

Synthesis and Glycosidase Inhibitory Studies of Pentahydroxyindolizidines: D-Glucose-Derived Aziridine-2-carboxylate Approach

K. S. Ajish Kumar,^[a] Vinod D. Chaudhari,^[a] Vedavati. G. Puranik,^[b] and Dilip D. Dhavale*^[a]

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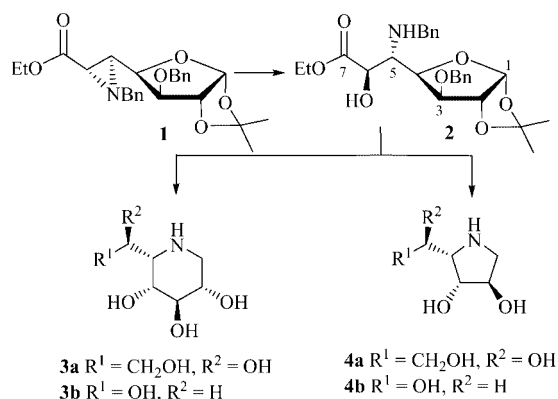
D-Glucose-derived aziridine-2-carboxylate **1** was converted into α -amino aldehyde **7**, which, after Wittig olefination, asymmetric dihydroxylation, hydrogenation followed by LiAlH₄ reduction, and *N*-Cbz protection, afforded two diastereomeric pyrrolidines **11a** and **11b** with sugar appendages. Removal of the 1,2-acetonide functionality in **11a/11b**

and reductive amination gave the pentahydroxyindolizidine alkaloids **6g** and **6h**, respectively, with (*S*) absolute configurations at the ring junctions. The glycosidase inhibitory activities of these compounds were studied.

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Introduction

Among strained ring systems, the three-membered nitrogen atom ring compounds – aziridines and aziridinecarboxylates^[1] – have found wide utility as intermediates in the synthesis of a variety of amino compounds, including natural alkaloids and unnatural analogues. In this context, we have recently reported the synthesis of the D-glucose-derived aziridinecarboxylate **1**, which undergoes highly regioselective nucleophilic ring-opening at the position α to the carboxylate group under acidic conditions in the presence of water as nucleophile, to afford aminol **2**. This in turn was elaborated for the synthesis of the piperidine and pyrrolidine iminosugars **3a/b** and **4a/b**, respectively (Scheme 1).^[2] As a part of our continuing interest in the area of iminosugars,^[3] we envisioned the potential of aziridinecarboxylate **1** in the synthesis of polyhydroxylated indolizidine alkaloids. This class of compounds (e.g., castanospermine **5**; Figure 1) and their analogues^[4] have the ability to inhibit a specific class of hydrolytic enzymes that cleave different types of glycosidic linkages and have therefore been found to have applications in the treatment of diabetes, obesity, and viral infection.^[5] In the search for structure–activity relationships and in order to find more potent and specific glycosidase inhibitors, a number of analogues of **5** have been either synthesized or isolated from natural sources and screened in biological assays.



Scheme 1. Piperidine and pyrrolidine alkaloids.

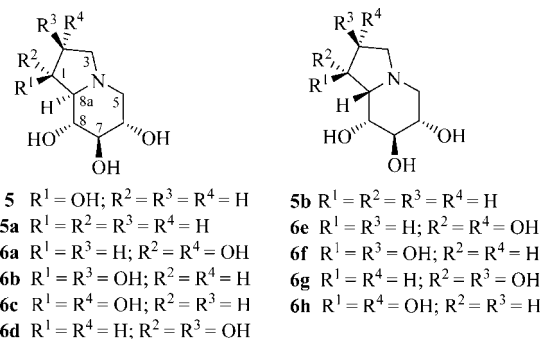


Figure 1. Indolizidine alkaloids.

In this context, in 2000 Arisawa et al. isolated uniflorine A from the Paraguayan natural medicine *namgapiry* – the leaves of *Eugenia uniflora* L. – and assigned its structure

[a] Garware Research Centre, Department of Chemistry, University of Pune, Pune-411 007, India

[b] Centre for Material Characterization, National Chemical Laboratory, Pune-411 008, India

E-mail: ddd@chem.unipune.ernet.in

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as (*R*)-2-hydroxy-1-*epi*-castanospermine (**6a**) on the basis of spectral and nOe data.^[6] The isolated uniflorine A was found to be a promising inhibitor of maltase and sucrase, with IC₅₀ values in the μM range.

In 2004, Pyne and co-workers reported the total synthesis of putative uniflorine A using the Petasis reaction, ring-closing metathesis and asymmetric dihydroxylation as key steps, and the pentahydroxyindolizidine ring structure **6a** was confirmed by X-ray crystallographic analysis of its peracetyl derivative.^[7] However, the authors have noticed considerable variation in the ¹H and ¹³C NMR spectroscopic data for the synthetic and the naturally occurring product. In 2005, in another report, Mariano and co-workers reported the synthesis of **5** and the pentahydroxyindolizidine alkaloids **6b**^[8a] and **6c**, using a photochemical reaction to construct a 4-aminocyclopentene-3,5-diol derivative from pyridine as a precursor of the piperidine ring through ring-rearrangement metathesis.^[8] Both compounds **6b** and **6c**, however, showed deviation in their spectroscopic data from those for the isolated uniflorine A. Recently, our group have

attempted to resolve this ambiguity by synthesizing **6a** and its analogues **6e** and **6f** using 1,3-addition of vinylmagnesium bromide to a D-glucose-derived nitron, *N*-allylation and ring-closing metathesis as key steps; however, the analytical and spectroscopic data once again did not match those reported for the isolated uniflorine A.^[9] In order to resolve the structural anomaly of uniflorine A, we thought of synthesizing new pentahydroxyindolizidine analogues **6g** and **6h** using the D-glucose-derived aziridinecarboxylate **1** as the precursor and of studying their glycosidase inhibitory activities.^[10] Regioselective nucleophilic ring-opening of **1**, followed by reduction of the ester, protection of the amine and oxidative cleavage of the diol should thus afford aminal **7** (Scheme 2) with the *L-ido* configuration at C-5, necessary for generation of the 8a-*epi* configuration at the ring junction. The Wittig olefination of **7**, asymmetric dihydroxylation (AD) and hydrogenation should give access to the pyrrolidine ring skeleton with a sugar appendage and with the requisite relative *anti* stereochemistry at the pyrrolidine ring, a true intermediate for the synthesis of the pentahydroxylated indolizidines **6g** and **6h**. Our results in the successful implementation of this methodology are discussed here.

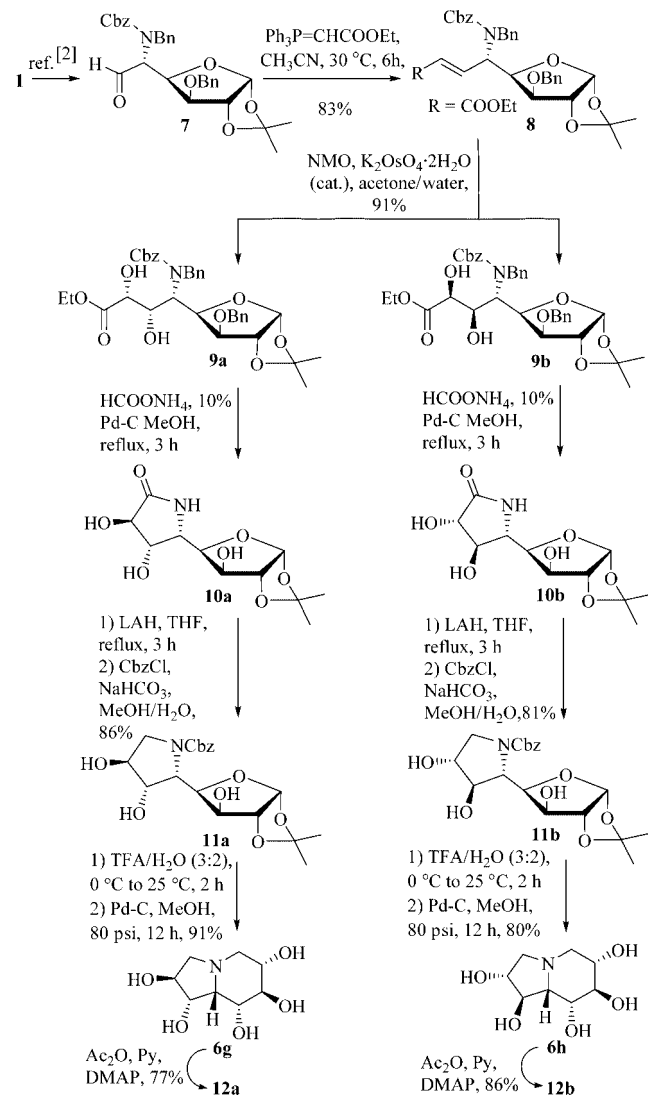
Results and Discussion

The aziridinecarboxylate **1** was converted into the aminal **7** as reported earlier by us.^[2] The Wittig olefination of **7** with Ph₃P=CHCOOEt afforded the γ -amino α,β -unsaturated ester **8** exclusively with the (*E*) geometry, as confirmed by ¹H NMR studies, which showed a large coupling constant of *J* = 16.1 Hz for protons 7-H and 6-H (Scheme 2). Dihydroxylation of **8** with potassium osmate (catalytic) and *N*-methylmorpholine *N*-oxide (NMO) in acetone/water (8:1) afforded a diastereomeric mixture of the vicinal diols **9a** and **9b** in a ratio of 7:3 (Table 1).^[11] The very similar *R_f* values of **9a** and **9b** did not permit us to separate the diastereomers by column/flash chromatography. Fortunately, however, crystallization of a diastereomeric mixture of **9a** and **9b** from ethyl acetate/hexane (2:8) and keeping the solution at 5 °C for 12 h afforded **9a** as a crystalline solid.^[12] Its single-crystal X-ray analysis (Figure 2) established the absolute configurations at the newly generated stereocenters as (6*S*) and (7*R*), so the minor isomer **9b** could then be assigned (6*R*) and (7*S*) absolute configurations.^[13]

Table 1. Dihydroxylation of **8**.

Entry	Ligand	Ratio of 9a/9b	Yield [%]
1	no ligand	70:30	91
2	(DHQ) ₂ PHAL	83:17	78
3	(DHQD) ₂ PHAL	52:48	82

The formation of **9a** as a major product was against our expectations (Kishi's empirical rule, applicable mainly to allylic alcohols), as **9a** was obtained by *syn*-dihydroxylation from the same side (α -face) as the pre-existing bulky *N*-



Scheme 2. Synthesis of indolizidine alkaloids **6g** and **6h**.

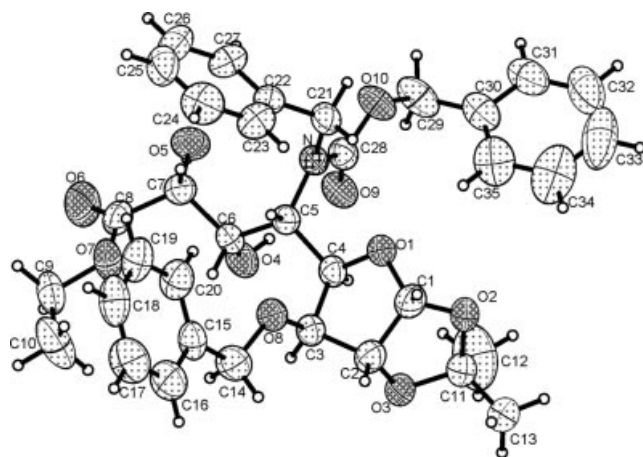


Figure 2. ORTEP diagram of the molecule **9a**.

(benzyl)benzyloxycarbonyl group, while the minor product **9b** was obtained from the side opposite (β -face).^[14] Analogous results were observed when we attempted to improve the diastereoselectivity using cinchona alkaloids as chiral ligands (Table 1).

Thus, the use of AD-mix- α [10 mol-% (DHQ)₂PHAL, 1 mol-% K₂OsO₂(OH)₄, K₃Fe(CN)₆, K₂CO₃, MeSO₂NH₂] in the osmylation afforded only a marginal increase in the diastereoselectivity in favour of **9a** (Entry 2), whereas the use of AD-mix- β [10 mol-% (DHQD)₂PHAL, 1 mol-% K₂OsO₂(OH)₄, K₃Fe(CN)₆, K₂CO₃, MeSO₂NH₂] did not afford any selectivity as determined from the ¹H NMR spectrum of the crude mixture (Entry 3). It is worth mentioning that although the presence of the *N*-(Bn)Cbz functionality hindered the α -face of the double bond, the dihydroxylation occurred preferentially from the same side as this bulky group to give **9a** as a major product. We presume that the amide C–N bond (of the *N*-Cbz group) has more double bond character,^[15] giving a net negative charge on the amide oxygen that complexes with potassium osmate (Figure 3), favouring the dihydroxylation taking place from the same side as the *N*-Cbz functionality. However, the reasons for the loss of diastereoselectivity on using AD-mix- β and the small increment in selectivity while using AD-mix- α during the dihydroxylation reaction are not clear to us.

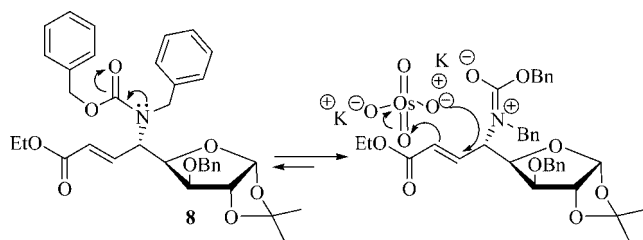


Figure 3. Plausible transition state for the observed selectivity.

In the next step, the aminodiol **9a** was subjected to hydrogenolysis (10% Pd–C and ammonium formate in methanol at reflux) to give the γ -lactam **10a** in quantitative yield. Reduction of the lactam functionality in **10a** with LiAlH₄

in THF gave the pyrrolidine, which on treatment with CbzCl in methanol afforded **11a**. In the subsequent steps, removal of the 1,2-acetonide functionality, followed by hydrogenation and purification by chromatography, afforded **6g** as a white solid. The analytical and ¹H and ¹³C NMR spectroscopic data were in accordance with the structure **6g**, but the data were not found to be in agreement with those for the isolated uniflorine A. The structure of **6g** was further confirmed by converting it into the peracetylated derivative **12a**, which also helped in assigning the conformation (vide supra).

The same sequence of reactions was repeated with the dihydroxylated compound **9b** (Scheme 2). The corresponding C-6, C-7 diepimeric compounds **10b** and **11b** were isolated and characterized by their spectral and analytical data. Subsequently, the *N*-Cbz-protected pyrrolidine **11b** afforded **6h** as a thick liquid on removal of the 1,2-acetonide group with TFA/H₂O and reductive aminocyclization by hydrogenation. To our disappointment, the spectral and the analytical data for **6h** were also inconsistent with those for the isolated uniflorine A. The pentahydroxyindolizidine **6h** was also further characterized as its pentaacetyl derivative **12b**.

Conformational Analysis

It is known that 1-deoxycastanospermine (**5a**) exists in the ⁸C₅ conformation A (Figure 4) in solution, while its 8a-epimer **5b** adopts the ⁵C₈ conformation B.^[3a] We thought of carrying out a conformational analysis of the newly synthesized pentahydroxyindolizidines **6g** and **6h**, which have 8a-*epi* configurations at their ring fusions with relative *anti*-hydroxy groups in the pyrrolidine ring. The ¹H NMR spectroscopic data for **6g** and **6h** were not informative due to the broadening of signals, so **6g** and **6h** were converted into the corresponding pentaacetyl derivatives **12a** and **12b** and the assignments of signals and coupling constant information were determined from decoupling experiments (Table 2). In **12a**, the appearance of the C5-methylene protons as two doublet of doublets at δ = 2.84 and 3.11 ppm with small coupling constants ($J_{5a,6}$ = 4.1, $J_{5e,6}$ = 3.6 Hz) indicates an equatorial orientation of the 6-H proton. A doublet of doublets at δ = 3.29 ppm for 8a-H, with $J_{8a,1}$ = 6.3 and $J_{8a,8}$ = 3.0 Hz, requires an axial–equatorial relationship between 8a-H and 8-H (small coupling), while the coupling constant of 6.3 Hz between 8a-H and 1-H indicates a *syn* relationship with a dihedral angle of ca. 20°. The initial geometry in the precursor **11a** ensures that the substituents at C6/C7/C8 in the product **12a** are *trans*. As 8-H is equatorial, the protons at 7-H and 6-H should also be equatorial, and this was confirmed by the low coupling constants (ca. 3 Hz) observed for these protons. These data indicated the ⁵C₈ conformation of **12a** with the (8a*S*) absolute configuration. In the ¹H NMR spectrum of **12b** the appearance of 8a-H at δ = 2.58 ppm ($J_{8a,1}$ = 8.8 and $J_{8a,8}$ = 2.2 Hz) suggests an axial–equatorial relationship between 8a-H and 8-H, while the large coupling of 8.8 Hz

indicated an *anti* relationship between 8a-H and 1-H with a dihedral angle of ca. 180°. Both 5-H methylene protons showed small coupling constants with 6-H, suggesting an equatorial orientation of 6-H. The appearance of 6-H, 7-H and 8-H as narrow multiplets suggested the relative *trans* equatorial disposition of these protons, indicating the 5C_8 conformation of **12b**. As **12a** and **12b** are acetylated derivatives of **6g** and **6h**, respectively, the same conformation (5C_8) was assigned to the pentahydroxyindolizidines **6g** and **6h**.

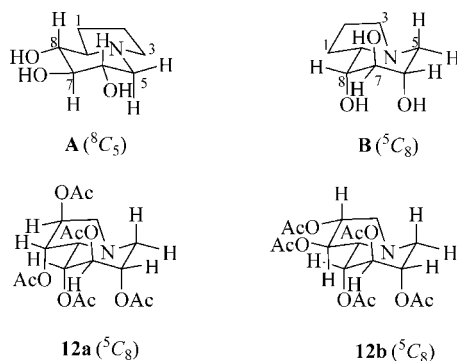


Figure 4. Conformations of indolizidines.

Table 2. Chemical shifts and coupling constant values for pentaacetoxy indolizidines **12a** and **12b**.

Chemical shifts [ppm]			Coupling constants, J [Hz]		
	12a	12b		12a	12b
1-H	5.37 (dd)	5.25 (dd)	1-H,2-H	2.7	4.1
2-H	5.19 (ddd)	5.08 (ddd)	1-H,8a-H	6.3	8.8
3-H	3.71 (dd)	2.75 (dd)	2-H,3-H	7.4	7.7
3-H	2.46 (dd)	3.10 (t)	2-H,3-H	5.7	1.6
5-H	3.11 (dd)		8a-H,8-H	3.0	2.2
5-H	2.84 (dd)	2.50 (dd)	8-H,7-H	4.9	$W_H = 5.4$
6-H	4.86 (br. d)	4.85 (narrow multiplet)	7-H,6-H	4.2	$W_H = 5.4$
7-H	5.07–5.12 (m)	5.02 (narrow multiplet)	6-H,5-H	4.1	$W_H = 5.4$
8-H		4.90 (narrow multiplet)	6-H,5-H	3.6	2.7
8a-H	3.29 (dd)	2.58 (dd)	3-H,3-H	11.0	11.0
			5-H,5-H	12.9	12.9

Glycosidase Inhibitory Activity

The isolated uniflorine A has been found to show inhibition of maltase and sucrase. In view of the potency of these types of molecules, we performed a glycosidase inhibition study with pentahydroxylated indolizidine alkaloids **6g** and **6h**.

As shown in Table 3, **6g** and **6h** exhibited selective inhibition towards β -glucosidase (sweet almonds) and β -xylanase (*Thermomyces ianuginosus*) in the millimolar range while no inhibition was observed with α -glucosidase (yeast) and α -mannosidase (jack bean) under the assay conditions.

Table 3. Inhibitory studies with indolizidine alkaloids **6g** and **6h**.

Enzyme	IC ₅₀ [mM]	
	6g	6h
α -Mannosidase (jack bean)	—[a]	—[a]
β -Glucosidase (sweet almonds)	12.35	22.28
α -Glucosidase (yeast)	—[a]	—[a]
β -Xylanase (<i>Thermomyces ianuginosus</i>)	51.81	0.05

[a] Inhibition not observed under assay conditions. Data are averages of three sets of assay performed.

Conclusions

In conclusion, we have successfully demonstrated the utility of the sugar-derived aziridinecarboxylate **1** as a valuable starting material in the synthesis of new pentahydroxyindolizidine alkaloids **6g** and **6h**. The glycosidase inhibitory activity studies indicate that **6g** and **6h** inhibit β -xylanase and β -glucosidase in the millimolar range. Work is in progress to utilize **1** in the synthesis of other iminosugars such as lentiginosine and swainsonine and will be reported in due course.

Experimental Section

Single crystals of compound **9a** suitable for X-ray diffraction were selected directly from the analytical samples.

Crystal Structure Determination of Compound 9a: $C_{35}H_{41}NO_{10}$, $M = 635.69$, orthorhombic, $a = 11.8806(6)$, $b = 11.9104(6)$, $c = 23.6172(11)$ Å, $V = 3341.9(3)$ Å³, $T = 293(2)$ K, space group $P2_12_12_1$, $Z = 4$, μ (Mo- $K\alpha$) = 0.092 mm⁻¹, 29957 reflections measured, 5864 unique [$I > 2\sigma(I)$], R value 0.0502, $wR_2 = 0.1180$. The Flack parameter 0.4251 (with esd 1.091) is inconclusive and therefore no conclusions on the absolute structure can be drawn.

General Remarks: Melting points were recorded with a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded by FTIR as thin films or in Nujol mulls or as KBr pellets and are expressed in cm⁻¹. ¹H (300 MHz), ¹³C (100 MHz) and ¹³C (75 MHz) NMR spectra were recorded in CDCl₃ or D₂O as solvents. Chemical shifts are reported in δ units (ppm) with reference to TMS as an internal standard, and J values are given in Hz. Decoupling experiments confirmed the assignments of the signals. Elemental analyses were carried out with a C,H-analyzer. Optical rotations were measured with a polarimeter at 25 °C. 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). The reactions were carried out in oven-dried glassware under dry N₂. Methanol, pyridine and THF were purified and dried before use. *n*-Hexane used was the distillation fraction between 40–60 °C. (DHQD)₂PHAL and (DHQ)₂PHAL and Pd-C (10%) were purchased from Aldrich and/or Fluka. After decomposition of the reaction mixtures with water, the workups involved washing of the combined organic layers with water and brine, drying over anhydrous sodium sulfate and evaporation of solvent at reduced pressure. For enzyme inhibition studies, substrates were purchased from Sigma Chemicals Co., USA. α -Glucosidase from yeast α -mannosidase from jack bean and β -xylanase from *Thermomyces ianuginosus* were purchased from Sigma Chemicals Co., USA. β -Glucosidase was extracted and purified from sweet almonds and used.

CCDC-644419 contains the supplementary crystallographic data for this paper. Data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(E)-Ethyl 3-O-Benzyl-1,2-O-isopropylidene-5-[benzyl(benzyloxycarbonyl)amino]-5,6,7-trideoxy-β-L-ido-6-eno-octafuranuronate (8): The phosphorane $\text{Ph}_3\text{P}=\text{CHCOOEt}$ (0.73 g, 2.08 mmol) was added at 25 °C to a solution of aminoaldehyde **7** (0.92 g, 1.73 mmol) in dry acetonitrile (20 mL), and the mixture was stirred well for 8 h. It was then concentrated, and on purification by column chromatography (*n*-hexane/ethyl acetate, 9:1), gave **8** as a thick liquid (0.89 g, 86%). $R_f = 0.54$ (*n*-hexane/ethyl acetate, 7:3). $[\alpha]_D = -18.1$ ($c = 0.59$, CHCl_3). ^1H NMR (300 MHz, CDCl_3 ; due to doubling of signals only prominent signals are mentioned): $\delta = 1.25$ (s, 3 H, CH_3), 1.28 (t, $J = 6.2$ Hz, 3 H, OCH_2CH_3), 1.43 (s, 3 H, CH_3), 3.77 (d, $J = 16.1$ Hz, 1 H, 5-H), 4.12 (m, 2 H, OCH_2CH_3), 4.25–4.45 (m, 2 H, NCH_2Ph), 4.49–4.90 (m, 5 H, OCH_2Ph , 3-H, 4-H, 2-H), 5.12 (d, $J = 16.1$ Hz, 2 H, NCOOCH_2Ph), 5.65 (d, $J = 16.1$ Hz, 1 H, 6-H), 5.92 (d, $J = 3.6$ Hz, 1 H, 1-H), 6.83 (dd, $J = 6.7$, 16.1 Hz, 1 H, 7-H), 7.13–7.40 (m, 15 H, $15 \times \text{ArH}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 14.1$ (OCH_2CH_3), 26.3 (CH_3), 26.7 (CH_3), 51.2 (NCH_2Ph), 56.2 (C-5), 57.8 (NCOOCH_2Ph), 60.2 (OCH_2CH_3), 67.1 (OBn), 71.6 (C-3), 81.1 (C-4), 81.6 (C-2), 104.6 (C-1), 111.7 $[(\text{CH}_3)_2\text{C}(\text{O})_2]$, 124.0 (C-7), 126.9 (ArC), 127.4 (s, $2 \times \text{ArC}$), 127.6 (s, $2 \times \text{ArC}$), 127.7 (s, $2 \times \text{ArC}$), 127.8 (s, $2 \times \text{ArC}$), 127.9 (ArC), 128.1 (s, $3 \times \text{ArC}$), 128.2 (s, $3 \times \text{ArC}$), 136.4 (ArC), 137.7 (ArC), 141.4 (C-6), 155.4 (CON), 165.5 (COOEt) ppm. IR (neat): $\tilde{\nu} = 2929$, 1712 cm^{-1} . $\text{C}_{35}\text{H}_{39}\text{NO}_8$ (601.69): calcd. C 69.87, H 6.53; found C 69.57, H 6.44.

Ethyl 3-O-Benzyl-5-[benzyl(benzyloxycarbonyl)amino]-5-deoxy-1,2-O-isopropylidene-β-L-threo-L-ido-heptofuranuronate (9a) and Ethyl 3-O-Benzyl-5-[benzyl(benzyloxycarbonyl)amino]-5-deoxy-1,2-O-isopropylidene-α-D-threo-L-ido-heptofuranuronate (9b): A catalytic amount of potassium osmate (0.06 g, 0.017 mmol) was added at 0 °C to a mixture of $\text{K}_3\text{Fe}(\text{CN})_6$ (3.35 g, 10.20 mmol), K_2CO_3 (3.57 g, 10.20 mmol) and (DHQD)₂PHAL or (DHQ)₂PHAL (0.026 g, 0.034 mmol, 1 mol-%) or without ligand in *t*BuOH/ H_2O (1:1, 80 mL), followed by methanesulfonamide (0.32 g, 3.40 mmol). After stirring for 5 min at 0 °C, compound **8** (2.00 g, 3.40 mmol) in *t*BuOH/ H_2O (1:1, 20 mL) was added over a period of 5 min. The reaction mixture was stirred at 0 °C for 24 h and quenched with solid sodium sulfite (3.00 g). The stirring was continued for another 45 min and the reaction mixture was extracted with ethyl acetate (5×40 mL). The combined organic phase was washed with KOH (10%) and worked up to afford a diastereomeric mixture of diols **9a** and **9b**. Recrystallization from *n*-hexane/ethyl acetate (2:8) gave **9a** as a white solid (1.31 g, 71%), m.p. 91–93 °C. $R_f = 0.60$ (*n*-hexane/ethyl acetate, 5:5). $[\alpha]_D = -27.2$ ($c = 0.52$, CHCl_3). The ^1H (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) spectra of **9a** were found to be very complicated, due to the doubling of signals as a result of restricted rotation in the urethane functionality. IR (neat): $\tilde{\nu} = 3500$, 3141, 1743, 1664, 1448, 1228 cm^{-1} . $\text{C}_{35}\text{H}_{41}\text{NO}_{10}$ (635.70): calcd. C 66.13, H 6.50; found C 65.96, H 6.37.

Procedure for 9a and 9b with NMO as the Cooxidant: NMO (0.29 g, 2.19 mmol) and potassium osmate (0.012 g) were added at 0 °C to a solution of conjugate ester **8** (0.60 g, 0.99 mmol) in acetone/water (8:1, 9 mL), and the system was stirred for 6 h. The reaction mixture was quenched with solid sodium sulfite (1.70 g). The stirring was continued for another 45 min, and the reaction mixture was extracted with ethyl acetate (5×20 mL). The combined organic phase was washed with KOH (10%) and worked up to afford a diastereomeric mixture of diols **9a** and **9b**.

α-L-threo-L-ido-Oct-1,4-furan-8-ulose 10a and α-D-threo-L-ido-Oct-1,4-furan-8-ulose 10b: A mixture of ammonium formate (0.35 g, 5.60 mmol) and Pd-C (10%, 0.10 g) was added to a solution of **9a**/**9b** (0.50 g, 0.80 mmol) in dry methanol (15 mL) at reflux and heating at reflux was continued for 5 h. The reaction mixture was filtered, concentrated and purified by column chromatography.

Elution (*n*-hexane/ethyl acetate, 2:8) gave **10b** as a white solid (0.05 g, 26%), m.p. 190–192 °C. $R_f = 0.65$ (MeOH/ CHCl_3 , 2:8). $[\alpha]_D = +6.4$ ($c = 0.02$, CHCl_3). ^1H NMR (300 MHz, D_2O): $\delta = 1.37$ (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 3.74 (dd, $J = 1.3$, 7.4 Hz, 1 H, 5-H), 4.12 (t, $J = 7.4$ Hz, 1 H, 6-H), 4.23 (dd, $J = 2.4$, 5.5 Hz, 1 H, 4-H), 4.32 (dd, $J = 1.3$, 7.9 Hz, 1 H, 7-H), 4.37 (d, $J = 2.4$ Hz, 1 H, 3-H), 4.71 (d, $J = 3.5$ Hz, 1 H, 2-H), 6.02 (d, $J = 3.5$ Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, D_2O): $\delta = 25.3$ (CH_3), 25.8 (CH_3), 53.5 (C-5), 73.5 (C-7), 74.3 (C-3), 75.4 (C-6), 77.7 (C-2), 85.1 (C-4), 104.3 (C-1), 112.6 $[(\text{CH}_3)_2\text{C}(\text{O})_2]$, 175.9 (C=O) ppm. IR (neat): $\tilde{\nu} = 3365$, 2983, 1679, 1452 cm^{-1} . $\text{C}_{11}\text{H}_{17}\text{NO}_7$ (275.26): calcd. C 48.00, H 6.23; found C 47.83, H 6.27.

Further elution with ethyl acetate gave **10a** as a white solid (0.14 g, 73%), m.p. 189–190 °C. $R_f = 0.60$ (MeOH/ CHCl_3 , 2:8). $[\alpha]_D = +20.8$ ($c = 1.24$, CHCl_3). ^1H NMR (300 MHz, D_2O): $\delta = 1.36$ (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 4.05 (dd, $J = 3.4$, 6.3 Hz, 1 H, 5-H), 4.37–4.45 (m, 4 H, 3-H, 4-H, 6-H, 7-H), 4.67 (d, $J = 3.8$ Hz, 1 H, 2-H), 6.00 (d, $J = 3.8$ Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 25.3$ (CH_3), 25.7 (CH_3), 55.5 (C-5), 74.4 (C-7), 75.0 (C-3), 76.1 (C-6), 80.2 (C-2), 84.9 (C-4), 104.5 (C-1), 112.7 $[(\text{CH}_3)_2\text{C}(\text{O})_2]$, 175.3 (C=O) ppm. IR (neat): $\tilde{\nu} = 3366$, 2984, 1683, 1452, 1074 cm^{-1} . $\text{C}_{11}\text{H}_{17}\text{NO}_7$ (275.26): calcd. C 48.00, H 6.23; found C 47.77, H 6.11.

α-L-threo-L-ido-Oct-1,4-furanose 11a: A solution of lactam **10a** (0.12 g, 0.44 mmol) in THF (5 mL) was added dropwise at 0 °C to a slurry of LAH (0.05 g, 1.30 mmol) in THF (6 mL) and the mixture was stirred well. The reaction mixture was brought to room temperature and heated at reflux for another 3 h. The reaction was quenched with ethyl acetate (5 mL) and saturated ammonium chloride solution (1 mL). The reaction mixture was filtered through a celite bed, concentrated and dried, and MeOH (5 mL), water (1 mL), NaHCO_3 (0.07 g, 0.87 mmol) and CbzCl (0.08 mL, 0.60 mmol) were added at 0 °C. The reaction mixture was stirred at 25 °C for 3 h. Concentration under vacuum, extraction with CHCl_3 , adsorption onto silica and column purification (*n*-hexane/ethyl acetate, 8.5:1.5) afforded **11a** (0.14 g, 86%) as a thick liquid. $R_f = 0.34$ (ethyl acetate). $[\alpha]_D = +13.0$ ($c = 0.23$, CHCl_3). ^1H NMR (300 MHz, CDCl_3): $\delta = 1.38$ (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 3.10 (br. d, $J = 0.09$ Hz, exchangeable with D_2O , 3-OH, 3-H), 3.36 (dd, $J = 6.8$, 11.2 Hz, 1 H, 8a-H), 3.76 (dd, $J = 7.6$, 11.2 Hz, 1 H, 8b-H), 4.20 (t, $J = 7.6$ Hz, 1 H, 5-H), 4.26 (d, $J = 2.3$ Hz, 1 H, 3-H), 4.30–4.38 (m, 1 H, 6-H), 4.44 (s, 1 H, 4-H), 4.46–4.52 (m, 1 H, 7-H), 4.54 (d, $J = 3.8$ Hz, 1 H, 2-H), 5.15 (ABq, $J = 12.3$ Hz, 2 H, NCOOCH_2Ph), 5.91 (d, $J = 3.8$ Hz, 1 H, 1-H), 7.38 (s, 5 H, $5 \times \text{ArH}$) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 25.9$ (CH_3), 26.5 (CH_3), 50.1 (C-8), 56.9 (C-5), 67.9 (NCOOCH_2Ph), 73.6 (C-7), 75.5 (C-3), 76.3 (C-6), 77.2 (C-4), 84.8 (C-2), 104.3 (C-1), 111.5 $[(\text{CH}_3)_2\text{C}(\text{O})_2]$, 127.9 (ArC), 128.2 (ArC), 128.5 (s, $3 \times \text{ArC}$), 135.7 (ArC), 157.5 (NCO) ppm. IR (neat): $\tilde{\nu} = 1676$, 1253, 1026 cm^{-1} . $\text{C}_{19}\text{H}_{25}\text{NO}_8$ (395.40): calcd. C 57.71, H 6.37; found C 57.52, H 6.26.

α-L-threo-L-ido-Oct-1,4-furanose 11b: A solution of lactam **10b** (0.05 g, 0.19 mmol) in THF (5 mL) was added dropwise at 0 °C to a slurry of LAH (0.02 g, 1.3 mmol) in THF (6 mL) and the system was stirred well. The reaction mixture was brought to room temperature and heated at reflux for another 3 h. The reaction was

quenched and worked up as for **11a**. NaHCO₃ (0.03 g, 0.40 mmol) and CbzCl (0.04 mL, 0.26 mmol) were added at 0 °C to the amino alcohol in MeOH (5 mL) and water (1 mL). The reaction mixture was stirred at 25 °C for 3 h. Concentration under vacuum, extraction with CHCl₃, adsorption onto silica and column purification (*n*-hexane/ethyl acetate, 6:4) afforded **11b** (0.06 g, 81%) as a white solid, m.p. 63–64 °C. *R*_f = 0.23 (ethyl acetate). [*a*]_D = –68.46 (*c* = 0.55, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.33 (s, 3 H, CH₃), 1.49 (s, 3 H, CH₃), 2.94 (br. s, 3 H, exchangeable with D₂O, 3-OH), 3.43 (d, *J* = 12.0 Hz, 1 H, 8a-H), 4.05 (dd, *J* = 6.1, 12.7 Hz, 1 H, 8b-H), 4.15 (d, *J* = 6.1 Hz, 1 H, 7-H), 4.20–4.30 (m, 3 H, 3-H, 4-H, 5-H), 4.40 (br. s, 1 H, 6-H), 4.50 (d, *J* = 3.5 Hz, 1 H, 2-H), 5.15 (ABq, *J* = 12.4 Hz, 2 H, NCOOCH₂Ph), 5.96 (d, *J* = 3.5 Hz, 1 H, 1-H), 7.28 (s, 5 H, 5 × ArH) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 26.2 (CH₃), 26.7 (CH₃), 54.4 (C-8), 63.8 (C-5), 67.8 (NCOOCH₂Ph), 75.1 (C-7), 75.4 (C-6), 77.2 (C-3), 80.5 (C-4), 84.8 (C-2), 104.4 (C-1), 112.0 [(CH₃)₂C(O)₂], 127.8 (s, 2 × ArC), 128.1 (ArC), 128.5 (s, 2 × ArC), 135.8 (ArC), 157.5 (NCO) ppm. IR (neat): ν̄ = 1685, 1232 cm^{–1}. C₁₉H₂₅NO₈ (395.40): calcd. C 57.71, H 6.37; found C 57.48, H 6.22.

(1S,2S,6S,7R,8R,8aS)-1,2,6,7,8-Pentahydroxyindolizidine (6g): A solution of **11a** (0.04 g, 0.11 mmol) in TFA/H₂O (3 mL, 2:1) was stirred at 20 °C for 3 h. Trifluoroacetic acid was co-evaporated with benzene to furnish a thick liquid. Pd-C (10%, 0.05 g) was added to a solution of the above product in methanol (5 mL). The solution was hydrogenated at 80 psi for 24 h. The catalyst was filtered through a celite bed and washed with methanol (15 mL). The filtrate was concentrated, and on column purification afforded **6g** as a crystalline solid (0.018 g, 91%), m.p. 163–165 °C. *R*_f = 0.20 (chloroform/methanol, 4:6). [*a*]_D = +2.1 (*c* = 1.93, MeOH). ¹H NMR (300 MHz, D₂O): δ = 2.86 (br. d, *J* = 11.0 Hz, 1 H, 5-Ha), 3.11–3.36 (m, 2 H, 3a-H, 3b-H), 3.44 (narrow multiplet, *W*_H = 16.4 Hz, 1 H, 8a-H), 3.70–3.84 (m, 2 H, 5-Hb, 2-H), 3.91 (t, *J* = 5.2 Hz, 1 H, 7-H), 4.22 (s, *W*_H = 13.7 Hz, 1 H, 8-H), 4.27–4.32 (m, 1 H, 6-H), 4.35 (d, *J* = 4.1 Hz, 1 H, 1-H) ppm. ¹³C NMR (75 MHz, D₂O): δ = 54.9 (C-3), 60.0 (C-5), 63.2 (C-6), 67.8 (C-8a), 69.1 (C-2), 69.8 (C-8), 74.7 (C-1), 77.7 (C-7) ppm. IR (KBr): ν̄ = 3400–3600 (br. band) cm^{–1}. C₈H₁₅NO₅ (205.21): calcd. C 46.82, H 7.37; found C 46.68, H 7.27.

(1R,2R,6S,7R,8R,8aS)-1,2,6,7,8-Pentahydroxyindolizidine (6h): A solution of **11b** (0.05 g, 0.12 mmol) in TFA/H₂O (3 mL, 2:1) was stirred at 25 °C for 2.5 h. Trifluoroacetic acid was co-evaporated with benzene to furnish a thick liquid. Pd-C (10%, 0.05 g) was added to a solution of the above product in methanol (5 mL). The solution was hydrogenated at 80 psi for 24 h. The catalyst was filtered through a celite pad and washed with methanol (15 mL). The filtrate was concentrated to give a thick light brown liquid of **6h** (0.02 g, 80%). *R*_f = 0.30 (chloroform/methanol, 4:6). [*a*]_D = +40.0 (*c* = 0.01, MeOH). ¹H NMR (300 MHz, D₂O): δ = 3.04–3.18 (m, 2 H, H5a, 3a-H), 3.22–3.40 (m, 3 H, 3b-H, 5b-H, 8a-H), 4.00 (narrow multiplet, *W*_H = 7.8 Hz, 1 H, 6-H), 4.07 (narrow multiplet, *W*_H = 5.8 Hz, 2 H, 8-H, 7-H), 4.24 (dd, *J* = 4.1, 13.2 Hz, 1 H, 2-H), 4.31–4.35 (m, 1 H, 1-H) ppm. ¹³C NMR (100 MHz, D₂O): δ = 53.7 (C-5), 59.5 (C-3), 66.7 (C-6/C-2), 66.8 (C-6/C-2), 68.0 (C-8/C-8a), 68.1 (C-8/C-8a), 74.7 (C-7), 76.1 (C-1) ppm. IR (Nujol): ν̄ = 3410–3600 (br. band) cm^{–1}. C₈H₁₅NO₅ (205.21): calcd. C 46.82, H 7.37; found C 46.68, H 7.15.

(1S,2S,6S,7R,8R,8aS)-1,2,6,7,8-Pentaacetoxyindolizidine (12a): Acetic anhydride (0.09 mL, 1.01 mmol) and catalytic 4-(dimethylamino)pyridine were added to an ice-cooled solution of **6g** (0.02 g, 0.10 mmol) in dry pyridine (1 mL). The reaction mixture was stirred at room temperature for 6 h. Ice water (5 mL) was

added and the mixture was extracted with chloroform (3 × 10 mL). Usual workup and chromatographic purification (*n*-hexane/ethyl acetate, 3:2) afforded the pentaacetate **12a** (0.03 g, 77%) as a thick liquid. *R*_f = 0.25 (*n*-hexane/ethyl acetate, 4:6). [*a*]_D = +37.2 (*c* = 0.19, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 2.04 (s, 3 H, COCH₃), 2.09 (s, 9 H, 3 × COCH₃), 2.10 (s, 3 H, COCH₃), 2.46 (dd, *J* = 5.7, 11.0 Hz, 1 H, 3e-H), 2.84 (dd, *J* = 3.6, 12.9 Hz, 1 H, 5e-H), 3.11 (dd, *J* = 4.1, 12.9 Hz, 1 H, 5a-H), 3.29 (dd, *J* = 3.0, 6.3 Hz, 1 H, 8a-H), 3.71 (dd, *J* = 7.4, 11.0 Hz, 1 H, 3a-H), 4.86 (br. d, *J* = 3.8 Hz, 1 H, 6-H), 5.07–5.12 (m, 2 H, 7-H, 8-H), 5.19 (ddd, *J* = 2.7, 5.7, 7.4 Hz, 1 H, 2-H), 5.37 (dd, *J* = 2.7, 6.3 Hz, 1 H, 1-H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 20.9 (s, 2 × COCH₃), 21.0 (COCH₃), 21.1 (COCH₃), 21.2 (COCH₃), 51.2 (C-5), 58.2 (C-3), 60.7 (C-8a), 66.9 (C-2), 67.9 (C-6), 68.1 (C-8), 77.7 (s, C-7, C-1), 168.7 (COCH₃), 169.3 (COCH₃), 169.6 (COCH₃), 169.7 (COCH₃), 170.0 (COCH₃) ppm. IR (neat): ν̄ = 1743, 1210 cm^{–1}. C₁₈H₂₅NO₁₀ (415.39): calcd. C 52.05, H 6.07; found C 52.04, H 6.06.

(1R,2R,6S,7R,8R,8aS)-1,2,6,7,8-Pentaacetoxyindolizidine (12b): Acetic anhydride (0.11 mL, 1.21 mmol) and a catalytic amount of 4-(dimethylamino)pyridine were added to an ice-cooled solution of **6h** (0.02 g, 0.10 mmol) in dry pyridine (1 mL). The reaction mixture was stirred at room temperature for 6 h. Ice water (5 mL) was added and the system was extracted with chloroform (3 × 10 mL). Usual workup and chromatographic purification (*n*-hexane/ethyl acetate, 3:2) afforded the pentaacetate **12b** (0.04 g, 86%) as a thick liquid. *R*_f = 0.44 (*n*-hexane/ethyl acetate, 4:6). [*a*]_D = –0.2 (*c* = 0.25, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 2.04 (s, 3 H, COCH₃), 2.06 (s, 3 H, COCH₃), 2.09 (s, 6-H, 2 × COCH₃), 2.10 (s, 3 H, COCH₃), 2.50 (dd, *J* = 2.7, 12.9 Hz, 1 H, 5e-H), 2.58 (dd, *J* = 2.2, 8.8 Hz, 1 H, 8a-H), 2.75 (dd, *J* = 7.7, 11.0 Hz, 1 H, 3a-H), 3.10 (t, *J* = 11.0 Hz, 2 H, 3e-H, 5a-H), 4.85 (narrow multiplet, *W*_H = 5.4 Hz, 1 H, 6-H), 4.90 (narrow multiplet, *W*_H = 5.4 Hz, 1 H, 8-H), 5.02 (narrow multiplet, *W*_H = 5.4 Hz, 1 H, 7-H), 5.08 (ddd, *J* = 1.6, 4.1, 7.7 Hz, 1 H, 2-H), 5.25 (dd, *J* = 4.1, 8.8 Hz, 1 H, 1-H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 20.8 (s, 2 × COCH₃), 20.9 (COCH₃), 21.0 (COCH₃), 21.3 (COCH₃), 51.9 (C-5), 58.9 (C-3), 63.4 (C-8a), 65.5 (C-2), 66.2 (C-6), 67.1 (C-8), 75.5 (C-7), 75.6 (C-1), 168.1 (COCH₃), 169.7 (COCH₃), 169.8 (s, 2 × COCH₃), 170.6 (COCH₃) ppm. IR (neat): ν̄ = 1740, 1218 cm^{–1}. C₁₈H₂₅NO₁₀ (415.39): calcd. C 52.05, H 6.07; found C 51.80, H 6.00.

General Procedure for Inhibition Assay: The inhibition potencies of **6g** and **6h** were determined by measuring the residual hydrolytic activities of the glycosidases.^[16] Substrates purchased from Sigma Chemicals Co., USA – namely *p*-nitrophenyl α-D-glucopyranoside and *p*-nitrophenyl β-D-glucopyranoside – of 2 mM concentration were prepared in 0.025 M citrate buffer of pH 6.0. *p*-Nitrophenyl α-D-mannopyranoside (2 mM) was prepared in 0.025 M citrate buffer of pH 4.0. The test compound was preincubated with the appropriate enzyme buffered at the optimal pH for 1 h at 25 °C. The enzyme reaction was initiated by the addition of substrate (100 μL). Controls were run simultaneously in the absence of test compound. The reaction was terminated at the end of 10 min by the addition of borate buffer (0.05 M, pH 9.8), and absorbance of the liberated *p*-nitrophenol was measured at 405 nm with a Shimadzu Spectrophotometer UV-1601. One unit of glycosidase activity is defined as the amount of enzyme that hydrolysed 1 μmol of *p*-nitrophenyl pyranoside per minute at 25 °C. Xylanase assay was carried out at pH 6.0 by mixing a 2 μM concentration of the enzyme with 0.5 mL of oat spelt xylan (10 mg mL^{–1}) in a reaction mixture of 1 mL and incubation at 50 °C for 30 min, with the reducing sugar released being determined by the dinitrosalicylic method.^[16b] One unit of xylanase activity is defined as the amount of enzyme that produced 1 μmol

of xylose equivalent per unit using oat spelt xylan as the substrate under assay conditions.

Supporting Information (see also the footnote on the first page of this article): This include ^1H NMR and ^{13}C NMR spectra of compounds **6g**, **6h**, **8**, **10a**, **10b**, **11a**, **11b**, **12a** and **12b**.

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