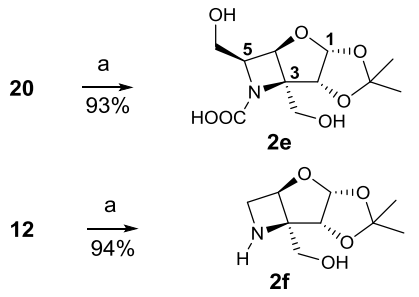


Figure 2. Plausible mechanism for formation of **22**

In order to obtain the azetidine iminosugar without *N*-COOH functionality, compound **20** was hydrogenated using 10% Pd/C in methanol at 100 psi (to remove *N*-Cbz and -*O*Bn groups). To our surprise, hydrogenolysis of **20** afforded compound **2e** in which *N*-Cbz functionality was converted to *N*-COOH along with the deprotection of 3- and 5-*O*Bn groups (Scheme 5). Owing to this unusual observation, we performed similar experiment with **12** wherein 5-CH_2*O*Bn group is absent. However, hydrogenolysis of **12** with 10% Pd/C in methanol proceeded with usual

deprotection of 3-CH_2*O*Bn and *N*-Cbz groups to give **2f** (Scheme 5). These results may be attributed to the presence of an additional 5-CH_2*O*Bn group in **20** wherein Pd(0) can act as Lewis acid. This study thus provides an access to two new azetidine scaffolds **2e** and **2f** for evaluation of glycosidase inhibitory activity.



Reaction conditions: a. H_2, 10% Pd/C, MeOH, 100 psi.

Scheme 5. Hydrogenolysis of **12** and **20**

Biological Activity

Azetidine iminosugars (**2a-2d**), and bicyclic furanose fused azetidine ring intermediates (**2e** and **2f**) were evaluated for inhibitory activity against a series of commercially available glycosidases such as α-glucosidase (rice) [E.C.3.2.1.20], β-glucosidase (rat intestine) [E.C.3.2.1.21], α- galactosidase (coffee beans) [E.C.3.2.1.22], β- galactosidase (bovine liver, cytosolic) [E.C.3.2.1.23], α-mannosidase (Jack beans) [E.C.3.2.1.24],and amyloglucosidase (*Aspergillus niger*) [EC 3.2.1.3] with reference to known standards *N*-hydroxyethyl deoxynojirimycin (trade name Miglitol) and 1- deoxynojirimycin (DNJ)[23]. The corresponding IC_{50} values and inhibition constants (Ki) were determined from Lineweaver-Burk plots (see the Supporting information) and the results are summarized in Table 1.

Azetidine iminosugars are known to be amyloglucosidase inhibitors[5,6] amongst various glycosidases and the same trend was noticed with **2a-2d** and showed good to moderate inhibition of amyloglucosidase with competitive type of inhibition. Amongst these, **2a** and **2b** were found to be weak inhibitors of amyloglucosidase while **2c** was found to inhibit α-galactosidase

significantly along with moderate inhibition of amyloglucosidase. The furanose fused azetidine intermediate **2f** displayed strong inhibition of amyloglucosidase with IC_{50} and K_i values 10.5 and 5.3μM respectively. Effect of *N*-COOH group and an additional 4-hydroxymethyl in **2d** was impressive since this molecule inhibited amyloglucosidase with IC_{50} and K_i values 1.5 and 0.8 μM respectively and found to be relatively more active than DNJ (IC_{50} = 2.8 and Ki = 1.5 μM) and Miglitol (IC_{50} = 2.8 and K_i = 1.5 μM). The acetonide analogue **2e** also showed strong inhibition against amyloglucosidase (IC_{50} = 2.8 and Ki = 1.5 μM) along with significant inhibition of α-galactosidase and weak inhibition of α-and β-glucosidase.

Enzyme (Source)		α-glucosidase (Rice)	β-glucosidase (Rat intestine)	α-galactosidase (Coffee Beans)	β-galactosidase (Bovine Liver)	α-manosidase (Jack Beans)	Amylo-glucosidase (A.Niger)
Miglitol	IC_{50}	0.1	70	NI	NI	NI	24
	K_i	0.056	32	NI	NI	NI	13
DNJ	IC_{50}	0.05	327	NI	NI	NI	1.7
	K_i	0.15	0.45	NI	NI	NI	2.1
2a	IC_{50}	NI	NI	NI	NI	NI	415
	K_i	NI	NI	NI	NI	NI	322
2b	IC_{50}	NI	NI	NI	NI	NI	522
	K_i	NI	NI	NI	NI	NI	421
2c	IC_{50}	NI	NI	103	NI	NI	201
	K_i	NI	NI	89	NI	NI	145
2d	IC_{50}	NI	NI	NI	NI	NI	1.5
	K_i	NI	NI	NI	NI	NI	0.8
2e	IC_{50}	NI	384	45	NI	NI	2.8
	K_i	NI	254	35	NI	NI	1.5
2f	IC_{50}	NI	NI	NI	NI	NI	10.5
	K_i	NI	NI	NI	NI	NI	5.3

[a]NI: No inhibition at 1mM concentration of inhibitor. Data is average of five sets of assay performed.

Table1. IC_{50} (μM) and K_i (μM) values for **2a-2f** and standards Miglitol and DNJ[a]

Molecular Docking

The molecular docking studies of azetidine iminosugar **2d** as well as bicyclic furanose fused azetidine ring intermediates **2e** and **2f** was performed in order to know their interactions with the amino acid residues of amyloglucosidase. Homology modeling was performed using Swiss Model server to predict three dimensional structure of *Aspergillus niger* amyloglucosidase (AgAmy, Accession No.: EHA21384). The X ray crystal structure of *Aspergillus awamori* glucoamylase (PDB:1DOG) was used as template for homology modeling.[24] Predicted model was energy minimized using GROMOS 43BI force field[25] and then assessed for its quality and Ramachandran plot analysis. Binding pockets of enzymes and docking simulations were predicted using AutoDock 4.2 version. [26] The grid was set around active site residues of AgAmy (Trp144, Glu200, Asp203) with dimension of 20 x 20 x 20 Å. The docking parameters were set to a LGA calculation of 10,000 runs. The energy evaluations were set to 1,500,000 and 27,000 generations. Population size was set to 150 and the rate of gene mutation and the rate of gene crossover were set to 0.02 and 0.8, respectively.[27] Conformations thus obtained were summarized, collected and extracted by using Autodock Tool. The geometry of resulting complexes was studied using the PyMol Molecular Viewer utility (The PyMOL Molecular Graphics System, Version 1.5.0.4 Schrödinger, LLC).

The molecular docking study of azetidine iminosugar **2d**, **2e** and **2f** showed atomic interactions with several amino acid residues of amyloglucosidase enzyme (Figure 3). Binding scores for **2d**, **2e** and **2f** were **-6.3**, **-5.7** and **-5.3** kcal/mol, respectively (Table 2), thus specifying highest binding affinity of **2d** for amino acid residues of amyloglucosidase. Binding pose analysis showed that **2d** and **2f** bind deep inside the active site while; **2e** at the mouth region of the binding pocket (Figure 3A). Analysis of polar contacts displayed that **2d** forms multiple

hydrogen bonds with Tyr72, Glu203 and Arg329 residue of binding pocket of AgAmy, which signifies the strong interaction between enzyme and **2d**. Compounds **2e** and **2f** form hydrogen bonds with Tyr72 while; **2e** forms single polar contact with Arg329 (Figure 3B-D). Higher density of hydrogen bonding in case of **2d** renders strong complex formation and attributed to the higher binding affinity. At the same time **2e** and **2f** showed weak interaction compared to **2d**, leading to lower binding score. Binding energies obtained for all complexes showed positive correlation with *in vitro* inhibition data. Interaction between AgAmy and **2d- 2f** exhibit similar strength of Van der Waals and electrostatic interactions, hence difference in the binding energy is solely contributed by the variations in polar contacts (Table 2). *In silico* analysis and *in vitro* validations suggest that binding of **2d** to the active site of AgAmy results in inaccessibility of active site for substrate which in turn marks **2d** as more active and competitive inhibitor of amyloglucosidase.

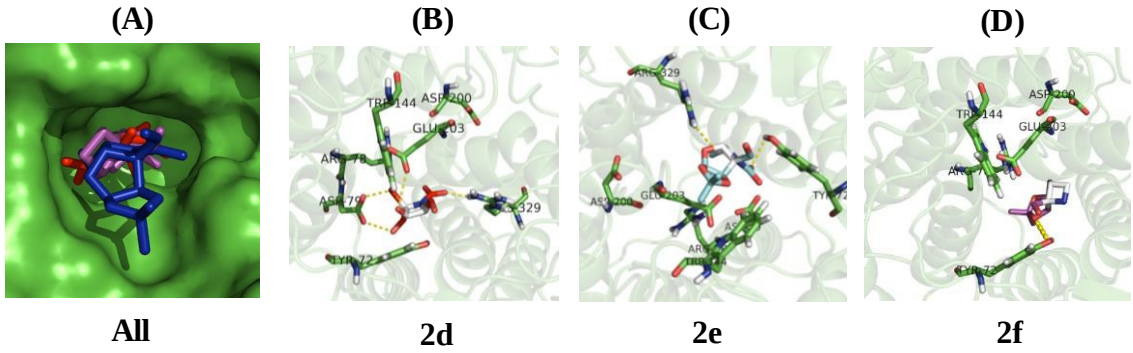


Figure 3. (**A**) Molecular interaction of **2d-2f** with *Aspergillus niger* amyloglucosidase (green colored), **2d** is represented in red while **2e** and **2f** are represented in blue and magneta colour respectively. (**B-D**) Binding poses of **2d-2f** in binding pockets of enzyme. Compounds and residue of binding site are represented in stick format with standard element colours. Intermolecular hydrogen bonding in binding pocket residues and functional group of compounds is represented by yellow dashed line.

Compound	H-bond energy (kcal/mol)	E_{vdw} (kcal/mol)	E_{elec} (kcal/mol)	E_{total} (kcal/mol)
2d	- 1.243	- 2.61	- 2.53	**- 6.38**
2e	- 0.52	-2.52	- 2.39	**- 5.43**
2f	- 0.75	-2.2	- 2.15	**-5.10**

Table 2: The H-bond energy, Van der Waals energy (E_{vdw}), electrostatic energy (E_{elec}) and total energy (E_{total}) in Kcal/mol between active site residues of *Aspergillus awamori* glucoamylase and **2d-2f**.

CONCLUSIONS

In conclusion, we have demonstrated the utility of the Jocic-Reeve and modified Corey-Link approach with 3-keto functionality of D-glucose for the synthesis of four new azetidine imninosugars **2a-2d**. The key azetidine ring skeleton was build up by nucleophilic displacement of the 5-*O*Ts/5-*O*Ms with *in situ* generated 3-amino functionality that consistently proceeded in high yields. Hydrolysis of *N*-Cbz group in **20** to *N*-COOH functionality under TFA:H_2O condition is unprecedented in the literature that was attributed to the presence of an additional 5-CH_2OR moiety. This led to an unusual formation of *N*-carboxylic azetidine iminosugar **2d**. Competitive inhibition of amyloglucosidase shown by azetidine iminosugars **2** is noteworthy, that was supported by the *in silico* molecular docking analysis. The *N*-carboxylic azetidine iminosugar **2d** was found to be relatively more active amyloglucosidase inhibitor than the miglitol and DNJ.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out with distilled and dried solvents using oven-dried glassware. All reagents were purchased from commercial sources (Aldrich or Fluka). ^{1}H NMR (200MHz/300MHz/400MHz/500MHz) and ^{13}C NMR (50MHz/75MHz/100MHz/125MHz) were recorded in $CDCl_3$ and D_2O as solvents. Chemical shifts were reported in δ unit (parts per million) with reference to TMS as an internal standard. Melting points were recorded using Thomas Hoover melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO P-1020 digital polarimeter with sodium light (589.3 nm) at 24–35 °C. High resolution mass spectra (HRMS) were obtained in positive ion electrospray (ESI) mode using TOF (time of flight) analyser. Thin layer Chromatography was performed on precoated plates (0.25 mm, silica gel 60 F254). Column chromatography was carried out with silica gel (100-200 mesh). IR spectra were obtained using FTIR spectrophotometer as a thin film or using KBr pellets and recorded in cm^{-1}. After neutralization workup involves washing of combined organic layer with water, brine, drying over anhydrous sodium sulphate and evaporation of solvent under reduced pressure.

1,2:5,6-Di-*O*-isopropylidene-3-*C*-(dichloromethyl)-α-D-allofuranose (**4**). To a stirred solution of diisopropylamine (6.78 mL, 48.39 mmol) in dry THF (60 mL), 1.6 M solution of n-butyllithium in hexane (7.3 mL, 48.39 mmol) was added under nitrogen atmosphere and stirred for 30 min at room temperature. The solution was cooled to -78 °C and ketone **3** (5.00 g, 19.35 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise. The temperature was then allowed to rise slowly to 20 °C and stirred. TLC analysis (Hexane/EtOAc: 3/2) after 3 h indicated disappearance of the starting material. Reaction was quenched by adding saturated aq. NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (100 mL × 2) and concentrated. Purification by column chromatography (hexane/ ethyl acetate, 9.5:0.5) afforded **4** (3.97 g, 60%) as a white solid: R_f =

0.56 (hexane/ EtOAc, 9:1); m.p 133-135 °C; $[\alpha]_D^{24}$ = +27.7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, ν, cm^{-1}) 3482 (br), 1220, 1079,789 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.23 (s, 1H, $CHCl_2$), 5.93 (d, *J* = 4.3 Hz, 1H, 1CH), 4.81 (d, *J* = 4.3 Hz, 1H, 2CH), 4.41 (ddd, *J* = 9.8, 5.8, 4.1 Hz, 1H, 5CH), 4.14 (dd, *J* = 8.8, 5.9 Hz, 1H, 6CHa), 4.06 (d, *J* = 9.8 Hz, 1H, 4CH), 3.96 (dd, *J* = 8.8, 4.1 Hz, 1H, 6CHb), 3.51 (s, 1H, exchangeable with D_2O, OH), 1.61 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.44 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 112.9 ($\underline{C}(CH_3)_2$), 110.2 ($\underline{C}(CH_3)_2$), 105.4 (C1), 84.7 (C2), 81.5 (C3), 79.4 (C4), 73.2 ($CHCl_2$), 73.1 (C5), 68.5 (C6), 27.0 (CH_3), 26.8 (CH_3), 26.5 (CH_3), 25.4 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{13}H_{20}Cl_2O_6Na$ [M + Na]: 365.0529; found: 365.0526 [M + Na].

3-Azido-3-deoxy-3-*C*-(formyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**5**). To a stirred solution of **4** (4.00 g, 11.68 mmol) in dry DMF (20 mL), sodium azide (2.28 g, 35.06 mmol), TBAI (2.16 g, 5.84 mmol) were added and the mixture was heated at 110 °C. TLC analysis (Hexane/ EtOAc: 9/1) after 4 h indicated disappearance of the starting material, DMF was evaporated at reduced pressure and the residue was extracted with EtOAc (30 mL × 3) and concentrated. Purification by column chromatography (hexane/ ethyl acetate: 9/1) afforded **5** (3.00 g, 82%) as a thick liquid: R_f = 0.5 (hexane/ EtOAc: 4/1); $[\alpha]_D^{25}$ = +75.70 (*c* 0.38, $CHCl_3$); IR ($CHCl_3$, ν, cm^{-1}) 2123, 1734, 1456, 1379, 844, 758; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.64 (s, 1H, CHO), 5.94 (d, *J* = 3.6 Hz, 1H, 1CH), 4.63 (d, *J* = 3.6 Hz, 1H, 2CH), 4.55 (d, *J* = 8.8 Hz, 1H, 4CH), 4.23 (ddd, *J* = 3.8, 6.1, 8.8 Hz, 1H, 5CH), 4.12 (dd, *J* = 3.8, 6.1 Hz, 1H, 6CHa), 4.06 (dd, *J* = 3.8, 8.8 Hz, 1H, 6CHb), 1.61 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 194.5 (CHO), 114.1 ($\underline{C}(CH_3)_2$), 109.9 ($\underline{C}(CH_3)_2$), 105.7 (C1), 86.2 (C2), 81.0 (C4), 76.5 (C3), 72.5 (C5), 67.2 (C6), 26.7 (CH_3),

26.6 (CH_3), 26.1 (CH_3), 24.6 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{13}H_{20}N_3O_6$ [M + H]: 314.1352; found: 314.1343 [M + H].

3-Azido-3-deoxy-3-*C*-(hydroxymethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**). To an ice-cooled stirred solution of **5** (3.00 g, 9.57 mmol) in methanol (20 mL), sodium borohydride (0.362 g, 9.57 mmol) was added in two portions. TLC analysis (Hexane/ EtOAc: 4/1) after 1 h indicated disappearance of the starting material and formation of a single product. Reaction was quenched by adding saturated aq. NH_4Cl solution (5 mL) and methanol was evaporated under reduced pressure. The residue was extracted with EtOAc (30 mL × 3) and concentrated. Purification by column chromatography (hexane/ ethyl acetate: 9/1) afforded **6** (2.81 g, 93%) as a thick liquid: R_f = 0.4 (hexane/ EtOAc: 4/1); $[\alpha]_D^{30}$ = −6.3 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$, ν, cm^{-1}) 3421 (br), 2986, 2116; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.86 (d, *J* = 3.9Hz, 1H, 1CH), 4.63 (d, *J* = 3.9Hz, 1H, 2CH), 4.30-4.20 (m, 1H, 5CH), 4.15 (dd, *J* = 9.0, 4.3 Hz, 1H, 6CHa), 4.06 (ABq, *J* = 12.9 Hz, 2H, 3C($C\underline{H}_2$OH)), 4.02 (dd, *J* = 9.0, 4.3Hz, 1H, 6CHb), 3.84 (d, *J* = 9.1Hz, 1H, 4CH), 2.91 (br, exchangeable with D_2O, 1H, OH), 1.54 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 113.1 ($\underline{C}(CH_3)_2$), 109.9 ($\underline{C}(CH_3)_2$), 104.3 (C1), 84.4 (C3), 81.8 (C2), 74.4 (C4), 72.5 (C5), 67.7 (C6), 62.1 (C3$\underline{C}H_2$OH), 26.7 (CH_3), 26.6 (CH_3), 26.3 (CH_3), 25.0 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{13}H_{21}N_3O_6Na$ [M + Na]: 338.1327; found: 338.1332 [M + Na].

3-Azido-3-deoxy-3-*C*-(benzyloxymethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**). To an ice-cooled solution of **6** (2.81 g, 8.91 mmol) in dry THF (15 mL), sodium hydride (0.445 g, 11.13 mmol) was added slowly and stirred for 15 min. Benzyl bromide (1.16 mL, 9.80 mmol) and catalytic amount of TBAI (0.329 g, 0.89 mmol) were added and stirred at room temperature. TLC analysis (Hexane/ EtOAc: 4/1) after 5 h indicated disappearance of the starting material and

formation of a single product. Reaction was quenched by adding saturated aq. NH_4Cl solution (5 mL) and THF was evaporated under reduced pressure. The residue was extracted with DCM (30 mL × 3) and concentrated. Purification by column chromatography (hexane/ EtOAc: 9.5/0.5) afforded **7** (3.32 g, 92%) as a thick liquid: R_f = 0.8 (hexane/ EtOAc: 4/1); $[\alpha]_D^{30}$ = +7.36 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 2116; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.44-7.26 (m, 5H, Ph), 5.84 (d, *J* = 3.6 Hz, 1H, 1CH), 4.72 (d, *J* = 3.6 Hz, 1H, 2CH), 4.68-4.56 (m, 2H, OCH_2Ph), 4.26-4.16 (m, 1H, 5CH), 4.07 (dd, *J* = 8.8, 6.5 Hz, 1H, 6CHa), 4.04-3.90 (m, 2H, 6CHb and 3C(CH_2O)), 3.86 (d, *J* = 9.9Hz, 1H, 4CH), 3.70 (d, *J* = 8.3Hz, 1H, 3C(CH_2O)), 1.51 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 137.9 (Ph), 128.9 (Ph), 127.7 (Ph), 127.6 (Ph), 112.9 ($\underline{C}(CH_3)_2$), 109.5 ($\underline{C}(CH_3)_2$), 104.6 (C1), 83.4 (C3), 80.8 (C2), 73.8 (O$\underline{C}H_2Ph$), 73.6 (C4), 73.0 (C5), 69.3 (C6), 67.6 (C3$\underline{C}H_2O$), 27.0 (CH_3), 26.7 (CH_3), 26.6 (CH_3), 25.1 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{20}H_{27}N_3O_6Na$ [M + Na]: 428.1797; found: 428.1796 [M + Na].

3-Azido-3-deoxy-3-*C*-(benzyloxymethyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (**8**). Compound **7** (3.32 g, 81.88 mmol) was dissolved in acetic acid:water (3:2, 30 mL) and stirred at 55 °C. TLC analysis (Hexane/ ethyl acetate: 4/1) after 3 h indicated disappearance of the starting material and formation of a single product. Acetic acid was evaporated under reduced pressure and the residue was neutralized by saturated aq. $NaHCO_3$ solution and extracted with ethyl acetate (30 mL × 3). Combined organic layer was dried over sodium sulphate and concentrated. Purification by column chromatography (hexane/ ethyl acetate: 7/3) afforded **8** (2.73 g, 91%) as a thick liquid: R_f = 0.5 (hexane/ EtOAc: 1/1); $[\alpha]_D^{30}$ = +26.05 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 3401(br), 2117, 1613, 1455, 1253; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.42-7.30 (m, 5H, Ph), 5.85 (d, *J* = 3.8 Hz, 1H, 1CH), 4.66 (ABq, J = 11.4 Hz, 2H, O$\underline{CH_2}$Ph), 4.60 (d, *J* = 3.8 Hz,

1H, 2CH), 4.04-3.90 (m, 3H, 6CHa and 3C(C$\underline{H_2}$O)), 3.89-3.83 (m, 1H, 5CH), 3.80 (d, *J* = 3.3 Hz, 1H, 4CH), 3.70 (dd, *J* = 11.4, 4.7 Hz, 1H, 6CHb), 2.04-1.80 (br, 2H, exchangeable with D_2O, OH), 1.50 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 136.8 (Ph), 128.6 (Ph), 128.1 (Ph), 127.9 (Ph), 113.1 ($\underline{C}(CH_3)_2$), 104.0 (C1), 84.2 (C2), 81.2 (C3), 74.0 (C4), 73.6 (C5), 69.1 (O$\underline{C}H_2$Ph), 68.8 (C3$\underline{C}H_2$O), 64.1 (C6), 26.8 (CH_3), 26.5 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{17}H_{23}N_3O_6Na$ [M + Na]: 388.1484; found: 388.1485 [M + Na].

3-Azido-3-deoxy-3-*C*-(benzyloxymethyl)-1,2-*O*-isopropylidene-α-D-xylofuranose (**9**). To an ice-cooled stirred solution of **8** (2.00 g, 5.47 mmol) in acetone/water (9:1, 20 mL), sodium metaperiodate (1.75 g, 8.21 mmol) was added slowly. TLC analysis (Hexane/EtOAc: 1/1) after 3 h indicated disappearance of the starting material. The reaction mixture was quenched with ethylene glycol (2 mL), acetone was evaporated under reduced pressure and the reaction mixture was filtered through celite and washed with EtOAc. The solvent was evaporated under reduced pressure to afford a thick liquid (crude weight 1.74 g, 5.24 mmol). To an ice cold stirred solution of the above crude product in methanol (15 mL), sodium borohydride (0.2 g, 5.24 mmol) was added slowly. TLC analysis (Hexane/EtOAc: 7/3) after 15 min indicated disappearance of the starting material and formation of a single product. Reaction was quenched by adding saturated aq. NH_4Cl solution (3 mL) and methanol was evaporated under reduced pressure. The residue was extracted with EtOAc (30 mL × 2) and concentrated. Purification by column chromatography (hexane/ EtOAc: 7/3) afforded **9** (1.50 g, 85%) as a thick liquid; R_f = 0.45 (Hexane/ EtOAc: 3/2); $[\alpha]_D^{30}$ = +18.73 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 3482(br), 2112, 1541, 1456; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.42-7.28 (m, 5H, Ph), 5.89 (d, *J* = 3.6 Hz, 1H, 1CH), 4.63 (ABq, *J* = 11.3 Hz, 2H, OC$\underline{H_2}$Ph), 4.58 (d, *J* = 3.6 Hz, 1H, 2CH), 4.10 (t, J = 5.7 Hz, 1H, 4CH), 3.93 (d, *J* = 10.3 Hz, 1H, 3C(C$\underline{H_2}$O)), 3.80 (d, *J* = 10.3 Hz, 1H, 3C(C$\underline{H_2}$O)), 3.82-3.77

(m, 2H, 5CHa and 5CHb), 2.67 (br t, 1H, exchangeable with D_2O, OH), 1.51 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 136.9 (Ph), 128.6 (Ph), 128.2 (Ph), 127.9 (Ph), 113.1 ($\underline{C}(CH_3)_2$), 104.2 (C1), 84.2 (C2), 82.0 (C4), 74.1 ($O\underline{C}H_2Ph$), 73.0 (C3), 69.1 ($C3\underline{C}H_2O$), 60.3 (C5), 26.8 (CH_3), 26.5 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{16}H_{21}N_3O_5Na$ [M + Na]: 358.1378; found: 358.1384 [M + Na].

3-Azido-3-deoxy-3-*C*-(benzyloxymethyl)-5-*O*-*p*-tolylsulfonyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**10**). To a stirred solution of **9** (1.50 g, 4.47 mmol) in dry pyridine (10 mL), tosyl chloride (1.02 g, 5.36 mmol) and catalytic amount of DMAP (0.053 g, 0.44 mmol) were added. The reaction mixture was heated at 60 °C. TLC analysis (Hexane/ EtOAc: 4/1) after 5 h indicated disappearance of the starting material and formation of a single product. Pyridine was removed under reduced pressure. Purification by column chromatography (hexane/ EtOAc: 9/1) afforded **10** (1.95 g, 88%) as a thick liquid; R_f = 0.65 (Hexane/ EtOAc: 4/1); $[\alpha]_D^{29}$ = +46.88 (*c* 0.27, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 2115, 1597, 1496, 1454, 1177; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.74 (d, *J* = 8.1 Hz, 2H, Ph), 7.41-7.29 (m, 7H, Ph), 5.84 (d, *J* = 3.4 Hz, 1H, 1CH), 4.61-4.58 (d, 3H, 2CH and $OC\underline{H_2}Ph$), 4.29 (dd, *J* = 9.1, 3.3Hz, 1H, 4CH), 4.11-4.023 (m, 2H, 5CHa and 5CHb), 3.87 (d, *J* = 10.5 Hz, 1H, $3C(C\underline{H_2}O)$), 3.73 (d, *J* = 10.5 Hz, 1H, $3C(C\underline{H_2}O)$), 2.43 (s, 3H, $PhC\underline{H_3}$), 1.46 (s, 3H, (CH_3)), 1.32 (s, 3H, (CH_3)); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 145.1 (Ph), 137.3 (Ph), 132.5 (Ph), 129.9 (Ph), 128.5 (Ph), 128.1 (Ph), 127.9 (Ph), 127.8 (Ph), 113.3 ($\underline{C}(CH_3)_2$), 104.6 (C1), 83.3 (C2), 78.5 (C4), 73.9 ($O\underline{C}H_2Ph$), 73.0 (C3), 69.0 (C5), 68.1 ($3C(\underline{C}H_2O)$), 26.9 (CH_3), 26.6 (CH_3), 21.7 ($Ph\underline{C}H_3$); HRMS (ESI-TOF) m/z calculated for $C_{23}H_{27}N_3O_7SNa$ [M + Na]: 512.1462; found: 512.1461 [M + Na].

3,5-Dideoxy-3-*C*-(benzyloxymethyl)-3,5-imino1,2-*O*-isopropylidene-α-D-xylofuranose (**11**).

To a solution of **10** (1.95 g, 3.98 mmol) in methanol, (15 mL) 10% Pd/C (0.042 g, 0.39 mmol) was added and the reaction mixture was hydrogenated at 100 psi at room temperature. TLC analysis (Hexane/ EtOAc: 4/1) after 3 h indicated disappearance of the starting material and formation of a single product. The catalyst was filtered through celite, washed with methanol and the solvent was evaporated under reduced pressure. Purification by column chromatography afforded **11** as thick liquid (0.94 g, 79%); R_f = 0.32 (EtOAc); $[\alpha]_D^{29}$ = +26.74 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 3331(br), 1652, 1456; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.40-7.30 (m, 5H, Ph), 6.27 (d, *J* = 3.8 Hz, 1H, 1CH), 4.76 (dd, , *J* = 5.2, 1.0 Hz, 1H, 4CH), 4.62 (ABq, *J* = 11.0 Hz, 2H, $OC\underline{H_2}Ph$), 4.43 (d, *J* = 3.8 Hz, 1H, 2CH), 3.80 (ABq, *J* = 10.5 Hz, 2H, $3C(C\underline{H_2}O)$), 3.70 (dd, *J* = 9.0, 5.2 Hz, 1H, 5CHa), 3.08 (dd, *J* = 9.0, 1.0 Hz, 1H, 5CHb), 2.23 (br, 1H, exchangeable with D_2O, NH), 1.43 (s, 3H, CH_3), 1.36 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 137.9 (Ph), 128.4 (Ph), 127.8 (Ph), 127.6 (Ph), 114.2 ($\underline{C}(CH_3)_2$), 108.9 (C1), 86.1 (C2), 79.8 (C4), 73.4 ($O\underline{C}H_2Ph$), 73.3 (C3), 68.8 ($3C(\underline{C}H_2O)$), 51.0 (C5), 28.1 (CH_3), 27.3 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{16}H_{22}NO_4$ [M + H]: 292.1549; found: 292.1552 [M + H].

***N*-Benzyloxycarbonyl-3-*C*-(benzyloxymethyl)-3,5-dideoxy--3,5-imino-1,2-*O*-isopropylidene-α-D-xylofuranose** (**12**). To an ice cold stirred solution of **11** (0.30 g, 1.02 mmol) in methanol:water (9:1, 10 mL) sodium bicarbonate (0.095 g, 1.13 mmol) was added, followed by slow drop wise addition of carbobenzyloxy chloride 50% solution (0.35 mL, 1.23 mmol) and reaction mixture was stirred. TLC analysis (Hexane/ EtOAc, 2:3) after 2 h indicated disappearance of the starting material and formation of a single product. The solvent was evaporated under reduced pressure and the resulting residue was extracted with chloroform (20 ml x 2) and concentrated. Purification by column chromatography (hexane/ EtOAc: 4/1) afforded **12** as a thick liquid (0.39 g, 89%); R_f = 0.55 (Hexane/EtOAc: 4/1); $[\alpha]_D^{29}$ = +11.0 (*c* 0.7, $CHCl_3$);

IR ($CHCl_3$, ν, cm^{-1}) 1706, 1497, 1454; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.36-7.20 (m, 10H, Ph), 6.17-6.15 (m, 1H, 1CH), 5.10-5.02 (m, 2H, NCOOC$\underline{H_2}$Ph), 4.85-4.75 (m, 1H, 4CH), 4.65-4.30 (m, 3H, 2CH and OC$\underline{H_2}$Ph), 4.10-3.97 (m, 2H, 5CHa and 5CHb), 3.91-3.70 (m, 1H, 3C(C$\underline{H_2}$O)), 3.57-3.47 (m, 1H, 3C(C$\underline{H_2}$O), 1.43 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 155.7 (N$\underline{C}$OO), 137.8 (Ph), 136.2 (Ph), 128.4 (Ph), 128.3 (Ph), 128.1 (Ph), 127.9 (Ph), 127.7 (Ph), 127.6 (Ph), 127.5 (Ph), 127.3 (Ph), 114.8 ($\underline{C}(CH_3)_2$), 108.9 (C1), 83.2 (C3), 78.9 (C2), 77.1 (C4), 73.3 (NCOO$\underline{C}H_2$Ph), 66.8 (O$\underline{C}H_2$Ph), 65.7 (C5), 56.6 (C6), 27.8 (CH_3), 27.2 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{24}H_{28}NO_6$ [M + H]: 426.1916; found: 426.1921 [M + H].

(2*S*,3*R*)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-2-hydroxylmethyl-azetidin-3-ol (**13**). A solution of **12** (0.39 g, 0.91 mmol) in TFA:H_2O (4 mL, 3:1) was stirred at 0 °C. TLC analysis (Hexane/ EtOAc: 4/1) after 2 h indicated disappearance of the starting material. TFA was co-evaporated with toluene under reduced pressure. The residue obtained (crude weight 0.35 g, 0.91 mmol) was dissolved in acetone/water (9:1, 10 mL), cooled to 0 °C, to this stirred solution, $NaIO_4$ (0.29 g, 1.09 mmol) was added slowly. TLC analysis (Hexane/EtOAc, 7:3) after 3 h indicated disappearance of the starting material. The reaction mixture was quenched with ethylene glycol (1 mL), acetone was evaporated under reduced pressure and filtered through celite and washed with EtOAc. The solvent was evaporated under reduced pressure to afford a thick liquid (crude weight 0.29 g, 0.75 mmol). To an ice cold stirred solution of above crude product in methanol (10 mL), sodium borohydride (0.043 g, 1.13 mmol) was added. TLC analysis (Hexane/EtOAc: 7/3) after 2 h indicated disappearance of the starting material and formation of a single product. Reaction was quenched by adding saturated aq. NH_4Cl solution (3 mL) and methanol was evaporated under reduced pressure. The residue was extracted with

EtOAc (20 mL × 2) and concentrated. Purification by column chromatography (hexane/EtOAc: 3/2) gave **13** (0.23 g, 72%) as a thick liquid; R_f = 0.57 (Hexane/EtOAc 1:4); $[\alpha]_D^{29}$ = -3.91 (*c* 0.44, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 3412 (br), 1682, 1425; ^1H NMR (200 MHz, $CDCl_3$+ D_2O) δ (ppm) 7.59-7.05 (m, 10H, Ph), 5.20-4.97 (m, 2H, NCOOC$\underline{H_2}$Ph), 4.65-4.33 (m, 3H, 3CH and OC$\underline{H_2}$Ph), 4.25-4.05 (m, 1H, 4CHa), 4.04-3.80 (m, 2H, 2C(C$\underline{H_2}$O)), 3.79-3.35 (m, 3H, 4CHb and 2C(C$\underline{H_2}$OH)); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 156.1 (N$\underline{C}$OO), 137.8 (Ph), 136.4 (Ph), 128.4 (Ph), 128.1 (Ph), 127.9 (Ph), 127.7 (Ph), 127.5 (Ph), 75.5 (NCOO$\underline{C}H_2$Ph), 73.5 (2C(O$\underline{C}H_2$Ph)), 69.2 (C2), 67.3 (C3), 66.9 (2C($\underline{C}H_2$O)), 61.7 (2C($\underline{C}H_2$OH)), 57.6 (C4); HRMS (ESI-TOF) m/z calculated for $C_{20}H_{24}NO_5$ [M + H]: 358.1654; found: 358.1663 [M + H].

(3*R*)-2,2-Bis(hydroxymethyl)-azetidin-3-ol (**2a**). To a solution of **13** (0.23 g, 0.64 mmol) in methanol (10 mL), 20% $Pd(OH)_2/C$ (0.009 g, 0.06 mmol) was added and the reaction mixture was hydrogenated at 100 psi. TLC analysis (Hexane/EtOAc: 1/4) after 12 h indicated disappearance of the starting material and formation of a single product. The reaction mixture was filtered through celite, washed with methanol and the solvent was evaporated under reduced pressure. Purification by column chromatography (chloroform/methanol: 4/1) afforded **2a** (0.082 g, 95%) as a sticky solid, R_f = 0.2 ($CHCl_3$/MeOH: 3/2); $[\alpha]_D^{29}$ = -19.93 (*c* 0.3, H_2O); IR (MeOH, *v*, cm^{-1}) 3310 (br); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.59 (dd, *J* = 7.8 and 6.5 Hz, 1H, 3CH), 4.02 (dd, *J* = 12.0, 7.8 Hz, 1H, 4CHa), 3.96 (d, *J* = 16.0 Hz, 1H, C$\underline{H_2}$OH), 3.77 (d, *J* = 16.0 Hz, 1H, C$\underline{H_2}$OH), 3.76 (dd, *J* = 12.0, 7.8 Hz, 1H, 4CHb), 3.68 (ABq, *J* = 12 Hz, 2H, C$\underline{H_2}$OH); ^{13}C NMR (100 MHz, D_2O) δ (ppm), 77.3 (C2), 64.6 (C3), 59.9 ($\underline{C}H_2$OH), 57.6 ($\underline{C}H_2$OH), 50.4 (C4); HRMS (ESI-TOF) m/z calculated for $C_5H_{12}NO_3$ [M + H]: 134.0817; found: 134.0822 [M + H].

***N*-Benzyloxycarbonyl-3-*C*-(benzyloxymethyl)-1,3-dideoxy-1,3-imino-D-xylitol** (**14**). Compound **12** (0.39 g, 0.91 mmol scale) on reaction with TFA:H_2O as described for **13** afforded

a mixture of hemiacetals (crude weight 0.30 g, 0.77 mmol). That was dissolved in THF/water (9:1, 10 mL), cooled to 0 °C and $NaBH_4$ (0.058 g, 1.55 mmol) were slowly added and stirred. TLC analysis (Hexane/EtOAc: 7/3) after 12 h indicated disappearance of the starting material and formation of a single product. Reaction was quenched by adding saturated aq. NH_4Cl solution (3 mL) and THF was evaporated under reduced pressure. The residue was extracted with EtOAc (20 mL × 2) and concentrated. Purification by column chromatography (hexane/EtOAc: 3/2) afforded **14** (0.25 g, 78%) as a thick liquid; R_f = 0.5 (EtOAc); $[\alpha]_D^{29}$ = −42.22 (*c* 0.13, $CHCl_3$); IR ($CHCl_3$, *v*, cm−1) 3364 (br), 1670, 1497, 1420; ^{1}H NMR (500 MHz, $CDCl_3$+D_2O) δ (ppm) 7.35-7.24 (m, 10H, Ph), 5.15 (d, *J* = 12.0 Hz, 1H, NCOOC$\underline{H_2}$Ph), 5.04 (d, *J* = 12.0 Hz, 1H, NCOOC$\underline{H_2}$Ph), 4.64 (dd, *J* = 7.8, 4.5 Hz, 1H, OC$\underline{H_2}$Ph), 4.54 (d, *J* = 12.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.45 (d, *J* = 12.0 Hz, 1H, 1CHa), 4.27 (dd, *J* = 9.5, 7.8 Hz, 1H, 4CH), 3.90 (d, *J* = 10.0 Hz, 1H, 3C(C$\underline{H_2}$O), 3.81 (bd, 1H, *J* = 12.5 Hz, 1H, 5CHa), 3.68 (dd, *J* = 9.5, 4.5 Hz, 1H, 1CHb), 3.62 (dd, *J* = 12.5, 4.5 Hz, 1H, 5CHb), 3.57 (d, *J* = 10.0 Hz, 1H, 3C(C$\underline{H_2}$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.5 (NCOO), 137.7 (Ph), 136.1 (Ph), 128.5 (Ph), 128.3 (Ph), 127.9 (Ph), 127.5 (Ph), 77.2 (C2), 73.5 (NCOO$\underline{C}H_2$Ph), 70.5 (O$\underline{C}H_2$Ph), 67.8 (C3), 67.4 (C4), 67.3 (3C(CH_2O)), 60.9 (C5), 58.9 (C1); HRMS (ESI-TOF) m/z calculated for $C_{21}H_{26}NO_6$ [M + H]: 388.1760; found: 388.1770 [M + H].

3-Hydroxymethyl-1,3-dideoxy-1,3-imino-D-xylitol (**2b**). Compound **14** (0.25 g, 0.66 mmol scale) on reaction with 20% $Pd(OH)_2$/C and on purification by column chromatography as described for **2a** afforded **2b** (0.10 g, 93%) as a sticky solid; R_f = 0.25 ($CHCl_3$/MeOH: 1/1); $[\alpha]_D^{28}$ = −8.7 (*c* 0.2, H_2O); IR (MeOH, *v*, cm^{-1}) 3309 (br); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm), 4.83 (m, 1H, merged in D_2O peak, 2CH), 4.36 (dd, *J* = 5.7, 2.7 Hz, 1H, 4CH), 4.21 (dd, *J* = 12.6, 5.7 Hz, 1H, 1CHa), 3.94 (d, *J* = 6.0 Hz, 1H, 1CHb), 3.99 (d, *J* = 6.0 Hz, 2H, 3C(C$\underline{H_2}$OH), 3.81

(dd, *J* = 12.2, 2.7 Hz, 1H, 5CHa), 3.65 (dd, *J* = 12.2, 5.8 Hz, 1H, 5CHb); ^{13}C NMR (125 MHz, D_2O) δ (ppm), 78.4 (C3), 67.9 (C4), 65.1 (C2), 61.6 3 (C($\underline{C}H_2OH$)), 58.9 (C5), 50.7 (C1); HRMS (ESI-TOF) m/z calculated for $C_6H_{14}NO_4$ [M + H]: 164.0923; found: 164.0922 [M + H].

(2*S*,3*R*)-1-(Benzyloxycarbonyl)-2-(benzyloxymethyl)-3-hydroxy-azetidine-2-carboxylic acid (**15**). Compound **12** (0.30 g, 0.70 mmol scale) on reaction with TFA:H_2O as described for **13** afforded a mixture of hemiacetals (crude weight 0.25 g, 0.64 mmol). This crude mixture was dissolved in acetone/water (9:1, 10 mL), cooled to 0 °C and $NaIO_4$ (0.21 g, 0.97 mmol) was added slowly and stirred. TLC analysis (Hexane/EtOAc: 7/3) after 3 h indicated disappearance of the starting material. The reaction mixture was quenched with ethylene glycol (1 mL), acetone was evaporated under reduced pressure and the reaction mixture was filtered through celite and washed with EtOAc. The solvent was evaporated under reduced pressure to afford a thick liquid (crude weight 0.22 g, 0.71 mmol). To a stirred solution of the above crude product in acetonitrile (5 mL), solution of sodium dihydrogen phosphate (0.018 g, 0.12 mmol) in water (3 mL) and 30% H_2O_2 (0.06 mL, 0.64 mmol) were added and cooled to −10 °C. To this stirred reaction mixture, solution of $NaClO_2$ (0.084 g, 0.93 mmol) in water (2.5 mL) was added dropwise over 15 min and stirred at 15 °C and the reaction was monitored by the evolution of oxygen with bubbler connected to the apparatus. After 10 h, the reaction was decomposed by addition of small amount of Na_2SO_3 (0.02 g), acidified with 10% HCl (5 mL) and extracted with EtOAc (3× 20 mL). The combined organic layer was concentrated. Purification by column chromatography (hexane/ EtOAc: 7/3) afforded **15** (0.18 g, 69% from **12**) as a thick liquid, R_f = 0.26 (EtOAc); $[\alpha]_D^{29}$ = -35.45 (*c* 0.11, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 3419(br), 1700; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.53-9.25 (br, 1H, exchangeable with D_2O, COOH), 7.98-7.45 (br, 1H, exchangeable with D_2O, OH), 7.38-7.12 (m, 10H, Ph), 5.15-5.03 (m, 2H, NCOOC$\underline{H_2}$Ph), 4.65-

4.63 (m, 1H, 3CH), 4.62-4.32 (m, 3H, 4CHa and OC$\underline{H_2}$Ph), 4.15-3.80 (m, 3H, 4CHb and 2C(C$\underline{H_2}$O)); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 174.7 (COOH), 156.5 (NCOO), 136.9 (Ph), 135.6 (Ph), 128.9 (Ph), 128.8 (Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (Ph), 128.3 (Ph), 128.2 (Ph), 127.9 (Ph), 77.3 (C2), 73.6 (NCOO$\underline{C}H_2$Ph), 73.5 (O$\underline{C}H_2$Ph), 69.7 (C3), 68.5 (3C($\underline{C}H_2$O)), 58.4 (C4); HRMS (ESI-TOF) m/z calculated for $C_{20}H_{22}NO_6$ [M + H]: 372.1447; found: 372.1453 [M + H].

(2*S*,3*R*)-2-Hydroxymethyl-3-hydroxy-azetidine-2-carboxylic acid (**2c**). Compound **15** (0.20 g, 0.56 mmol scale) on reaction with 20% $Pd(OH)_2$/C as described for **2a** afforded **2c** as a sticky solid (0.065 g, 92%) and no further purification was needed, R_f = 0.35 (NH_4OH/MeOH: 0.5/9.5); $[\alpha]_D^{29}$ = -51.36 (*c* 0.26, H_2O); IR (neat, *v*, cm^{-1}) 1619; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.71 (t, *J* = 6.4 Hz, 1H, 3CH), 4.29 (dd, *J* = 11.3, 6.0 Hz 1H, 4CHa), 4.10 (s, 2H, C$\underline{H_2}$OH), 3.90 (dd, *J* = 11.3, 6.0 Hz, 1H, 4CHb); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 168.8 (COOH), 80.2 (C2), 64.9 (C3), 60.7 ($\underline{C}H_2$OH), 50.9 (C4); HRMS (ESI-TOF) m/z calculated for $C_5H_{10}NO_4$ [M + H]: 148.0610; found: 148.0616 [M + H].

3,5-Dideoxy-3-*C*-(hydroxymethyl)-3,5-imino-1,2-di-*O*-isopropylidene-α-D-xylofuranose (**2f**). To a solution of **12** (0.20 g, 0.47 mmol) in methanol (15 mL), 10% Pd/C (0.01 g, 0.094 mmol) was added and the reaction mixture was hydrogenated at 100 psi at room temperature. TLC analysis (Hexane/ EtOAc: 4/1) after 12 h indicated disappearance of the starting material and formation of a single product. The catalyst was filtered through celite, washed by methanol and solvent was evaporated under reduced pressure. Purification by column chromatography afforded **2f** (0.088 g, 94%) as a sticky solid; R_f = 0.5 ($CHCl_3$/MeOH: 4/1); $[\alpha]_D^{25}$ = +36.0 (*c* 0.14, H_2O); IR (MeOH, *v*, cm^{-1}) 3309 (br); ^{1}H NMR (500 MHz, D_2O) δ (ppm), 6.39 (d, *J* = 3.7 Hz, 1H, 1CH), 5.05 (d, *J* = 3.7 Hz, 1H, 2CH), 4.93 (dd, *J* = 5.2, 2.1 Hz, 1H, 4CH), 4.13 (dd, *J* = 12.3,

2.1 Hz, 1H, 5CHa), 4.07 (ABq, *J* = 15.0 Hz, 2H, 3C(C$\underline{H_2}$OH)), 3.66 (dd, *J* = 12.3, 2.1 Hz, 1H, 5CHb); ^{13}C NMR (125 MHz, D_2O) δ (ppm), 116.1 (C$\underline{(CH_3)_2}$), 108.2 (C1), 82.2 (C2), 79.3 (C3), 77.6 (C4), 57.8 (3C(C$\underline{H_2}$OH)), 50.6 (C5), 26.5 (CH_3), 26.1 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_9H_{16}NO_4$ [M + H]: 202.1073; found: 202.1089 [M + H].

3-Azido-3-deoxy-3-*C*-benzyloxymethyl-6-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**16**). To a mixture of compound **8** (1.0 g, 2.73 mmol), dibutyltin oxide (0.068 g, 0.27 mmol) and tetrabutylammonium bromide (0.264 g, 0.82 mmol), diisopropyl ethyl amine (1.12 mL, 6.84 mmol) and benzyl bromide (0.81 mL, 6.84 mmol) were added sequentially under air. The reaction mixture was then heated at 70 °C (neat), TLC analysis (Hexane/ EtOAc: 7/3) after 5 h indicated disappearance of the starting material and formation of a single product. Reaction was quenched by adding 5 ml of water and extracted with DCM (30 mL × 3) and concentrated. Purification by column chromatography (hexane/ EtOAc: 9/1) afforded **16** (1.19 g, 95%) as a thick liquid: R_f = 0.48 (hexane/ EtOAc: 4/1); $[\alpha]_D^{28}$ = +15.50 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 3431(br), 2116, 1261, 1095, ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.45-7.26 (m,10H, Ph), 5.86 (d, *J* = 3.5 Hz, 1H, 1CH), 4.71 (d, *J* = 10.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.70 (d, *J* = 3.5 Hz, 1H, 2CH), 4.65-4.55 (m, 3H, OC$\underline{H_2}$Ph), 4.08 (d, *J* =10.5 Hz, 1H, 4CH), 4.05-3.98 (m, 1H, 5CH), 3.97-3.90 (m, 2H, 3C(C$\underline{H_2}$O)), 3.75 (dd, *J* = 9.8, 2.6 Hz, 1H, 6CHa), 3.58 (dd, *J* = 9.8, 5.8 Hz, 1H, 6CHb), 2.96 (d, *J* = 4.4 Hz, 1H, exchangeable with D_2O, OH), 1.38 (s, 3H, CH_3), 1.53 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 137.9 (Ph), 137.4 (Ph), 128.5 (Ph), 128.4 (Ph), 127.7 (Ph), 127.6 (Ph), 112.9 (C$\underline{(CH_3)_2}$), 104.2 (C1), 83.8 (C2), 80.1 (C4), 74.0 (C3), 73.7 (C5), 73.4 (OC$\underline{H_2}$Ph), 71.7 (OC$\underline{H_2}$Ph), 69.1 (3C(C$\underline{H_2}$O), 68.1 (C6), 26.9 (CH_3), 26.6 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{24}H_{29}N_3O_6Na$ [M + Na]: 478.1953; found: 478.1951 [M + Na].

3-Azido-3-deoxy-3-*C*-benzyloxymethyl-6-*O*-benzyl-5-*O*-methanesulfonyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**17**). To an ice-cooled solution of **16** (0.30 g, 0.65 mmol) in dry DCM (10 mL), triethyl amine (0.38 mL, 1.97 mmol) was added slowly and stirred for 15 min. To this stirred solution, methane sulfonyl chloride (0.07 mL, 0.98 mmol) was added. TLC analysis (Hexane/ EtOAc: 4/1) after 1 h indicated disappearance of the starting material and formation of a single product. Reaction was quenched by adding 3 ml of water, extracted with DCM (20 mL × 3) and concentrated. Purification by column chromatography (hexane/ EtOAc: 9/1) afforded **17** (0.34 g, 97%) as a thick liquid: R_f = 0.5 (hexane/ EtOAc: 4/1); $[\alpha]_D^{28}$ = +23.56 (*c* 0.46, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 2118, 1651, 1359, 1261, 800, ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.50 – 7.30 (m,10H, Ph), 5.88 (d, *J* = 3.4 Hz, 1H, 1CH), 5.02 (dt, *J* = 6.6, 1.9 Hz, 1H, 5CH), 4.80 (d, *J* = 3.4 Hz, 1H, 2CH), 4.65 (ABq, *J* = 15.0 Hz, 2H, OC$\underline{H_2}$Ph), 4.64 (d, *J* =11.8 Hz, 1H, OC$\underline{H_2}$Ph), 4.53 (d, *J* =11.8 Hz, 1H, OC$\underline{H_2}$Ph), 4.09 (d, *J* = 7.1 Hz, 1H, 4CH), 3.96 (ABq, *J* = 10.0 Hz, 2H, 3C(C$\underline{H_2}$O)), 3.92 (dd, *J* = 11.7, 1.9 Hz, 1H, CHa), 3.73 (dd, *J* = 11.7, 6.6 Hz, 1H, CHb), 2.94 (s, 3H, $OSO_2C\underline{H_3}$), 1.53 (s, 3H, CH_3), 1.39 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 137.7 (Ph), 137.4 (Ph), 128.5 (Ph), 128.4 (Ph), 127.9 (Ph), 127.8 (Ph), 113.2 ($\underline{C}(CH_3)_2$), 104.2 (C1), 83.1 (C4), 78.6 (C2), 78.3 (C3), 73.7 (C5), 73.3 (O$\underline{C}H_2$Ph), 73.1 (O$\underline{C}H_2$Ph), 69.6 (C6), 69.4 (3C($\underline{C}H_2$O)), 38.9 ($OSO_2\underline{C}H_3$), 27.0 (CH_3), 26.7 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{25}H_{31}N_3O_8SNa$ [M + Na]: 556.1729; found: 556.1733 [M + Na].

3-*C*-[(Benzyloxymethyl)-*N*-benzyloxycarbonyl]-3-deoxy-6-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**18**). To a stirred solution of **17** (1.19 g, 2.61 mmol) in dry MeOH (15 mL), triethyl amine (0.72 mL, 5.22 mmol) and 1,3-dithiane (0.52 mL, 5.22 mmol) were added sequentially under nitrogen atmosphere. TLC analysis (Hexane/ EtOAc: 4/1) after 48 h indicated disappearance of the starting material and formation of a single product. The reaction mixture

was filtered through celite, washed with methanol and concentrated. The crude residue obtained (crude weight 1.01 g, 2.35 mmol) was dissolved in 20 mL methanol:water (9:1) and cooled to 0 °C. To this cooled solution, sodium bicarbonate (0.59 g, 7.05 mmol) was added followed by slow drop wise addition of carbobenzyloxy chloride 50% solution (0.60 mL, 3.52 mmol) and the reaction mixture was stirred. TLC analysis (Hexane/ EtOAc, 3:2) after 2 h indicated disappearance of the starting material and formation of a single product. The solvent was evaporated under reduced pressure, resulting residue was extracted with chloroform (30 ml x 2) and concentrated. Purification by column chromatography (hexane/ EtOAc: 4/1) afforded **18** (1.21 g, 92%) as a thick liquid: R_f = 0.5 (hexane/ EtOAc, 4:1); $[\alpha]_D^{25}$ = +12.09 (*c* 0.21, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 3417(br), 3358(br), 1728,^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.37-7.17 (m,15H, Ph), 5.81 (d, *J* = 3.5 Hz, 1H, 1CH), 5.25 (s, 1H, exchangeable with D_2O, NH), 5.03 (d, *J* = 12.2 Hz, 1H, NCOOC$\underline{H_2}$Ph), 4.95 (d, *J* = 12.2 Hz, 1H, NCOOC$\underline{H_2}$Ph), 4.90 (d, *J* = 3.5 Hz, 1H, 2CH), 4.52 – 4.42 (m, 4H, OC$\underline{H_2}$Ph), 4.22 – 4.16 (m, 2H, one is exchangeable with D_2O and becomes multiplet corresponding to 1H, 5CH and OH), 4.02 (d, *J* = 8.6 Hz, 1H, 4CH), 3.79 - 3.72 (m, 2H, 3C(C$\underline{H_2}$O)), 3.69 (dd, *J* = 10.0 and 2.4 Hz, 1H, 6CHa), 3.53 (dd, *J* = 10.0, 5.7 Hz, 1H, 6CHb), 1.42 (s, 3H, CH_3) ,1.23 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 155.4 (NCOO), 138.2 (Ph), 136.7 (Ph), 136.1 (Ph), 128.6 (Ph), 128.5 (Ph), 128.3 (Ph), 128.1 (Ph), 128.0 (Ph), 127.8 (Ph), 127.5 (Ph), 112.5 ($\underline{C}(CH_3)_2$), 104.3 (C1), 82.2 (C4),84.6 (C2), 77.2 (C3), 73.9 (NCOO$\underline{C}H_2$Ph), 73.5 (O$\underline{C}H_2$Ph), 71.6 (O$\underline{C}H_2$Ph), 68.1 (3C($\underline{C}H_2$O)), 68.0 (C5), 66.8 (C6), 26.7 (CH_3),26.4 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{32}H_{37}NO_8Na$ [M + Na]: 586.2411; found: 586.2410 [M + Na].

3-*C*-[(Benzyloxymethyl)-*N*-benzyloxycarbonyl]-3-deoxy-6-*O*-benzyl-5-*O*-methanesulfonyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**19**). To an ice-cooled solution of **18** (1.21 g, 2.14

mmol) in dry DCM (10 mL), triethyl amine (0.89 mL, 6.44 mmol) was added slowly and stirred for 15 min. To this solution, methane sulfonyl chloride (0.25 mL, 3.21 mmol) was added. TLC analysis (Hexane/ EtOAc: 4/1) after 1 h indicated disappearance of the starting material and formation of a single product. Reaction was quenched by adding 5 mL of water, extracted with DCM (30 mL × 3) and concentrated. Purification by column chromatography afforded **19** (1.25 g, 91%) as a thick liquid: R_f = 0.6 (hexane/ EtOAc: 4/1); $[\alpha]_D^{25}$ = +28.18 (*c* 0.17, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 3367, 1728, 1541,1456, 1261, ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.41 – 7.25 (m,10H, Ph), 6.23 (s, 1H, exchangeable with D_2O, NH), 6.02 (d, *J* = 3.5 Hz, 1H, 1CH), 5.17 (ddd, *J* = 6.5, 5.2, 4.0 Hz, 1H, 5CH), 5.07 (d, *J* = 10.0 Hz, 1H, NCOOC$\underline{H_2}$OPh), 5.02 (d, *J* = 3.5 Hz, 1H, 2CH), 5.0 (d, *J* = 10.0 Hz, 1H, NCOOC$\underline{H_2}$OPh), 4.61 – 4.46 (m, 4H, OC$\underline{H_2}$Ph), 4.21 (d, *J* = 5.2 Hz, 1H, 4CH), 4.08 (d, *J* = 9.9 Hz, 1H, 3C(C$\underline{H_2}$O)), 3.90 (dd, *J* = 10.9, 5.2 Hz, 1H, 6CHa), 3.73 – 3.67 (m, 2H, 6CHb and 3C(C$\underline{H_2}$O)), 2.92 (s, 3H, OSO_2CH_3), 1.47 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 155.6 (NCOO), 137.7 (Ph), 136.9 (Ph), 136.5 (Ph), 128.5 (Ph), 128.4 (Ph), 128.0 (Ph), 127.9 (Ph), 127.8 (Ph), 112.2 ($\underline{C}(CH_3)_2$), 105.4 (C1), 84.5 (C4), 82.1 (C2), 78.2 (C5), 77.2 (C3), 73.7 (NCOO$\underline{C}H_2$Ph), 73.4 (O$\underline{C}H_2$Ph), 69.1 (O$\underline{C}H_2$Ph), 68.7 (3C($\underline{C}H_2$O)), 66.7 (C6), 38.6 ($OSO_2\underline{C}H_3$), 26.9 (CH_3), 26.4 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{33}H_{39}NO_{10}SNa$ [M + Na]: 664.2186; found: 664.2189 [M + Na].

***N*-Benzyloxycarbonyl-3-*C*-(benzyloxymethyl)-6-*O*-benzyl-3,5-dideoxy--3,5-imino-1,2-*O*-isopropylidene-α-D-glucofuranose** (**20**). To a stirred solution of **19** (1.25 g, 1.94 mmol) in MeOH (10 mL), K_2CO_3 (0.40 g, 2.92 mmol) was added and the suspension was stirred at reflux under nitrogen atmosphere. TLC analysis (Hexane/ EtOAc: 4/1) after 1 h indicated disappearance of the starting material and formation of a single product. Reaction mixture was filtered through celite, washed by methanol and concentrated. Purification by column

chromatography afforded **20** (1.01 g, 95%) as a thick liquid: R_f = 0.6 (hexane/ EtOAc: 4/1); $[\alpha]_D^{25}$ = -17.0 (*c* 0.14, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 1672, ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.34-7.13 (m,15H, Ph), 5.47 (d, *J* = 3.3 Hz, 1H, 1CH), 5.07 (ABq, *J* = 15.0 Hz, 2H), 4.66 (t, *J* = 6.2 Hz, 1H, 5CH), 4.53 (d, *J* = 15.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.46 (d, *J* = 15.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.41 (ABq, *J* = 15.0 Hz, 2H, 3C(C$\underline{H_2}$O)), 4.23 – 4.19 (m, 2H, 2CH and 4CH), 3.72 - 3.64 (m, 4H, 6CHa, 6CHb and OC$\underline{H_2}$Ph), 1.40 (s, 3H, CH_3), 1.21 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 152.7 (NCOO), 138.1 (Ph), 137.9 (Ph), 136.5 (Ph), 128.4 (Ph), 128.3 (Ph), 128.0 (Ph), 127.9 (Ph), 127.7 (Ph), 127.6 (Ph), 127.5 (Ph), 112.9 ($\underline{C}(CH_3)_2$), 104.9 (C1), 86.6 (C4), 75.4 (C2), 74.2 (C3), 73.6 (C5), 73.5 (NCOO$\underline{C}H_2$Ph), 71.2 (3C($\underline{C}H_2$O)), 69.4 (O$\underline{C}H_2$Ph), 68.9 (O$\underline{C}H_2$Ph), 65.9 (C6), 27.3 (CH_3), 26.5 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{32}H_{36}NO_7$ [M + H]: 546.2492; found: 546.2487 [M + H].

(2*S*,3*R*,4*S*)-2,4-Bis(benzyloxymethyl)-2-hydroxymethyl-3-hydroxy-azetidine-1-carboxylic acid (**21a**).

Compound **20** (0.5 g, 0.91 mmol scale) on reaction with TFA:H_2O as described for **13** afforded a mixture of hemiacetals (crude weight 0.38 g, 0.91 mmol). This crude mixture was dissolved in acetone/water (9:1, 10mL), cooled to 0 °C and $NaIO_4$ (0.29 g, 1.37 mmol) were added slowly and stirred. TLC analysis (Hexane/EtOAc: 2/3) after 3 h indicated disappearance of the starting material. The reaction mixture was quenched with ethylene diol (1 mL), acetone was evaporated under reduced pressure and the reaction mixture was filtered through celite and washed with EtOAc. The solvent was evaporated under reduced pressure to afford a thick liquid (crude weight 0.37 g, 0.75 mmol). To an ice cold stirred solution of above crude product in methanol (10 mL), sodium borohydride (0.051 g, 1.36 mmol) was added. TLC analysis (Hexane/EtOAc: 2/3) after 3 h indicated disappearance of the starting material and formation of a single product. Reaction

was quenched by adding saturated aq. NH_4Cl solution (3 mL) and methanol was evaporated under reduced pressure. The residue was extracted with EtOAc (20 mL × 3) and concentrated. Purification by column chromatography (Hexane/EtOAc: 1/4) afforded **21a** (0.31 g, 88% from **20**) as a thick liquid: R_f = 0.3 (EtOAc); $[\alpha]_D^{25}$ = -87.63 (*c* 0.05, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 3398(br), 1730, ^{1}H NMR (500 MHz, $CDCl_3$+D_2O) δ (ppm) 7.29-7.13 (m, 10H, Ph), 4.50 – 4.32 (m, 5H, 3CH and OC$\underline{H_2}$Ph), 4.06 – 4.02 (m, 1H, 4CH), 3.83 (d, *J* = 11.7 Hz, 1H, 2C(C$\underline{H_2}$O)), 3.75 (dd, *J* = 10.0, 5.0 Hz, 1H, 4C(C$\underline{H_2}$O)), 3.71 (d, *J* = 11.7 Hz, 1H, 2C(C$\underline{H_2}$O)), 3.67 (dd, *J* = 10.0, 4.7 Hz, 1H, 4C(C$\underline{H_2}$O)), 3.35 (d, *J* = 9.8 Hz, 1H, C$\underline{H_2}$OH), 3.26 (d, *J* = 9.8 Hz, 1H, C$\underline{H_2}$OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 154.9 (NCOO), 137.9 (Ph), 137.4 (Ph), 128.5 (Ph), 127.9 (Ph), 127.8 (Ph), 127.7 (Ph), 75.8 (C2), 73.8 (O$\underline{C}H_2$Ph), 73.5 (O$\underline{C}H_2$Ph), 71.9 (C3), 69.2 (C4), 64.9 (2C($\underline{C}H_2$O), 63.4 (4C($\underline{C}H_2$O), 60.2 ($\underline{C}H_2$OH),; HRMS (ESI-TOF) m/z calculated for $C_{21}H_{26}NO_6$ [M + H]: 388.1760; found: 388.1756 [M + H].

(3*R*,4*S*)-3-Hydroxy-2,2,4-tris(hydroxymethyl)-azetidine-1-carboxylic acid (2d).

Compound **21a** (0.31 g, 0.80 mmol scale) on reaction with 20% $Pd(OH)_2$/C and on purification by column chromatography as described for **2a** afforded **2d** (0.15 g, 93%) as a sticky solid: R_f = 0.4 (chloroform/MeOH: 3/2); $[\alpha]_D^{25}$ = +22.26 (*c* 0.15, MeOH); IR (neat, *v*, cm^{-1}) 3253 (br), 1672, ^{1}HNMR (500 MHz, D_2O) δ (ppm) 4.65 (ddd, *J* = 7.4, 4.5, 1.3Hz, 1H, 4CH), 4.05 (d, *J* = 1.3Hz, 1H, 3CH), 3.90 (dd, *J* = 15.0, 10.0 Hz, 1H, 4C(C$\underline{H_2}$OH)), 3.84 (dd, *J* = 15.0, 4.0 Hz, 1H, 4C(C$\underline{H_2}$OH)), 3.79 (d, *J* = 11.3 Hz, 1H, 2C(C$\underline{H_2}$OH)), 3.70 (d, *J* = 11.3 Hz, 1H, 2C(C$\underline{H_2}$OH)), 3.66 (s, 2H, 2C(C$\underline{H_2}$OH)); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 155.9 (NCOO), 78.5 (C3), 62.8 (C2), 62.2 (4C($\underline{C}H_2$OH)), 61.0 (2C($\underline{C}H_2$OH)), 60.8 (2C($\underline{C}H_2$OH)), 60.7 (C4); HRMS (ESI-TOF) m/z calculated for $C_7H_{14}NO_6$ [M + H]: 208.0821; found: 208.0805 [M + H].

***N*-Carboxylic-3-*C*-(benzyloxymethyl)-6-*O*-benzyl-3,5-dideoxy--3,5-imino-1,2-*O*-isopropylidene-α-D-glucofuranose** (**22**). A solution of **20** (0.3 g, 0.55 mmol) in TFA:H_2O (3:1, 5 mL) was stirred at 0 °C. TLC analysis (Hexane/ EtOAc: 4/1) after 30 min indicated disappearance of the starting material and formation of a single product. TFA was co-evaporated with toluene under reduced pressure. Purification by column chromatography (Hexane/ EtOAc: 7/3) afforded **22** (0.24 g, 96%) as a thick liquid: R_f = 0.6 (Hexane/ EtOAc: 1/1); $[\alpha]_D^{25}$ = -24.75 (*c* 0.08, $CHCl_3$); IR ($CHCl_3$, *v*, cm^{-1}) 3132, 1713, 1406, 1101, 1014 ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.36-7.25 (m,10H, Ph), 6.73- 6.65 (br, 1H, exchangeable with D_2O, NCOOH), 5.89 (d, *J* = 3.4 Hz, 1H, 1CH), 4.60 – 4.51 (m, 5H, 5CH and OCH_2Ph), 4.41 (d, *J* = 3.4 Hz, 1H, 2CH), 4.27 (d, *J* = 1.8 Hz, 4CH), 3.79 - 3.72 (m, 3H, 6CHa and 3C(CH_2O)), 3.56 (d, *J* = 9.6 Hz, 1H, 6CHb), 1.49 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 152.7 (NCOOH), 137.7 (Ph), 137.3 (Ph), 128.5 (Ph), 128.4 (Ph), 127.9 (Ph), 127.8 (Ph), 127.7 (Ph), 113.5 (C$(CH_3)_2$), 104.9 (C1), 85.2 (C2), 74.8 (C4), 73.7 (OCH_2Ph), 73.6 (OCH_2Ph), 72.8 (C3), 69.9 (C5), 68.5 (3C(CH_2O)), 65.5 (C6), 27.1 (CH_3), 26.6 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{25}H_{30}NO_7$ [M + H]: 456.2022; found: 456.2026 [M + H].

***N*-Carboxylic-3-*C*-(hydroxymethyl)-3,5-dideoxy--3,5-imino-1,2-*O*-isopropylidene-α-D-glucofuranose** (**2e**). To a solution of **20** (0.3 g, 0.55 mmol) in methanol (10 mL), 10% Pd/C (0.012 g, 0.11 mmol) was added and the reaction mixture was hydrogenated at 100 psi at room temperature. TLC analysis (Hexane/ EtOAc: 4/1) after 12 h indicated disappearance of the starting material and formation of a single product. The catalyst was filtered through celite, washed with methanol and the solvent was evaporated at reduced pressure. Purification by column chromatography afforded **2e** (0.14 g, 93%) as a sticky solid: R_f = 0.43 (chloroform/ MeOH: 9/1); $[\alpha]_D^{25}$ = -16.17 (*c* 0.18, MeOH); IR (neat, *v*, cm^{-1}) 3261, 1685,^{1}H NMR (500 MHz,

D_2O) δ (ppm) 5.94 (d, *J* = 3.6 Hz, 1H, 1CH), 4.56 (d, *J* = 3.6 Hz, 1H, 2CH), 4.51 (ddd, *J* = 4.5, 3.5, 2.0 Hz, 1H, 5CH), 4.40 (d, *J* = 2.0 Hz, 1H, 4CH), 3.84 (d, *J* = 12.0 Hz, 1H, 3C(CH_2OH)), 3.80-3.73 (m, 2H, 6CHa and 6CHb), 3.70 (d, *J* = 12.0 Hz, 1H, 3C(CH_2OH)), 1.46 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); ^{13}C NMR (125 MHz, D_2O) δ (ppm), 154.9 (NCOOH), 114.3 ($C(CH_3)_2$), 104.7 (C1), 83.9 (C2), 76.5 (C4), 72.6 (C5), 66.3 (3C(CH_2OH)), 61.5 (C3), 60.8 (C6), 25.8 (CH_3), 25.3 (CH_3); HRMS (ESI-TOF) m/z calculated for $C_{11}H_{18}NO_7$ [M + H]: 276.1077; found: 276.1080 [M + H].

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of compounds **4-22** and **2a-2f**. Glycosidase inhibition assay as well as Lineweaver-Burk plots.

AUTHOR INFORMATION

Corresponding Author

*E-mail: ddd@chem.unipune.ac.in

Notes

The authors declare no competing financial interest.

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