Stereoisomeric Imidazolo-Pentoses − Synthesis, Chiroptical Properties, and Evaluation as Glycosidase Inhibitors

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The syntheses of all four imidazolo-piperidino-pentoses in the L-series *ent*-**2** to *ent*-**5**, and of three out of the four possible stereomers in the D-series **3**, **4**, and **5**, are reported. The linear imidazolo sugar precursors were prepared, either by double condensation of formamidine with protected aldohexoses, or by nucleophilic addition of a lithiated imidazole derivative to protected aldotetroses. Cyclisation of these linear imidazolo-carbohydrates was performed by intramolecular S_N2 reactions. These were followed by deprotection to the target molecules. The four pairs of opposite enantiomers showed pronounced mirror-image-type Cotton effects in their CD spectra. All stereomers of the D-series show a negative rotatory power ($[\alpha]_D$), while the stereomers of the L-series show a positive one. None of the eight imidazolo sugars inhibited the replication of HIV-1. Some of them proved to be rather selective but only moderately potent inhibitors of α-glycosidases, as determined by Michaelis-Menten kinetics.

Introduction

In a recent article dealing with glycosidase-catalysed hydrolysis mechanisms of polysaccharides, Zechel and Withers reviewed the finely tuned action of these enzymes, and postulated that polysaccharide hydrolases lead to transition states having a pronounced oxocarbonium character, both with retaining and with inverting glycosidases.[1] Since most natural polysaccharides are chair-conformed pyranoses, the postulated cyclic oxocarbonium-type transition states appear as flattened-, i.e. as half-chair conformations.

In 1992 Aoyagi, Aoyama and their co-workers published the structure of the natural product nagstatine (**1**) and showed that this imidazolo sugar is a very potent inhibitor of some glucosaminidases, e.g. with a K_i value of 4 nM for the *N*-acetyl-β-D-glucosaminidase of bovine kidney enzyme.[2] The discovery of **1** proved to be of interest for the refined deciphering of glycosidase-catalysed hydrolysis of polysaccharides by way of the so-called lateral protonation mechanism.[3] The imidazole ring forces the six-membered piperidinose ring of **1** to occur as a half-chair conformation. Once protonated at the site of the most basic nitrogen atom (i.e. by "lateral protonation" of the pseudoanomeric N-atom [3]), **1** leads to an imidazolium cation, which mimics rather well the postulated oxocarbonium ion intermediates. The often higher potency displayed by **1** and by similar artificial bicyclic mimics [4] has been attributed to their greater rigidity, the polyhydroxylated heterocyclic moiety being effectively locked in a conformation favouring inhibition.[5] As a matter of fact, several nonnatural azolo-piperidinoses have been synthesized, some of which showed remarkably strong inhibition properties.[3,4,6]

We set out in 1988 to incorporate an imidazole ring into a pyranose, the azole moiety having to induce a half-chair conformation of the attached piperidinose moiety. The first compound we synthesized along these lines was the D-*arabino*-imidazolo sugar **2**.[7] Tested by Bryan Winchester against eleven human liver glycosidases, **2** turned out to be a potent and selective inhibitor of α-D-mannosidase at pH = 4.0.[8] Compound **2** seemed to be of some interest as, unlike other azasugar derivatives known at that time, it selectively inhibited α-D-mannosidase. Such a selectivity was believed to be due to the planar imidazole ring (N.B.: structure and properties of nagstatine were published in 1992). A brief search of the literature furthermore suggested that **2** represented a novel class of α-D-mannosidase inhibitors. Molecular modelling showed that **2** (with the reverse D-*lyxo*-type configuration; see Scheme 1) closely resembled the geometry of the D-mannosyl cation.[8] We surmised that some stereomers of **2** would also be selective glycosidase inhibitors, e.g. those corresponding to the D-glucosyl or D-galactosyl cations, which could be of interest as antiviral and antitumour agents.

In some preceding publications we reported the synthesis of the L-*xylo* (*ent*-**3**),[9] the L-*lyxo* (*ent*-**4**),[10] and in a preliminary communication the synthesis of the D-*xylo* (**3**) stereomer.[11] We describe herein the detailed syntheses of the

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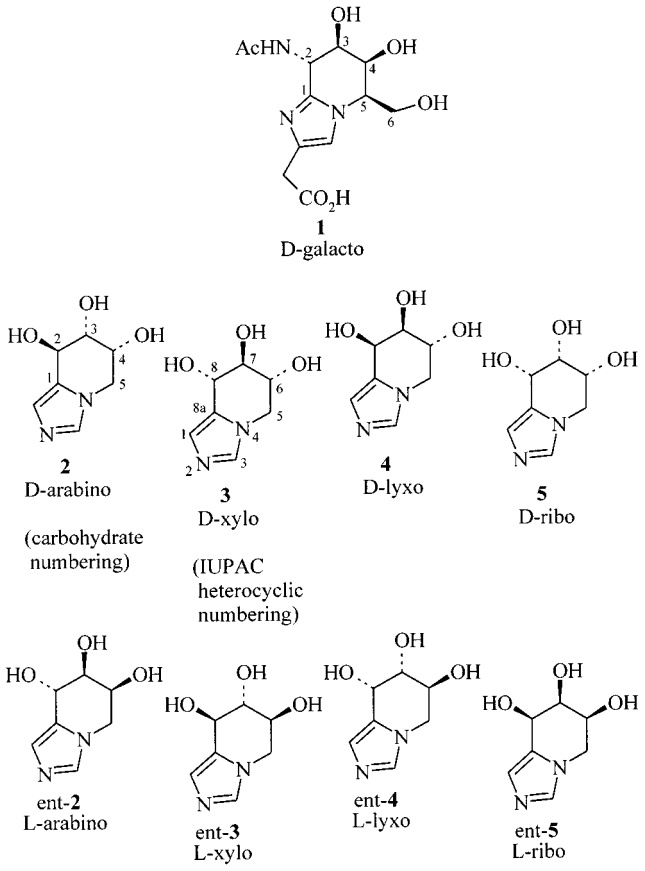


Scheme 1. Nagstatine (**1**) and the eight imidazolo-piperidinoses

five remaining stereomers (Scheme 1), as well as an improved synthesis of *ent*-**3** and *ent*-**4**. Chiroptical properties, i.e. $[\alpha]_D$ and CD data of all eight stereomers, are reproduced; they corroborate the expected absolute configurations. Inhibition assays of all eight stereomers against several glycosidases, as well as in vitro anti-HIV tests are reported.

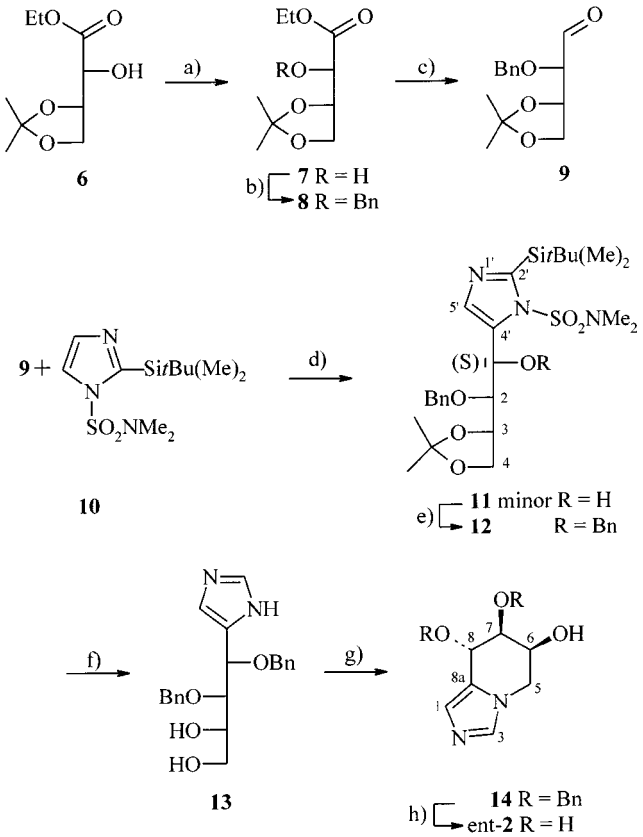
Results

Syntheses of Imidazolo-Piperidinoses

Arabinose Series 2

Two syntheses of the D-*arabino*-imidazolo sugar **2** have been described. The first one had been performed in poor overall yield by applying a known and rather old methodology (overall yield from D-glucose 2%).[7] In the second one the imidazole moiety had been introduced by condensation of formamidine with 3-*O*-benzyl-D-glucose in a pressure vessel under ammonia, a method we had developed previously.[12] The resulting linear imidazolo sugar, submitted to intramolecular cyclisation by Appel and Wihler's procedure ($CBr_4/Ph_3P/Et_3N$), followed by debenzylation (H_2/Pd/C), gave **2** in less time and in better yield (overall yield from D-glucose 8%[12]) than the previous procedure. Azasugar **2** is levorotatory ($[\alpha]_D = -9$) with a positive Cotton effect in CD [213.5 nm ($\Delta\varepsilon = +5.20$), and 197.0 nm ($\Delta\varepsilon = -2.05$)].

The L-*arabino* enantiomer *ent*-**2** was synthesized according to Scheme 2 from L-threose derivative **6**, which had been obtained from L-ascorbic acid (vitamin C) according to a known procedure.[13] Sequential reaction of **6** with triflic anhydride and pyridine, followed by an S_N2 reaction of the corresponding triflate with a nitrite salt (Bu_4NNO_2/CH_2Cl_2/H_2O), led to the L-*erythro* diastereomer **7** (78% from **6**). *O*-Benzylation (BnBr/Ag_2O/KI/toluene) gave **8** (88%), which was reduced quantitatively to the corresponding L-erythrose derivative **9** (DIBAH/toluene; −78 °C). The known imidazole derivative **10**,[14] after a site-specific lithiation at C-5 (BuLi/hexane/THF; −78 °C) that had already been reported,[15] was added to the aldehyde **9** (THF; −50 °C) leading thereby to a mixture of two diastereomers, which were separated by chromatography. The minor L-*arabino* isomer (1*S*)-**11** (absolute configuration as determined with the final bicyclic compound *ent*-**2**; see below) was *O*-benzylated (NaH/Bu_4NI/BnBr/THF) giving **12**, which was at once deprotected with acid (1 N HCl/THF) to yield the key intermediate **13**. This latter compound was *N*- and *O*-tosylated (−10 °C; TsCl, 2.7 equiv./NEt_3/DMAP/CH_2Cl_2), in order to orient the sulfonylation process toward the

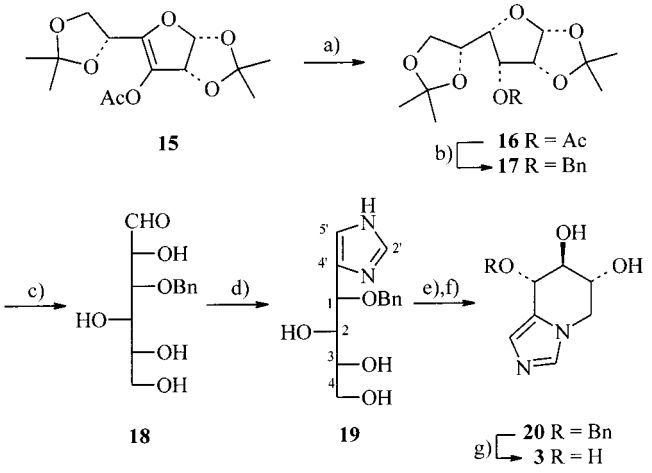


Scheme 2. Reagents and conditions: a) 1. Tf_2O, pyridine, CH_2Cl_2, 0 °C; 2. Bu_4NNO_2, CH_2Cl_2, 40 °C; b) BnBr, Ag_2O, KI (cat.), MS (4 Å), toluene, reflux; c) DIBAH, toluene, −78 °C; d) 1. **10** in THF, *n*BuLi, −78 °C; 2. + **9** in THF at −65 °C to room temp.; e) BnBr, NaH, NBu_4I, THF; f) 6 N HCl, 45 °C; g) 1. TsCl (2.3 equiv.), NEt_3, DMAP, CH_2Cl_2; 2. NaOH (1 M), acetone; h) H_2, $Pd(OH)_2$/C, MeOH

primary alcohol. The expected crude *N*,*O*-ditosyl derivative dissolved slowly in sodium hydroxide at 60 °C and led indeed to bicyclic compound **14**. Hydrogenolysis [H_2/$Pd(OH)_2$/C; 30 bar] of **14** gave the expected L-*arabino* enantiomer *ent*-**2** ($[\alpha]_D$ = +4). ORD and CD (negative CE) spectra of **2** and *ent*-**2** proved their mirror image relationship.

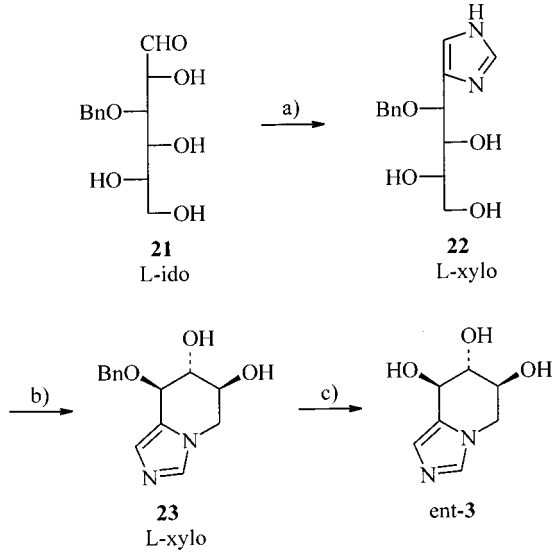
Xylose Series 3

The synthesis of the D-*xylo*-imidazolo sugar **3** (Scheme 3) required configurational inversion both of C-3 and C-4 of D-glucose into the known 3-*O*-benzyl-D-gulose derivative **18**,[16,17] according to *cis*-hydrogenation of the known intermediate enol acetate **15** from the least-hindered side. This rather critical *cis*-hydrogenation was achieved successfully with a rhodium/alumina catalyst, the crystalline D-*gulo* stereoisomer **16** being formed as the only reaction product (96% after crystallisation). Reaction of **16** with sodium methoxide in THF using PTC conditions (Bu_4NI) gave the corresponding alkoxide (not isolated), to which benzyl bromide was added at once to yield the *O*-benzyl derivative **17**, which is a known compound.[17] Removal of the acetonide protecting groups of **17** with an acid resin (Dowex) gave the desired D-gulose derivative **18** as a mixture of furanose and pyranose isomers. Once crystallized (EtOH/acetone, 9:1) **18** occurs in its β-pyranose form (see Exp. Sect.). For the sake of convenience **18** is represented in Scheme 3 in its acyclic linear Fischer projection, instead as a mixture of the furanose and pyranose anomers. Condensation of **18** with formamidine, according to a method we had described previously,[12] led in moderate yield to the imidazole derivative **19**. Ditosylation (TsCl, pyridine; −10 °C) of the latter occurred both at the remote nitrogen atom, and selectively at the primary alcohol function. The crude ditosyl derivative dissolved slowly in sodium hydroxide at 60 °C and led to bicyclic compound **20**. Hydrogenolysis of the benzyl ether derivative **20** gave target molecule **3** ($[\alpha]_D$ = −68) (Scheme 3).[11]



Scheme 3. Conditions and reagents: a) H_2, Rh/Al_2O_3, AcOEt, 50 bar; b) 1. NaOMe, Bu_4NI, THF, 0 °C; 2. BnBr, 50 °C; c) Dowex, EtOH/H_2O (1:1), 75 °C; d) $H_2NCH{=}NH$/AcOH, NH_3 liq., 80 °C, 45 bar; e) TsCl, pyridine, −10 °C; f) NaOH (1 M), acetone, 60 °C, 14 h; g) H_2, $Pd(OH)_2$, AcOH

The synthesis of the L-*xylo* derivative *ent*-**3** had already been described by making use of van Leusen's methodology (tosmic reagent) to construct the imidazole moiety.[9] A second approach based on formamidine condensation to a carbohydrate starting material is described below (Scheme 4). L-Idose configuration being essential for our purposes, carbon atom C-5 of D-glucose had to be inverted. Furthermore, the 3-OH group had to be protected by benzylation, in order to orient the final cyclisation into the right direction. As a matter of fact, the synthesis of 3-*O*-benzyl-L-idose (**21**) had already been described.[18,19] For the sake of simplicity, **21** is represented in Scheme 4 in its acyclic linear Fischer projection, instead as a furanose/pyranose mixture. Compound **21** was condensed with formamidine in a pressure vessel under ammonia, leading to the imidazolo sugar derivative **22** in 45% yield. Intramolecular cyclisation of the latter was best accomplished by applying Appel and Wihler's methodology ($CBr_4/Ph_3P/Et_3N$ in DMF),[20] which led to **23** (40% after recrystallisation). Debenzylation of **23** gave the target molecule *ent*-**3** (84%) ($[\alpha]_D$ = +69) (ref.[9] $[\alpha]_D$ = +69) (Scheme 4). The overall yield for the formation of *ent*-**3** from D-glucofuranose diace-



Scheme 4. Conditions and reagents: a) $H_2NCH{=}NH$/AcOH, NH_3 liq., 90 °C, 40 bar; b) Ph_3P, CBr_4, DMF, NEt_3, 0 °C; c) H_2, $Pd(OH)_2$/C, AcOH

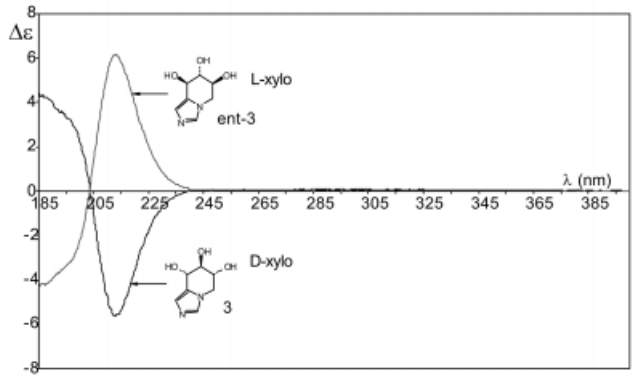
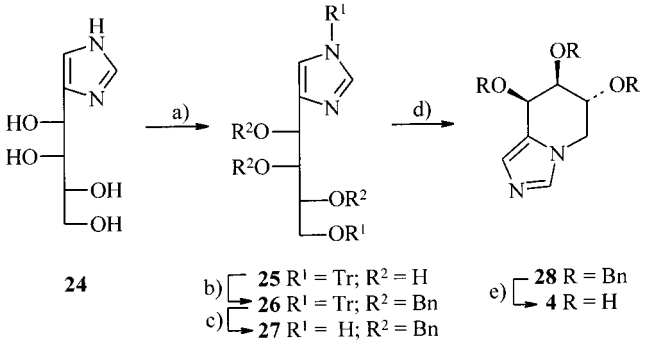


Figure 1. Circular dichroism of D- and L-imidazolo-*xylo*-piperidinose

tonide was about 8%, as compared to the 2% yield of the preceding synthesis.[9] Both $[\alpha]_D$ and CD spectral data of **3** and of *ent*-**3** proved their enantiomeric relationship (see Figure 1).

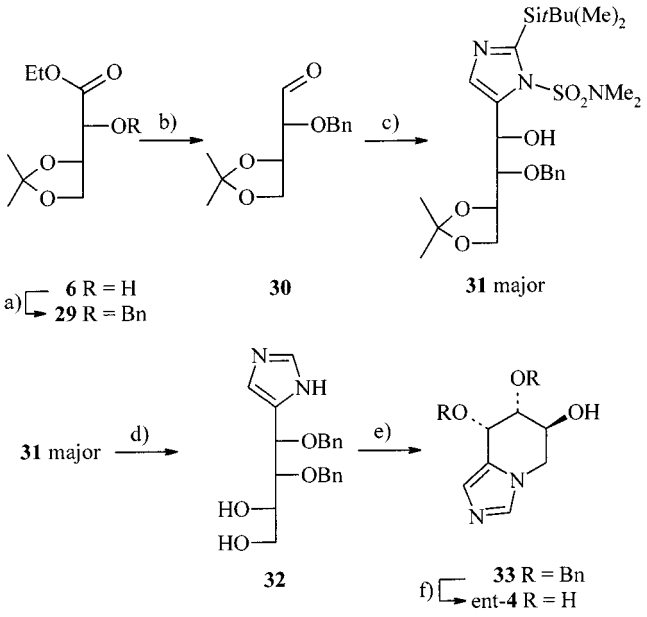
Lyxose Series 4

The synthesis of the D-*lyxo*-imidazolo sugar **4** from imidazolo-tetrol **24**, the formation of which we had described previously,[12] was straightforward (Scheme 5). Bis(tritylation) (TrCl/pyridine/DMAP) led specifically to **25**, which was transformed into the tris(benzyl ether) **26** (NaH/BnBr/Bu_4NI/THF). Removal of both trityl protections of **26** was performed under rather harsh acidic conditions (8 N HCl/THF; 2 d reflux), and led to **27** (83%). Intramolecular cyclisation was performed according to a standard procedure (α-tosyl chloride/pyridine followed by Ac_2O) and gave **28** (92%). Hydrogenolysis of the latter (H_2/$Pd(OH)_2$/C/AcOH; 8 bar) gave the target imidazolo sugar **4** (56%) ($[\alpha]_D = -13$).



Scheme 5. Conditions and reagents: a) TrCl, pyridine, DMAP, 70−75 °C: b) BnBr, NaH, Bu_4NI, THF, 60 °C; c) 8 M HCl, THF; d) 1. TsCl, pyridine, 0 °C to room temp., 2. Ac_2O, 80 °C; e) H_2, $Pd(OH)_2$/C, PdO/C, AcOH, 8 bar, room temp.

The synthesis of the L-*lyxo* enantiomer *ent*-**4** had already been described, albeit in poor overall yield in a previous publication, by taking advantage of the van Leusen methodology for the built-up of the imidazole ring.[10] The synthesis described below proved to be more convenient. The L-*threo-seco* derivative **6** of L-ascorbic acid acetonide (see above, Scheme 2) was *O*-benzylated ($BnBr/Ag_2O$/KI) in toluene leading to **29** (90%), which was reduced to the aldehyde **30** (DIBAH; 98%). A solution of **30** was added to the cooled lithio complex of imidazole derivative **10**. Two diastereoisomers formed quantitatively that were separated by chromatography, the major isomer being **31**. This latter compound was *O*-benzylated (NaH/BnBr/Bu_4NI) in THF, and the acid-sensitive protection groups removed (2 N HCl), thereby leading to compound **32** (90% overall yield from **31**). Intramolecular cyclisation to **33** was performed in a standard way (TsCl/pyridine at 0 °C; then 1 N NaOH at room temp.), the best yield being only 36%. Catalytic hydrogenolysis of the two benzyl ethers (H_2/Pd/C; 20 bar) gave *ent*-**4** in 9.8% overall yield ($[\alpha]_D = +11$) (Scheme 6). The

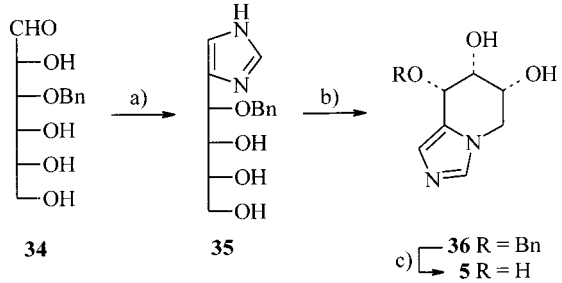


Scheme 6. Conditions and reagents: a) BnBr, Ag_2O, KI, MS (4 Å), toluene, reflux; b) DIBAH, toluene, −78 °C; c) 1. **10** in THF, *n*BuLi, −78 °C; 2. + **30** in THF at −65 °C, then room temp.; d) 1. BnBr, NaH, Bu_4NI, THF, 40 °C; 2. 2 M HCl, THF, 70 °C; e) Tf_2O, pyridine, CH_2Cl_2, −30 °C; f) H_2, Pd/C 20%, MeOH

$[\alpha]_D$ and CD spectral data of **4** and of *ent*-**4** are definite proof for them being enantiomers (see Exp. Sect.).

Ribose Series 5

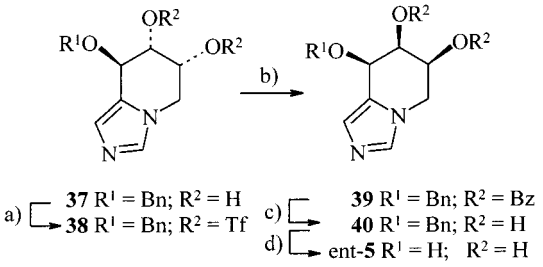
For the synthesis of the D-*ribo*-imidazolo sugar **5** we applied a reaction sequence similar to the one used for the preparation of **3** and of *ent*-**3**. In the present instance this required a configurational inversion in position C-3 of D-glucose, actually the formation of 3-*O*-benzyl-D-allose (**34**) which had already been described by Fleet.[22] Condensation of **34** with formamidine in a pressure vessel as described above led to **35** (53%), which was cyclised to **36** according to the Appel and Wihler procedure (49%). Palladium-catalysed debenzylation gave **5** (81%) as colourless crystals ($[\alpha]_D = -40$) (Scheme 7).



Scheme 7. Conditions and reagents: a) $HN{=}CHNH_2$/AcOH, NH_3 liq., 80 °C, 40 bar; b) Ph_3P, CBr_4, NEt_3, DMF, 40 °C; c) H_2, $Pd(OH)_2$/C, AcOH

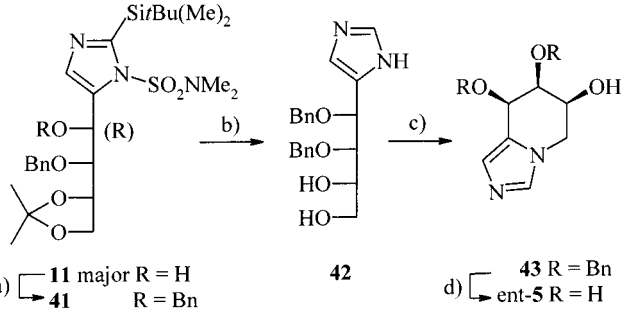
In order to prepare the L-*ribo* enantiomer *ent*-**5** we started from the monobenzyl-imidazolo-D-*arabino*-piperidinose derivative **37**, whose synthesis we had already described previously.[12] Reaction of **37** with triflic anhydride

gave bis(triflate) **38**, which was submitted in a one-pot procedure to two Walden inversions with tetrabutylammonium benzoate. The resulting bis(benzoate) **39** was at once saponified (Na_2CO_3) to give the crystalline benzyl derivative **40**. Hydrogenolysis of **40** [H_2/Pd(OH)$_2$/C] led in 25% overall yield to *ent*-**5** as a colourless oil ($[\alpha]_D = +34$) (Scheme 8).



Scheme 8. a) Tf_2O, pyridine, CH_2Cl_2, 0 °C; b) $Bu_4N^+C_6H_5CO_2^-$, toluene, 75 °C, 15 h; c) Na_2CO_3, MeOH, reflux, 6 h; d) H_2, Pd(OH)$_2$/C, AcOH

A second synthesis of *ent*-**5** was based on the major L-*ribo* adduct (1*R*)-**11** we had obtained along with the minor L-*arabino* adduct (1*S*)-**11** (see above and Scheme 2). *O*-Benzylation of the alcohol (1*R*)-**11** gave **41**, which was not isolated. It was followed by acid-promoted deprotection of the imidazole moiety of (the fully protected) compound **41**, thereby leading to the "linear" imidazole, which was cyclised (via the monotosyl derivative of the primary alcohol) to **43** (Scheme 9). Catalytic hydrogenolysis of both benzyl ether functionalities of **43** gave a triol that proved to be identical with compound *ent*-**5** we had already obtained in the above described synthesis ($[\alpha]_D = +34$); ^1H and ^{13}C NMR spectra are superimposable. Both $[\alpha]_D$ and CD spectral data of **5** and of *ent*-**5** demonstrate their enantiomeric relationship (see Exp. Sect.).



Scheme 9. a) BnBr, NaH, Bu_4NI, THF, 40 °C; b) 6 N HCl, 45 °C; c) 1. TsCl, NEt_3, DMAP, CH_2Cl_2, −10 °C, 2. 1 M NaOH, acetone, room temp.; d) H_2, Pd(OH)$_2$/C, MeOH, 30 bar

Spectral Properties and Structure Analyses

Structure and absolute configuration assignments − particularly of the eight target imidazolo carbohydrates **2** to **5** and *ent*-**2** to *ent*-**5** − were performed using standard ^1H and ^{13}C NMR spectroscopic analyses, in conjunction with chiroptical data, i.e. optical rotations ($[\alpha]_D$ values) and Cotton effects (CE), as determined by circular dichroism (CD).

Let us consider the D-*xylo* (**3**) and the L-*xylo* (*ent*-**3**) azasugars. Both have been obtained by condensation of well-defined aldohexoses with formamidine; compound **3** had been synthesised starting from the known D-*gulo* derivative **18**, *ent*-**3** from the known L-*ido* derivative **21**. Neither the cyclisation steps, nor the deprotection steps affected the absolute configuration of carbon atoms C-6, -7, and -8, neither of **18**, nor of **21** on their way to **3** and to *ent*-**3**, respectively. This was corroborated by the ^1H and ^{13}C NMR spectra of *ent*-**3**, which proved to be identical, i.e. superimposable, with those of **3**. Furthermore the rotatory powers had the same magnitude but were of opposite sign for the two enantiomers: $[\alpha]_D = -68$ for **3**; $[\alpha]_D = +69$ for *ent*-**3**. Last, but not least, the CD spectra were of the mirror-image type, **3** occurring with a pronounced negative Cotton effect, *ent*-**3** with a positive one (Figure 1).

Structure and absolute configuration of the three remaining enantiomeric pairs, whose formulae are reproduced in Scheme 1, could be ascertained using similar spectroscopic arguments. For each pair of enantiomers: i) the ^1H and ^{13}C NMR spectra are identical and superimposable; ii) optical rotations ($[\alpha]_D$ values) have similar magnitudes and are of opposite sign; iii) CD spectra show well-defined mirror-image-type Cotton effects (CE), their shapes being very similar to those reproduced in Figure 1.

All stereoisomeric imidazolo sugars of the D-series (see Scheme 1) are levorotatory, their L-enantiomers being dextrorotatory ($[\alpha]_D$ values). These data seem to indicate that the chirality of carbon atom C-6 plays a dominant role in optical rotation. As would have been expected in CD spectroscopy, the sign of the CE is determined by the chirality of the asymmetric carbon atom which is nearest to the imidazole chromophore, i.e. by C-8. As a matter of fact the D-*arabino* (**2**), L-*xylo* (*ent*-**3**), D-*lyxo* (**4**), and L-*ribo* (*ent*-**5**) stereoisomers all occur with a pronounced *positive CE* as a consequence of the (*R*) configuration of C-8. The corresponding opposite enantiomers − i.e. L-*arabino* (*ent*-**2**), D-*xylo* (**3**), L-*lyxo* (*ent*-**4**), and D-*ribo* (**5**), respectively − all appear with a pronounced mirror-image *negative CE*, obviously as a consequence of the (*S*) configuration of C-8 (see Exp. Sect.).

Enzymatic Assays

The enzymatic assays were performed as indicated in the Exp. Sect. with imidazolo-piperidinoses **2**, **3**, **4**, **5** (D-series), and with their enantiomers *ent*-**2**, *ent*-**3**, *ent*-**4**, and *ent*-**5** (L-series), respectively. Most kinetic measurements have been performed in Lausanne using two dozens of glycosidases[24] with azasugars **2**, **5**, *ent*-**3**, *ent*-**4**, and *ent*-**5**. Some kinetic data have been measured in Mulhouse using seven glycosidases[25] with azasugars **3**, **4**, and *ent*-**2**. Five azasugars (i.e. **2**, **3**, *ent*-**3**, *ent*-**4**, and *ent*-**5**) showed modest inhibitory properties of a few enzymes. The three remaining azasugars (*ent*-**2**, **4**, and **5**) did not exhibit any inhibitory properties.

The D-*arabino* isomer **2** (BpKa = 6.22; calculated 6.00) proved to be a moderate inhibitor of α-mannosidase of jack beans (K_i = 54 μM), a weaker one of α-mannosidase of almonds (K_i = 1 mM). The L-*xylo* isomer *ent*-**3** showed some activity against α-mannosidase of jack beans (K_i = 360 μM) and against α-galactosidase of *Escherichia coli* (K_i = 380

μM), whereas its D-enantiomer **3** is a rather weak inhibitor of α-galactosidase of green coffee beans (IC_{50}= 1 mM). The L-*lyxo* azasugar *ent*-**4** proved to be a weak inhibitor of β-galactosidase of jack beans (K_i = 1.3 mM) and of α-glucosidase of baker yeast (K_i = 580 μM). Eventually L-*ribo* azasugar *ent*-**5** inhibits α-galactosidase of *Escherichia coli* (K_i = 89 μM). One tends to reach the conclusion that where inhibition is indeed observed, it occurs with α-glycosidases (i.e. with inverting glycosidases). In one instance though a β-glycosidase was slightly inhibited: L-*lyxo* azasugar *ent*-**4** inhibited β-galactosidase to a moderate extent. The nature of these inhibitions proved to be competitive in all instances, as shown by Lineweaver−Burk plots.

Anti-HIV and Toxicity Assays

The compounds of both D- and L-series were evaluated in vitro for a potential antiviral activity against human immunodeficiency virus type 1 (HIV-1) multiplication in two different cell lines CEM-SS and MT4 as described in the Exp. Sect. None of the test compounds inhibited the replication of HIV-1 when added to the culture medium at concentrations ranging from 100 μg/mL to 1 ng/mL. The eight azasugar derivatives had no toxicity for these cells of lymphocytic origin within the range of concentrations indicated above (data not shown).

Conclusion

All eight stereoisomeric imidazolo-pentoses shown in Scheme 1 have been synthesised by now. Introduction of the imidazole ring was achieved, either by condensation of formamidine with a hexose derivative, or by nucleophilic addition of a metallated imidazole to a tetrose derivative. Intramolecular cyclisation of the resulting linear imidazolo sugar derivatives was performed using some known methods. The chiroptical properties of the imidazolo sugar target molecules proved to be of interest: (i) the four stereomers of the L-series are dextrorotatory, each one having roughly the same magnitude as its corresponding levorotatory enantiomer of the D-series; (ii) in the CD spectra the sign of the Cotton effect (CE) is determined by the chirality of the carbon atom which is nearest to the imidazole chromophore, i.e. C-8, the (*R*) configuration leading to a positive CE, the (*S*) configuration to a negative one.

None of these eight imidazolo carbohydrates showed any activity as an anti-HIV agent in vitro. Some of them proved to be selective, but only moderate to poor inhibitors of α-glycosidases. It should, however, be pointed out that these azasugars have at least one shortcoming, of which we became aware when the structure of nagstatine was published:[2] The most basic nitrogen atom of our azasugars is not located in the pseudoanomeric position like in nagstatine **1**, but rather one bond farther away. Furthermore, these azasugars are derivatives of pyranopentoses, i.e. they lack the hydroxymethylene handle that may be of some use for docking purposes. As a consequence, it was unlikely that they would show optimal geometric complementarity with the glycosidase active site. Nevertheless, it is worth noticing that those azasugars that are potent inhibitors inhibit α-glycosidases more easily than β-glycosidases.

Experimental Section

General: Flash chromatography (FC): silica gel (Merck 60; 230−400 mesh). − TLC: aluminium sheets silica gel (Merck 60 HF_{254}); the spots were revealed by UV or by heating with a thermogun after spraying with a solution of $KMnO_4/Na_2CO_3$ (20 g/40 g) in H_2O (1 l) or a solution of phosphomolybdic acid (5% in 96% EtOH). − M.p.: Kofler hot-bench or Büchi-SMP apparatus; corrected values. − Optical rotations were all measured at +20 °C: Schmidt-Haensch Polartronic Universal polarimeter. CD spectra were measured in H_2O solution between 185 and 400 nm under nitrogen with a Jobin Yvon CD6 Dichrographe (Δε values) at the Roche research center of the pharmaceutical division in Basle. − ^1H and ^{13}C NMR spectra: 250 MHz and 62.9 MHz, respectively; Bruker ACF-250 spectrometer at 300 K. Internal references for ^1H NMR: $Si(Me)_4$, $CDCl_3$ (δ = 7.26), CD_3OD (δ = 3.30), [D_4]TSP for spectra in D_2O (δ = 0.00); for ^{13}C NMR: $CDCl_3$ (δ = 77.03), CD_3OD (δ = 49.02); δ in ppm and *J* in Hz. − HR-MS data were measured with a MAT-311 or with a Zabspec TOF spectrometer at the University of Rennes. Microanalyses were carried out by the Service Central de Microanalyses of the CNRS, 69390 Vernaison, France. The H^+ ion exchange resin Amberlit CG 6000 was from Rohm & Haas.

Inhibition of Glycosidase Activity: Inhibition tests were performed with all eight imidazolo-piperidinoses on commercially available glycosidases (from Sigma)[24] with the appropriate *p*-nitrophenyl glycosyl substrates in 96-well microplates. Inhibitors were dissolved in water to give a 60 mM final concentration. The reaction mixtures for assays of the enzymes contained the enzyme in a buffer, at the appropriate optimum pH value, 5 mM pNp glycoside, and the potential inhibitor in a final volume of 0.01 mL. Enzyme and inhibitor were pre-incubated for 5 min at room temp. in the buffer, and the reaction was started by addition of the substrate. After 20 min incubation at 37 °C, the reaction was stopped by addition of 0.25 mL 0.2 M sodium borate buffer (pH = 9.8). In Lausanne the *p*-nitrophenol liberated was monitored at 405 nm on a microplate reader (Digiscan). In the Mulhouse experiments[25] the release of *p*-nitrophenol was measured continuously at 405 nm in order to determine initial velocities. All kinetic measurements were performed at 25 °C, the reaction being started by adding an enzyme in 1 mL of an assay medium (acetate or phosphate buffer) and using substrate concentrations of ca. the K_m value of each enzyme. When inhibition was indeed observed, its percentage was measured for a concentration of 1 mM. − In Lausanne the kinetic measurements were performed with azasugars **2**, **5**, *ent*-**3**, *ent*-**4**, and *ent*-**5**; in Mulhouse with azasugars *ent*-**2**, **3**, and **4**. − In some preliminary screenings, the enzymatic activity was determined in the presence of high inhibitor concentration (1 mM) and the rate of enzymatic inhibition (expressed in %) was obtained as follows: Percentage of inhibition = activity in the presence of 1 mM inhibitor × 100/activity without inhibitor. Only inhibitions superior to 50% at 1 mM of product were considered to be significant. For such products, the IC_{50} value (concentration of inhibitor required for 50% inhibition of enzyme activity) was calculated by measuring the glycosidase activity in the presence of various concentrations of inhibitor. − The inhibition constant K_i was determined for the products showing inhibition between 60 and 100% at 1 mM concentration. The

nature of the inhibition was deduced from the Lineweaver−Burk plots.

Virology − Materials and Experimental Procedures: The cultures of CEM-SS and MT4 cells were maintained at 37 °C under 5% CO_2 in RPMI 1640 medium supplemented with 10% decomplemented fetal bovine serum (FBS). The antiviral activity against HIV-1 of a given compound in CEM-SS cells was measured by quantification of the reverse transcriptase activity (room temp.) associated with virus particles released from HIV1 Lai infected cells in the culture medium. CEM-SS cells were infected with 100 $TCID_{50}$ (the virus was titrated under the same experimental conditions); after 30 min of adsorption, free virus particles were washed out and the cells resuspended in RPMI-10% SVF at the final concentration of 10^5 cells/mL in the presence of different concentrations of test compounds. After 5 d, virus production was measured by room temp. assay as described.[26] The 50% inhibitory concentration (IC_{50}) was derived from the computer-generated median effect plot of the dose-effect data.[27] The cytotoxicity of the drugs was evaluated in parallel by incubating uninfected cells in the presence of different concentrations of antiviral products. The cell viability was determined by a measure of mitochondrial dehydrogenase activity, enzymes reducing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into formazan (which quantity was given by the optical density at 540 nm).[28] The 50% cytotoxic concentration (CC_{50}) is the concentration of drug which reduces cell viability by 50% and was calculated with the program used in the determination of the IC_{50} values. *anti*-HIV1 activity was also measured in HIV IIIB infected MT4 cells and was based on the inhibition of virus-induced cytopathogenicity as described.[26,29] − The CEM-SS cells were obtained from P. Nara through the AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH.

Ethyl L-Erythronate Derivative 7: Tf_2O (7.7 mL, 94 mmol) was added slowly to a solution of **6** (6.4 g, 62.6 mmol)[13] and of pyridine (7.6 mL, 280 mmol, 4 equiv.) in anhydrous CH_2Cl_2 at 0 °C. The reaction was monitored by TLC and quenched after 30 min with a saturated Na_3PO_4 solution (buffer). The resulting mixture was extracted with CH_2Cl_2, the organic solution concentrated to 25 mL and treated with Bu_4NNO_2 (36.2 g, 125 mmol) at 40 °C. After 1 h, the mixture was extracted with CH_2Cl_2, the resulting organic solution was dried with $MgSO_4$, filtered, and concentrated at room temp. (the product being volatile). The crude product was purified by FC (Et_2O) to give **7** as a slightly-yellow oil (4.93 g, 78%). − $[\alpha]_D^{20} = +26$ ($c = 2.0$, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 4.28 [m, 2 H, H−C(2), H−C(3)], 4.26 (q, 2 H, C*H*$_2$−CH$_3$), 4.03 [dd, 1 H, H$_a$−C(4)], 4.00 [dd, 1 H, H$_b$−C(4)], 1.43 (s, 3 H, C*H*$_3$ *isoprop.*), 1.35 (s, 3 H, C*H*$_3$ *isoprop.*), 1.31 (t, 3 H, CH$_2$−C*H*$_3$), $J_{3,4a} = 5.5$, $J_{3,4b} = 6.7$, $J_{4a,4b} = 8.6$; $J_{CH2CH3} = 7.1$. − ^{13}C NMR ($CDCl_3$): δ = 172.1 (*C*O$_2$Et), 109.9 [*C*(CH$_3$)$_2$], 77.0 [C(2)], 71.1 [C(3)], 65.0 [C(4)], 61.9 (O*C*H$_2$CH$_3$), 26.3 and 25.1 (2 *C*H$_3$ *isoprop.*), 14.1 (OCH$_2$ *C*H$_3$).

Ethyl L-Erythronate Derivative 8: A mixture of freshly prepared anhydrous Ag_2O (1.17 g, 5.1 mmol), powdered 4-Å molecular sieves (ca. 1 g), and KI (10 mg) was heated under vacuum at 300 °C. After cooling to room temp., a solution of **7** (690 mg, 3.38 mmol) in anhydrous toluene (25 mL) and BnBr (440 μL, 635 mg, 3.7 mmol) were added to the powdery mixture. The resulting mixture was heated under reflux for 90 min, the reaction being monitored by TLC (AcOEt/cyclohexane, 3:7). After cooling to room temp., the mixture was filtered through a small column of silica gel, concentrated to dryness and the crude residue separated by FC (AcOEt/cyclohexane, 1:9, then 2:8) to yield **8** as a slightly yellow syrup (875 mg, 88%). − $[\alpha]_D^{20} = -46$ ($c = 2.0$, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 7.35−7.29 (m, 5 H, H-*arom*), 4.68 and 4.49 (2 H, *AB*, $J = 11.6$ Hz, OC*H*$_2$Ph), 4.34 [ddd, 1 H, H−C(3)], 4.23 (2 H, *ABX*$_3$, OC*H*$_2$CH$_3$), 4.04 [dd, 1 H, H$_a$−C(4)], 4.00 [dd, 1 H, H$_b$−C(4)], 3.95 [d, 1 H, H−C(2)], 1.42 (s, 3 H, CH$_3$ *isoprop.*), 1.33 (s, 3 H, CH$_3$ *isoprop.*), 1.29 (t, 3 H, OCH$_2$C*H*$_3$), $J_{2,3} = 6.4$, $J_{3,4a} = 5.8$, $J_{3,4b} = 5.3$, $J_{4a,4b} = 8.8$, $J_{CH2,CH3} = 7.1$ Hz. − ^{13}C NMR ($CDCl_3$): δ = 170.2 (*C*O$_2$Et), 136.9 (C$_s$ Ph), 129−128 (5C, Ph), 109.6. [*C*(CH$_3$)$_2$], 78.9 [C(2)], 75.8 (O*C*H$_2$Ph), 72.6 [C(3)], 66.0 [C(4)], 60.8 (O*C*H$_2$CH$_3$), 26.4 and 25.1 (2 CH$_3$ *isoprop.*), 14.0 (OCH$_2$*C*H$_3$).

L-Erythrose Derivative 9: To a stirred solution of **8** (2.5 g, 8.60 mmol) in anhydrous toluene (55 mL) at −78 °C was added dropwise a 1.5 M solution of DIBAH (8.6 mL, 12.9 mmol, 1.5 equiv.) in toluene. The reaction was monitored by TLC (AcOEt/cyclohexane, 5:5). After 25 min at −78 °C, the reaction was complete, excess DIBAH was slowly neutralised with MeOH (ca. 25 mL), and the solution was allowed to warm to room temp. The solution was treated sequentially with a saturated aq. Seignette salt (K and Na tartrate) solution (2 mL) and some brine (4 mL) leading thereby to the precipitation of the aluminium salts, which were filtered and washed with AcOEt. The stirred filtrates were dried ($MgSO_4$), filtered and concentrated to dryness. The resulting syrup was dissolved in anhydrous toluene and the solution concentrated in vacuo; this procedure was repeated three times in order to obtain the free aldehyde instead of the hydrate. The final syrup was put under vacuum over fresh P_2O_5 in a dessicator for 20 h to yield **9** as an oil (2.06 g, 96%), which crystallised in the freezer. − ^{1}H NMR ($CDCl_3$): δ = 9.70 [d, 1 H, H−C(1)], 7.40−7.15 (m, 5 H, H-*arom*), 4.74 and 4.60 (2 H, *AB*, $J = 11.6$ Hz, OC*H*$_2$Ph), 4.35 [td, 1 H, H−C(3)], 4.07 [dd, 1 H, H$_a$−C(4)], 3.93 [dd, 1 H, H$_b$−C(4)], 3.81 [dd, 1 H, H−C(2)], 1.43 (s, 3 H, CH$_3$ *isoprop.*), 1.35 (s, 3 H, CH$_3$ *isoprop*), $J_{1,2} = 2.1$, $J_{2,3} = 6.2$, $J_{3,4a} = 6.2$, $J_{3,4b} = 5.5$, $J_{4a,4b} = 8.6$ Hz. − ^{13}C NMR ($CDCl_3$): δ = 201.4 (*C*HO), 152.3 (*Cs* Ph), 128.6, 128.3, 128.2 (5C, Ph), 109.4 [*C*(CH$_3$)$_2$], 83.1 [C(2)], 75.1 (O*C*H$_2$Ph), 73.4 [C(3)], 66.3 [C(4)], 26.5 and 25.1 (2C, *C*H$_3$ *isoprop.*).

The Coupling Reaction: To a solution of the sulfonamide **10** (2.68 g, 9.25 mmol, 1.4 equiv.)[14,15] in anhydrous THF (35 mL) at −78 °C was added dropwise a 1.6 M solution of *n*BuLi in hexane (8.0 mmol, 1.2 equiv.). After 25 min at −78 °C, the reddish solution was allowed to warm to −50 °C. To this latter solution a solution of **9** (1.65 g, 6.60 mmol) in anhydrous THF (35 mL) at room temp. was quickly added and the resulting mixture allowed to warm slowly to room temp., the reaction medium being monitored by TLC (AcOEt/cyclohexane, 3:7). The reaction mixture was quenched with H_2O, extracted with CH_2Cl_2, the organic solution dried ($MgSO_4$) and concentrated to dryness which led to an orange oil. The two diastereoisomers (2.77 g, 77%, ratio 73:27) were separated by FC (AcOEt/cyclohexane, 2:8, then 3:7), the minor L-*arabino* compound **11** (740 mg) being the more polar one.

Minor L-*arabino* Diastereomer (1*S*)-11: ^{1}H NMR ($CDCl_3$): δ = 7.35−7.10 [m, 6 H, H *arom* Ph and H−C(4′)], 5.02 [ddd, 1 H, H−C(1)], 4.56−4.29 (2 H, *AB*, $J = 10.8$ Hz, OC*H*$_2$Ph), 4.15 [td, 1 H, H−C(3)], 4.00 [dd, 1 H, H$_a$−C(4)], 3.86 [dd, 1 H, H−C(2)], 3.81 [dd, 1 H, H$_b$−C(4)], 2.86 (d, 1 H, −OH), 2.76 [s, 6 H, SO$_2$N(C*H*$_3$)$_2$], 1.39 and 1.28 (2 × 3 H, 2 CH$_3$ *isoprop.*), 0.91 [br. s, 9 H, SiMe$_2$C(C*H*$_3$)$_3$], 0.34 and 0.35 (6 H, Si(C*H*$_3$)$_2$*t*Bu), $J_{1,OH} = 7.8$, $J_{1,2} = 3.3$, $J_{1,4'} = 0.5$, $J_{2,3} = 5.3$, $J_{3,4a} = J_{3,4b} = 6.6$, $J_{4a,4b} = 8.4$ Hz. − ^{13}C NMR ($CDCl_3$): δ = 155.8 [C(2′)], 137.0 (Cs Ph), 134.7 [C(4′)], 131.6, 128.2, 128.0 (5C, Ph), 127.9 [C(5′)], 108.8 [*C*(CH$_3$)$_2$], 80.8 [C(2)], 75.6 (O*C*H$_2$Ph), 74.9 [C(3)], 65.9 [C(4)], 65.3

[C(1)], 37.4 [$SO_2N(CH_3)_2$], 27.1 [Si*t*Bu(CH_3)$_2$], 26.1 (CH_3 *isoprop.*), 25.5 [$SiMe_2C(CH_3)_3$], 24.9 (CH_3 *isoprop.*), −3.5 and −3.7 [$SiMe_2C(CH_3)_3$].

Major L-*ribo* Diastereomer (1*R*)-11: − ^{1}H NMR ($CDCl_3$): δ = 7.53 [s, 1 H, H−C(4′)], 7.38−7.22 (m, 5 H, Ph), 5.18 [t, 1 H, H−C(1)], 4.83 and 4.72 (2 H, *AB*, *J* = 11.4 Hz, OCH_2Ph), 4.10 [q, 1 H, H−C(3)], 4.01 [dd, 1 H, H−C(2)], 3.97 [dd, 1 H, H_a−C(4)], 3.88 [dd, 1 H, H_b−C(4)], 2.97 (d, 1 H, OH), 2.80 [s, 6 H, $SO_2N(CH_3)_2$], 1.41 (s, 3 H, CH_3 *acetonide*), 1.28 (s, 3 H, CH_3 *acetonide*), 1.01−0.98 [m, 9 H, $SiMe_2C(CH_3)_3$], 0.42 and 0.39 [2 s, 6 H, Si*t*Bu(CH_3)$_2$], $J_{1,2} = J_{1,OH} = 4.3$, $J_{2,3} = J_{3,4a} = J_{3,4b} = 6.4$, $J_{4a,4b} = 8.3$ Hz. − ^{13}C NMR ($CDCl_3$): δ = 155.7 [C(2′)], 138.0 (Cs Ph), 133.3 [C(5′)], 131.9, 130.6, 128.3, 127.8, 127.7 (5C, C-*arom*), 120.1 [C(4′)], 108.9 [*C*(CH_3)$_2$ *acetonide*), 82.0 [C(2)], 75.7 (O*C*H_2Ph), 74.7 [C(3)], 66.5 [C(4)], 65.5 [C(1)], 38.2 and 37.3 [$SO_2N(CH_3)_2$], 29.2 [$SiMe_2C(CH_3)_3$], 27.2 and 26.9 [SiMe_2*t*Bu(CH_3)$_2$], 26.6 and 25.2 [C(CH_3)$_2$ *acetonide*), − 3.6, − 3.7 and − 4.0 ($SiMe_2C(CH_3)_3$].

Imidazolo-L-arabinose Derivative 13: To a stirred solution of **11** (462 mg, 0.86 mmol) in anhydrous THF (14 mL) were added at room temp. a catalytic amount of Bu_4NI (13 mg, 0.04 mmol) and NaH (65 mg, 2.6 mmol, 3.0 equiv.). The reaction mixture was heated to 35 °C for 30 min and became dark red. BnBr (220 mg, 150 µL, 1.29 mmol, 1.5 equiv.) was added and the mixture heated to 40 °C for 15 h until completion of the reaction as monitored by TLC (AcOEt/cyclohexane, 3:7). After cooling to room temp., the reaction was quenched with H_2O (1 mL), 6 N HCl (4.5 mL) was added and the reaction mixture heated to 45 °C for 14 h. After cooling, the medium was extracted with CH_2Cl_2 to remove any apolar by-products and the aq. phase was neutralised with ammonia. The resulting cloudy solution was extracted with AcOEt, the organic phase dried with $MgSO_4$, filtered and concentrated to dryness to yield a slightly orange oil which was purified by FC (Et_2O/MeOH, 98:2 then 95:5 and finally 90:10, with small amounts of NH_3 in MeOH). Compound **13** (243 mg, 76%) was isolated as a colourless syrup. − $[\alpha]_D^{20}$ = +40 (*c* = 0.95, MeOH). − ^{1}H NMR ($CDCl_3$): δ = 7.52 [s, 1 H, H−C(2′)], 7.35−7.21 [11 H, H-*arom* and H−C(4′)], 4.73 [d, 1 H, H−C(1)], 4.54 (br. s, 2 H, OCH_2Ph), 4.54−4.31 (2 H, *AB*, *J* = 11.8, OCH_2Ph), 3.84 [t, 1 H, H−C(2)], 3.75−3.60 [m, 3 H, H−C(3), H_a−C(4), H_b−C(4)], $J_{1,2} = J_{2,3} = 4.4$ Hz. − ^{13}C NMR (CD_3OD): δ = 139.9 (Cs Ph), 139.7 [Cs Ph), 137.1 [C(2′)], 129.4−128.8 (10C, Ph), 120 [C(4′)], 84.5 [C(2)], 76.9 [C(1)], 76.0 (O*C*H_2Ph), 73.1 [C(3)], 72.4 (O*C*H_2Ph), 64.1 [C(4)]. − HR-MS: $[M + H]^+$ ion 369.1815 ($C_{21}H_{25}N_2O_4$, calcd. 369.1814).

L-*arabino*-Imidazolo-piperidinose Derivative 14: − To a stirred solution of **13** (315 mg, 0.85 mmol) and Et_3N (365 µL, 260 mg, 2.6 mmol, 3.0 equiv.) in CH_2Cl_2 (6 mL) at −10 °C were added catalytic amounts of DMAP (ca. 5 mg) and TsCl (440 mg, 2.3 mmol, 2.7 equiv.). The reaction mixture was monitored by TLC (CH_2Cl_2/MeOH/NH_4OH_{conc}, 95:5:0.2), quenched after 14 h with H_2O (2 mL) for 1 h at −5 °C and then extracted with CH_2Cl_2. The organic solution was concentrated to dryness and the residue taken up in 1 M NaOH (5 mL) and acetone (5 mL). The resulting solution was stirred for 14 h at room temp.; acetone was evaporated and the aq. phase was extracted with CH_2Cl_2. The organic phase was dried with $MgSO_4$ and concentrated to dryness, leading thereby to a slightly yellow oil. The crude oil was purified by FC (Et_2O, then Et_2O/MeOH, 95:5 and finally 90:10, MeOH containing small amounts of NH_4OH_{conc}) and led to **14** as a white sticky foam (172 mg, 0.49 mmol). − $[\alpha]_D^{20}$ = +63 (*c* = 1.15, MeOH). − ^{1}H NMR ($CDCl_3$): δ = 7.38 [s, 1 H, H−C(3)], 7.30−7.10 (10 H, H-*arom*), 7.00 [s, 1 H, H−C(1)], 4.66 [d, 1 H, H−C(8)], 4.62−4.53 (2 H, *AB*, *J* = 11.8, OCH_2Ph), 4.58−4.41 (2 H, *AB*, *J* = 11.8, OCH_2Ph), 4.44 [ddd, 1 H, H−C(6)], 4.12 [dd, 1 H, H_a−C(5)], 3.98 [dd, 1 H, H−C(7)], 3.86 [dd, 1 H, H_b−C(5)], $J_{5a,5b} = 11.9$, $J_{5a,6} = 5.6$, $J_{5b,6} = 9.0$, $J_{6,7} = 2.4$, $J_{7,8} = 4.0$ Hz. − ^{13}C NMR ($CDCl_3$): δ = 139.5 [C(3)], 139.3 [C(1)], 129.4, 129.4, 129.0, 128.8 (12C *arom*), 79.9 [C(7)], 73.6 (O*C*H_2Ph), 72.1 (O*C*H_2Ph), 70.7 [C(6)], 65.8 [C(8)], 46.5 [C(5)]. − HR-MS: M^+ ion 350.1646 ($C_{21}H_{22}N_2O_3$, calcd. 350.16304).

L-*arabino*-Imidazolo-piperidinose (*ent*-2): −A stirred solution of **14** (166 mg, 0.47 mmol) in MeOH (4 mL) was put under H_2 pressure (30 bar) at room temp. in the presence of moist (20% H_2O) $Pd(OH)_2$/C ("Pearlman's catalyst", 150 mg). After 7 d the suspension was centrifuged and the catalyst was rinsed several times with MeOH. The combined organic solution was concentrated in vacuo to ca. 2 mL and filtered through Celite to remove the last trace amounts of catalyst. Concentration of the solution to dryness gave an oil, which was purified by FC ($CHCl_3$/MeOH, 95:5) yielding thereby *ent*-**2** (45 mg, 56%) as a slightly beige resin. − $[\alpha]_D^{20}$ = +6 (*c* = 1.9, MeOH). − CD (H_2O): 213.5 (−4.25), 197.0 (+1.70). − ^{1}H NMR (CD_3OD): δ = 7.57 [s, 1 H, H−C(3)], 6.98 [s, 1 H, H−C(1)], 4.82 [d, 1 H, H−C(8)], 4.35 [ddd, 1 H, H−C(6)], 4.12 [dd, 1 H, H_a−C(5)], 4.03 [dd, 1 H, H_b−C(5)], 3.92 [dd, 1 H, H−C(7)], $J_{5a,5b} = 12.4$, $J_{5a,6} = 4.4$, $J_{5b,6} = 6.8$, $J_{6,7} = 1.8$, $J_{7,8} = 5.8$ Hz. − ^{13}C NMR (CD_3OD): δ = 136.8 [C(3)], 131.4 [C(8a)],127.0 [C(1)], 74.3 [C(7)], 67.4 [C(6)], 66.2 [C(8)], 47.0 [C(5)]. − These two NMR spectra are identical with those we had reported for the D-*arabino*-imidazolo-piperidinose **2**.[7,12] − HR-MS: M^+ ion 170.0687 ($C_7H_{10}N_2O_3$, calcd. 170.06914).

D-Gulofuranose Derivative 16: A stirred solution of the known product **15** (34.2 g, 114 mmol)[16] in AcOEt (700 mL) containing catalytic amounts of 5% Rh/Al_2O_3 (17.5 g) in suspension was put under H_2 pressure (50 bar) at room temp. for 45 min. After filtration and concentration of the resulting solution to dryness, the crude crystalline residue was recrystallised [Et_2O/petroleum ether (30−60 °C)] to give **16** as colourless crystals (33.7 g, 98%), m.p. 75−76 °C. − ^{1}H NMR ($CDCl_3$): δ = 5.80 [d, 1 H, H−C(1)], 5.06 [dd, 1 H, H−C(3)], 4.80 [dd, 1 H, H−C(2)], 4.61 [ddd, 1 H, H−C(5)], 4.10 [dd, 1 H, H_a−C(6)], 4.07 [dd, 1 H, H−C(4)], 3.52 [dd, 1 H, H_b−C(6)], 2.12 (s, 3 H, COCH_3), 1.57 (s, 3 H, CH_3 *acetonide*), 1.43 (s, 3 H, CH_3 *acetonide*), 1.38 (s, 3 H, CH_3 *acetonide*), 1.34 (s, 3 H, CH_3 *acetonide*), $J_{1,2} = 4.1$, $J_{2,3} = 5.7$, $J_{3,4} = 6.7$, $J_{4,5} = 9.3$, $J_{5,6a} = 6.7$, $J_{5,6b} = 7.2$, $J_{6a,6b} = 8.4$ Hz. − $C_{14}H_{22}O_7$ (302.32): C 55.62, H 7.33, found C 55.4, H 7.6.

D-Gulofuranose (17): To a stirred solution of **16** (5.00 g, 16.5 mmol) and Bu_4NI (630 mg, 1.70 mmol, 0.1 equiv.) in THF (40 mL) at 0 °C was added NaOMe (970 mg, 18.0 mmol, 1.10 equiv.). After 30 min, the reaction medium was left to warm to room temp. and was monitored by ^{1}H NMR of hydrolysed aliquots. After 4 h, BnBr (3.25 g, 19.0 mmol, 1.15 equiv.) was added and the reaction mixture heated to 50 °C for 14 h. The mixture was cooled to room temp., treated with 0.1 N NaOH (20 mL) to destroy excess BnBr, and extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$), filtered and concentrated to dryness to yield a crude solid whose recrystallisation (MeOH/H_2O) gave **17** as colourless crystals (5.30 g, 92%), m.p. 128 °C (ref.[17] m.p. 128.5−129.5 °C). − ^{1}H NMR ($CDCl_3$): δ = 7.40−7.20 (5 H, H-*arom*), 5.78 [d, 1 H, H−C(1)], 4.79 and 4.46 [2 H, *AB*, *J* = 11.7 Hz, OCH_2Ph), 4.71 (m, 1 H, H−C(5)], 4.63 [t, 1 H, H−C(2)], 4.15−3.95 [m, 3 H, H−C(3), H−C(4) and H_a−C(6)], 3.56 [dd, 1 H, H_a−C(6)], 1.63 (s, 3 H, CH_3 *acetonide*), 1.43 (s, 3 H, CH_3 *acetonide*), 1.37 (s, 3 H, CH_3 *acetonide*), 1.34 (s, 3 H, CH_3 *acetonide*), $J_{1,2} = 4.0$, $J_{2,3} = 4.0$, $J_{5,6a} = 6.6$, $J_{5,6b} = 7.3$, $J_{6a,6b} = 8.5$ Hz.

D-Gulose Derivative 18: A suspension of Dowex (5X28) beads (10 mL) in a solution of **17** (8.51 g, 24.3 mmol) in EtOH/H_2O, 1:1 (80 mL) was stirred at 75 °C, the reaction being monitored by TLC (AcOEt/MeOH, 9:1). After 4 h, the reaction mixture was cooled to room temp., filtered and the resin rinsed with AcOEt. The organic solution was dried ($MgSO_4$) and filtered through a silica bed (AcOEt/MeOH, 9:1) to yield **18** as a crude yellow syrup (5.58 g, ca. 85%) which is a mixture of furanose and pyranose isomers. A small amount of it was crystallised (EtOH/acetone, 9:1) as the β-D-gulopyranose (deliquescent crystals). − ^{1}H NMR (CD_3OD) of the latter: δ = 7.45−7.25 (m, 5 H, H-*arom*), 4.84 [d, 1 H, H−C(1)], 4.75 and 4.64 (2 H, *AB*, *J* = 11.6 Hz, OC*H*$_2$Ph), 3.90 [td, 1 H, H−C(5)], 3.82 [dd, 1 H, H−C(4)], 3.79 [dd, 1 H, H−C(3)], 3.75 and 3.60 [2 H, *AB*, $J_{6a,6b}$ = 11.3, H_a−C(6) and H_b−C(6)], 3.65 [dd, 1 H, H−C(2)]. $J_{1,2}$ = 8.2, $J_{2,3}$ = 3.2, $J_{3,4}$ = 3.6, $J_{4,5}$ = 1.3, $J_{5,6a}$ = $J_{5,6b}$ = 6.1 Hz.

D-Imidazolo-xylose (19): Compound **18** (5.58 g, 20.6 mmol) and formamidine acetate (3.00 g, 28.9 mmol, 1.40 equiv.) were dissolved in liquid ammonia (ca. 30 mL) at −78 °C in a pressure vessel. The sealed vessel was heated to 80 °C whereby the pressure rose to 45 bar. After 48 h, the pressure vessel was cooled to −78 °C, opened, and the ammonia was evaporated by a stream of N_2. The crude residue was dissolved in 0.5 N HCl (4 mL) and treated with cationic CG-6000 (Na^+) exchange resin in order to remove AcOH. The reaction product was eluted from the resin by washing with a 15% ammonia solution. After concentration to dryness, the residue was purified by FC (CH_2Cl_2/MeOH/NH_4OH_{conc}, 75:20:5) to yield **19** (2.30 g, 40%) as a slightly yellow foam. − $[\alpha]_D^{20}$ = +51 (*c* = 1.23, MeOH). − ^{1}H NMR (CD_3OD): δ = 7.83 [s, 1 H, H−C(2′)], 7.30−7.15 (m, 5 H, H-*arom*), 7.16 [s, 1 H, H−C(4′)], 4.66 [d, 1 H, H−C(1)], 4.48 and 4.36 (2 H, *AB, J* = 11.7 Hz, OC*H*$_2$Ph), 3.97 [dd, 1 H, H−C(2)], 3.65−3.50 [m, 2 H, H_a−C(4) and H_b−C(4)], 3.42 [td, 1 H, H−C(3)], $J_{1,2}$ = 7.6,. $J_{2,3}$ = 2.3, $J_{3,4a}$ = $J_{3,4b}$ = 5.9 Hz. − ^{13}C NMR (CD_3OD): δ = 139.8 [C_s Ph), 137.0 [C(2′)], 129.4, 129.2, and 129.0 (C-*arom*), 120.0 [1 H, br. *s*, C(4′)], 78.0 [C(1)], 76.5 (O*C*H$_2$Ph), 75.3 [C(2)], 72.7 [C(3)], 64.6 [C(4)]. − HR-MS: [M + H]$^+$ ion 279.1347 ($C_{14}H_{19}N_2O_4$, calcd. 279.1345).

D-*xylo*-Imidazolo-piperidinose Derivative 20: To a stirred solution of **19** (1.10 g, 3.95 mmol) in pyridine (30 mL) at −10 °C was added TsCl (2.10 g, 11.0 mmol, 2.8 equiv.). The reaction was monitored by TLC (Et_2O/MeOH/NH_4OH_{conc}, 80:15:5). After 14 h, H_2O (2 mL) and MeOH (2 mL) were added and the reaction was left to react for 1 h at −5 °C. The resulting solution was extracted with $CHCl_3$, concentrated to near dryness, some acetone (ca. 50 mL) was added, and the resulting mixture treated with 1 M NaOH (100 mL). This solution was heated to 60 °C for 14 h, adjusted to pH = 9 (1 N HCl; then Na_2CO_3), extracted with AcOEt, dried ($MgSO_4$) and concentrated to give a brownish oil which was purified by FC (Et_2O/MeOH/NH_4OH_{conc}, 85:13:2). Compound **20** (542 mg, 52%) was obtained as a slightly beige foam. − $[\alpha]_D^{20}$ = +5 (*c* = 0.6, MeOH). − ^{1}H NMR (CD_3OD): δ = 7.61 [s, 1 H, H−C(3)], 7.30−7.10 (m, 5 H, H-*arom*), 6.97 [s, 1 H, H−C(1)], 4.75 (2 H, br. *s*, OC*H*$_2$Ph), 4.60 [d, 1 H, H−C(8)], 4.30 [dd, 1 H, H_a−C(5)], 4.01 [dd, 1 H, H−C(7)], 3.93 [td, 1 H, H−C(6)], 3.86 [dd, 1 H, H_b−C(5)], $J_{7,8}$ = 5.1, $J_{5a,5b}$ = 11.2, $J_{5a,6}$ = 3.3, $J_{6,7}$ = 7.2, $J_{5b,6}$ = 7.2 Hz. − ^{13}C NMR (CD_3OD): δ = 139.3 (C_s Ph), 129.4, 129.4, and 128.8 (C-*arom*), 72.6 [C(7)], 70.4 (O*C*H$_2$Ph), 69.9 [C(8)], 66.9 [C(6)], 46.7 [C(5)].

D-*xylo*-Imidazolo-piperidinose (3): A solution of **20** (480 mg, 1.80 mmol) in AcOH (12 mL), containing moist (31% H_2O) 20% $Pd(OH)_2$/C (200 mg), was stirred for 16 h under H_2 (1 bar) at room temp.; the reaction medium being monitored by TLC ($CHCl_3$/MeOH/NH_4OH_{conc}, 60:35:5). The suspension was centrifuged, the catalyst washed several times with MeOH and the combined organic solutions concentrated to dryness. The resulting acetate salt of the imidazolo sugar was dissolved in 0.5 N HCl and the solution percolated on the cationic CG-6000 (Na^+) exchange resin (10 mL by volume). The resin was rinsed with a 5% to 15% ammonia solution. After concentration to dryness, the residue was purified by FC ($CHCl_3$/MeOH/NH_4OH_{conc}, 65:30:5) to yield a brownish crystalline solid (190 mg, 60%) which was recrystallized (MeOH/H_2O) to give **3** (97 mg, 30%), m.p.$_{dec.}$ 240 °C. − $[\alpha]_D^{20}$ = −68 (*c* = 0.89, H_2O). − CD: 213.0 (−5.60), 192.5 (+3.60). − ^{1}H NMR (CD_3OD): δ = 7.57 [s, 1 H, H−C(3)], 6.98 [s, 1 H, H−C(1)], 4.61 [d, 1 H, H−C(8)], 4.32 [dd, 1 H, H_a−C(5)], 3.97 [td, 1 H, H−C(6)], 3.84 [dd, 1 H, H_b−C(5)], 3.73 [dd, 1 H, H−C(7)], $J_{7,8}$ = 6.5. $J_{5a,5b}$ = 12.2, $J_{5a,6}$ = 4.5. $J_{6,7}$ = $J_{5b,6}$ = 7.9 Hz. − ^{13}C NMR (CD_3OD): δ = 137.5 [C(3)], 131.0 [C(8a)], 126.2 [C(1)], 76.3 [C(7)], 68.4 [C(6)], 68.0 [C(8)], 47.5 [C(5)]. − $C_7H_{10}N_2O_3$ (170.17): C 49.40, H 5.92, N 16.46; found C 49.4, H 6.0, N 16.3.

D-*xylo*-Imidazole Derivative 22: A pressure vessel, which had been prepared according to ref.[17,18], containing a mixture of **21** (3.73 g, 13.8 mmol), formamidine acetate (2.50 g, 23.9 mmol), and some liquid ammonia (ca.40 mL), was heated to 90 °C for 15 h under stirring whereby the pressure rose to 40 bar. Workup as for **19** (see above). The resulting brownish oil was dissolved in MeOH (100 mL), the solution concentrated to dryness and the residue stripped off the ammonia in vacuo. The crude oil residue was taken up in H_2O and percolated on a CG-6000 resin (acid form, 40 g) with H_2O to remove AcOH. Desorption was performed with 10% aq. ammonia, the solution concentrated to dryness and the residue separated by FC (AcOEt/MeOH, 10:1 then 8:2 with some conc. aq. ammonia) to give **22** as a yellow oil (1.75 g, 45%). − $[\alpha]_D^{20}$ = −48 (*c* = 1.0, MeOH). − ^{1}H NMR (CD_3OD): δ = 7.74 [d, 1 H, H−C(2′)], 7.31−7.22 (m, 5 H, H-*arom*), 7.11 [d, 1 H, H−C(5′)], 4.63 [d, 1 H, H−C(1)], 4.47 and 4.36 (2 H, *AB*, *J* = 11.6 Hz, C*H*$_2$Ph), 3.92 [dd, 1 H, H−C(2)], 3.58 [dd, 1 H, H_a−C(4)], 3.52 [dd, 1 H, H_b−C(4)], 3.36 [td, 1 H, H−C(3)], $J_{1,2}$ = 7.6, $J_{2,3}$ = 2.4, $J_{2',5'}$ = 1.3, $J_{4a,4b}$ = 11.2, $J_{3,4a}$ = 6.2, $J_{3,4b}$ = 6.2 Hz. − ^{13}C NMR (CD_3OD): δ = 139.4, 129.2, 129.1, 128.6 (C-*arom* Ph), 137.0 [C(2′)], 135.9 [C(5′)], 120.4 [C(4′)], 77.1 [C(1)], 74.5 [C(2)], 72.3 [C(3)], 71.6 (*C*H$_2$Ph), 64.6 [C(4)].

L-*xylo*-Imidazolo-piperidinose Derivative 23: To a stirred solution of **22** (240 mg, 0.86 mmol) in DMF (1 mL) under Ar at 0 °C was added CBr_4 (330 mL). After 15 min, Ph_3P (490 mg, 1.87 mmol) was added in small portions over 10 min, followed by addition of Et_3N (0.4 mL, 2.9 mmol). The reaction mixture was directly put on top of a silica gel column and eluted with Et_2O, then with Et_2O/MeOH/NH_4OH_{conc}, 70:30:1 to give **23** (90 mg, 40%) as a colourless crystalline compound, which was rinsed with *i*PrOH, m.p. 170−172 °C. − $[\alpha]_D^{20}$ = −9 (*c* = 1.0, MeOH). − ^{1}H NMR and ^{13}C NMR spectra superimposable with those of **20**. − $C_{14}H_{16}N_2O_3$ (260.29): C 64.60, H 6.20, N 10.76; found C 64.4, H 6.2, N 10.9.

L-*xylo*-Imidazolo-piperidinose (*ent*-3): A stirred solution of **23** (107 mg, 0.41 mmol) in AcOH (3 mL) containing some $Pd(OH)_2$/C, was put under H_2 (1 bar) until complete disappearance of **23** as monitored by TLC (AcOEt/MeOH, 1:1). The suspension was filtered and the resulting solution concentrated to dryness in vacuo. The crude residue was purified by FC (Et_2O/MeOH/NH_4OH_{conc}, 70:30:1) leading to *ent*-**3** (59 mg, 84%) as a colourless powder, m.p.$_{dec.}$ 238 °C. − $[\alpha]_D^{20}$ = +69 (*c* = 0.55, H_2O) [ref.[9] $[\alpha]_D^{20}$ = +69 (*c* = 0.55, H_2O)]. − CD: 213.0 (+6.20), 185.0 (−4.15). − ^{1}H NMR and ^{13}C NMR spectra superimposable with those of **3**. − HR-MS

$[M + H]^+$ 171.0770 ($C_7H_{11}N_2O_3$); found 171.0770. − $C_7H_{10}N_2O_3$ (170.17): C 49.40, H 5.92, N 16.46; found C 49.5, H 6.0, N 16.3.

D-*lyxo*-Imidazole Derivative 25: A stirred solution of the known tetritol **24** (2.93 g, 15.57 mmol),[12] DMAP (200 mg), and TrCl (9.55, 34 mmol) in pyridine (65 mL) was heated to 70−75 °C and the reaction monitored by TLC (AcOEt, then AcOEt/MeOH/NH_4OH_{conc}, 5:5:0.5). After 3.5 h, pyridine was distilled off under vacuum (60 °C, 0.7 Torr), the residue taken up in CH_2Cl_2, and the resulting solution washed with H_2O, dried ($MgSO_4$), filtered and concentrated to dryness. The crude reaction product was purified by FC (AcOEt) leading to **25** (7.43 g, 71%) as a colourless powder. − ^{1}H NMR ($CDCl_3$): δ = 7.58 [d, 1 H, H−C(2′)], 7.44−7.00 (30 H, H-*arom*), 6.85 [d, 1 H, H−C(5′)], 4.76 [d, 1 H, H−C(1)], 4.02 [td, 1 H, H−C(3)], 3.90 [dd, 1 H, H−C(2)], 3.29 [dd, 1 H, H_a−C(4)], 3.23 [dd, 1 H, H_b−C(4)], 2.9 (3 H, large peak, OH), $J_{1,2}$ = 6.0, $J_{2,3}$ = 2.4, $J_{3,4a}$ = 5.4, $J_{3,4b}$ = 5.8, $J_{4a,4b}$ = 9.4, $J_{2',5'}$ = 1.4 Hz. − ^{13}C NMR ($CDCl_3$): δ = 143.8, 142.0, 141.1, 138.4, 129.7, 128.7, 128.2, 128.1, 127.8, 127.0, 119.5 (C-*arom* of *trityl* and *imidazole*), 86.8 (O*C*Ph_3), 75.6 (N*C*Ph_3), 74.4, 70.1, 69.7, 65.2 [C(1), C(2), C(3), C(4)]. − HR-MS: $(M + H)^+$ ion 673.3067 ($C_{45}H_{41}N_2O_4$, calcd. 673.3066).

D-*lyxo*-Imidazole Derivative 26: To a stirred solution of triol **25** (7.15 g, 10.63 mmol) in anhydrous THF (120 mL) was added at 0 °C NaH/oil (1.7 g, 55−65% NaH). When the evolution of H_2 had ceased, Bu_4NI (60 mg) and BnBr (4.5 mL, 38 mmol) were added. The solution was warmed to room temp., heated to 60 °C for 4 h, cooled to room temp. and H_2O (4 mL) was added slowly. The solution was concentrated to dryness, the residue taken up in CH_2Cl_2 and H_2O and the mixture extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), concentrated to dryness and the residue was purified by FC (AcOEt/cyclohexane, 2:8) to give **26** (5.28 g, 53%) as a solid foam. − ^{1}H NMR ($CDCl_3$): δ = 7.44−6.83 (45 H, H-*arom* of *trityl* and *benzyl* groups), 6.83 [d, 1 H, H−C(5′)], 4.62 [d, 1 H, H−C(1)], 4.63 and 4.50 (2 H, *AB*, *J* = 11.5 Hz, CH_2Ph), 4.39 and 4.20 (2 H, *AB*, *J* = 12.0 Hz, CH_2Ph), 4.34 and 4.27 (2 H, *AB*, *J* = 11.5, CH_2Ph), 4.17 [dd, 1 H, H−C(2)], 4.01 [ddd, 1 H, H−C(3)], 3.41 [dd, 1 H, H_a−C(4)], 3.30 [dd, 1 H, H_b−C(4)], $J_{1,2}$ = 7.4, $J_{2,3}$ = 3.4, $J_{3,4a}$ = 6.2, $J_{3,4b}$ = 5.3, $J_{4a,4b}$ = 9.7, $J_{2',5'}$ = 1.2 Hz. − ^{13}C NMR ($CDCl_3$): δ = 144.1, 142.3, 139.0, 138.7, 138.6, 129.6, 128.7, 128.1, 128.0, 127.9, 127.8, 127.7, 127.2, 127.0, 126.8, and 122.4 (C-*arom* of *trityl*, *benzyl*, and *imidazole*), 87.0 (O*C*Ph_3), 80.6 [C(2)], 78.3 [C(3)], 75.3 (N*C*Ph_3), 74.2 [C(1)], 73.9 (CH_2Ph), 73.6 (CH_2Ph), 69.7 (CH_2Ph), 64.3 [C(4)]. − HR-MS: $[M + H]^+$ ion 943.4472 ($C_{66}H_{59}N_2O_4$, calcd. 943.4475).

D-*lyxo*-Imidazole Derivative 27: A solution of **26** (2.50 g, 2.65 mmol) in THF (50 mL) and 6 N HCl (50 mL) was heated under reflux for 24 h, 8 N HCl (8 mL) was added and reflux was pursued for another 24 h, the reaction being monitored by TLC (AcOEt/MeOH, 9:1). The reaction mixture was neutralised with 2 N NaOH at 0 °C, the organic phase separated and the aq. phase extracted with CH_2Cl_2. The combined organic phases were dried (MgSO4), filtered and concentrated to dryness. The crude residue was purified by FC (AcOEt, then AcOEt/MeOH, 9:1) leading to **27** (1.013 g, 83%) as a colourless foam. − ^{1}H NMR ($CDCl_3$): δ = 7.58 [s, 1 H, H−C(2′)], 7.29−7.26 (15 H, H-*arom*), 7.08 [s, 1 H, H−C(5′)], 4.70 [d, 1 H, H−C(1)], 4.72 and 4.63 (2 H, *AB*, *J* = 11.0 Hz, CH_2Ph), 4.59 and 4.53 (2 H, *AB*, *J* = 11.4 Hz, CH_2Ph), 4.49 and 4.35 (2 H, *AB*, *J* = 11.8 Hz, CH_2Ph), 4.15 [dd, 1 H, H−C(2)], 3.66 [dd, 1 H, H_a−C(4)], 3.53 and 3.50 [m, 2 H, H−C(3) and H_b−C(4)], $J_{1,2}$ = 4.0, $J_{2,3}$ = 6.0, $J_{3,4a}$ = 4.0, $J_{4a,4b}$ = 11.8 Hz. − This latter ^{1}H NMR spectrum, albeit more detailed here, is identical with the one of *ent*-**27** we had described in a preceding publication.[10] The ^{13}C NMR spectrum is identical with the one of *ent*-**27.**[10]

D-*lyxo*-Imidazolo-piperidinose Derivative 28: To a stirred solution of **27** (738 mg, 1.61 mmol) in pyridine (12 mL) at 0 °C was added α-tosyl chloride (735 mg, 3.86 mmol, 2.4 equiv.). After 10 min, the reaction mixture − which was monitored by TLC (AcOEt) − was left to warm to room temp. and stirred for another 30 min. A new and less polar compound appeared. Excess Ac_2O was added and the mixture heated to 80 °C for 1 h. MeOH (excess) was added, the reaction mixture was stirred for 30 min, the mixture concentrated to dryness and the residue separated by FC (AcOEt, then AcOEt/MeOH, 9.5:0.5) to yield **28** (652 mg, 92%) as a colourless resin. The ^{1}H NMR spectrum (C_6D_6) is identical to the one of *ent*-**28** we had described previously.[10]

D-*lyxo*-Imidazolo-piperidinose (4): A stirred solution of **28** (422 mg, 0.97 mmol) in AcOH (30 mL) was put under H_2 pressure (8 bar) in an autoclave at room temp. for 20 h in the presence of 20% $Pd(OH)_2$/C (containing 50% water) (200 mg) and PdO/C (150 mg). The catalyst was removed by centrifugation, and washed with AcOH. The combined organic phases were concentrated to dryness, the residue was taken up in MeOH, the solution concentrated to dryness, and the residue put on an ion exchange column (Amberlit CG 6000, H^+). Desorption was performed with aq. NH_4OH (ca 10%). After removal of the solvents, the crude residue was purified by FC (Et_2O/MeOH/NH_4OH_{conc}, 8:2:0.5 to 6:4:0.5) to yield **4** (92 mg, 56%) as a colourless powder, m.p.$_{dec.}$ 214 °C (MeOH/*i*PrOH). − $[\alpha]_D^{20}$ = −13 (*c* = 0.8, MeOH). − CD: 215.0 (+3.85), 198.0 (−4.40), 188.5 (−1.75). − ^{1}H NMR (D_2O): δ = 7.64 [d, 1 H, H−C(1)], 7.07 [t, 1 H, H−C(3)], 5.06 [dd, 1 H, H−C(8)], 4.40* [m, 1 H, H_a−C(5)], 4.39* [m, 1 H, H−C(6)], 4.08* [dd, 1 H, H−C(7)], 3.95 [dd, 1 H, H_b−C(5)], $J_{1,3}$ = 0.7, $J_{1,8}$ = 0.8, $J^*_{5a,5b}$ = 13.2, $J^*_{5a,6}$ = 4.7, $J^*_{6,7}$ = 7.2, $J^*_{5b,6}$ = 5.9, $J_{7,8}$ = 3.8 Hz (*: calculated from a simulated spectrum with Bruker's PANIC program). This latter ^{1}H NMR spectrum as well as the ^{13}C NMR spectrum are identical to the ones reported for *ent*-**4**.[10] − $C_7H_{10}N_2O_3$ (170.17): C 49.41, H 5.92, N 16.46; found C 49.5, H 6.0, N 16.3.

Ethyl L-Threonate Derivative 29: A mixture of freshly prepared anhydrous Ag_2O (8.50 g, 36.6 mmol), powdered 4-Å molecular sieves (ca. 2 g), and KI (500 mg) were activated at 300 °C under vacuum. After cooling to room temp., these solids were poured into a stirred solution of **6** (5.00 g, 24.5 mmol) in anhydrous toluene (120 mL), the mixture was heated to 50 °C, and BnBr (3.4 mL, 28.6 mmol) added dropwise.[23] The resulting mixture was heated to reflux, the reaction being monitored by TLC (AcOEt/cyclohexane, 2:8). After 2 h the reaction mixture was cooled to room temp., filtered through a silica bed, the filtrate concentrated to dryness and the crude residue purified by FC (AcOEt/cyclohexane, 1:9 then 2:8) leading thereby to the oily product **29** (6.55 g, 91%) which crystallised in the freezer, m.p. 37 °C. − $[\alpha]_D^{20}$ = +59 (*c* = 2.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 7.38−7.26 (m, 5 H, H-*arom*), 4.78 and 4.52 (2 H, *AB*, *J* = 11.9, CH_2Ph), 4.39 [q, 1 H, H−C(3)], 4.22 (q, 2 H, CH_2−CH_3), 4.01 [dd, 1 H, H_a−C(4)], 3.98 [d, 1 H, H−C(2)], 3.95 [dd, 1 H, H_b−C(4)], 1.39 (s, 3 H, CH_3 *acetonide*), 1.35 (s, 3 H, CH_3 *acetonide*), 1.29 (t, 3 H, CH_2−CH_3),. $J_{3,4}$ = $J_{3,2}$ = 6.2, J_{CH2CH3} = 7.1, $J_{3,4a}$ = 6.5, $J_{4a,4b}$ = 8.7, $J_{2,3}$ = 5.9, $J_{3,4b}$ = 6.4 Hz.− ^{13}C NMR ($CDCl_3$): δ = 170.1 [C(1)], 137.1 (Cs *arom*), 128.4 to 128.0 (5 C-*arom*), 109.9 [C(6)], 78.6 [C(2)], 75.9 [C(3)], 72.8 [C(5)], 65.5 [C(4)], 61.2 (*C*H_2CH$_3$), 25.3 and 26.3 (2 *C*H_3 *isoptop.*), 14.2 (CH_2*C*H_3). − $C_{16}H_{22}O_5$ (294.35): C 65.29, H 7.53; found C 65.5, H 7.8.

L-Threose Derivative 30: − To a stirred solution of ester **29** (4.16 g, 14.1 mmol) in anhydrous toluene (76 mL) at −78 °C was added

dropwise 1.5 M DIBAH in toluene (20 mL, 30 mmol). After 20 min at −78 °C, MeOH (7 mL) was added dropwise and the reaction allowed to warm to room temp. To this stirred solution a saturated potassium sodium tartrate solution (7 mL) and AcOEt (40 mL) were added. After 10 min, the solution was dried ($MgSO_4$), the suspension filtered and the filtrate dried once more ($MgSO_4$), the resulting suspension was filtered and the filtrate concentrated to dryness. The residue was dissolved in toluene, centrifuged and the filtrate concentrated to dryness, the residue taken up once more in anhydrous toluene, and the solution concentrated to dryness, leading to the pure aldehyde **30** (ca. 3.5 g, quantitative; aldehyde hydrate being no longer detected by ^{1}H NMR), which was used as such for the following step. − ^{1}H NMR ($CDCl_3$): δ = 9.72 [d, 1 H, H−C(1)], 7.38−7.26 (m, 5 H, H-*arom*), 4.79 and 4.66 (2 H, *AB*, *J* = 11.9, C*H*$_2$Ph), 4.38 [m, 1 H, H−C(3)], 4.06 [dd, 1 H, H$_a$−C(4)], 3.95 [dd, 1 H, H$_b$−C(4)], 3.86 [dd, 1 H, H−C(2)], 1.43 (s, 3 H, C*H*$_3$ *acetonide*), 1.35 (s, 3 H, C*H*$_3$ *acetonide*), $J_{1,2}$ = 1.5, $J_{3,4a}$ = 6.6, $J_{4a,4b}$ = 8.8, $J_{3,4b}$ = 5.9, $J_{2,1}$ = 1.5, $J_{2,3}$ = 5.4 Hz. − ^{13}C NMR ($CDCl_3$): δ = 202.1 [C(1)], 136.9 (C$_s$ *arom*), 128.6−128.1 (5C *arom*), 109.8 (*C*Me$_2$*acetonide*), 82.8 [C(2)], 75.3 [C(3)], 73.3 (*C*H$_2$Ph), 65.3 [C(4)], 26.1 and 25.1 [C(*C*H$_3$)$_2$ *acetonide*).

The Coupling Reaction: To a stirred solution of **10** (4.81 g, 16.6 mmol) in anhydrous THF (70 mL) at −78 °C was added dropwise a 1.6 M solution of *n*BuLi in hexane (11.4 mL, 18.3 mmol). After 30 min, a solution of **30** (3.33 g, 13.3 mmol) in anhydrous THF (10 mL) was added and the mixture was left to warm to room temp. After ca. 1 h, a sat. aq. solution of Na_2CO_3 was added, the mixture extracted with AcOEt and the organic solution washed with H_2O, dried ($MgSO_4$) and concentrated to dryness. The resulting brownish oil (two diastereoisomers) was separated by FC (AcOEt/cyclohexane, 2:8 then 5:5), the major product **31** (3.29 g, 46%) being the less polar one as a yellow oil, and its more polar diastereoisomer (2.44 g, 34%) as an orange oil.

Major L-*lyxo*-Diastereoisomer (1*S*)-31: ^{1}H NMR ($CDCl_3$): δ = 7.47 [s, 1 H, H−C(5′)], 7.37−7.24 (m, 5 H, H-arom), 5.09 [dd, 1 H, H−C(1)], 4.84 and 4.61 (2 H, *AB*, *J* = 11.4, C*H*$_2$Ph), 4.23 [ddd, 1 H, H−C(3)], 3.89 [dd, 1 H, H$_a$−C(4)], 3.82 [t, 1 H, H−C(2)], 3.75 [dd, 1 H, H$_b$−C(4)], 3.23 (d, 1 H, O*H*), 2.77 [s, 6 H, N(C*H*$_3$)$_2$], 1.45 and 1.35 (2 × 3 H, C*H*$_3$ *isoprop*), 1.00 [s, 9 H, SiC(C*H*$_3$)$_3$], 0.39 [s, 6 H, Si(C*H*$_3$)$_2$], $J_{1,OH}$ = 7.0, $J_{1,2}$ = 5.4, $J_{2,3}$ = 5.5, $J_{3,4a}$ = 6.5, $J_{3,4b}$ = 7.4, $J_{4a,4b}$ = 8.5 Hz. − ^{13}C NMR ($CDCl_3$): δ = 156.1, 138.1, 134.2, 131.9, 128.4−127.8, 109.5, 81.6, 76.9, 74.0, 66.0, 64.9, 37.5, 27.3, 26.4, 25.6, 18.4, −3.4 and −3.6.

Minor L-*xylo*-Diastereoisomer (1*R*)-31: ^{1}H NMR ($CDCl_3$): δ = 7.33−7.30 [m, 6 H, H-*arom* and H−C(4′)], 5.00 [ddd, 1 H, H−C(1)], 4.73 and 4.43 (2 H, *AB*, *J* = 10.8 Hz, OC*H*$_2$Ph), 4.38 [dt, 1 H, H−C(3)], 3.97 [dd, 1 H, H$_a$−C(4)], 3.81 [dd, 1 H, H$_b$−C(4)], 3.75 [dd, 1 H, H−C(2)], 3.17 (d, 1 H, −O*H*), 2.82 [s, 6 H, N(C*H*$_3$)$_2$], 1.44 and 1.38 [2 s, 6 H, C(C*H*$_3$)$_2$], 0.99 [s, 9 H, SiC(CH$_3$)$_3$], 0.41 and 0.40 [2 s, 6 H, Si*t*Bu(C*H*$_3$)$_2$], $J_{1,5'}$ = 0.6, $J_{1,OH}$ = 7.2, $J_{1,2}$ = 2.8, $J_{2,3}$ = 6.2, $J_{3,4a}$ = 6.3, $J_{3,4b}$ = 7.4, $J_{4a,4b}$ = 8.3 Hz. − ^{13}C NMR ($CDCl_3$): δ = 156.1, 137.5, 134.7, 128.5−128.0, 109.5, 80.9, 77.5, 74.9, 65.8, 65.7, 37.6, 27.3, 26.5, 25.7, 18.3, −3.4, −3.6.

L-Imidazolo-lyxose Derivative 32: To a stirred solution of (1*S*)-**31** (1.735 g, 3.21 mmol) in anhydrous THF (60 mL) was added a catalytic amount of Bu_4NI (200 mg) and 50% NaH in oil (450 mg, 18.8 mmol) at room temp. The reaction mixture was heated to 40 °C and BnBr (0.8 mL, 6.77 mmol) was added. After 2 h, the reaction mixture was cooled to room temp. and MeOH (5 mL) and H_2O (5 mL) were added. The organic solvents were evaporated in vacuo and the residue was extracted with AcOEt, the organic phase washed with brine, dried ($MgSO_4$), filtered and concentrated to dryness whereby an orange oil was obtained. This oily residue was dissolved in THF (1.5 mL) and 2 N HCl (65 mL) was added. The resulting mixture was heated to 70 °C for 3 h, cooled to room temp. and extracted with AcOEt, the aq. phase was adjusted with NH_4OH to pH = 10, and extracted again with AcOEt. The combined organic phases were washed with brine, dried ($MgSO_4$), concentrated to dryness, and the oily residue was purified by FC (Et_2O/MeOH/NH_4OH_{conc}, 9:1:0.5) leading thereby to **32** (938 mg, 90%) as colourless crystals (AcOEt/pentane), m.p. 132 °C. − $[\alpha]_D^{20}$ = +20 (*c* = 1, MeOH). − ^{1}H NMR ($CDCl_3$): δ = 7.63 [s, 1 H, H−C(2′)], 7.37−7.21 (10 H, H-*arom*), 7.07 [s, 1 H, H−C(5′)], 4.74 [d, 1 H, H−C(1)], 4.62 and 4.51 (2 H, *AB*, *J* = 11.3 Hz, C*H*$_2$Ph), 4.57 and 4.42 (2 H, *AB*, *J* = 11.7 Hz, C*H*$_2$Ph), 3.96 [t, 1 H, H−C(2)], 3.80 [m, 1 H, H−C(3)], 3.63−3.61 [m, 2 H, H$_a$−C(4) and H$_b$−C(4)], $J_{1,2}$ = 4.6, $J_{2,3}$ = 4.6 Hz. − Anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found C 68.3, H 6.3, N 7.4.

L-*lyxo*-Imidazolo-piperidinose Derivative 33: To a stirred solution of **32** (792 mg, 2.15 mmol) in CH_2Cl_2 (15 mL) and pyridine (770 μL, 9.5 mmol) at −30 °C was added Tf_2O (760 μL, 4.63 mmol) dropwise. After 30 min, the reaction mixture was left to warm to room temp., H_2O was added and the solution extracted with CH_2Cl_2. The organic solution was dried ($MgSO_4$), filtered, concentrated to dryness and the oily residue purified by FC (Et_2O/MeOH/NH_4OH_{conc}, 9:1:0.5), which led to **33** (244 mg, 32%) as a colourless resin that crystallised, m.p. 129 °C. − $[\alpha]_D^{20}$ = +57 (*c* = 1, MeOH). − ^{1}H NMR ($CDCl_3$): δ = 7.50 [s, 1 H, H−C(3)], 7.38 (10 H, H-*arom*), 7.08 [s, 1 H, H−C(1)], 4.77 [d, 1 H, H−C(8)], 4.70 and 4.47 (2 H, *AB*, *J* = 11.8 Hz, C*H*$_2$Ph), 4.64 and 4.40 (2 H, *AB*, *J* = 12.2 Hz, C*H*$_2$Ph), 4.69 [td, 1 H, H−C(6)], 4.52 [dd, 1 H, H$_a$−C(5)], 3.74 [dd, 1 H, H$_b$−C(5)], 3.60 [dd, 1 H, H−C(7)], $J_{5a,6}$ = 6.6, $J_{5a,5b}$ = 12.2, $J_{5b,6}$ = 9.5, $J_{6,7}$ = 9.5, $J_{7,8}$ = 3.3 Hz. − ^{13}C NMR ($CDCl_3$): δ = 140.1 [C(3)], 136.9 (2 C$_s$), 129.3 [C(1)], 128 to 128.6 (C-*arom*), 127.8 [C(8$_a$)], 79.9 [C(7)], 71.5 (*C*H$_2$Ph), 69.7 (*C*H$_2$Ph), 65.1 [C(8)], 64.5 [C(6)], 47.5 [C(5)].

L-*lyxo*-Imidazolo-piperidinose (*ent*-4): A stirred solution of **33** (175 mg, 0.50 mmol) in MeOH (3 mL) was put under H_2 (20 bar) for 4 d in the presence of 10% Pd/C (200 mg) at room temp. The suspension was filtered through Clarcel, the solution concentrated to dryness and the residue purified by FC (Et_2O/MeOH/NH_4OH_{conc}, 6:4:0.5) leading to *ent*-**4** (54 mg, 63%) as a colourless powder, m.p.$_{dec.}$ 205 °C (MeOH/*i*PrOH). − $[\alpha]_D^{20}$ = +11 (*c* = 0.5, MeOH). − CD: 215.0 (−3.45), 199.5 (+4.75), 188.5 (+2.10). − The ^{1}H NMR and ^{13}C NMR spectra are identical and superimposable with those of **4** and with those reported previously.[10]

D-*ribo*-Imidazole Derivative 35: A pressure vessel, which had been prepared according to ref.[21,22], containing 3-*O*-benzyl-D-allose (**34**) (6.15 g, 22.8 mmol), formamidine acetate (3.32 g, 31.9 mmol), and liquid ammonia (ca. 40 mL), was heated to 80 °C for 15 h under stirring whereby the pressure rose to 40 atm. The workup was performed as for **22** and gave **35** (3.34 g, 53%) as a yellow oil which was purified by FC (AcOEt/MeOH/NH_4OH_{conc}, 8:1:0.1 then 4:1:0.1). − $[\alpha]_D^{20}$ = +52 (*c* = 1.0, MeOH). − ^{1}H NMR (CD_3OD): δ = 7.68 [d, 1 H, H−C(2′)], 7.30−7.20 (m, 5 H, H-*arom*), 7.08 [d, 1 H, H−C(5′)], 4.69 [d, 1 H, H−C(1)], 4.46 and 4.35 (2 H, *AB*, *J* = 11.6 Hz, C*H*$_2$Ph), 3.99 [dd, 1 H, H−C(2)], 3.71 [dd, 1 H, H$_a$−C(4)], 3.59 [dd, 1 H, H$_b$−C(4)], 3.41 [ddd,1 H, H−C(3)], $J_{2',5'}$ = 1.2, $J_{1,2}$ = 4.7, $J_{2,3}$ = 7.4, $J_{3,4a}$ = 3.4, $J_{3,4b}$ = 6.1, $J_{4a,4b}$ = 11.4 Hz. − ^{13}C NMR (CD_3OD): δ = 139.5, 129.3, 129.0, 128.6 (C-*arom*), 136.8 [C(2′)], 134.2 [C(4′)], 122.6 [C(5′)], 76.3 [C(1)], 75.0 [C(2)], 73.4 [C(3)], 71.4 (*C*H$_2$Ph), 64.5 [C(4)].

D-*ribo*-Imidazolo-piperidinose Derivative 36: To a stirred solution of **35** (458 mg, 1.65 mmol) in DMF (4 mL) under Ar at 0 °C was added CBr_4 (988 mg, 2.95 mmol). After 15 min, Ph_3P (907 mg, 3.45 mmol) was added in small portions over 10 min, the solution kept for 3 h at 0 °C, then left to warm to room temp. overnight, then heated to 45 °C for 5 h. After cooling to room temp., Et_3N (0.6 mL) was added, the reaction mixture stirred overnight and the reaction mixture was separated by column chromatography (Et_2O, then Et_2O/MeOH/NH_4OH_{conc}, 70:30:1), whereby **36** (209 mg, 49%) formed as a colourless crystalline compound, m.p. 177−179 °C (AcOEt/MeOH). − $[\alpha]_D^{20}$ = −15 (*c* = 1.2, MeOH). − ^{1}H NMR (CD_3OD): δ = 7.57 [d, 1 H, H−C(3)], 7.46−7.20 (m, 5 H, H-*arom*), 6.94 [dd, 1 H, H−C(1)], 4.81 and 4.72 (2 H, *AB*, *J* = 12.0 Hz, C*H*$_2$Ph), 4.67 [dd, 1 H, H−C(8)], 4.30* [dd, 1 H, H−C(7)], 4.13* [1 H, H_a−C(5)], 4.06* [1 H, H−C(6)], 4.01* [1 H, H_b−C(5)], $J_{1,3}$ = 1.0, $J_{1,8}$ = 1.2, $J_{5a,5b}$ = 10.5*, $J_{5a,6}$ = 4.6*, $J_{5b,6}$ = 8.5*, $J_{6,7}$ = 2.0* , $J_{3,8}$ = 3.6* Hz (*: values calculated from a simulated spectrum with Bruker's PANIC program). − ^{13}C NMR (CD_3OD): δ = 139.3, 129.5, 129.1, 128.9 (C-*arom*), 136.9 [C(3)], 129.2 [C(1)], 126.7 [C(8a)], 73.0 [C(8)], 72.1 (*C*H$_2$Ph), 69.5 [C(7)], 68.3 [C(6)], 45.8 [C(5)]. − Anal. calcd. for $C_{14}H_{16}N_2O_3$ (260.29): C 64.60, H 6.20, N 10.76; found C 64.3, H 6.2, N 10.7.

D-*ribo*-Imidazolo-piperidinose (5): A stirred solution of **36** (191 mg, 0.734 mmol) in AcOH (5 mL) was put under H_2 in the presence of 20% $Pd(OH)_2$/C at atmospheric pressure. After complete disappearance of **36**, as monitored by TLC (AcOEt/MeOH, 1:1), the suspension was filtered through Celite, the resulting solution concentrated to dryness and the crude residue purified by FC ($CHCl_3$/MeOH/NH_4OH_{conc}, 7:3:0.2) leading to **5** (101 mg, 81%) as colourless crystals, m.p. 225 °C$_{dec.}$ − $[\alpha]_D^{20}$ = −40 (*c* = 0.5, MeOH). − CD: 215.5 (−5.20), 198.5 (+5.65), 190.0 (+4.80). − ^{1}H NMR (D_2O): δ = 7.66 [s, 1 H, H−C(3)], 7.06 [s, 1 H, H−C(1)], 4.96 [d, 1 H, H−C(8)]*, 4.31 [ddd, 1 H, H−C(6)]*, 4.29 [dd, 1 H, H−C(5)]* , 4.24 [dd, 1 H, H−C(7)]*, 4.01 [dd, 1 H, H_b−C(5)]*, $J_{5a,5b}$ = 12.0* , $J_{5a,6}$ = 8.8*, $J_{5b,6}$ = 5.9*, $J_{6,7}$ = 1.8*, $J_{7,8}$ = 3.8* Hz (*: values calculated from a simulated spectrum with Bruker's PANIC program). − ^{13}C NMR (CD_3OD): δ = 136.6 [C(3)], 131.8 [C(8a)], 126.2 [C(1)], 72.2 [C(7)], 68.5 [C(6)], 65.8 [C(8)], 45.8 [C(5)]. − Anal. calcd. for $C_7H_{10}N_2O_3$ (170.17): C 49.41, H 5.92, N 16.46; found C 49.2, H 5.9, N 16.3.

D-*arabino*-Imidazolo-piperidinose Derivative 38: − To a stirred solution of the known D-*arabino* derivative **37** (220 mg, 0.845 mmol) [12] in anhydrous CH_2Cl_2 (8 mL) and pyridine (0.35 mL) under Ar at 0 °C, was added dropwise Tf_2O (0.39 mL, 2.37 mmol). After 20 min, H_2O (10 mL) was added and the resulting solution extracted with $CHCl_3$, the organic phase was dried ($MgSO_4$) and concentrated to dryness to lead to **38** as a colourless oil which was used without any purification for the next step. − ^{1}H NMR ($CDCl_3$): δ = 7.66 [s, 1 H, H−C(3)], 7.43−7.25 (5 H, H-*arom*), 7.15 [s, 1 H, H−C(1)], 5.77 [ddd, 1 H, H−C(6)], 5.40 [dd, 1 H, H−C(7)], 4.93 [d, 1 H, H−C(8)], 4.70 and 4.59 (2 H, *AB*, *J* = 12.0 Hz, C*H*$_2$Ph), 4.61 [dd, 1 H, H_a−C(5)], 4.30 [dd, 1 H, H_b−C(5)], $J_{5a,5b}$ = 13.0, $J_{5a,6}$ = 6.0, $J_{5b,6}$ = 9.3, $J_{6,7}$ = 2.0, $J_{7,8}$ = 5.0 Hz.

8-*O*-Benzyl-L-*ribo*-imidazolo-piperidinose (40): A stirred solution of the preceding crude bis(triflate) **38** and $Bu_4NOCOPh$ (1.02 g, 2.80 mmol) in toluene (5 mL) was heated at 75 °C for 15 h. The solvent was evaporated in vacuo and the resulting crude residue **39** dissolved in MeOH (15 mL). To this stirred solution Na_2CO_3 (1 g) was added and the reaction mixture heated under reflux for 6 h. The MeOH solution was concentrated, and the crude residue purified by FC (Et_2O/MeOH/NH_4OH_{conc}, 8:2:0.2) to yield **40** (64 g, 29% overall yield from **37**) as beige crystals, m.p. 179−181 °C (*i*PrOH). − $[\alpha]_D^{20}$ = +10 (*c* = 1.2, MeOH). − ^{1}H NMR and ^{13}C NMR spectra are identical with those of **36** (see above). − HR-MS: $[M]^+$ ion 350.1629 ($C_{21}H_{22}N_2O_3$, calcd. 350.16304).

L-*ribo*-Imidazolo-piperidinose (*ent*-5): A stirred solution of **40** (54 mg, 0.207 mmol) in AcOH (2 mL) was put under H_2 in the presence of 20% $Pd(OH)_2$/C (50 mg), the reaction being monitored by TLC (AcOEt/MeOH, 1:1). After disappearance of **40**, the suspension was filtered through Celite, the solution concentrated to dryness and the residue purified by FC ($CHCl_3$/MeOH/NH_4OH_{conc}, 7:3:0.2) leading thereby to *ent*-**5** (31 mg, 88%) as a colourless powder, m.p.$_{dec.}$ 210 °C. − $[\alpha]_D^{20}$ = +34 (*c* = 0.8, MeOH). − CD: 215.5 (+5.65), 198.5 (−6.10), 190.0 (−5.20). − ^{1}H NMR and ^{13}C NMR spectra are identical to those of **5** (see above). − HR-MS: $[M + H]^+$ ion 171.0770 ($C_7H_{11}N_2O_3$, calcd. 171.0770).

L-Imidazolo-ribose Derivative 42: To a stirred solution of (1*R*)-**11** (400 mg, 0.77 mmol) in anhydrous THF (14 mL), were added at room temp. a catalytic amount of Bu_4NI (10 mg, 0.03 mmol) and NaH (55 mg, 2.3 mmol, 3 equiv.). The mixture was heated to 35 °C for 30 min and became dark red. BnBr (170 mg, 120 μL, 1.00 mmol, 1.3 equiv.) was added and the mixture heated to 40 °C for 15 h until completion (as monitored by TLC: AcOEt/cyclohexane, 3:7), the target molecule **41** being not isolated. After cooling the reaction mixture to room temp., H_2O (1 mL) and 6 N HCl (4 mL) were added and the resulting reaction mixture was heated to 45 °C for 14 h. After cooling, the reaction medium was extracted with CH_2Cl_2 to discard any polar by-products and the aq. phase was neutralised with ammonia. The resulting cloudy solution was extracted with AcOEt, the organic phase dried ($MgSO_4$), filtered and concentrated to dryness to yield a slightly orange oil, which was purified by FC (CH_2Cl_2/MeOH/NH_4OH_{conc}, 98:2:0.5 then 95:5:0.5 and finally 90:10:0.5) to yield **42** (202 mg, 71%) as a white sticky foam. − $[\alpha]_D^{20}$ = −52 (*c* = 0.90, MeOH). − ^{1}H NMR ($CDCl_3$): δ = 7.36 [s, 1 H, H−C(2′)], 7.30−7.05 (10 H, H-*arom*), 6.85 [s, 1 H, H−C(4′)], 4.74 [d, 1 H, H−C(1)], 4.67 and 4.58 (2 H, *AB*, *J* = 10.9 Hz, OC*H*$_2$Ph), 4.49 and 4.33 (2 H, *AB*, *J* = 11.9, OC*H*$_2$Ph), 3.84 [dd, 1 H, H−C(2)], 3.62 [dd, 1 H, H_a−C(4)], 3.51 [dd, 1 H, H_b−C(4)], 3.50 [ddd, 1 H, H−C(3)], $J_{1,2}$ = 3.7, $J_{2,3}$ = 8.2, $J_{4a,4b}$ = 11.3, $J_{3,4a}$ = 3.5, $J_{3,4b}$ = 5.2 Hz. − ^{13}C NMR (CD_3OD): δ = 139.9 and 139.7 (2 C$_s$, *phenyl*), 136.6 [C(2′)], 135.5 [C(2′)], 129.3, 129.2, 129.1, 128.9, 128.6, 128.6 (10 C-*arom*), 122.1 [C(4′)], 83.2 [C(2)], 76.5 [C(1)], 75.6 (O*C*H$_2$Ph), 73.5 [C(3)], 71.6 (O*C*H$_2$Ph), 64.3 [C(4)]. − HR-MS: $[M + H]^+$ ion 369.1812 ($C_{21}H_{25}N_2O_4$, calcd. 369.1814).

L-*ribo*-Imidazolo-piperidinose Derivative 43: To a stirred solution of **42** (180 mg, 0.49 mmol) and Et_3N (190 μL, 130 mg, 1.3 mmol, 2.7 equiv.) in CH_2Cl_2 (4 mL) at − 10 °C were added catalytic amounts of DMAP (ca. 3 mg) and TsCl (235 mg, 1.15 mmol, 2.4 equiv.). The reaction mixture was monitored by TLC (CH_2Cl_2/MeOH/NH_4OH_{conc}, 95:5:0.2), quenched after 14 h with H_2O (2 mL) at −5 °C for 2 h and then extracted with CH_2Cl_2. The organic solution was concentrated to dryness and the residue taken up in 1 M NaOH (4 mL) and in acetone (5 mL). The resulting solution was stirred for 14 h at room temp. and extracted with CH_2Cl_2, the organic phase was dried (MgSO4) and concentrated to dryness, leading to a slightly yellow oil, which was purified by FC (Et_2O, then Et_2O/MeOH/NH_4OH_{conc}, 95:5:0.2 then 90:10:0.2) to yield **43** (131 mg, 75%) as colourless crystals (toluene), m.p. 139 °C. − $[\alpha]_D^{20}$ = +3 (*c* = 1.72, MeOH). − ^{1}H NMR ($CDCl_3$): δ = 7.47 [s, 1 H, H−C(3)], 7.35−7.10 (10 H, H-*arom*), 6.97 [s, 1 H, H−C(1)], 4.71 [d, 1 H, H−C(8)], 4.67 and 4.47 (2 H, *AB*, *J* = 12 Hz, OC*H*$_2$Ph), 4.66 and 4.57 (2 H, *AB*, *J* = 12.1 Hz, OC*H*$_2$Ph), 4.25 [m, 1 H, H−C(6)], 4.19 [dd, 1 H, H_a−C(5)], 3.82 [dd, 1 H, H_b−C(5)], 3.76

[dd, 1 H, H−C(7)], $J_{5a,5b}$ = 12.5, $J_{7,8}$ = 3.3, $J_{6,7}$ = 2.2, $J_{5a,6}$ = 3.7, $J_{5b,6}$ = 3.7 Hz. − ^{13}C NMR (CD_3OD): δ = 139.8 and 139.2 (2 C_s *arom*), 137.2 [C(3)], 129.5, 129.3, 129.1, 129.1, 128.9, 128.7 (10 C-*arom*), 126.8 [C(1)], 76.9 [C(7)], 74.1 (O*C*H_2Ph), 72.8 [C(8)], 72.4 (O*C*H_2Ph), 68.3 [C(6)], 47.0 [C(5)]. − HR-MS: 350.1629 ($C_{21}H_{23}N_2O_3$, calcd. 350.16304).

L-*ribo*-Imidazolo-piperidinose (*ent*-5): A stirred solution of **43** (125 mg, 0.36 mmol) in MeOH (3 mL) was put under H_2 (30 bar) in the presence of 20% $Pd(OH)_2$/C at room temp. After 3 d, the suspension was centrifuged and the catalyst rinsed with MeOH. The organic solution was dried ($MgSO_4$), concentrated to dryness, and the resulting oil purified by FC (Et_2O, then Et_2O/MeOH/NH_4OH_{conc}, 80:20:0.2) to yield *ent*-**5** (29 mg, 47%) as a colourless resin, m.p.$_{dec.}$ 210 °C. − $[\alpha]_D^{20}$ = +34 (*c* = 0.75, MeOH). − CD spectrum as above (positive CE). − ^{1}H and ^{13}C NMR spectra were superimposable with those measured with **5** (see above). − HR-MS: $[M + H]^+$ ion 171.0773 ($C_7H_{11}N_2O_3$, calcd. 171.0770).

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[25] Glycosidases from SIGMA used for the inhibition assays at Mulhouse: α-D-mannosidase EC 3.2.1.24 (Jack beans); α-D-glucosidase EC 3.2.1.20 [(maltose);yeast); β-D-glucosidase EC 3.2.1.21 (almond); α-D-galactosidase 3.2.1.22 (green coffee beans); β-D-galactosidase EC 3.2.1.23 (*Escherichia coli*); β-D-mannosidase EC 3.2.1.25 (snail acetone powder); α-L-fucosidase 3.2.1.51 (bovine kidney).
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