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Synthesis of an Imidazolo-L-*lyxo*-Piperidinose Derivative

by **Andrzej Frankowski**[a)*], **Dariusz Deredas**[a)], **Jacques Streith**[b)] and **Théophile Tschamber**[b)*].

[a)]Institute of Organic Chemistry, Technical University, ul. Zwirki 36, PL- 90-924 Lodz, Poland.
[b)] Ecole Nationale Supérieure de Chimie, Université de Haute-Alsace, 3, rue Alfred Werner, F- 68093 Mulhouse, France.

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Abstract. - Imidazolo-L-lyxo-piperidinose **4** was synthesised from the D-galactose derivative **8** by two reaction sequences, via removal of a terminal carbon atom, stepwise incorporation of an imidazole moiety, and eventually intramolecular S_N2 reaction to the corresponding piperidine ring. Piperidinose **4** proved to be a poor glycosidase inhibitor. © 1998 Elsevier Science Ltd. All rights reserved.

Introduction. - In recent years piperidinose type amino-deoxysugars, which bear five-membered aromatic heterocycles condensed to the piperidine ring, have been the subject of several investigations. Such bicyclic azasugars mimic the half-chair oxocarbonium ion which is usually postulated as the "transition state" in enzymatic glycoside hydrolyses. For that reason they may be considered as potential inhibitors of glycosidases. Indeed and quite often they behave as such. In the imidazolo-piperidinose series, the naturally occurring nagstatine, which was discovered in 1992, is a potent glycosidase inhibitor.[1] *Tatsuta* and coworkers described the synthesis of **1** and of some of its analogues.[2,3] Furthermore *Burgess* and his coworkers synthetized several imidazolo-piperidinoses.[4] Some time ago we prepared two imidazolo-piperidinoses belonging to the D-arabino **2**[5] and to the L-xylo series **3**.[6] All the aminosugars we alluded to above have in common an imidazole ring fused to a piperidine ring in the 1 and 2 positions. As to piperidinoses which are condensed with a tetrazole ring, they were the target-molecules of some of *Vasella's*[7,8,9] and *Fleet's*[10,11] synthetic endeavours.

As pointed out recently by Vasella, there seems to be good evidence that the catalytically active carboxy group of lysozyme does not protonate the glycosidic O-atom from above – i.e. perpendicular to the pyranose ring, as proposed initially by Koshland[12]– but rather in the plane of that piperidine ring[13] . Vasella pointed out furthermore that such a lateral orientation of the protonating carboxy group would also appear to be a feature of several retaining β-glycosidases. He inferred this latter hypothesis from a comparison of inhibitory properties of some bicyclic aromatic piperidinoses possessing an sp^2-hybridized N-atom in lieu of the glycosidic O-atom, and of some similar aminosugars which do not possess such a heteroatom on that very site.[13] That the imidazolosugar nagstatine **1** is a strong inhibitor of N-acetyl-β-D-glucosaminidase from bovine kidney (IC_{50} = 13 nM) fits these predictions rather well.

Fax : (33) 1 89 43 77 90 ; Email : T.Tschamber@ univ-mulhouse.fr

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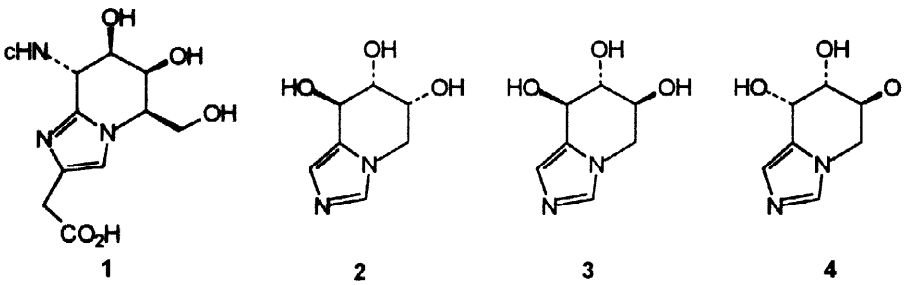
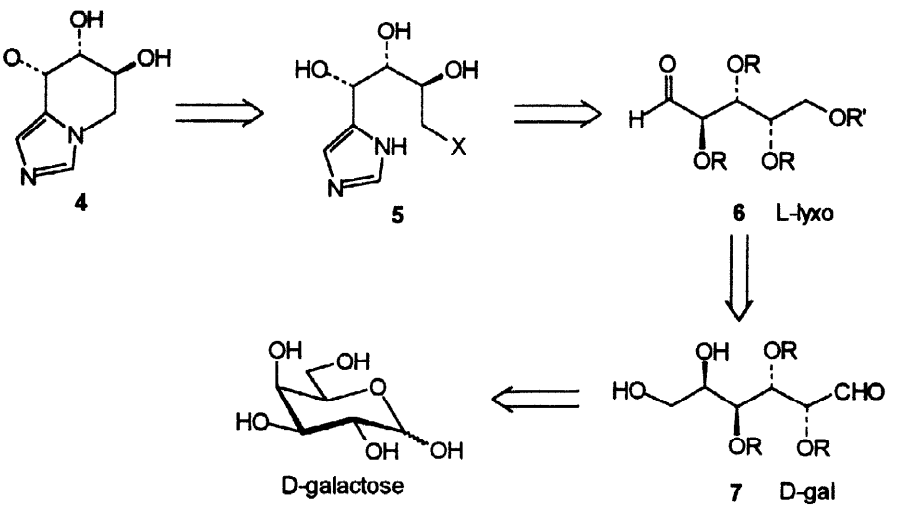
Since the imidazolo-D-arabino-piperidinose **2** turned out to be a potent and specific inhibitor both of jack beans α-mannosidase (K_i = 50 μM)[14], and of human liver α-mannosidase,[15] we decided to prepare some stereoisomers of **2** hoping to attain some glycosidase inhibitors having different specificities which would be related to their absolute configuration. Nevertheless as of today and in view of Vasella's recent comments, it seemed unlikely to attain strong inhibitory properties, since the glycosidic O-atom of our target molecules is replaced by an sp^2 C-atom instead of the required sp^2 N-atom, as in nagstatine **1**.[13]



Scheme 1

Results and Discussion.

We describe herein two synthetic strategies leading from D-galactose to the imidazolo-L-lyxo-piperidinose derivative **4**, our target molecule.



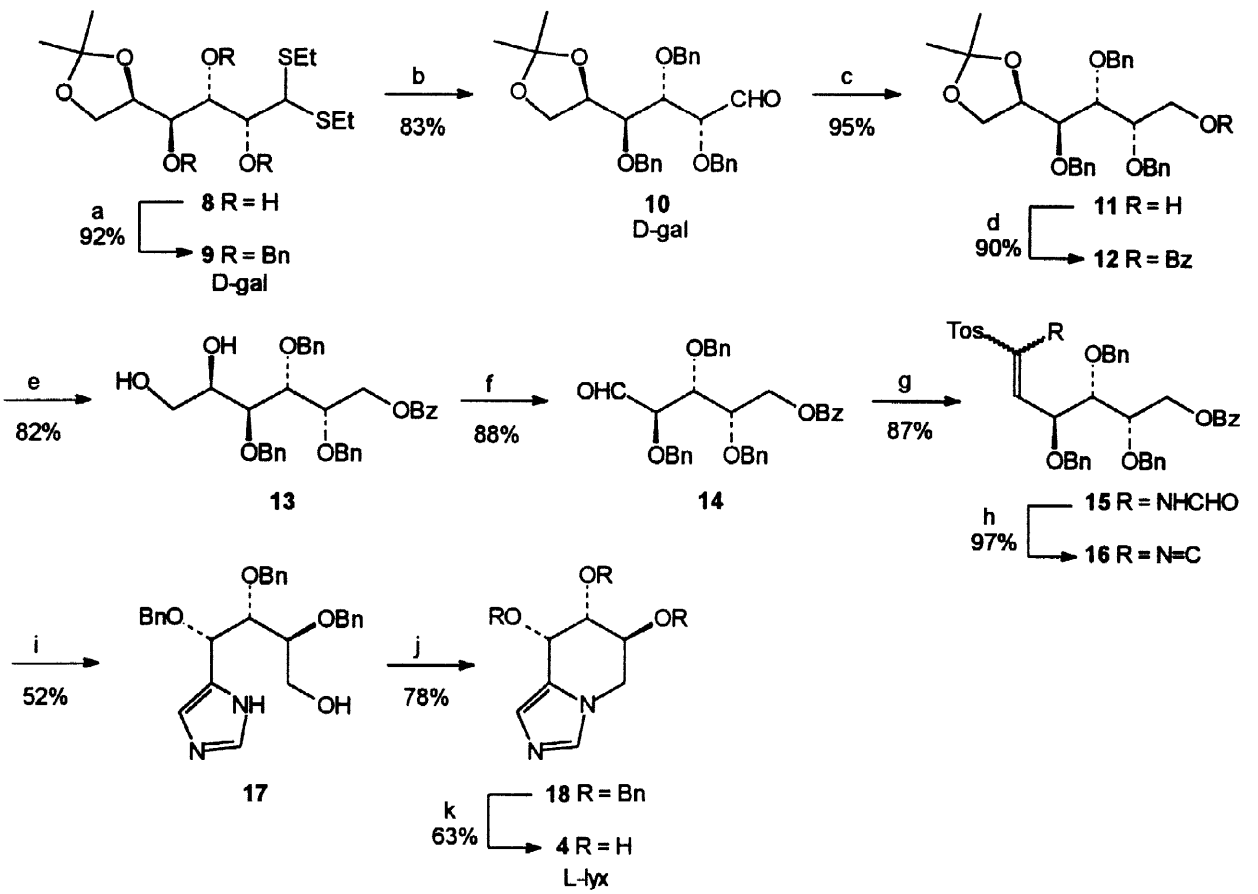
Scheme 2

The overall retrosynthetic analysis of our planned syntheses is delineated in Scheme 2. Aminosugar **4** could

in principle be obtained by an intramolecular S_N2 cyclisation of the appropriate derivative of imidazolyl-L-*lyxo*-butanetetrol **5**. The hemisynthesis of **5** was to be achieved by a stepwise van Leusen type incorporation (with the TosMIC reagent) of the imidazole moiety into the chain of L-*lyxose* derivative **6**, this latter one being readily available from the D- *galactose* configurated compound **7** via sequential reduction of its aldehyde function and oxidative cleavage of the terminal free diol.

In actual fact we synthesized target compound **4** from D-galactose in two different ways (Scheme 3) starting from the known 5,6-O-isopropylidene-D-galactose diethyldithioacetal.[16] Dithioacetal **8** was perbenzylated to give the fully protected tribenzyl derivative **9** which we used as the common precursor for both synthetic sequences.

First synthetic sequence (Scheme 3). Removal of the dithioacetal protection of **9** with mercury salts (HgO/$HgCl_2$) in acetonitrile led easily to the rather unstable aldehyde **10**. This latter compound was reduced at once with $NaBH_4$ in



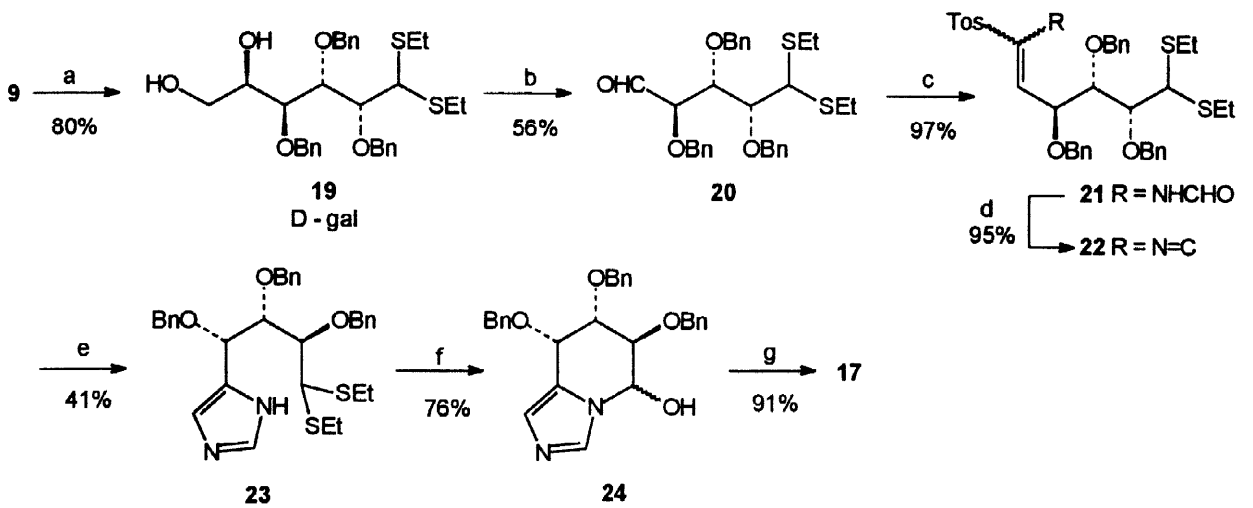
a. BnBr, NaH, THF b. HgO, $HgCl_2$, MeCN c. $NaBH_4$, MeOH d. BzCl, Py e. AcOH aq. f. $NaIO_4$, acetone
g. DME, TosMIC, t-BuOK h. $POCl_3$, NEt_3, DME i. NH_3, MeOH j. 1) $BnSO_2Cl$, Py 2) Ac_2O k. $Pd(OH)_2$ / C, H_2

Scheme 3

methanol and the corresponding alcohol **11** was benzoylated to give compound **12** in good yield. Removal of the isopropylidene protection of **12** in acetic acid followed by oxidative cleavage of the resulting diol **13** with sodium periodate gave the L-lyxose derivative **14** in good overall yield. The van Leusen methodology[17] was then applied as follows : aldehyde **14** in dimethoxyethane (DME) was treated in the cold with toluene-4-sulfonylmethyl isocyanide (TosMIC) in the presence of potassium t-butoxide; this led in good yield to a mixture of the two Z/E isomers **15** which were treated sequencially with triethylamine and $POCl_3$ to give the corresponding Z/E isocyanides **16** in excellent yield. Finally treatment of this latter mixture with ammonia in methanol led slowly, and in moderate yield only, to the imidazole derivative **17** in which the benzoyl protection had also been removed by ammonia. Reaction of the primary alcohol of **17** with phenylmethanesulfonyl chloride (α-tosyl chloride) in pyridine and subsequent treatment with acetic anhydride led directly to intramolecular SN2 cyclisation (78%) ; the resulting tribenzyl derivative **18** was deprotected by hydrogenolysis in the presence of Pearlman's catalyst ($Pd(OH)_2/C$) to give the target piperidinose **4** in moderate yield.

Structure and configuration of imidazolosugar **4** could easily be determined from the corresponding ^1H- and ^{13}C NMR spectral data whose first order interpretations do not require any further comments (Table 1).

Second synthetic sequence (Scheme 4). Removal of the isopropylidene moiety of **9** in aqueous acetic acid gave diol **19** in good yield. Periodate oxidative cleavage of the terminal free diol of **19** gave the pentanal derivative **20** in



a. AcOH aq. b. $NaIO_4$, acetone c. TosMIC, t-BuOK d. $POCl_3$, Et_3N, DME
e. NH_3/MeOH f. $Ce(NH_4)_2(NO_3)_6$, MeCN g. $NaBH_4$, MeOH

Scheme 4

moderate yield. Incorporation of the imidazole ring via the *van Leusen* methodology was very similar to the one described above and led in moderate overall yield to the imidazolyl-tetritol **23**. Removal of the dithioacetal function by mercury salts failed in this case, presumably because of mercury ions' propensity to complex the imidazole ring. Therefore we used the oxidant $Ce(NH_4)_2(NO_3)_6$ (CAN) as a deprotecting agent[18] which led directly to the product of intramolecular cyclisation *i.e.* hemiaminal **24** as a mixture of two anomers in a *ca.* 1:1 ratio (according to ^1H – NMR). Reduction of hemiaminal **24** with $NaBH_4$ gave imidazolyl-L-*lyxo*-tetritol derivative **17** in good yield. The transformation of **17** into the target imidazolo-L-lyxo-piperidinose derivative **4** proceeded as above (first synthetic sequence).

Table 1. *^1H - NMR (250 MHz) and ^{13}C - NMR (62.9 MHz) Data of Imidazolo-L-lyxo-piperidinose* (**4**) *in D_2O (^1H - NMR) and in CD_3OD (^{13}C - NMR)* [a]

H-C (1)	H-C (3)	H_a-C (5)	H_b-C (5)	H-C (6)	H-C (7)	H-C (8)
7.09	7.66	3.97	4.41	4.40	4.09	5.07
$J_{(5a,5b)}$	$J_{(5a,6)}$	$J_{(5b,6)}$	$J_{(6,7)}$	$J_{(7,8)}$		
14.4	7.2	4.8	7.0	3.9		
C(1)	C(3)	C(5)	C(6)	C(7)	C(8)	C(8a)
126.55	136.97	47.15	68.07	71.79	63.98	131.60

[a] - Assignment of ^1H and ^{13}C - NMR signals by selective decoupling experiments.

Biological assays and Conclusions. -The inhibitory activities of compound **4** against 24 commercially available glycosidases were determined. Only in two instances some rather modest inhibitory activities were observed : *K_i = 1.3 mM against the β-galactosidase of jack beans; K_i = 0.6 mM against the α-glucosidase (isomaltase) of baker's yeast.*[14] *Quite obviously the imidazolo-L-lyxo-piperidinose 4 is but a poor glycosidase inhibitor. This may be due to several factors. To begin with sugars having the lyxo configuration do not seem to occur in nature, neither in the D- nor in the L-series. Furthermore to be a potent glycosidase inhibitor a piperidinose usually requires a CH_2OH group to be present in the C(5) position; if only to induce its proper docking into the enzyme's active site . Finally, and notwithstanding imidazolosugar 2, which happens to be a potent inhibitor of α-mannosidases, the presence of an sp^2 N-atom in lieu of the glycosidic O-atom may be a prerequisite for an imidazolo-piperidinose to be a potent glycosidase inhibitor (see above).*

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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-250 spectrometer using double-irradiation techniques; tetramethylsilane (TMS; ^1H - NMR) and $CDCl_3$ (δ ($CDCl_3$) = 77.00 with respect to TMS; ^{13}C - NMR) as internal references; δ in ppm and J in Hz. Mass spectra (MS and HRMS) were measured on a ZabSpec TOF Micromass spectrometer at 8 kV (source temp. 40 °C) in a meta-nitrobenzylic alcohol matrix in the FAB^+ mode (ionisation with Cs^+) and were performed at the Centre Régional de Mesures Physiques de l'Ouest at the University of Rennes I.

2,3,4-Tri-O-benzyl-5,6,-O-isopropylidene-D-galactose diethyldithioacetal **9**.
To a stirred soln. of 5,6-O-isopropylidene D-galactose diethyldithioacetal **8**[16] (5.49 g, 16,8 mmol) in anh. THF (50 ml) was added portionwise 50% NaH in oil (2.9 g, *ca.* 60 mmol) at 0 °C. When the evolution of H_2 ceased, Bu_4NI (20 mg) and BnBr (6.0 ml, ca.50 mmol) were added at 0 °C. Stirring was continued at r.t. overnight until complete disappearence of starting material (TLC), and the mixture was treated with MeOH (20 ml). The solvents were evaporated. The residue was dissolved in CH_2Cl_2 (200 ml), and washed with water. The org. layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by FC (hexane/AcOEt 4:1) to obtain **9** (R_f = 0.65) (9.19 g, 92%) as a pale yellow oil. $[\alpha]^{20}_D$ = -3.7 (c = 1.0, $CHCl_3$). IR (film) : 3100, 3080, 3050, 3000, 2940, 2880, 1505, 1445, 1380, 1270, 1220, 1170, 1120, 1075, 1030, 980, 920, 870, 700. ^1H - NMR ($CDCl_3$) : 7.37 - 7.24 (m, 15H, arom.) ; 4.77 (dd, AB, J = 11.2, PhC*H*$_2$) ; 4.75 (dd, AB, J = 11.3, PhC*H*$_2$) ; 4.73 (dd, AB, J = 11.6, PhC*H*$_2$) ; 4.29 (ddd, H-C(5)) ; 4.12 (dd, H-C(3)) ; 4.09 (d, H-C(1)) ; 3.99 (dd, Ha-C(6)) ; 3.97 (dd, H-C(2)) ; 3.78 (dd, Hb-C(6)) ; 3.68 (dd, H-C(4)) ; 2.72 - 2.52 (m, 4H, SCH_2) ; 1.42, 1.36 (2s, Me_2C); 1.19 (t, J = 7.5, C*H*$_3$CH$_2$S) ; 1.17 (t, J = 7.4, C*H*$_3$CH$_2$S). $J_{(1,2)}$ = 5.1, $J_{(2,3)}$ = 4.8, $J_{(3,4)}$ = 6.0, $J_{(4,5)}$ = 7.5, $J_{(5,6a)}$ = 6.4, $J_{(5,6b)}$ = 6.4, $J_{(6a,6b)}$ = 8.4. ^{13}C - NMR ($CDCl_3$) : 139.08, 138.83 (s arom.); 128.74, 128.61, 128.45, 128.31, 128.09, 128.02, 127.85 (arom. CH); 109.28 (*C*Me$_2$); 82.96 (C(2)) ; 81.29 (C(3)) ; 80.96 (C(4)) ; 77.99 (C(5)) ; 75.03, 74.94, 74.17 (CH_2Ph) ; 67.11 (C (6)) ; 54.32 (C(1) ; 26.99, 26.07 (*Me*$_2$C) ; 25.75, 25.44 (S*C*H$_2$) ; 14.86 (*C*H$_3$ - CH$_2$S). MS : m/z = 595.2 $[M-H]^+$, 535.2 $[M-SEt]^+$, 477.2 $[M-SEt-OC(CH_3)_2]^+$. HRMS calculated for $C_{34}H_{44}O_5S_2$ $[M]^+$: 596.2630, found : 596.2619.

2,3,4-Tri-O-benzyl-5,6-O-isopropylidene-D-galactose **10**.
To a stirred soln. of **9** (2.94 g, 4.9 mmol) in 80% aq. acetonitrile (40 ml) were added HgO (3.20 g, 14.8 mmol) and a soln. of $HgCl_2$ (1.34 g, 4.9 mmol) in 80% aq. acetonitrile (20 ml). The mixture was stirred at r.t. for 5 h, filtered and acetonitrile was evaporated. To this residue a 10% aq. soln. of KI was added in excess and the mixture was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and evaporated. The residue was purified by FC (hexane/AcOEt 4:1) and led to **10** (R_f= 0.4) (2.00 g, 83%) as a colourless and unstable syrup which was used immediately for the next reaction. $[\alpha]^{20}_D$ = +11.2 (c=1.85, $CHCl_3$). IR (film) : 3420, 3100, 3075, 3040, 2935, 2880,1730, 1610, 1580, 1500, 1450, 1370, 1270, 1215, 1100, 1080, 1030, 700. ^1H - NMR ($CDCl_3$) : 9.65 (s,C*H*O);7.42-7.11(m,15H, arom. H) ; 4.85 - 3.49 (6H, 3AB, $PhCH_2$ and m, 6H, sugar protons) ; 1.43, 1.37 (2s, Me_2C).

2,3,4-Tri-O-benzyl-5,6-O-isopropylidene-D-galactitol **11**.
To a stirred soln. of **10** (1.94 g, 3.95 mmol) in anh. ethanol (20 ml) $NaBH_4$ (0.75 g, 19.8 mmol) was added portionwise at -5°. The mixture was stirred under Ar at r.t. overnight, treated with an aq. NH_4Cl soln. (excess) and ethanol was evaporated. The residue was extracted with $CHCl_3$, and the solvent dried ($MgSO_4$) and evaporated.

Purification by FC (hexane/AcOEt 5:2) gave **11** (R_f = 0.4) (1.84 g, 94 %) as a colourless syrup. $[\alpha]_D^{20}$ = +26.5 (c =0.88, $CHCl_3$). IR (film) : 3470, 3100, 3075, 3050, 3000, 2950, 2900, 1500, 1455, 1375, 1260, 1220, 1165, 1125, 1090, 1075, 700. ^{1}H - NMR ($CDCl_3$) : 7.37 - 7.25 (m, 15H arom.) ; 4.70 (dd, AB, J = 11.5, CH_2Ph) ; 4.62 (dd, AB, J = 10.0, CH_2Ph) ; 4.60 (dd, AB, J = 11.5, CH_2Ph) ; 4.42 (dt, H-C(5)) ; 3.96 (dd, Ha-C(6)) ; 3.83 - 3.62 (m, 6H, sugar protons) ; 1.42, 1.36 (2s, Me_2C). $J_{(5,6a)}$ = 6.5, $J_{(4,5)}$ = 7.3, $J_{(6a,6b)}$ = 8.2. ^{13}C - NMR ($CDCl_3$) : 138.61, 138.25 (s arom.) ; 128.67, 128.73, 128.53, 128.39, 128.35, 128.21, 128.08 (arom, CH) ; 109.30 (*C*Me_2) ; 80.42 (C(4)) ; 80,23 (C(2)) ; 79.56 (C(3)) ; 77.44 (C(5)) ; 74.77, 74.24, 72.48 (CH_2Ph) ; 66.90 (C(1)) ; 61.43 (C(6)) ; 27.02, 26.02 (*Me*$_2$C). MS : m/z = 493.3 $[M+H]^+$, 435.2 $[M-OC(CH_3)_2+H]^+$. HRMS calculated for $C_{30}H_{37}O_6$ $[M+H]^+$: 493.2590, found : 493.2579.

1-O-Benzoyl-2,3,4-tri-O-benzyl-5,6-O-isopropylidene-D-galactitol **12**.

To a stirred soln. of **11** (1.27 g, 2.58 mmol) in anh. pyridine (5 ml) some freshly distilled benzoyl chloride (1.2 ml, *ca.* 10 mmol) was added dropwise at 0°. The mixture was stirred at r.t. overnight, pyridine was evaporated, then evaporated three times along with toluene and the residue dissolved in CH_2Cl_2 (20 ml). The CH_2Cl_2 soln. was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by FC (hexane/AcOEt 5:2) and led to **12** (R_f = 0.7) (1.39 g, 90 %) as a colourless syrup. $[\alpha]^{20}_D$ = -26.1 (c = 1.5, $CHCl_3$). IR (film) : 3100, 3070, 3015, 2970, 2920, 1735, 1620, 1600, 1515, 1470, 1380, 1330, 1285, 1230, 1180, 1130, 1115, 1085, 1055, 1030, 750, 725, 650. ^{1}H - NMR ($CDCl_3$) : 8.20 -7.96 (m, 3H, o-H, p-H,Bz) ; 7.71 - 7.23 (m, 17H arom. H) ; 4.68 (dd, AB, J = 11.2, $PhCH_2$) ; 4.67 (dd, AB, J = 11.7, $PhCH_2$) ; 4.60 (dd, AB, J = 11.5, $PhCH_2$) ; 4.61 - 4.34 (m, 4H, sugar protons) 4.08 - 3.71 (m, 4H, sugar protons) ; 1.43, 1.36 (2s, Me_2C). ^{13}C - NMR ($CDCl_3$: 166.64 (CO) ; 138.77, 138.49, 138.11 (s arom.) ; 134.95, 134.07, 133.48, 133.21, 130.99, 130.58, 130.39, 130.08, 129.95, 129.78, 129.30, 128.87, 128.82, 128.71, 128.64, 128.44, 128.35, 128.25, 128.19, 127.98 ; (arom. CH) ; 109.23 (CMe_2) ; 79.71 (C(3)) ; 79.50 (C(2)) ; 77.45 (C(4)) ; 76.94 (C(5)) ; 74.90, 74.56, 73.19 (CH_2Ph) ; 66.81 (C(6)) ; 64.74 (C(1)) ; 26.98, 26.03 (*Me*$_2$C). MS : m/z = 597.3 $[M+H]^+$, 539.2 $[M-OC(CH_3)_2+H]^+$. HRMS calculated for $C_{37}H_{41}O_7$ $[M+H]^+$: 597.2852, found 597.2834.

1-O-Benzoyl-2,3,4-tri-O-benzyl-D-galactitol **13**.

A soln. of **12** (1.34 g, 2.24 mmol) in 75% aq. AcOH (10 ml) was stirred at 60° for 8 h. The mixture was neutralised with a saturated aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2. The CH_2Cl_2 solns. were dried ($MgSO_4$) and evaporated. The residue was purified by FC (AcOEt/EtOH 85:15) and gave **13** (R_f = 0.35) (1.03 g, 82 %) as a colourless syrup. $[\alpha]^{20}_D$ = -0.5 (c = 1.5, $CHCl_3$) IR (film) : 3470, 3080, 3040, 2930, 2880, 1725, 1605, 1585, 1500, 1450, 1390, 1280, 1180, 1115, 1100, 1080, 1025, 980, 720, 700. ^{1}H - NMR ($CDCl_3$) : 7.99 (d, 2H, J = 7.0, o-H, Bz) ; 7.58 (t, 1H, J = 7.0, p-H, Bz) ; 7.44 (t, 2H, J = 7.0, m-H, Bz) ; 7.34 - 7.22 (m, 15H arom.) ; 4.76 (dd, AB, J = 11.2, CH_2Ph) ; 4.71 (dd, AB, J = 11.2, CH_2Ph) ; 4.55 (dd, AB, J = 11.5, CH_2Ph) ; 4.58 (dd, Ha-C(1)) ; 4.55 (dd, Hb-C(1)) ; 4.05 (dt, H-C(2)) ; 3.97 (ddd, H-C(5)) ; 3.93 (dd, H-C(3)) ; 3.78 (dd, H-C(4)) ; 3.67 (dd, Ha-C(6)) ; 3.58 (dd, Hb-C(6)). $J_{(1a,1b)}$ = 12.0, $J_{(1a,2)}$ = 5.5, $J_{(1b,2)}$ = 5.3, $J_{(2,3)}$ = 5.0, $J_{(3,4)}$ = 5.0, $J_{(4,5)}$ = 2.5, $J_{(5,6a)}$ = 6.2, $J_{(5,6b)}$ = 4.8, $J_{(6a,6b)}$ = 11.2. ^{13}C - NMR ($CDCl_3$) : 166.65 (CO); 138.21, 138.01, 133.58,130.29, 130.07, 128.93, 128.88, 128.68, 128.43, 128.32 (arom. CH); 79.64 (C(4)); 78.28 (C(5)); 77.44 (C(3)); 75.14 (C(2)); 74.11, 73.33, 71.76 (*C*H_2Ph); 64.59 (C(1)); 64.39 (C(6)). MS : m/z = 557.2 $[M+H]^+$, 181.1 $[HOH_2C\text{-}CH(OH)\text{-}CH{=}O\text{-}CH_2Ph]^+$. HRMS calculated for $C_{34}H_{37}O_7$ $[M+H]^+$: 557.2539, found : 557.2522.

5-O-Benzoyl-2,3,4-tri-O-benzyl-L-lyxose **14**.

To a stirred soln. of **13** (1.00 g, 1.80 mmol) in acetone (10 ml) was added dropwise at r.t. $NaIO_4$ (0.58 g, 2.7 mmol) in water (10 ml). The mixture was stirred at r.t. overnight, acetone was evaporated and the residue was extracted with CH_2Cl_2. The CH_2Cl_2 solns. were dried ($MgSO_4$) and evaporated. Purification by FC (hexane/AcOEt 5:2) gave **14** (0.83 g, 88%) as a colourless syrup. $[\alpha]^{20}_D$ = +4.7 (c = 0.57, $CHCl_3$), IR (film) : 3450, 3080, 3050, 2940, 1735, 1610, 1590, 1505, 1455, 1280, 1220, 1185, 1120, 1100, 1075, 1030, 980, 720, 700. ^{1}H - NMR ($CDCl_3$) : 10.03 (s, C*H*O) ; 8.14 - 7.88 (m, 3H, o-H, p-H, Bz) ; 7.68 - 7.41 (m, 2H, m-H, Bz) ; 7.34 - 7.20 (m, 15H arom.) ; 4.70 (dd, AB, J = 11.7, CH_2Ph) ; 4.68 (dd, AB, J = 11.7, CH_2Ph) ; 4.58 (dd, AB, J = 12.0, CH_2Ph) ; 4.45 -3.95 (m, 5H, sugar

protons). ^{13}C - NMR ($CDCl_3$) : 192.83 (C (1)) ; 161.20 (CO) ; 137.61, 134.88, 133.52, 130.59, 130.17, 130.08, 129.41, 129.07, 129.00, 128.88, 128.83, 128.61, 128.09, 127.41 (arom. CH) ; 82.45 (C(4)) ; 79.85 (C(2)) ; 78.85 (C(3)) ; 74.45, 73.73, 73.52 (CH_2Ph) ; 65.81 (C(5)).

(3S,4S,5S)-N-(6-Benzoyloxy-3,4,5-tribenzyloxy-1-tosyl-hex-1-en-1-yl)formamide **15**.
To a stirred soln. of *t*-BuOK (0.20 g, 1.78 mmol) in dry 1,2-dimethoxyethane (DME) (5 ml) under Ar at -30° was added dropwise a soln. of toluene-4-sulfonylmethyl isocyanide (TosMIC) (0.3 g, 1.52 mmol) in dry DME (10 ml). After 15 min, a soln. of **14** (0.80 g, 1.52 mmol) in dry DME (10 ml) was added dropwise and the stirring was continued for 1.5 h at -30°. The reaction mixture was then poured into ice-water, acidified with AcOH at 0° and extracted with CH_2Cl_2. The organic solution was dried (Na_2SO_4), evaporated and the residue purified by FC (hexane / AcOEt 1 : 1). **15** (R_f = 0.6) (0.95 g, 87%) was obtained as a pale yellow foam (mixture of two geometric isomers in *ca.* 1 : 1 ratio according to ^1H - NMR) IR (film) : 3300, 3080, 3050, 2930, 1725, 1610, 1505, 1455, 1250, 1180, 1130, 1100, 1080, 1030, 980, 720, 700. MS : m/z = 720.2 $[M+H]^+$. HRMS calculated for $C_{42}H_{42}NO_8S$ $[M+H]^+$: 720.2631, found : 720.2604.

N2,3,4-Tri-O-benzyl-D-galactose diethyldithioacetal **19**.
A soln. of **9** (2.37g, 3.96 mmol) in 75% aq. AcOH (15 ml) was stirred at 60° for 8 h. Workup as for **13** : after FC (hexane / AcOEt 1:1) **19** (R_f = 0.55) (1.76 g, 80%) was obtained as a colourless syrup. $[\alpha]^{20}_D$ = -5.8 (c = 4.00, $CHCl_3$). IR (film) : 3470, 3050, 2990, 2945, 2900, 1615, 1590, 1565, 1505, 1445, 1410, 1260, 1220, 1120, 1080, 985, 705. ^1H - NMR ($CDCl_3$) : 7.39 - 7.26 (m, 15H arom.) ; 4.84 (dd, AB, J = 10.1, CH_2Ph) ; 4.81 (dd, AB, J = 10.9, CH_2Ph) ; 4.63 (dd, AB, J = 11.7, CH_2Ph) ; 4.36 (dd, H-C(3)) ; 3.99 (dd, H-C(2)) ; 3.96 (d, H-C(1)) ; 3.91 (dt, H-C(5)) ; 3.72 (dd, Ha-C(6)) ; 3.69 (dd, H-C(4)) ; 3.58 (dd, Hb-C(6)) : 2.83 - 2.57 (m, 4H, SCH_2) ; 1.22 (2t, 6H, J = 7.25, CH_3-CH_2S). J (1,2) = 3.0, $J_{(2,3)}$ = 3.8, $J_{(3,4)}$ = 3.3, $J_{(4,5)}$ = 3.0, $J_{(5,6b)}$ = 5.4, $J_{(5,6a)}$ = 5.1, $J_{(6a,6b)}$ = 11.3. ^{13}C - NMR ($CDCl_3$) : 138.87, 138.33, 138.17 (s arom.) ; 128.92, 128.86, 128.68, 128.60, 128.56, 128.44, 128.29, 128.15, 127.95 (arom, CH) ; 83.53 (C(2)) ; 82.25 (C(3)) ; 77.69 (C(4)) ; 76.30, 75.58, 72.80 (CH_2Ph) ; 71.93 (C(5)) ; 63.60, (C(6)) ; 54.13 (C(1)) ; 26.03, 25.49 (SCH_2) ; 14.89, 14.83 (SCH_2CH_3). MS : m/z = 555.2 $[M-H]^+$, 495.2 $[M-SEt]^+$, 433.2 $[M-SEt-EtSH]^+$, 267.1 $[H_2C-C(OCH_2Ph)=C(SEt)_2]^+$. HRMS calculated for $C_{31}H_{40}O_5S_2$ $[M]^+$: 556.2317, found : 556.2312.

(2R, 3S, 4R)-2,3,4-Tribenzyloxy-5,5-diethylthiopentanal **20**.
To a stirred soln. of **19** (1.7 g, 3.05 mmol) in acetone (15 ml) $NaIO_4$ (0,98 g, 4.56 mmol) in water (15 ml) was added dropwise at r.t. and stirring was continued overnight. Workup as for **14** : after FC (hexane / AcOEt 4:1) **20** (R_f = 0.5) (0.89 g, 56 %) was obtained as a colourless syrup. $[\alpha]^{20}_D$ = -1.9 (c = 2.51, $CHCl_3$). IR (film) : 3470, 3080, 3050, 2975, 2940, 2885, 1745, 1505, 1455, 1375, 1355, 1315, 1275, 1220, 1100, 1080, 1030, 980, 700. ^1H - NMR ($CDCl_3$) : 9.72 (s, CHO) ; 7.36 - 7.26 (m, 15H arom.) ; 4.80 (dd, AB, J = 11.0, CH_2Ph) ; 4.72 (dd, AB, J = 11.2, CH_2Ph) ; 4.62 (dd, AB, J = 11.8, CH_2Ph) ; 4.33 (dd, H-C(3)) ; 4.06 (dd, H-C(2)) ; 4.01 (d, H-C(5)) ; 3.96 (dd, H-C(4)) ; 2.71 - 2.57 (m, 4H, SCH_2) ; 1.22 (t, J = 7.3, CH_3) ; 1.19 (t, J = 7.4, CH_3). J (1,2) = 1.6, J (2,3) = 3.7, J (3,4) = 6.0, J (4,5) = 4.5. ^{13}C - NMR ($CDCl_3$) : 201.46 (C(1)) ; 138.28, 137.93, 137.11 (s, arom.) ; 128.48, 128.29, 128.22, 128.06, 127.97, 127.86, 127.71, 127.53 (arom.CH); 84.02 (C(4) ; 82.61 (C(2)) ; 81.21 (C(3)) ; 75.61, 74.58, 72.49 (CH_2Ph); 53.29 (C(5)) ; 25.54, 25.40 (S-CH_2); 14.52, 14.22 (CH_3). MS : m/z = 525.2 $[M+H]^+$, 463.2 $[M-SEt]^+$. HRMS calculated for $C_{30}H_{37}O_4S_2$ $[M+H]^+$: 525.2133, found :525.2129.

(3S,4S,5R)-N-(3,4,5-Tribenzyloxy-6,6-diethylthio-1-tosyl-hex-1-en-1-yl)formamide **21**.
To a stirred soln. of *t*-BuOK (0.81 g, 7.25 mmol) in dry 1,2-dimethoxyethane (DME) (10 ml) under Ar at -30° was added dropwise a soln. of toluene-4-sulfonylmethyl isocyanide (TosMIC) (1.24 g, 6.35 mmol) in dry DME (10 ml). After 15 min, a soln. of **20** (3.32 g, 6.33 mmol) in dry DME (15 ml) was added dropwise. Stirring was continued for 1.5 h at -30° 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), evaporated and the residue purified by FC (hexane / AcOEt 1:1, R_f = 0.65) which led to **21** (4.40 g, 97 %) as a pale yellow foam (mixture of two geometric isomers according to the ^1H - NMR). IR

(film) : 3080, 3045, 2975, 2940, 2880, 1720, 1600, 1500, 1450, 1230, 1210, 1155, 1090, 980, 700.

(1S, 2S, 3R)-1,2,3-Tribenzyloxy-4,4-diethylthio-1-(1H-imidazol-4(5)-yl) butane **23**.
To a stirred soln. of **21** (1.12 g, 1.55 mmol) in dry DME (5 ml) under Ar at -35° was added Et_3N (1.1 ml, 7.8 mmol) followed by slow addition of $POCl_3$ (0.16 ml, 1.72 mmol) in dry DME (5 ml). After stirring for 1.5 h at -5°, the mixture was poured into ice-water, extracted with CH_2Cl_2, dried (Na_2SO_4) and evaporated at r.t. : 10.04 g (95%) of **22** as a chromatographically pure sample (IR (film : 2110 (isocyanide)). The soln. of crude **22** (1.04 g) in dry 20% NH_3/MeOH (10 ml) was stirred at r.t. overnight. Evaporation and FC (hexane / AcOEt 1:4) gave **23** (R_f = 0.45) (0.36 g, 41% from **21**) as a colourless syrup. $[\alpha]^{20}_D$ = +26.3 (c = 0.25, $CHCl_3$). IR (film) : 3050, 2975, 2945, 2880, 1500, 1455, 1305, 1270, 1220, 1130, 1090, 1075, 1030, 980, 700. ^{1}H - NMR ($CDCl_3$) : 7.63 (br s, H-C(2')) ; 7.38 - 7.23 (m, 15H arom.) ; 7.07 (br s, H-C(5')) ; 4.75 (dd, AB, J = 11.4, CH_2Ph) ; 4.70 (dd, AB, J = 10.9, CH_2Ph) ; 4.61 (d, H-C(1)) ; 4.43 (dd, H-C(2)) ; 4.42 (dd, AB, J = 12.1, CH_2Ph) ; 3.80 (d, H-C(4)) ; 3.54 (dd, H-C(3)) ; 2.70 - 2.42 (m, 4H, S-CH_2) ; 1.17 (t, J = 7.4, CH_3) ; 1.15 (t, J = 7.4, CH_3). ^{13}C - NMR ($CDCl_3$) : 139.04, 138.89, 138.39 (s - arom.) ; 136.30 (C(2')) ; 128.84, 128.80, 128.69, 128.60, 128.18, 128.11, 128.05, 127.87 (arom.*C*H) ; 126.29 (C(5')) ; 84.14 (C(2)) ; 83.44 (C(3)) ; 76.42, 76.22, 70.30 (*C*H_2Ph) ; 73.18 (C(1)); 53.99 (C(4)); 26.01, 25.64 (SCH_2); 14.90, 14.76 (CH_3). MS : m/z = 563.6 $[M+H]^+$, 501.5 $[M-SEt]^+$, 455.5 $[M-OBn]^+$, 267.2 $[CH_2$-C(OCH_2Ph)=C($SEt)_2]^+$, 187.2 [Imidazole-CH(OCH_2Ph)]$^+$, 135.1 $[(SEt)_2CH]^+$. HRMS calculated for $C_{32}H_{39}N_2O_3S_2$ $[M+H]^+$: 563.2402, found : 563.2399.

(6S,7S,8S)-6,7,8-Tribenzyloxy-5,6,7,8-tetrahydroimidazo[1.5-a]pyridine-5-ol **24** (mixture of anomers).
To a stirred soln. of **23** (674 mg, 1.2 mmol) in 75% aq. acetonitrile (15 ml) solid $Ce(NH_4)_3(NO_3)_6$ (2.63 g, 4.8 mmol) was added. After stirring for 3 h at r. t. acetonitrile was evaporated and the mixture was diluted with water (20 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 soln. was dried ($MgSO_4$) and evaporated. The residue purified by FC ($CHCl_3$/MeOH 9 : 1) gave **24** (R_f = 0.55) (417 mg, 76%) as colourless foam (mixture of two anomers in *ca.* 1 : 1 ratio according to ^{1}H - NMR). $[\alpha]^{20}_D$ = +40.7 (c = 1.40, $CHCl_3$). IR (film) : 3170, 3100, 3085, 3050, 2950, 2885, 1510, 1485, 1460, 1380, 1345, 1250, 1220, 1180, 1140, 1120, 1075, 1035, 950, 710. ^{1}H - NMR ($CDCl_3$) :Common signals for anomers A and B : 7.43 - 7.14 (m, 15H, arom.) 4.84 - 4.52 (m, 6H, C*H*$_2$Ph) Anomer A : 8.45 (br s, H-C(3)) ; 7.08 (br s, H- (1)) ; 5.88 (d, H-C(5)) ; 4.83 (d, H-C(8)) ; 4.16 (dd, H-C(6)) ; 3.98 (dd, H-C (7). J(5,6)=3.4, J(6,7)=6.4, J(7,8) = 3.2. Anomer B : 8.07 (br s, H-C(3)); 7.06 (br s, H-C(1)) ; 5.56 (d, H-C(5); 4.80 (d, H-C(8)) ; 4.24 (dd, H-C(6)) ; 3.86 (dd, H-C(7)). $J_{(5,6)}$ = 3.2, $J_{(6,7)}$ = 6.6, $J_{(7,8)}$ = 3.2. MS : m/z = 457.2 $[M+H]^+$, 349.2 $[M-OBn]^+$. HRMS calculated for $C_{28}H_{29}N_2O_4$ $[M+H]^+$: 457.2127, found : 457.2120.

(1S,2S,3S) 1,2,3-Tri-O-benzyl 1-(1H-imidazol-4(5)-yl butane-tetrol **17**
***i) From* 15:** To a stirred soln. of **15** (0.93 g, 1.29 mmol) in dry DME (5 ml) under Ar at -35° was added Et_3N (0.9 ml, 6.5 mmol) followed by a slow addition of $POCl_3$ (0.13 ml, 1.42 mmol) in dry DME (5 ml). After stirring for 1.5 h at -5° , the mixture was poured into ice-water, extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated at r.t.: isocyanide **16** (0.88 g, 97%) was obtained (IR film : 2110 (N = C)). The soln. of crude **16** (0.88 g) in dry 20% NH_3 / MeOH (10 ml) was stirred at r.t. overnight. Evaporation and FC ($CHCl_3$ / MeOH 9 : 1) gave **17** (R_f = 0.45) (0.31 g, 53% from **15**) as a colourless foam. $[\alpha]^{20}_D$ = +42.9 (c = 0.75, $CHCl_3$), IR (film) : 3270, 3105, 3080, 3050, 2940, 2895, 1510, 1465, 1400, 1355, 1225, 1100, 1080, 710. ^{1}H - NMR ($CDCl_3$): 7.58 (br s, H-C(2')) ; 7.35 -7.22 (m, 15H arom.) ; 7.07 (br s, H-C(5')) ; 4.71 (d, H-C(1)) ; 4.68 (dd, AB, J = 11.0, CH_2Ph) ; 4.56 (dd, AB, J = 11.6, CH_2Ph) ; 4.41 (dd, AB, J = 12.2, CH_2Ph) ; 4.14 (dd, H-C(2)) ; 3.68 - 3.50 (m, 3H, sugar protons). $J_{(1,2)}$ = 4.1, $J_{(2,3)}$ = 5.9. ^{13}C - NMR ($CDCl_3$) : 138.27, 138.21, 138.04 (s - arom) ; 135.77 (C(2')) 132.04 (C(5')) ; 128.65, 128.59, 128.47, 128.39, 128.35, 127.94, 127.92, 127.84, 127.64, 127.37 (arom. CH) ; 82.22 (C(2)) ; 80.05 (C(3)) ; 75.25, 73.26, 70.22 (*C*H_2Ph) ; 73.13 (C(1)) ; 61.50 (C(4)). MS : m/z = 459.2 $[M + H]^+$, 351.2 $[M-OBn]^+$. HRMS calculated for $C_{28}H_{31}N_2O_4$ $[M+H]^+$:459.2284, found : 459.2295.
***ii) From* 24:** To a stirred soln. of **24** (350 mg, 0.77 mmol) in anh. EtOH (10 ml) $NaBH_4$ (145 mg, 3.83 mmol) was added portionwise at -5°. The mixture was stirred at r.t. overnight. Workup as for **11** : after FC ($CHCl_3$ / MeOH 9 : 1) **17** (R_f = 0.45) (320 mg, 91%) was obtained as a colourless foam, whose analytical data were

identical with those of the sample obtained from **15**.

(6S, 7R, 8S) - 6,7,8 - Tribenzyloxy - 5,6,7,8 - tetrahydro imidazo [1.5 - a] pyridine **18**.
To a stirred soln. of **17** (240 mg, 0.522 mmol) in dry pyridine (2 ml) a soln. of phenylmethanesulfonyl chloride (α-tosyl chloride) (209 mg, 1.1 mmol) in dry pyridine (1 ml) was added dropwise under Ar at -10°. Stirring was continued at -10° for 2 h, then Ac_2O (0.16 g, 0.57 mmol) was added and the mixture was stirred for another 1.5 h at 65°. After evaporation to dryness along with toluene (20 ml) FC ($CHCl_3$/MeOH 9 : 1) gave **18** (R_f = 0.5) (180 mg, 78%) as a colourless foam. $[\alpha]^{20}_D$ = +15.8 (c = 0.28, $CHCl_3$), ^{1}H - NMR ($CDCl_3$) : 7.34 - 7.08 (m, 17H, 3Ph, H-C (3), H-C (1)); 4.60 (d, H-C (8)); 4.45 (dd, AB, J = 11.9, CH_2Ph); 4.41 (dd, AB, J = 12.0, CH_2Ph); 4.39 (dd, AB, J = 12.2, CH_2Ph); 4.21 (ddd, H-C(6)); 3.62 (dd, Ha-C(5)); 3.53 (dd, H-C(7)); 3.19 (dd, Hb-C(5)); $J_{(5a,6)}$ = 6.0, $J_{(5b,6)}$ = 6.8, $J_{(5a,5b)}$ = 12.6, $J_{(6,7)}$ = 8.1, $J_{(7,8)}$ = 3.3.

(6S, 7R, 8S) - 5,6,7,8 - Tetrahydroimidazo [1.5 - a] pyridine - 6,7,8 - triol **4**.
A suspension of **18** (170 mg, 0.385 mmol) and 10% $Pd(OH)_2$/C *(Pearlman's catalyst)* (200 mg) in AcOH (5 ml) was stirred under H_2 (4 psi) at r.t. for 24 h until complete disappearance of **18**. The catalyst was filtered off over *Celite* and washed with AcOH. The combined filtrates were evaporated at 40° and the resulting residue was dissolved in H_2O (2 ml). This aq. soln. was passed over an *Amberlite CG 120 (H^+)* column. Elution of **4** was performed with 2N NH_3. After evaporation the residue was purified by FC (MeOH / 28% NH_4OH soln. 4 : 1, R_f = 0.7) to give **4** (41.5 mg, 63%), as a colourless foam after lyophilization. $[a]^{20}_D$ = -1.8 (c = 0.8, MeOH), IR (KBr) : 3300, 2900, 1600, 1540, 1450, 1325, 1120, 1090, 1070, 780, 640. ^{1}H - NMR and ^{13}C - NMR: *Table 2*. HR : m/z = 171.0 $[M+H]^+$. HRMS calculated for $C_7H_{11}N_2O_3$ $[M+H]^+$: 171.0770, found : 171.077

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