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 oxocarbonium ions which are the postulated intermediates in the glycoprocessing of the pyranose polysaccharides. This bicyclic azasugar should be a glycosidase inhibitor.

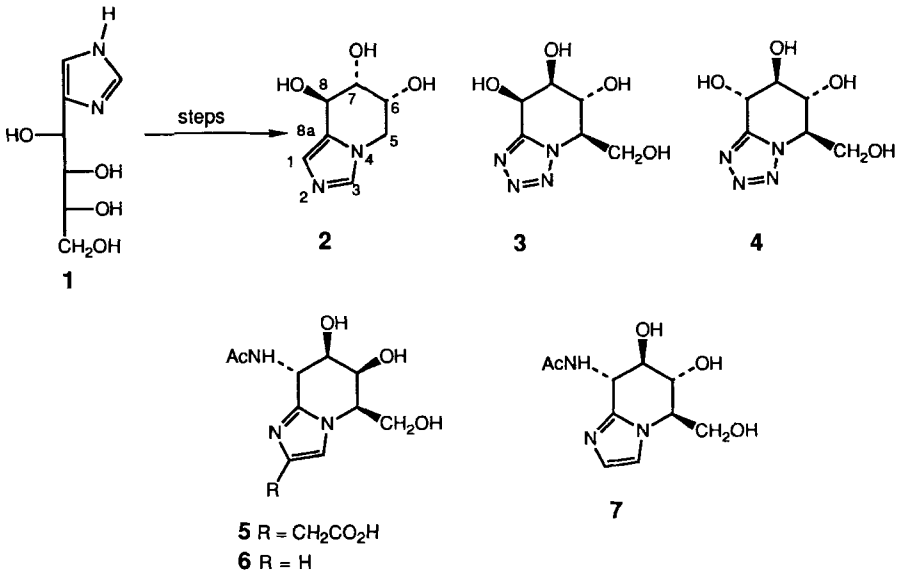
The enzymatic glycosidase mechanism of pyranosic polysaccharides is believed to involve a transient half-chair oxocarbonium ion which is stabilized by a complementary carboxylate anion of an active-site catalytic residue [1] [2]. Structural aza analogues of these glycosyl cations represent an attractive 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

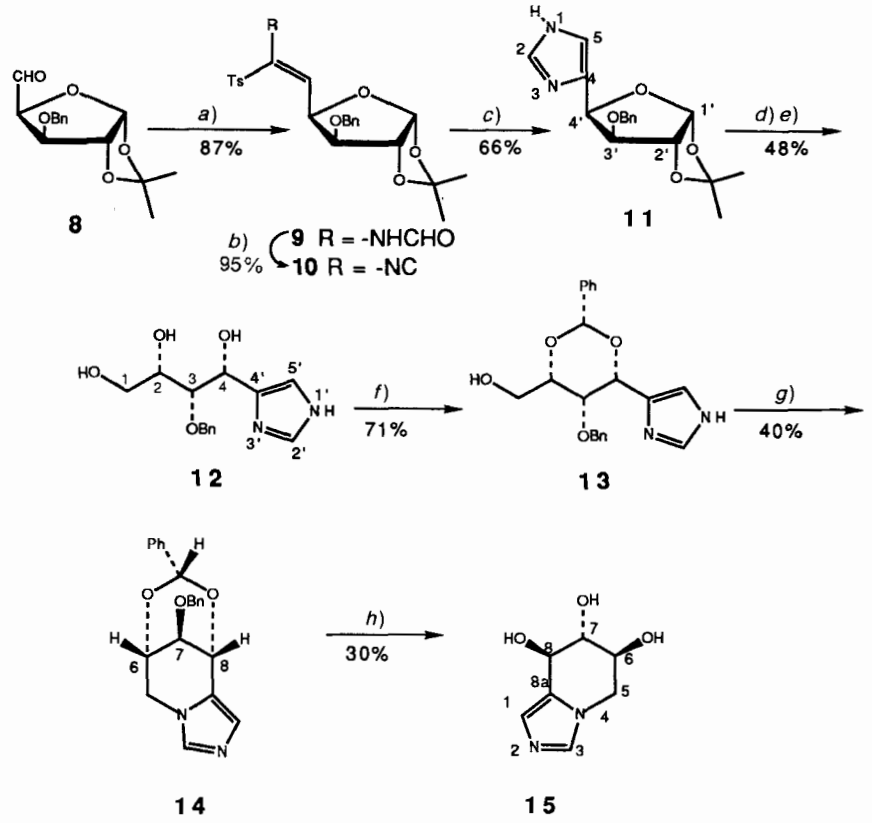


nose **15** from D-glucose. According to a straightforward retrosynthetic analysis, the terminal C(6) atom of D-glucose had to be removed and replaced by the imidazole ring (*via* C–C bond formation). The sugar moiety of the resulting imidazole derivative must then formally be turned upside down (in 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 H_2SO_4 in dioxane, followed by $NaBH_4$ reduction of the resulting hemiacetal, gave imidazolyl-L-*xylo*-tetritol derivative **12**. Reaction of **12** with benzaldehyde in the presence of anhydrous $ZnCl_2$ 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. ^{1}H-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 PhC*H*$(O)_2$ (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 PhC*H*$(O)_2$ (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*-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, $Pd(OH)_2/C$, AcOH.

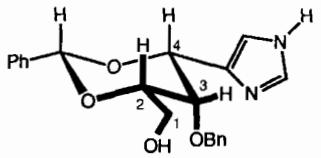


Fig. 1. *Chair conformation* **13A** *of compound* **13** *as determined by nuclear* Overhauser *measurements*

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 $PhCH(O)_2$ (5.87 ppm) → NOE at H–C(7) (4.27 ppm; 19%!; quasi flagpole-bowsprit interaction) and at H–C(6) (4.15 ppm; 3%)).

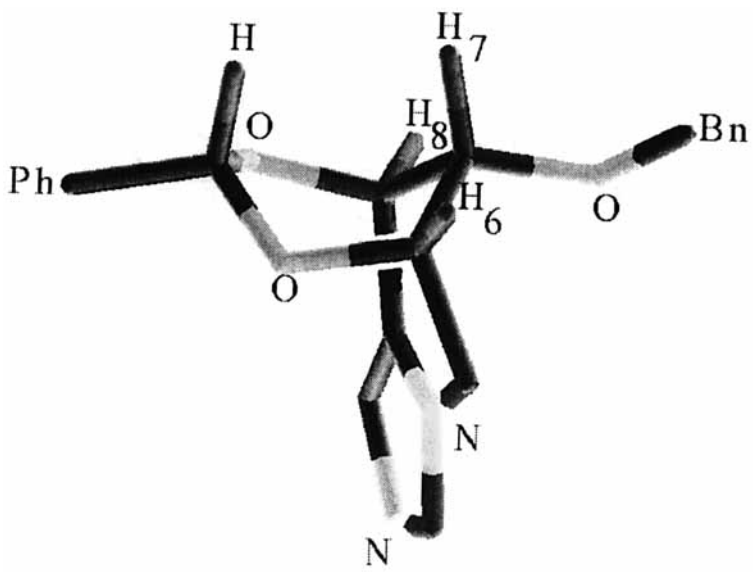


Fig. 2. *Boat conformation* **14A** *of compound* **14** *as determined by molecular modeling and by nuclear* Overhauser *effect measurements*

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*-piperidinose **15** is a C(6) diastereoisomer of its D-*arabino*-piperidinose stereoisomer **2** appears clearly when comparing the corresponding ^{1}H-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. *^{1}H-NMR* (250 MHz) *and ^{13}C-NMR* (62.9 MHz) *Data of Imidazopiperidinose Derivatives* **2** *and* **15** *in CD_3OD.* δ in ppm, internal standard CD_3OD ($\delta(CD_3OD)$ 3.30 ppm for ^{1}H, and $\delta(CD_3OD)$ 49.02 ppm for ^{13}C)[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 ^{1}H- and ^{13}C-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; $SiMe_4$ (^1H) and $CDCl_3$ ($\delta(CDCl_3)$ 77.00 ppm rel. to $SiMe_4$; ^{13}C) and CD_3OD ($\delta(CD_3OD)$ 3.30 ppm for ^1H and δ (CD_3OD) 49.02 ppm for ^{13}C) 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 isocyano[(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 CH_2Cl_2. The CH_2Cl_2 soln. was dried (Na_2SO_4) 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 ($CDCl_3$): *cis/trans*-**9** 1:1. Anal. calc. for $C_{24}H_{27}NO_7S$ (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]-1H-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 Et_3N (9.6 ml, 69 mmol), followed by slow addition of $POCl_3$ (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 CH_2Cl_2, dried (Na_2SO_4), 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% NH_3/MeOH (25 ml) was stirred at r.t. overnight. Evaporation and FC ($CHCl_3$/MeOH 9:1) gave **11** (2.78 g, 66%). Pale yellow foam. $[\alpha]_D^{20} = -45.5$ ($c = 0.9$, $CHCl_3$). IR (film): 3060, 3030, 2985, 2935, 2870, 1495, 1450, 1380, 1370, 1350, 1250, 1160, 1075, 1025, 1010, 910, 860, 735, 700. ^1H-NMR ($CDCl_3$): 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*, PhCH_2); 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 $C_{17}H_{20}N_2O_4$ (316.36): C 64.54, H 6.37, N 8.85; found: C 65.2, H 6.4, N 8.7.

(2S,3S,4R)-3-(Benzyloxy)-1-(1H-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. H_2SO_4 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 Na_2CO_3. The solid was filtered off and washed with dioxane. The filtrate and washings were evaporated. FC ($CHCl_3$/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), $NaBH_4$ (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. NH_4Cl soln., and evaporated. The residue was extracted with EtOH and filtered. The EtOH extract was evaporated and the residue purified by FC (MeOH/Et_2O/28% NH_4OH soln. 5:5:0.2): **12** (1.2 g, 71%). Pale yellow foam. ^1H-NMR (CD_3OD): 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*, PhCH_2); 3.80 (*dd*, H–C(3)); 3.70 (*m*, H–C(2)); 3.62 (*m*, 2 H–C(1)); $J(2',5') = 1.5$, $J(4,5') = 0.6$, $J(3,4) = 5.5$, $J(2,3) = 3.6$, $J(1,2) = 7.1$, $J(1,2) = 5.0$[1]), $J(1,1) = 9.0$[1]). ^{13}C-NMR (CD_3OD): 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 (PhCH_2); 73.0 (C(2)); 68.4 (C(4)); 64.2 (C(1)). Anal. calc. for $C_{14}H_{18}N_2O_4$ (278.31): C 60.42, H 6.52, N 10.07; found: C 59.7, H 6.6, N 9.9.

(2S,3S,4R)-3-Benzyl-2,4-(benzylidenedioxy)-4-(1H-imidazol-4-yl)butan-1-ol (**13**). To a stirred mixture of **12** (720 mg, 2.6 mmol) and anh. $ZnCl_2$ (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 ($CHCl_3$) (removal of excess PhCHO), then $CHCl_3$/MeOH 9:1): **13** (670 mg, 71%). Colourless syrup. $[\alpha]_D^{20} = -41.5$ ($c = 0.7$, $CHCl_3$). ^1H-NMR (CD_3OD, 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 (2*d* (*AB*),

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

J = 11.0, PhCH_2); 4.18 (*ddd*, H–C(2)); 3.81 (*t*, H–C(3)); 3.80 (*dd*, 1 H_a–C(1)); 3.65 (*dd*, 1 H_b–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 (C(4′)); 136.1 (C(2′)); 129.8, 129.5, 129.2, 129.0, 128.8, 127.7 (arom. CH); 117.8 (C(5′)); 102.8 (PhCH(O)$_2$); 81.9 (C(4)); 78.7 (PhCH_2O); 75.8 (C(2)); 74.7 (C(3)); 62.8 (C(1)). FAB-MS: 367 ([M + 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 anh. pyridine (0.46 ml, 5.54 mmol), then at –40° dropwise freshly distilled Tf_2O (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 ($CHCl_3$/MeOH 9:1): **14** (256 mg, 40%). Colourless thick syrup. $[\alpha]_D^{20}$ = +2.8 (c = 0.86, $CHCl_3$). ^{1}H-NMR (C_6D_6): 7.38–7.33 (*m*, H–C(3), 2 arom. H); 7.16–6.99 (*m*, H–C(1), 8 arom. H); 5.87 (*s*, PhCH(O)$_2$); 5.15 (*dd*, H–C(8)); 4.26 (*dd*, H–C(7)); 4.15, 4.04 (2*d* (*AB*), J = 12.0, PhCH_2); 4.15 (*dq*, H–C(6)); 3.65 (*dd*, H–C(5)); 3.56 (H′–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 (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 (C(1)); 127.5 (C(8a)); 93.5 (PhCH(O)$_2$); 72.0 (PhCH_2); 68.3 (C(6)); 67.3 (C(7)); 62.5 (C(8)); 45.2 (C(5)). FAB-MS: 349 ([M + 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% Pd(OH)$_2$/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 2N aq. NH_3. After evaporation, the residue was purified by prep. TLC (anal. silica gel plates (*Merck*), MeOH/Et_2O/28% NH_4OH soln. 5:5:0.2): **15** (25 mg, 42%). Colourless foam after lyophilization. R_f 0.60. $[\alpha]_D^{22}$ = +69 (c = 0.55, MeOH). ^{1}H-NMR: *Table*.

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