

137. On the Way to Glycoprocessing Inhibitors. Synthesis of an Imidazo-L-xylo-piperidinose Derivative

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An eight-step synthetic sequence led from the known D-xylo-pentodialdose **8** to imidazo-L-xylo-piperidinose **15**, the key steps being the build-up of imidazole compound **12** by a *van Leusen* methodology and the intramolecular S_N2 ring closure of the O-triflated benzylidene derivative **13**. xylo-Piperidinose **15** appears in a half-chair conformation like the oxocarbenium ions which are the postulated intermediates in the glycoprocessing of the pyranose polysaccharides. This bicyclic azasugar should be a glycosidase inhibitor.

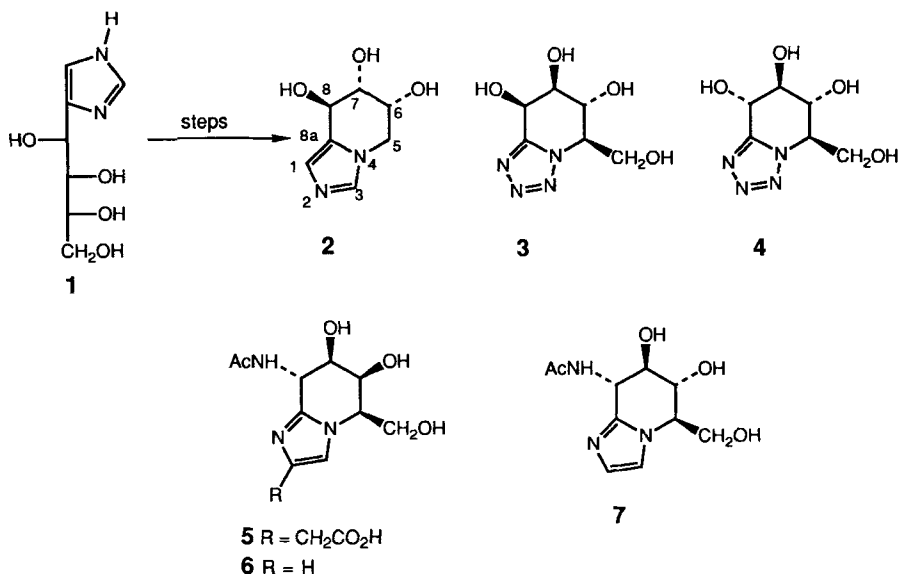
The enzymatic glycosidase mechanism of pyranosic polysaccharides is believed to involve a transient half-chair oxocarbenium ion which is stabilized by a complementary carboxylate anion of an active-site catalytic residue [1] [2]. Structural aza analogues of these glycosyl cations represent an attractive synthetic target for the design of potent glycoprocessing inhibitors [3] [4]. Imidazopiperidinoses possess the characteristic features which are required for glycosidase inhibitors: *i*) the half-chair conformation with a positive charge around the (protonated) ring heteroatoms; *ii*) the same topographic orientation of the OH groups, *i.e.*, the same absolute configuration as the corresponding monosaccharides [5]. Moreover, the imidazole moiety itself can interact with the active sites of glycosidases [6] [7].

Along these lines of thought, we described in 1991 the synthesis of imidazo-D-arabino-piperidinose **2** from D-fructose derivative **1** (*Scheme 1*) [8]. This latter chiral half-chair piperidinose transition-state analogue, when tested against a dozen human liver glycosidases, proved to be a potent mannosidase inhibitor [9]. Azasugar **2** seemed to be of interest as, unlike other azasugar derivatives, it selectively inhibits α -D-mannosidase but does not inhibit α -fucosidase [9].

In the meantime *Vasella*, *Withers*, and their coworkers published the synthesis of mannonojiritetrazole **3** and of nojiritetrazole **4**, both of which proved to be potent transition-state analogue inhibitors [10]. Quite recently, *Tatsuta et al.* reported the synthesis of some 'de-branched' nagstatin (**5**) analogues, *i.e.*, imidazo-N-acetyl-D-galactosamine analogue **6** and imidazo-N-acetyl-D-glucosamine analogue **7** both of which showed strong inhibiting activities against N-acetyl- β -D-glucosaminidase [11]. Last but not least, the naturally occurring nagstatin **5**, a half-chair galactosamine fused to an imidazole ring, was found to be an inhibitor of N-acetyl- β -D-glucosaminidase [12].

Since the imidazo-D-arabino-piperidinose **2** was of interest as a specific glycoprocessing inhibitor, we decided to synthesize some stereoisomers of it, *i.e.*, imidazosugars having different configurations. Herein, we describe the synthesis of imidazo-L-xylo-piperidi-

Scheme 1

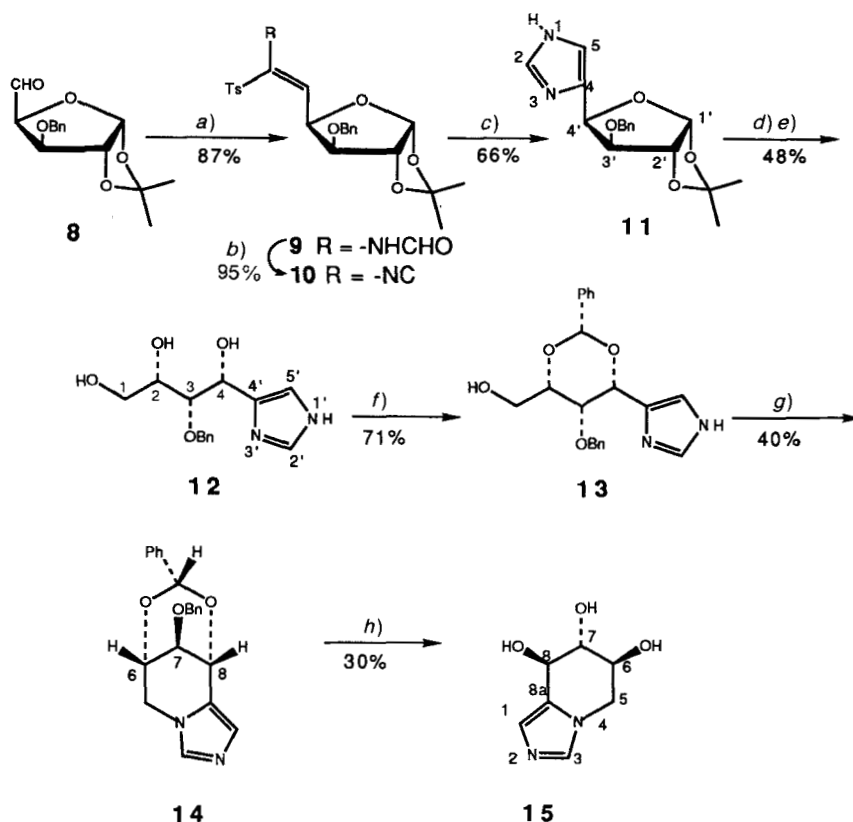


nose **15** from D-glucose. According to a straightforward retrosynthetic analysis, the terminal C(6) atom of D-glucose had to be removed and replaced by the imidazole ring (via C–C bond formation). The sugar moiety of the resulting imidazole derivative must then formally be turned upside down (in terms of the *Fischer* projection) in order to enter the L-xylose series.

Chiral aldehyde **8** was readily available from D-glucose according to a known three-step procedure [13]. Applying then a *van Leusen* methodology [14], **8** was transformed into the imidazole derivative **11** via formamide derivatives **9** (two geometric isomers) and isocyano(tosyl)alkane derivatives **10** (two geometric isomers; Scheme 2). Removal of the isopropylidene protection with dilute H₂SO₄ in dioxane, followed by NaBH₄ reduction of the resulting hemiacetal, gave imidazolyl-L-xylo-tetritol derivative **12**. Reaction of **12** with benzaldehyde in the presence of anhydrous ZnCl₂ led to the 1,3-dioxane derivative **13** whose treatment with trifluoromethanesulfonic(triflic) anhydride in pyridine gave tricyclic compound **14**. Removal of the protecting groups by hydrogenolysis eventually led to **15**.

The 1,3-dioxane ring obviously reduces the conformational lability of the polyhydroxylated side chain of **12**; furthermore, it protects the two secondary-alcohol functions, leaving the primary alcohol free. ¹H-Nuclear *Overhauser* effect (NOE) measurements indicate that this dioxane ring appears in chair conformation **13A**, as indicated in Fig. 1, the benzyloxy moiety being the only axial substituent (irradiation of ring atom PhCH(O)₂ (5.81 ppm) → NOE at H–C(4) (5.18 ppm; 9%) and H–C(2) (4.18 ppm; 9.5%); irradiation of H–C(4) (5.18 ppm) → NOE at PhCH(O)₂ (5.81 ppm; 15.5%), H–C(3) (3.80 ppm; 7%), and H–C(2) (4.18 ppm; 5%)). Chair conformation **13A** is obviously distorted, which explains the difference of NOE magnitudes between the three axial H-atoms.

Scheme 2



a) TsCH_2NC , $t\text{-BuOK}$, DME. b) POCl_3 , Et_3N , DME. c) NH_3 , MeOH, DME. d) H_2SO_4 , dioxane. e) NaBH_4 , EtOH. f) PhCHO , ZnCl_2 . g) Tf_2O , pyridine, CH_2Cl_2 . h) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, AcOH.

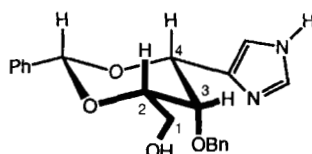


Fig. 1. Chair conformation **13A** of compound **13** as determined by nuclear Overhauser measurements

The triflate of **13** could not be isolated and gave instantaneously an intramolecular S_N2 reaction leading to **14**, whose 1,3-dioxane ring appears in a twisted-boat conformation **14A** (Fig. 2) as shown by *Dreiding* steel models, molecular modeling based on energy minimization of force field TRIPOS and CERIUS-*Dreiding* II programs, and NOE measurements (irradiation of the ring atom $\text{PhCH}(\text{O})_2$ (5.87 ppm) $\rightarrow$ NOE at $\text{H}-\text{C}(7)$ (4.27 ppm; 19%!; quasi flagpole-bowsprit interaction) and at $\text{H}-\text{C}(6)$ (4.15 ppm; 3%)).

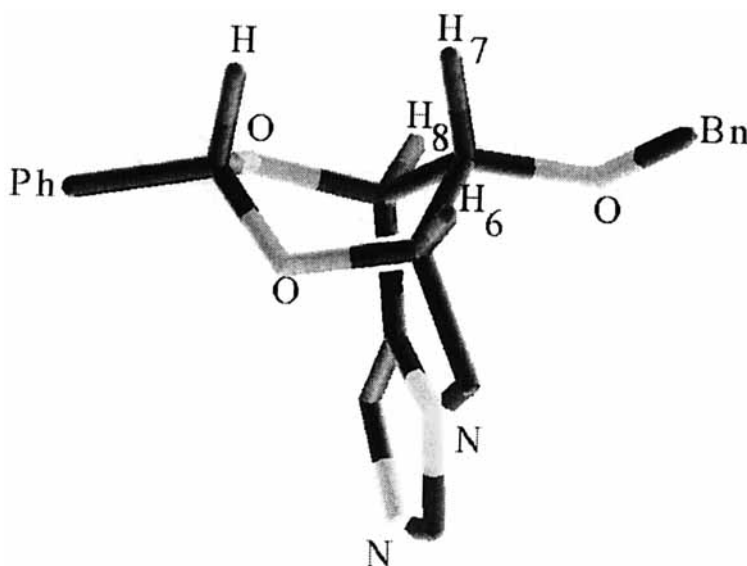


Fig. 2. Boat conformation **14A** of compound **14** as determined by molecular modeling and by nuclear Overhauser effect measurements

No NOE could be measured for H–C(8), due to the twisted-boat conformation, as also indicated by the TRIPOS and CERIUS programs.

That *L*-xylo-piperidine **15** is a C(6) diastereoisomer of its *D*-arabino-piperidine stereoisomer **2** appears clearly when comparing the corresponding ¹H-NMR spectra (Table). We notice in particular that H–C(6) is equatorial in compound **2** ($J(6,7) = 2.0$ Hz) and axial in **15** ($J(6,7) = 7.9$ Hz). In **15**, the three OH groups are either equatorial (H–C(6), H–C(7)) or pseudo-equatorial (H–C(8)) demonstrating thereby that the six-membered ring occurs predominantly, if not exclusively, in one of the two possible half-chair conformations.

Table. ¹H-NMR (250 MHz) and ¹³C-NMR (62.9 MHz) Data of Imidazopiperidine Derivatives **2** and **15** in CD₃OD. δ in ppm, internal standard CD₃OD (δ (CD₃OD) 3.30 ppm for ¹H, and δ (CD₃OD) 49.02 ppm for ¹³C)^a.

	H–C(1)	H–C(3)	H–C(5)	H'–C(5)	H–C(6)	H–C(7)	H–C(8)
2	6.96	7.54	4.16	4.04	4.34	3.91	4.82
15	6.97	7.54	4.32	3.84	3.97	3.74	4.61
	$J(1,3)$	$J(1,8)$	$J(5,5')$	$J(5,6)$	$J(5',6)$	$J(6,7)$	$J(7,8)$
2			12.5	4.5	7.0	2.0	5.5
15	1.0	1.2	12.1	4.6	7.8	7.9	6.4
	C(1)	C(3)	C(5)	C(6)	C(7)	C(8)	C(8a)
2	127.2	136.8	46.92	67.4	74.3	66.2	131.4
15	126.8	136.7	47.9	69.2	76.2	68.4	131.8

^a) Assignment of the ¹H- and ¹³C-NMR signals by selective decoupling experiments.

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Experimental Part

General. Flash chromatography (FC); silica gel (*Merck* 60; 230–400 mesh). TLC: silica gel *HF*₂₅₄ (*Merck*). Optical rotations: *Perkin-Elmer-241* polarimeter. IR Spectra: *Spectromom-2000-MOM* spectrophotometer. NMR Spectra: *Bruker-AC-200* and *-AC-250* spectrometers using double-irradiation techniques; SiMe₄ (¹H) and CDCl₃ (δ (CDCl₃) 77.00 ppm rel. to SiMe₄; ¹³C) and CD₃OD (δ (CD₃OD) 3.30 ppm for ¹H and δ (CD₃OD) 49.02 ppm for ¹³C) as internal references; δ in ppm and *J* in Hz. Fast atom bombardment (FAB) MS: modified FAB mass spectrometer *MI 1201 E* (*PO Electron*, Ukraine). Elemental analyses were carried out by the Microanalysis Service of the Technical University of Lodz.

N-{2-[(4' R)-3'-O-Benzyl-1',2'-O-isopropylidene- α -L-threofuranose-4-C-yl]-1-[(tol-4-yl)sulfonyl]-ethenyl}formamide (**9**). To a stirred soln. of *t*-BuOK (2.2 g, 19.6 mmol) in dry 1,2-dimethoxyethane (DME) (20 ml) under Ar at –30° was added dropwise a soln. of isocyanato[(tol-4-yl)sulfonyl]methane (3.32 g, 17 mmol) in dry DME (20 ml). After 15 min, a soln. of **8** (4.41 g, 5.85 mmol) in DME (20 ml) was added dropwise at –30°, the stirring continued for 1.5 h, and the mixture poured into ice-water, acidified with AcOH at 0° and extracted with CH₂Cl₂. The CH₂Cl₂ soln. was dried (Na₂SO₄) and evaporated and the residue purified by FC (AcOEt/hexane 1:1): **9** (6.32 g, 87%). Pale yellow foam. IR (film): 3280, 3085, 3065, 3030, 2985, 2935, 2870, 1710, 1690, 1660, 1595, 1485, 1380, 1370, 1320, 1300, 1290, 1215, 1145, 1080, 1025, 885, 855, 810, 750, 700. ¹H-NMR (CDCl₃): *cis/trans*-**9** 1:1. Anal. calc. for C₂₄H₂₇NO₇S (473.55): C 60.87, H 5.75, N 2.96; found: C 60.5, H 5.6, N 2.8.

4-[(4' R)-3'-O-Benzyl-1',2'-O-isopropylidene- α -L-threofuranose-4-C-yl]-1*H*-imidazole (**11**). To a stirred soln. of **9** (6.32 g, 13.74 mmol) in dry DME (20 ml) under Ar at –35° was added at once Et₃N (9.6 ml, 69 mmol), followed by slow addition of POCl₃ (1.39 ml, 16.9 mmol) in DME (5 ml). After stirring for 1.5 h at –5°, the mixture was poured into ice-water, immediately extracted with CH₂Cl₂, dried (Na₂SO₄), and evaporated at r.t.: **5.8 g** (95%) of **10** as a chromatographically pure sample (IR (film): 2110 (N=C)). The soln. of crude **10** (5.8 g) in dry 20% NH₃/MeOH (25 ml) was stirred at r.t. overnight. Evaporation and FC (CHCl₃/MeOH 9:1) gave **11** (2.78 g, 66%). Pale yellow foam. $[\alpha]_D^{20} = -45.5$ (*c* = 0.9, CHCl₃). IR (film): 3060, 3030, 2985, 2935, 2870, 1495, 1450, 1380, 1370, 1350, 1250, 1160, 1075, 1025, 1010, 910, 860, 735, 700. ¹H-NMR (CDCl₃): 7.63 (*d*, 1 H-C(2)); 7.32–7.26 (*m*, 3 arom. H); 7.14–7.10 (*m*, 2 arom. H, H-C(5)); 6.00 (*d*, H-C(1')); 5.34 (*d*, H-C(4')); 4.72 (*d*, H-C(2')); 4.42 (*AB*, PhCH₂); 4.05 (*d*, H-C(3')); 1.55 (*s*, Me); 1.35 (*s*, Me); *J*(2,5) = 0.5, *J*(1',2') = 3.8, *J*(2',3') = 0, *J*(3',4') = 2.9. Anal. calc. for C₁₇H₂₀N₂O₄ (316.36): C 64.54, H 6.37, N 8.85; found: C 65.2, H 6.4, N 8.7.

(2*S*,3*S*,4*R*)-3-(Benzyloxy)-1-(1*H*-imidazol-4-yl)butane-1,2,4-triol (**12**). To a soln. of **11** (2.85 g, 9 mmol) in dioxane (15 ml) was added a 4% aq. H₂SO₄ soln. (15 ml). The mixture was heated at reflux for 2 h, until complete disappearance of **11**, then neutralized with caution at r.t. with solid Na₂CO₃. The solid was filtered off and washed with dioxane. The filtrate and washings were evaporated. FC (CHCl₃/MeOH 9:1) led to a mixture of two anomers as a pale yellow foam (1.69 g, 68%). To this mixture (1.69 g, 6.12 mmol) in EtOH (15 ml), NaBH₄ (1.16 g, 30.6 mmol) was added at 0°. The mixture was stirred under Ar at r.t. for 24 h, then treated with sat. aq. NH₄Cl soln., and evaporated. The residue was extracted with EtOH and filtered. The EtOH extract was evaporated and the residue purified by FC (MeOH/Et₂O/28% NH₄OH soln. 5:5:0.2): **12** (1.2 g, 71%). Pale yellow foam. ¹H-NMR (CD₃OD): 8.11 (*d*, H-C(2)); 7.31–7.24 (*m*, arom. H); 7.16 (*dd*, H-C(5)); 5.05 (*dd*, H-C(4)); 4.66 (*s*, PhCH₂); 3.80 (*dd*, H-C(3)); 3.70 (*m*, H-C(2)); 3.62 (*m*, 2 H-C(1)); *J*(2',5') = 1.5, *J*(4,5') = 0.6, *J*(3,4) = 5.5, *J*(2,3) = 3.6, *J*(1,2) = 7.1, *J*(1,2) = 5.0¹⁾, *J*(1,1) = 9.0¹⁾. ¹³C-NMR (CD₃OD): 139.8 (C_{ipso}); 138.5 (C(4)); 135.5 (C(2)); 129.5, 129.3, 128.7 (arom. CH); 117.6 (C(5)); 82.8 (C(3)); 76.0 (PhCH₂); 73.0 (C(2)); 68.4 (C(4)); 64.2 (C(1)). Anal. calc. for C₁₄H₁₈N₂O₄ (278.31): C 60.42, H 6.52, N 10.07; found: C 59.7, H 6.6, N 9.9.

(2*S*,3*S*,4*R*)-3-Benzyl-2,4-(benzylidenedioxy)-4-(1*H*-imidazol-4-yl)butan-1-ol (**13**). To a stirred mixture of **12** (720 mg, 2.6 mmol) and anh. ZnCl₂ (1.86 g, 13.7 mmol) was added under Ar freshly distilled PhCHO (5 ml, 49 mmol) at r.t. The stirring was continued at r.t. for 24 h. The mixture was chromatographed by FC (CHCl₃) (removal of excess PhCHO), then CHCl₃/MeOH 9:1: **13** (670 mg, 71%). Colourless syrup. $[\alpha]_D^{20} = -41.5$ (*c* = 0.7, CHCl₃). ¹H-NMR (CD₃OD, 300 K): 7.67 (*d*, H-C(2)); 7.58 (*m*, 2 arom. H); 7.32 (*m*, 3 arom. H); 7.24 (*m*, 3 arom. H); 7.10 (*m*, 2 arom. H); 7.06 (*dd*, H-C(5)); 5.81 (*s*, PhCH(O)₂); 5.18 (*dd*, H-C(4)); 4.26, 4.04 (*2d* (*AB*),

¹⁾ Calculated with the PANIC simulation program from *Bruker*.

$J = 11.0$, PhCH_2); 4.18 (*ddd*, $\text{H}-\text{C}(2)$); 3.81 (*t*, $\text{H}-\text{C}(3)$); 3.80 (*dd*, 1 $\text{H}_a-\text{C}(1)$); 3.65 (*dd*, 1 $\text{H}_b-\text{C}(1)$); $J(2',5') = 1.2$, $J(5',4) = 0.8$, $J(3,4) = 1.6$, $J(2,3) = 1.6$, $J(2,1a) = 6.9$, $J(2,1b) = 5.8$, $J(1a,1b) = 11.2$. ^{13}C -NMR (CD_3OD , 300 K): 139.7, 139.3 (2 C_{ipso}); 137.3 ($\text{C}(4')$); 136.1 ($\text{C}(2')$); 129.8, 129.5, 129.2, 129.0, 128.8, 127.7 (arom. CH); 117.8 ($\text{C}(5')$); 102.8 ($\text{PhCH}(\text{O})_2$); 81.9 ($\text{C}(4)$); 78.7 (PhCH_2O); 75.8 ($\text{C}(2)$); 74.7 ($\text{C}(3)$); 62.8 ($\text{C}(1)$). FAB-MS: 367 ($[\text{M} + \text{H}]^+$).

(6*S*,7*R*,8*R*)-7-(*Benzyloxy*)-6,8-(*benzylidenedioxy*)-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine (**14**). To a stirred soln. of **13** (670 mg, 1.83 mmol) in CH_2Cl_2 (10 ml) was added at once under Ar anhyd. pyridine (0.46 ml, 5.54 mmol), then at -40° dropwise freshly distilled TiF_4 (0.42 ml, 4.18 mmol). Stirring was continued at -40° for 1 h until complete disappearance of **13**. The mixture was treated with aq. sat. NaHCO_3 soln. at 0° and extracted with CH_2Cl_2 , the org. layer dried (Na_2SO_4), filtered, and evaporated and the residue purified by FC ($\text{CHCl}_3/\text{MeOH}$ 9:1): **14** (256 mg, 40%). Colourless thick syrup. $[\alpha]_{\text{D}}^{20} = +2.8$ ($c = 0.86$, CHCl_3). ^1H -NMR (C_6D_6): 7.38–7.33 (*m*, $\text{H}-\text{C}(3)$, 2 arom. H); 7.16–6.99 (*m*, $\text{H}-\text{C}(1)$, 8 arom. H); 5.87 (*s*, $\text{PhCH}(\text{O})_2$); 5.15 (*dd*, $\text{H}-\text{C}(8)$); 4.26 (*dd*, $\text{H}-\text{C}(7)$); 4.15, 4.04 (*2d* (*AB*), $J = 12.0$, PhCH_2); 4.15 (*dq*, $\text{H}-\text{C}(6)$); 3.65 (*dd*, $\text{H}-\text{C}(5)$); 3.56 ($\text{H}'-\text{C}(5)$); $J(5,5') = 12.8$, $J(5,6) = 2.1$, $J(5',6) = 2.1$, $J(6,7) = 5.5$, $J(6,8) = 1.7$, $J(7,8) = 4.0$. ^{13}C -NMR (CDCl_3): 137.7, 136.8 (2 C_{ipso}); 136.4 ($\text{C}(3)$); 129.3, 128.7, 128.4, 128.3, 127.7, 126.4 (4 C_o , 4 C_m , 2 C_p); 128.2 ($\text{C}(1)$); 127.5 ($\text{C}(8a)$); 93.5 ($\text{PhCH}(\text{O})_2$); 72.0 (PhCH_2); 68.3 ($\text{C}(6)$); 67.3 ($\text{C}(7)$); 62.5 ($\text{C}(8)$); 45.2 ($\text{C}(5)$). FAB-MS: 349 ($[\text{M} + \text{H}]^+$).

(6*S*,7*R*,8*R*)-5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridine-6,7,8-triol (**15**). A suspension of **14** (124 mg, 0.356 mmol) and 10% $\text{Pd}(\text{OH})_2/\text{C}$ (150 mg) in AcOH (5 ml) was stirred under H_2 (4 psi) at r.t. for 16 h until complete disappearance of **14**. The catalyst was filtered off over *Celite* and washed with AcOH . The combined filtrates were evaporated at r.t., and the resulting residue was dissolved in H_2O (2 ml). This aq. soln. was passed over *Amberlite* *CG120* (H^+) columns. Elution of **15** was performed with 2*N* aq. NH_3 . After evaporation, the residue was purified by prep. TLC (anal. silica gel plates (*Merck*), $\text{MeOH}/\text{Et}_2\text{O}/28\% \text{NH}_4\text{OH}$ soln. 5:5:0.2): **15** (25 mg, 42%). Colourless foam after lyophilization. R_f 0.60. $[\alpha]_{\text{D}}^{25} = +69$ ($c = 0.55$, MeOH). ^1H -NMR: *Table*.

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