Synthesis of Imidazolo-Piperidinopentoses as Nagstatine Analogues[‡]

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Keywords: Azasugars / Circular dichroism / Enzyme inhibitors / Nitrogen heterocycles

The syntheses of the four imidazolo-piperidino-pentoses **3**–**6**, which belong to the D-series, and of their L-enantiomers, *ent*-**3** to *ent*-**6**, are reported. Ascorbic acid and isoascorbic acid were converted over several steps into the L-*threo*/L-*erythro*- and the D-*erythro*/D-*threo*-configured aldotetroses, respectively, which are the key building blocks for the eight target imidazolo-pentoses cited above. Nucleophilic addition of a metallated imidazole to any one of these four aldotetroses gave the corresponding two diastereomeric adducts, intramolecular cyclisation of which provided the expected bicyclic target molecules, with some protection and deprotection steps being unavoidable prerequisites. The structures and configurations of all eight piperidinoses in Scheme 1 were determined unambiguously, by a combination of ^{1}H/^{13}C NMR spectroscopy, circular dichroism (CD) and $[\alpha]_D$ values, in conjunction with single-crystal X-ray diffraction analyses of the L-*arabino* and D-*lyxo* azasugars *ent*-**3** and **6**. Although lacking the hydroxymethylene group in the C(5) position, the overall structure of these eight stereomers strongly resembles that of the natural product nagstatine (**1**), a potent inhibitor of *N*-acetyl-β-D-glucosaminidase. As a matter of fact, after examination of the inhibitory properties of these imidazolo-piperidinoses against six commonly encountered glycosidases, we observe that the L-*arabino* imidazolo-sugar *ent*-**3** is a potent inhibitor in this series, with K_i = 1 μM both with a β-glucosidase and with a β-galactosidase. The D-*ribo* and D-*xylo* stereomers **4** and **5** proved to be inhibitors of a β-glucosidase of similar magnitude (**4**: K_i = 20 μM; **5:** K_i = 17 μM), the other stereomers being either modest to poor inhibitors, or showing no inhibition at all.

Introduction

The mechanism of polysaccharide hydrolases (i.e., of glycosidases) is thought to produce transition states with pronounced oxocarbonium characters, both with retaining and with inverting glycosidases.[1] Since most natural oligo- and polysaccharides are chair conformer pyranoses, the ensuing oxocarbonium-type transition states appear as flattened, half-chair, conformations.

In 1992, Aoyagi, Aoyama and co-workers published the structure of the natural product nagstatine (**1**), and showed that this imidazole-sugar is a very potent inhibitor of some glucosaminidases, with a K_i value of 4 nM for the bovine kidney enzyme *N*-acetyl-β-D-glucosaminidase, for example.[2,3] The discovery of **1** heralded a new era for investigation of glycosidase-catalysed polysaccharide hydrolysis mechanisms.[4] The imidazole ring forces the six-membered piperidinose ring of **1** to occupy a half-chair conformation. As a result, azasugar **1** would seem to mimic the "activated complex" of the sugar moiety in the enzyme-substrate complex. Therefore, its *stereostructure* should be in agreement with Pauling's prediction of close similarity in the *structure* of the substrate − in its flattened transition state − and the enzyme's active site.[5,6] Once protonated at the most basic nitrogen atom − by "lateral protonation" of the pseudoanomeric N-atom inside the enzyme's active site[4] − **1** gives rise to an imidazolium cation that mimics the postulated oxocarbonium ion-type transition states rather well. The often higher potency displayed by **1** and by similar artificial bicyclic mimics has been attributed to their greater rigidity, the polyhydroxylated heterocyclic moiety being effectively locked in a conformation that favours inhibition.[4,7−9] In fact, several nonnatural azole-piperidinoses have been synthesized,[4,7,8] some of which have shown remarkably strong inhibition properties.[10]

In a preceding publication we reported the synthesis of all eight imidazolo-piperidinose stereomers − such as D-*arabino*-azasugar **2** (three asymmetric centres) − the overall structures of which are similar to those of Scheme 1, except for the basic nitrogen atom, which appears in the 2-position (heterocyclic numbering) in azasugar **2**,[11] while occupying the pseudoanomeric N(1) position in the series at hand. Similarities with nagstatine (**1**) in this latter series are hence rather obvious. For that reason, we surmised that some of the eight stereomers of Scheme 1 might show reasonably potent glycosidase inhibitory properties. As we see below, this assumption proved to be correct, at least for some of the eight target azasugars, as determined by Michaelis−Menten kinetics with six commonly encountered glycosidases. Single-crystal X-ray diffraction experiments with the L-*arabino* and D-*lyxo* stereomers *ent*-**3** and **6**, in combination with ^{1}H and ^{13}C NMR spectra, together

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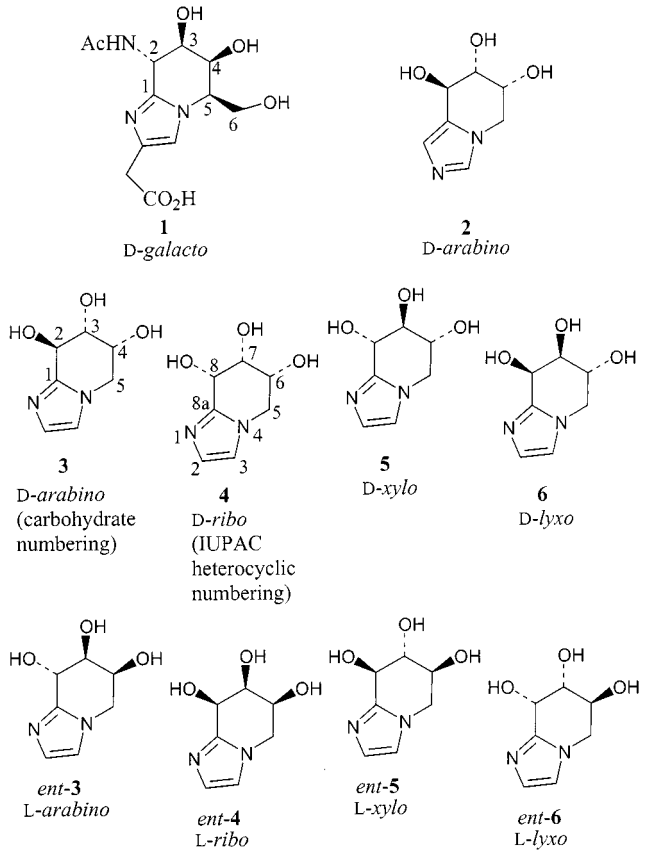
with the chiroptical data of all eight imidazolo-piperidinoses, allowed their absolute configurations to be determined unambiguously. It should be noted in particular that the circular dichroism (CD) spectra were in perfect agreement with the expected mirror-image relationships of the four pairs of opposite enantiomers **3**/*ent*-**3**, **4**/*ent*-**4**, **5**/*ent*-**5** and **6**/*ent*-**6**.



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

Results

Synthesis of Imidazolo-piperidinoses

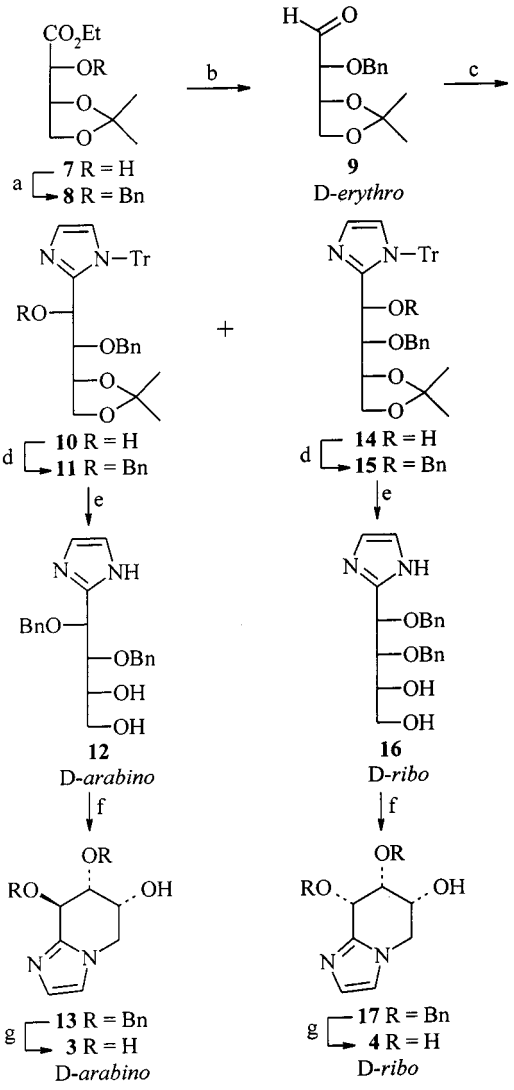
In order to prepare all eight stereomers in Scheme 1, we decided to use a classical approach, starting from D-erythrose **9** and L-erythrose (*ent*-**9**), and from D-threose **20** and L-threose (*ent*-**20**) − all four aldotetroses provided with appropriate protection groups − by nucleophilic addition of an *N*-protected and C(2)-metallated imidazole derivative to the aldehyde double bond, using a known method.[7] We expected that each of the four aldotetrose derivatives would afford a pair of diastereomeric imidazolo-pentoses, the nucleophilic addition process having little chance of being diastereoselective. This did indeed turn out to be the outcome of these nucleophilic coupling reactions, and resulted in the expected eight linear imidazolo stereomers *in toto*. These could be cyclised to the corresponding imidazolo-piperidinose derivatives, deprotection of which produced the target imidazolo-sugars shown in Scheme 1.

The primary starting materials, L-ethyl threonate and D-ethyl erythronate derivatives, were obtained from the easily available and inexpensive ascorbic acid and isoascorbic acid, respectively, according to known methodology based on the oxidative cleavage of the ene-diol double bond of the corresponding monoacetonides (see below). Walden inversions were performed, by which L-ethyl threonate (from ascorbic acid) provided L-ethyl erythronate, and D-ethyl erythronate (from isoascorbic acid) D-ethyl threonate.

Arabinose Series 3 and Ribose Series 4

Retrosynthetic analyses of the D-*arabino* **3** and D-*ribo* **4** target molecules suggested isoascorbic acid (D-*erythro* configuration) in its monoacetonide form as the starting material (see Scheme 2). Oxidative cleavage of the ene-diol double bond of this starting material, followed by esterification of the ensuing carboxylate to the corresponding ethyl D-erythronate **7**, had already been described by Abushanab and co-workers,[12] and Demuynck and co-workers.[13] *O*-Benzylation of **7** (BnBr/Ag_2O/KI/4Å MS/toluene) gave **8** (83%), which was quantitatively reduced (DIBAH/toluene at −78 °C) to aldehyde **9**, a compound that readily condenses with water to afford the hydrated form of the aldehyde. In order to avoid the formation of that (undesired) hydrate, the very dry aldehyde **9** was carefully prepared (see Exp. Sect.) and used directly in the next step without purification. C(2)-Lithiated *N*-trityl-imidazole was added under argon to aldehyde **9**, to give a mixture of adducts **10**, as the minor and less polar diastereomer, and **14** (major and most polar diastereomer). These stereomers could be separated to a large extent by chromatography. O-Benzylation (NaH/BnBr/toluene) of minor adduct **10** gave fully protected derivative **11** in good yield, but with small amounts of impurities. Partial deprotection of **11** in acidic medium (Dowex H^+/EtOH/H_2O) produced pure and crystalline D-*arabino* diol **12** (69%). A similar sequence of reactions, starting from the major and not entirely homogenous adduct **14**, gave dibenzyl ether **15**, and thence pure crystalline D-*ribo* diol **16**. Compound **12** was *N*- and *O*-tosylated (TsCl/NEt_3/DMAP/CH_2Cl_2) to direct the sulfonylation process toward the primary alcohol. The expected *N,O*-ditosyl derivative, without being purified, dissolved slowly in a NaOH/MeOH solution at room temp. for 12 h, and afforded bicyclic compound **13** (45%) in crystalline form. Hydrogenolysis of **13** (H_2/Pd(OH)$_2$/C/AcOH) gave the expected D-*arabino* target molecule **3** (45%) as a crystalline compound (Scheme 2). The chiroptical properties of **3** are shown in Figure 1 (CD spectrum) and in Table 1 ($[\alpha]_D$). A similar sequence of reactions, starting from the linear D-*ribo* derivative **16**, afforded di-*O*-benzyl-D-*ribo*-piperidinose **17**, and then D-*ribo*-piperidinose **4**, the chiroptical data of which are also shown in Figure 1 and in Table 1.

Retrosynthetic analyses of the L-*arabino* and L-*ribo* target enantiomers *ent*-**3** and *ent*-**4** suggested L-*erythro* aldehyde *ent*-**9** as the starting material (see Scheme 3). A multi-step synthesis of this compound had been described by us previously, starting from an L-threonate ethyl ester derivative (from ascorbic acid), followed by a Walden inversion at



Scheme 2. Synthesis of the imidazolo D-*arabino* and D-*ribo* piperidinoses **3** and **4**.
a) BnBr, KI, Ag_2O, MS (4 Å), toluene, reflux; b) toluene, −78 °C, DIBAH; c) 1. *N*-tritylimidazole in THF, *n*BuLi, −5 °C; 2. + **9** in THF at −5 °C, then stirring at 0 °C; 3. H_2O; d) NaH, THF, BnBr, nBu_4NI, 40 °C; e) EtOH/H_2O, Dowex 50WX8, 60 °C; f) 1. CH_2Cl_2, TsCl, NEt_3, DMAP, 0 °C, 24 h; 2. 2 M NaOH/MeOH, room temp., 12 h; g) H_2, $Pd(OH)_2$/C, AcOH

C(2) to give the corresponding ethyl L-erythronate, the *O*-benzyl derivative of which had been quantitatively reduced to *ent*-**9**.[11] Treatment of C(2)-lithiated *N*-trityl-imidazole with anhydrous aldehyde *ent*-**9** gave a mixture of the two expected diastereomeric adducts *ent*-**10** (minor and less polar compound) and *ent*-**14** (more polar and major adduct) which could be separated to a large extent by column chromatography. The chromatographic fraction containing the minor and almost pure L-*arabino* diastereomer *ent*-**10** was *O*-benzylated (NaH/BnBr/nBu_4NI/THF) to produce the homogenous derivative *ent*-**11**. This was deprotected in acidic medium (Dowex H^+/EtOH/H_2O) to give the crystalline L-*arabino* diol *ent*-**12** (83%). A similar reaction sequence, starting from the major and almost pure L-*ribo* adduct *ent*-**14**, provided the homogenous bis-benzyl derivative

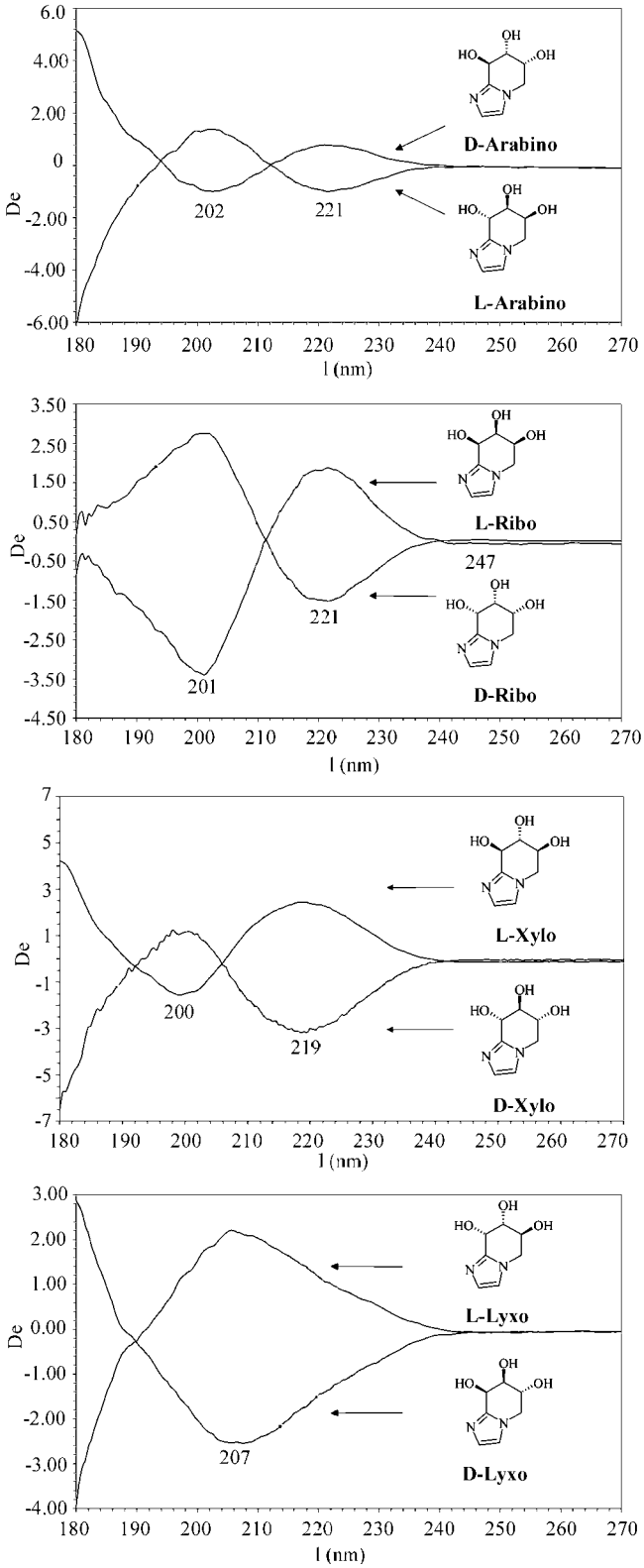


Figure 1. Circular dichroism of the eight imidazolo-piperidinoses

ent-**15**, followed by the crystalline L-*ribo* diol *ent*-**16** (87%). Intramolecular cyclisation of *ent*-**12** to the L-*arabino* piperidinose *ent*-**13** was performed (as above for **13**) by way of the *N,O*-ditosyl intermediate. Hydrogenolysis of *ent*-**13** (H_2/Pd/C/MeOH) gave *ent*-**3** (63%). The absolute configuration

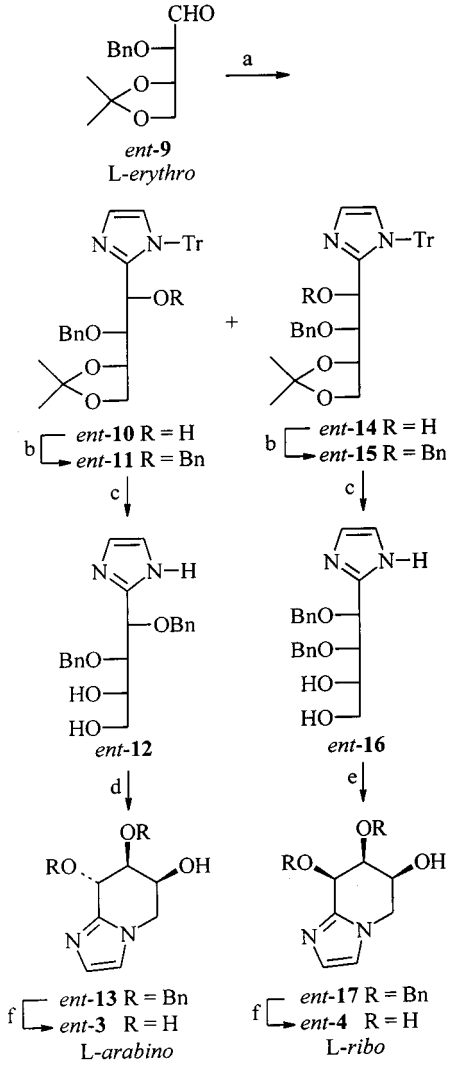
Table 1. Rotatory power data ($[\alpha]_D^{20}$ values) of the eight stereomers of Scheme 1.

D-*arabino* (**3**)	D-*ribo* (**4**)	D-*xylo* (**5**)	D-*lyxo* (**6**)
−23	−32	−56	−42
(c = 1.0, H_2O)	(c = 1.0, H_2O)	(c = 1.0, MeOH)	(c = 1.0, MeOH)
L-*arabino* (*ent*-**3**)	L-*ribo* (*ent*-**4**)	L-*xylo* (*ent*-**5**)	L-*lyxo* (*ent*-**6**)
+28	+32	+55	+42
(c = 1.0, H_2O)	(c = 1.0, H_2O)	(c = 1.0, MeOH)	(c = 1.0, MeOH)

of *ent*-**3** could be determined from its chiroptical properties (CD spectrum: Figure 1; optical rotatory power: Table 1) and by a single-crystal X-ray diffraction experiment (Figure 3). Comparison of chiroptical data clearly proved the mirror image relationship between **3** and *ent*-**3**. A similar reaction sequence with *ent*-**16** gave piperidinose derivative *ent*-**17**, which was deprotected to the L-*ribo* target molecule *ent*-**4**. This proved to be the enantiomer of the D-*ribo* compound **4** (Figure 1 and Table 1).

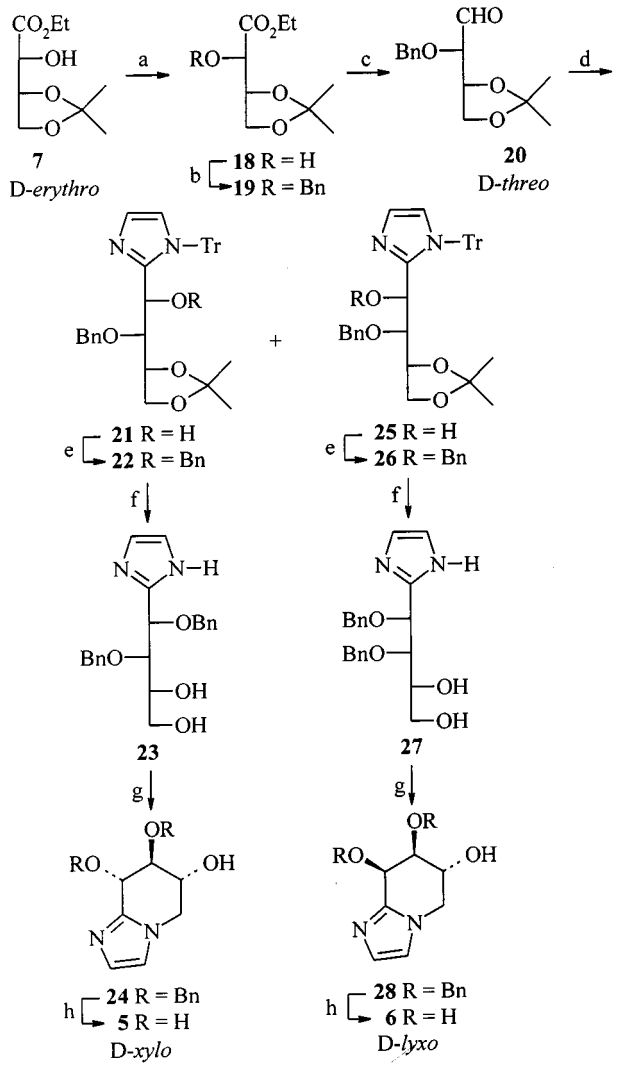
Xylose Series 5 and Lyxose Series 6

Retrosynthetic analysis of the D-*xylo* and D-*lyxo* target molecules **5** and **6** suggested D-*threo* aldehyde **20** as the starting material (see Scheme 4). This could be obtained from the known D-erythronate ethyl ester **7** (from isoascorbic acid)[12,13] by Walden inversion at C(2) and semireduction of the ensuing D-threonate ester **19** to the aldehyde **20** as follows. Sequential treatment of **7** with triflic anhydride and pyridine, followed by an S_N2 reaction between the corresponding triflate and a nitrite salt ($NaNO_2/CH_2Cl_2/H_2O$), produced the D-*threo* diastereomer **18** (74% from **7**). O-Benzylation ($BnBr/Ag_2O/KI$/toluene) gave **19** (77%), which was reduced (DIBAH/toluene; −78 °C) to the corresponding D-threose derivative **20** (85%). Treatment of C(2)-lithiated *N*-trityl-imidazole with anhydrous aldehyde **20** under argon atmosphere produced the diastereomeric adducts **21** (less polar and minor adduct) and **25** (more polar and major adduct), which were separated to a large extent by column chromatography, accompanied by some unchanged *N*-trityl-imidazole. The minor D-*xylo* isomer **21** was *O*-benzylated (NaH/Bu_4NI/BnBr/toluene) to give **22**, which was at once deprotected with acid (4 N HCl) to yield the key intermediate **23** as a crystalline compound. A similar sequence of reactions, starting from the major diastereomer **25**, enabled the linear D-*lyxo* diol **27** to be obtained as a crystalline compound, by way of intermediate **26**. Intramolecular cyclisations of the linear imidazolosugar derivatives **23** and **27** were performed as follows. Compound **23** was *N*- and *O*-tosylated ($TsCl/Et_3N/CH_2Cl_2$ in the presence of Bu_2SnO as a catalyst) in order to direct the sulfonylation process toward the primary alcohol. The expected *N*,*O*-ditosyl derivative, without being purified, dissolved slowly in 2 N NaOH/MeOH and afforded piperidinose derivative **24** (87%). A similar reaction sequence with the linear D-*lyxo* derivative **27** gave **28** (90%). Both **24** and **28** were deprotected ($H_2/Pd(OH)_2/C$), to afford the D-*xylo* and D-*lyxo* stereomers **5** and **6**, respectively. The stereostructure and absolute configuration of **6** were determined by a single-crystal X-ray diffraction experiment (Figure 2).



Scheme 3. Synthesis of the imidazolo L-*arabino* and L-*ribo* piperidinoses *ent*-**3** and *ent*-**4**. a) 1. *N*-Tritylimidazole in THF, *n*BuLi, −5 °C; 2. + *ent*-**9** in THF at −5 °C, then stirring at 0 °C; 3. H_2O; b) NaH, THF, BnBr, nBu_4NI, 40 °C; c) EtOH/H_2O, Dowex 50 WX8, 60 °C; d) 1. TsCl, NEt_3, DMAP, CH_2Cl_2, 0 °C; 2. 2 M NaOH/MeOH, room temp.; e) 1. Bu_2SnO, NEt_3,TsCl, CH_2Cl_2; 2. 2 M NaOH/MeOH, room temp.; f) H_2, Pd/C, 30 bar, MeOH.

Retrosynthetic analyses of the L-*xylo* and L-*lyxo* target molecules *ent*-**5** and *ent*-**6** suggested L-*threo* aldehyde *ent*-**20** (ex vitamin C) as the starting material (see Scheme 5). The preparation of *ent*-**20** had already been described by us in



Scheme 4. Synthesis of the imidazolo D-*xylo* and D-*lyxo* piperidinoses **5** and **6**. a) 1) Tf_2O, CH_2Cl_2, pyridine, −10 °C to room temp., 2. $NaNO_2$, DMF; b) Ag_2O, KI, MS 4A, BnBr toluene, reflux; c) DIBAH, toluene, −78 °C; d) *N*-tritylimidazole in THF, *n*BuLi, −5 °C, 2. + **20** in THF at −5 °C then stirring at 0 °C; e) NaH, nBu_4NI, THF, BnBr, 40 °C; f) 4 N HCl, reflux; g) 1. NEt_3, Bu_2SnO, CH_2Cl_2, TsCl, 2. 2 N NaOH/MeOH; h) H_2, $Pd(OH)_2/C$, EtOH/AcOH

a previous publication.[11] Anhydrous aldehyde *ent*-**20** was treated with C(2)-lithiated *N*-trityl-imidazole, under reaction conditions similar to those used for the coupling reactions described above. This resulted in a mixture of the two expected diastereomeric adducts *ent*-**21** (minor and less polar compound), and *ent*-**25** (major and more polar compound) which were separated to a large extent by chromatography. O-Benzylation of *ent*-**21** and *ent*-**25** produced the fully protected compounds *ent*-**22** and *ent*-**26**, respectively. Partial deprotection of these compounds in acidic media gave the corresponding crystalline diols *ent*-**23** and *ent*-**27**. Intramolecular cyclisation of the respective *N*,*O*-ditosyl derivatives of these two compounds in NaOH/MeOH solution gave the expected imidazolo-piperidinoses *ent*-**24** and *ent*-**28**, which were deprotected by hydrogenolysis to give target molecules L-*xylo* *ent*-**5** and L-*lyxo* *ent*-**6**, respectively

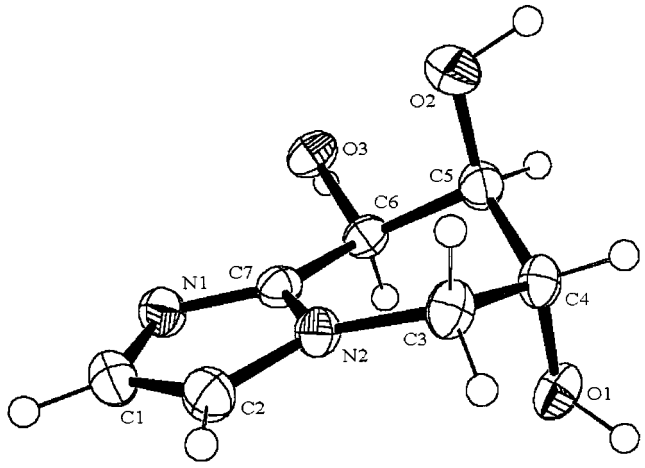


Figure 2. Molecular structure of **6;** selected bond lengths [Å), bond angles [°] and torsion angles [°]: N(1)−C(1) 1.385(2), N(1)−C(7) 1.325(2), C(1)−C(2) 1.353(2), C(2)−N(2) 1.375(2), N(2)−C(3) 1.464(2), N(2)−C(7) 1.356(2), C(3)−C(4) 1.521(2), C(4)−O(1) 1.426(2), C(4)−C(5) 1.534(2), C(5)−O(2) 1.421(2), C(5)−C(6) 1.532(2), C(6)−O(3) 1.425(2), C(6)−C(7) 1.500(2); C(1)−N(1)−C(7), 105.2(1), N(1)−C(1)−C(2) 110.3(1), C(1)−C(2)−N(2) 106.0(1), C(2)−N(2)−C(3) 127.3(1), C(2)−N(2)−C(7) 107.4(1), C(3)−N(2)−C(7) 125.0(1), N(2)−C(3)−C(4) 110.2(1), C(3)−C(4)−C(5) 110.6(1), C(4)−C(5)−C(6) 109.5(1), C(5)−C(6)−C(7) 110.7(1), N(1)−C(7)−N(2) 111.1(1), N(1)−C(7)−C(6) 127.0(1). N(2)−C(7)−C(6) 121.3(1); N(1)−C(7)−N(2)−C(3) −174.5, C(2)−N(2)−C(7)−C(6) −172.3, C(6)−C(7)−N(2)−C(3) 13.6, C(1)−N(1)−C(7)−N(2) 0.3, N(2)−C(3)−C(4)−C(5) 48.9, C(6)−C(5)−C(4)−C(3) −63.7, C(7)−C(6)−C(5)−C(4) 49.5, C(7)−N(2)−C(3)−C(4) −24.9, N(1)−C(1)−C(2)−N(2) 0.0, C(7)−N(1)−C(1)−C(2) −0.2, C(7)−N(2)−C(2)−C(1) 0.2

(Scheme 5). The chiroptical properties of these imidazolo-piperidinoses proved their mirror image relationship with respect to the D-*xylo* **5** and D-*lyxo* **6** stereomers, respectively (Table 1 and Figure 1).

Spectral Properties and Structure Analyses

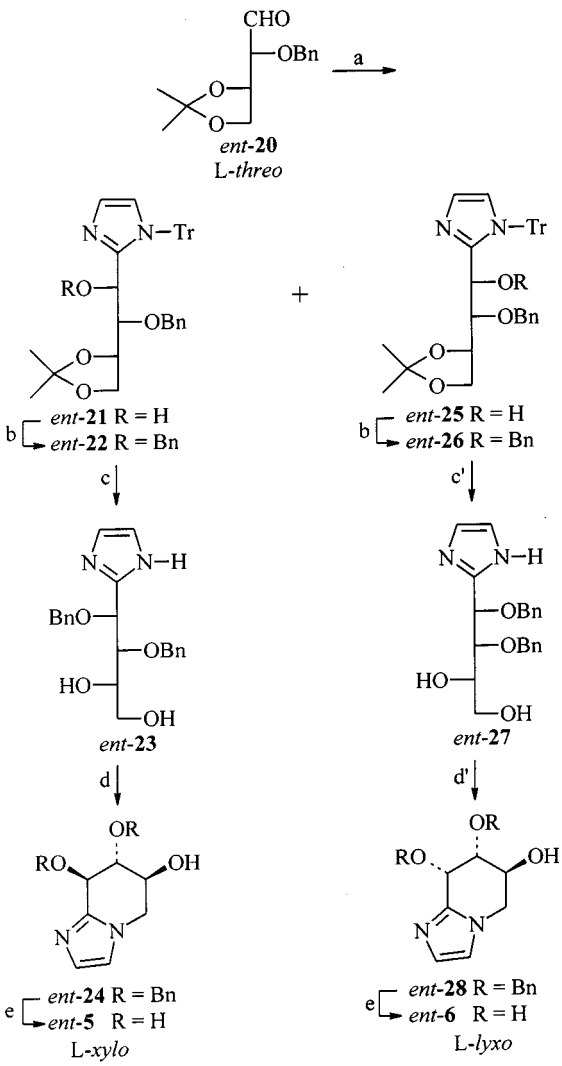
The structures and absolute configurations of imidazolo-sugars **3** to **6** and *ent*-**3** to *ent*-**6** could be assigned without any ambiguity, thanks to a combination of $^1H/^{13}C$ NMR spectroscopy and circular dichroism (CD) and rotatory power data, in conjunction with the single-crystal X-ray diffraction analyses of the L-*arabino* and D-*lyxo* imidazolosugars *ent*-**3** and **6**, as shown below.

X-ray diffraction analysis of *ent*-**3** clearly demonstrated its absolute L-*arabino* configuration, as shown in Figure 3. Let us now consider a "configuration retro-analysis" for the synthetic sequence of that azasugar (Scheme 3). Since *ent*-**3** has the L-*arabino* configuration, it follows that:

i) its precursor, minor adduct *ent*-**10**, exists in the same L-*arabino* configuration,

ii) as a consequence, the major adduct *ent*-**14** has the diastereomeric L-*ribo* configuration, and so does the corresponding target azasugar *ent*-**4**, as shown in Scheme 3,

iii) the Walden inversion we had described previously with the L-*threo* ester derivative obtained from ascorbic acid[11] ultimately affords the L-*erythro* intermediate *ent*-**9**, which is the immediate precursor of both *ent*-**10** and *ent*-**14**,



Scheme 5. Synthesis of the imidazolo L-*xylo* and L-*lyxo* piperidinoses *ent*-**5** and *ent*-**6**. a) *N*-tritylimidazole in THF, nBuLi, −5 °C, 2. + *ent*-**20** in THF at −5 °C, then stirring at 0 °C; b) NaH, nBu$_4$NI, THF, BnBr, 40 °C; c) 2 N HCl, reflux; c′) EtOH/H$_2$O, Dowex H+, 60 °C; d) 1. CH_2Cl_2, DMAP, NEt_3, TsCl, 0 °C, 2. 2 N NaOH/MeOH; d′) 1. NEt_3, Bu_2SnO, CH_2Cl_2, TsCl, 2. 2 N NaOH/MeOH; e) H_2, Pd/C, MeOH, 20−30 bar.

iv) since the ^{1}H and ^{13}C NMR spectra of azasugar **3** are identical to and superimposable on those of L-*arabino ent*-**3**, and since the CD spectra of these two stereomers are mirror images (Figure 1), it may be concluded that **3** has the D-*arabino* configuration,

v) since the ^{1}H and ^{13}C NMR spectra of azasugar **4** are identical to and superimposable on those of L-*ribo ent*-**4**, and since the CD spectra of these two stereomers are mirror images (Figure 1), it may be concluded that **4** has the D-*ribo* configuration.

That is to say that the X-ray diffraction analysis of L-*arabino* stereomer *ent*-**3**, taken in conjunction with the ^{1}H/^{13}C NMR and CD spectra of **3**, *ent*-**4** and **4**, permits the D-*arabino*, L-*ribo* and D-*ribo* configurations, respectively, to be assigned to these three stereomers. When considering the absolute 3D structure of *ent*-**3**, it is worth noting that the asymmetric centre C(2) has been created, and asymmetric

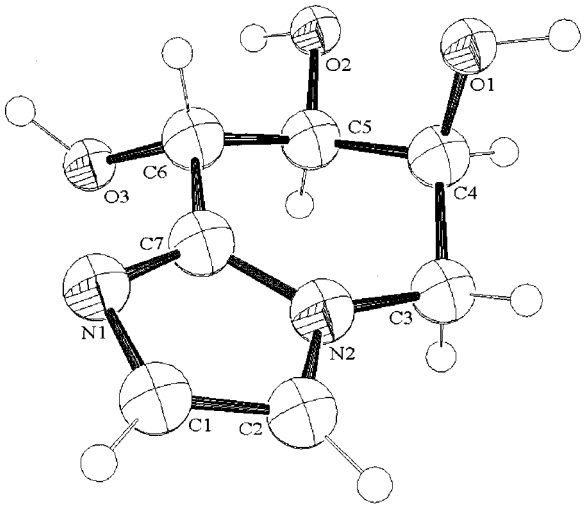


Figure 3. Molecular structure of *ent*-**3**; selected bond lengths [Å], bond angles[°] and torsion angles[°]: N(1)−C(1) 1.384(2), N(1)−C(7) 1.325(1), C(1)−C(2) 1.359(2), C(2)−N(2) 1.377(1), N(2)−C(3) 1.465(1), N(2)−C(7) 1.358(1), C(3)−C(4) 1.524(1), C(4)−C(5) 1.521(1), C(5)−O(2) 1.419(1), C(5)−C(6) 1.528(1), C(6)−C(7) 1.500(1); C(1)−N(1)−C(7) 105.43(9), N(1)−C(1)−C(2) 110.3(1), C(1)−C(2)−N(2) 105.7(1), C(2)−N(2)−C(3) 127.11(9), C(2)−N(2)−C(7) 107.64(9), C(3)−N(2)−C(7) 125.18(9), N(2)−C(3)−C(4) 110.05(8), C(3)−C(4)−C(5) 109.78(8), C(4)−C(5)−C(6) 113.34(8), C(5)−C(6)−C(7) 111.51(8), N(1)−C(7)−N(2) 110.99(9), N(1)−C(7)−C(6) 126.74(8), N(2)−C(7)−C(6) 122.23(8); N(1)−C(7)−N(2)−C(3) 177.4, C(2)−N(2)−C(7)−C(6) 178.1, C(6)−C(7)−N(2)−C(3) −4.8, C(1)−N(1)−C(7)−N(2) −0.5, N(2)−C(3)−C(4)−C(5) 50.5, C(6)−C(5)−C(4)−C(3) 60.5, C(7)−C(6)−C(5)−C(4) −39.2, C(7)−N(2)−C(3)−C(4) 24.7, N(1)−C(1)−C(2)−N(2)−0.3, C(7)−N(1)−C(1)−C(2) 0.5, C(7)−N(2)−C(2)−C(1) 0.0

centre C(3) modified, in the laboratory: i.e. in vitro. Only asymmetric centre C(4) has been left untouched and occurs in target molecule *ent*-**3** as created in vivo in nature (in vitamin C).

If we consider the X-ray diffraction analysis of stereomer **6,** which is in perfect agreement with its configuration as being D-*lyxo* (Figure 2), use of this in conjunction with the ^{1}H/^{13}C NMR and CD spectra (Figure 1) of all four stereomers **6**, *ent*-**6**, **5** and *ent*-**5** unambiguously gives their assignments as D-*lyxo*, L-*lyxo*, D-*xylo* and L-*xylo*, respectively. The arguments are similar to those outlined above for the D- and L-*arabino* and D- and L-*ribo* stereomers.

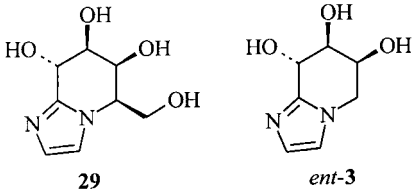
The chiroptical properties proved to be of great interest. The rotatory power data − in terms both of magnitude and sign − agreed rather well with the mirror image relationships between opposite enantiomers (Table 1). It is worth noting that all the D-configured imidazolosugars were levorotatory, and the L-stereomers dextrorotatory ($[\alpha]_D^{20}$ values). Furthermore, the magnitudes of the $[\alpha]_D$ values of opposite enantiomers were identical, or at least very similar. Last but not least, the circular dichroism (CD) spectra of all eight stereomers are definite testimony to the mirror image relationship between the pairs of opposite enantiomers **3**/*ent*-**3**, **4**/*ent*-**4**, **5**/*ent*-**5**, and **6**/*ent*-**6** (Figure 1).

Enzymatic Assays

The eight imidazolo-piperidinopentoses from Scheme 1 were evaluated as potential inhibitors of six commercially

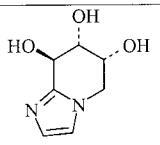
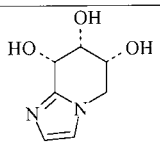
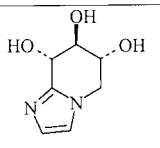
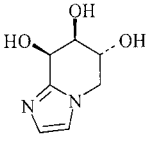
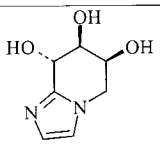
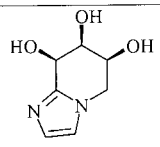
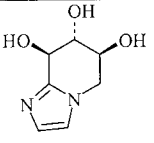
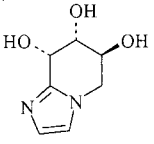
available glycosidases. A number of these stereomers showed some interesting inhibitory and selectivity properties, as reported in Table 2.

The D-*arabino* derivative **3** was inactive towards the pool of enzymes evaluated, whereas its L-*arabino* enantiomer *ent*-**3** was quite potent with respect to β-glucosidase from almonds and β-galactosidase from *E. coli*, with K_i values of 1μM in both cases. These are the most potent inhibitory effects observed for the whole series. This is most probably due to the chiral 3D structure of *ent*-**3**, since i) the three asymmetric carbon atoms C(2), C(3), and C(4) in *ent*-**3** (carbohydrate numbering, see: Scheme 1) have the same absolute configurations as the corresponding carbon atoms in β-D-*galacto*-pyranose; ii) the carbon atoms C(2) and C(3) of *ent*-**3** have the same absolute configurations as the corresponding carbon atoms in β-D-*gluco*-pyranose. It should be noted that manmade D-*galacto* imidazolo-piperidinose **29** − the (D-*galacto*) homologue of (L-*arabino*) *ent*-**3** (Scheme 6) − is the most powerful β-D-galactosidase inhibitor known so far (K_i ca. 2 nM), since Tatsuta and coworkers demonstrated that it was ca. five hundred times



Scheme 6. D-*galacto*-imidazolo-piperidinose **29** and L-*arabino*-imidazolo-piperidinose *ent*-**3**

Table 2. Inhibition constants (K_i) in μM measured at 22 °C. NI = no inhibition at [*I*] = 1 mM. ([*S*] = K_M)

	 D-*arabino* **3**	 D-*ribo* **4**	 D-*xylo* **5**	 D-*lyxo* **6**
α-D-Glucosidase Baker's Yeast EC 3.2.1.20	NI	NI	NI	K_i = 80 μM
β-D-Glucosidase Almonds EC 3.2.1.21	NI	K_i = 20 μM	K_i = 17 μM	NI
α-D-Galactosidase Green Coffee Beans EC 3.2.1.22	NI	NI	NI	NI
β-D-Galactosidase (VI) *Escherichia coli* EC 3.2.1.23	NI	NI	NI	K_i = 65 μM
α-D-Mannosidase Jack beans EC 3.2.1.24	NI	NI	NI	K_i = 360 μM
β-D-Mannosidase Snail Acetone Powder EC 3.2.1.25	NI	NI	NI	NI
	 L-*arabino ent*-**3**	 L-*ribo ent*-**4**	 L-*xylo ent*-**5**	 L-*lyxo ent*-**6**
α-D-Glucosidase Baker's Yeast EC 3.2.1.20	NI	NI	NI	NI
β-D-Glucosidase Almonds EC 3.2.1.21	K_i = 1 μM	NI	NI	NI
α-D-Galactosidase Green Coffee Beans EC 3.2.1.22	NI	NI	NI	NI
β-D-Galactosidase (VI) *Escherichia coli* EC 3.2.1.23	K_i = 1 μM	NI	NI	NI
α-D-Mannosidase Jack beans EC 3.2.1.24	NI	K_i = 285 μM	K_i = 280 μM	NI
β-D-Mannosidase Snail Acetone Powder EC 3.2.1.25	NI	NI	NI	NI

more active than *ent*-**3** with the same β-D-galactosidase (from *E. coli*).[7] Comparison of the K_i values of *ent*-**3** and **29** clearly shows that the CH_2OH "handle" is of great importance for strong docking of an imidazolo-piperidinose in the active site of the corresponding enzyme.

The D-*xylo* stereomer **5** is a good example of configurational fit with respect to a particular glycosidase (almond β-glucosidase), with a K_i value of 17 μM. Indeed, in terms of absolute configuration, the three asymmetric centres C(2), C(4) and C(5) in **5** are identical to those in D-*gluco*-pyranose. The L-*xylo* enantiomer *ent*-**5** was a weak inhibitor (K_i = 280 μM) of α-D-mannosidase from Jack beans, nevertheless showing an interesting selectivity for this particular enzyme.

The D-*ribo* stereomer **4** proved to be as potent (K_i = 20 μM) as **5** with the almond β-glucosidase. To interpret this result, it may be argued that C(2) and C(4) of **4** have the same absolute configurations as the corresponding carbon atoms in β-D-*gluco*-pyranose. The L-*ribo* stereomer *ent*-**4** only weakly inhibited the α-mannosidase of Jack beans (K_i = 285 μM). Nevertheless, *ent*-**4** is selective for this particular hydrolytic enzyme. Once again we note that C(2) and C(3) of *ent*-**4** have the same absolute configurations as the corresponding carbon atoms in α-D-*manno*-pyranose.

Finally, the D-*lyxo* stereomer **6** was shown to have moderate inhibitory effects on α-glucosidase from bakers' yeast (K_i = 80 μM) and β-galactosidase from *E. coli* (K_i = 65 μM), again with some 3D complementarities. If configurational complementarity were to be operative throughout the whole series, **6** would be expected to be an inhibitor of α- or β-mannosidase. This is indeed observed but only to a moderate extent, since **6** is an (albeit rather poor) inhibitor of α-D-mannosidase of Jack beans. As for L-*lyxo* stereomer *ent*-**6**, it had no significant effect at a concentration of 1 mM on any of the enzymes studied.

In a preceding publication we described the syntheses and enzymatic assays of all eight imidazolo-piperidinose stereomers, of which D-*arabino* compound **2** in Scheme 1 is representative.[11] Note that the basic nitrogen atom occupies a different position in these compounds, all other structural parameters being identical. When comparing the inhibition properties of azasugars **3**−**6** and *ent*-**3**−*ent*-**6**, with those previously described for their type **2** N-positional isomers, several characteristic differences are evident:

i) the half-chair inhibiting imidazolo-sugars described here are configurationally selective and seem to be true transition state analogue inhibitors of glycosidases (Table 2), whereas active type **2** imidazolo-sugars as a rule inhibit quite different glycosidases,[11]

ii) the active azasugars described here inhibit β-glycosidases to a greater extent than they inhibit α-glycosidases, whereas active type **2** azasugars as a rule inhibit α-glycosidases, albeit rather poorly,

iii) the pseudoanomeric N(1) atom appears to represent a key factor in the − most probably lateral[4] − binding of the inhibiting imidazolo-sugars described here.

Experimental Section

General: − Flash chromatography (FC): silica gel (*Merck 60*; 230−400 mesh). − TLC: aluminium sheets precoated with silica gel (*Merck 60 F_{254}*); spots were viewed by UV or by heating with a thermogun after spraying with a solution of $KMnO_4$ (20 g) and Na_2CO_3 (40 g) in H_2O (1 L) or a solution of phosphomolybdic acid (5% in 96% EtOH). − M.p.: Kofler hot-bench or Mettler FP-51 apparatus; corrected. − 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 atmosphere on a Jobin Yvon CD6 Dichrographe (Δε values). − ^1H and ^{13}C NMR spectra: 250 MHz and 400 MHz, and 62.9 and 100.6 MHz, respectively; Bruker ACF 250 and Bruker DSX 400 spectrometers at 300 K. Internal references for ^1H NMR: $Si(Me)_4$, $CDCl_3$ (δ = 7.26), CD_3OD (δ = 3.30), dioxane (δ = 3.75) 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. − Microanalyses were carried out by the Service Central de Microanalyses of the CNRS, F-69390 Vernaison or by the Institut de Chimie des Substances Naturelles du CNRS, F-91198 Gif-sur-Yvette. MeOH−NH_3 stands for a solution of pure MeOH saturated with NH_3 (gas) at room temp.

Enzymatic Assays

Glycosidases [α-mannosidase (EC 3.2.1.24) from jack beans, β-mannosidase (EC 3.2.1.25) from snails, α-glucosidase (EC 3.2.1.20) from bakers' yeast, β-glucosidase (EC 3.2.1.21) from almonds, α-galactosidase (EC 3.2.1.22) from green coffee beans, β-galactosidase from *E. coli* (EC 3.2.1.23)] and their corresponding substrates were purchased from Sigma Co.

Spectrophotometric assays were performed at the optimum pH for each enzyme[14] with *p*-nitrophenyl-α-D-mannopyranoside as a substrate for α-mannosidase (K_m = 2 mM, pH = 4.5), *p*-nitrophenyl-β-D-mannopyranoside for β-mannosidase (K_m= 1.3 mM, pH = 4.0), *p*-nitrophenyl-α-D-glucopyranoside for α-glucosidase (K_m = 0.3 mM, pH = 7.0), *p*-nitrophenyl-β-D-glucopyranoside for β-glucosidase (K_m = 2 mM, pH = 5.0), *p*-nitrophenyl-β-D-galactoside (K_m = 0.3 M, pH = 7.0) and *p*-nitrophenyl-α-D-galactoside (K_m = 0.3 mM, pH = 6.5) as substrates for the corresponding galactosidases. The release of *p*-nitrophenol was measured continuously at 405 nm to determine initial velocities. All kinetics studies were performed at 25 °C and the reaction was started by addition of enzyme in a 1 mL assay medium (acetate buffer 50 mM, or phosphate buffer 20 mM according to the desired pH value) using substrate concentrations around the K_m value of each enzyme. The K_i values were determined for the most potent inhibitors, by use of the Dixon graphical procedure.[15,16]

Ethyl D-Erythronate Derivative 8: A mixture of freshly prepared anhydrous Ag_2O (10.21 g; 44.1 mmol), powdered molecular sieves (4Å, 3.7 g), and KI (570 mg) was heated under vacuum at 300 °C. After the mixture had cooled to room temp., a solution of **7** (6.00 g; 29.4 mmol)[12,13] in anhydrous toluene (230 mL) and BnBr (3.80 mL, 31.8 mmol) were added. The resulting suspension was heated under reflux for 2 h. After cooling to room temp., the suspension was filtered, the resulting solution was evaporated to dryness under vacuum, and the residue was purified by chromatography (AcOEt/cyclohexane, 2:8) to yield **8** (7.14 g, 83%) as a slightly yellow syrup. − $[\alpha]_D^{20}$ = +37 (*c* = 2, $CHCl_3$). − ^1H NMR and ^{13}C NMR spectra were identical to those we had reported previously for the *ent*-**8** enantiomer.[11] − $C_{16}H_{22}O_5$ (294.34): calcd. C 65.29, H 7.53; found C 65.3, H 7.5.

D-Erythrose Derivative 9: A solution of DIBAH (1.6 M, 8.5 mL, 12.7 mmol; 1.5 equiv.) in toluene was added dropwise at −78 °C to a stirred solution of **8** (2.50 g, 8.49 mmol) in anhydrous toluene (55 mL). The reaction was complete after 15 min at −78 °C, excess DIBAH was slowly neutralised with MeOH (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), resulting in the precipitation of the aluminium salts, which were filtered and washed with AcOEt (ca. 70 mL). The 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 kept under vacuum over P_2O_5 in a dessicator for 20 h to yield **9** as an oil (2.07 g, 97%). − The ^{1}H NMR spectrum was superimposable on the one that we had reported in a preceding publication for the L-erythrose derivative *ent*-**9**.[11]

Coupling Reaction Between a Lithio-imidazole and D-Erythrose Derivative 9: (Scheme 2). A solution of BuLi in hexane (1.6 M, 10.8 mL, 17.2 mmol) was added dropwise under argon atmosphere at −5 °C over a period of 15 min to a stirred solution of *N*-trityl-imidazole (4.71 g, 15.8 mmol) in anhydrous THF (180 mL). A solution of aldehyde **9** (3.58 g, 14.3 mmol) in THF (14 mL) was added dropwise to this stirred mixture, which was further stirred for 2 h at 0 °C. The reaction was quenched with ice, the mixture was concentrated in vacuo and dissolved in AcOEt (160 mL), and the aqueous phase was extracted several times with AcOEt. The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvents were evaporated to dryness. The resulting crude oil (yellow) was separated by careful column chromatography (AcOEt/cyclohexane, 4:6 then 1:1), which produced two fractions, the first one containing mostly the minor adduct **10** (1.90 g), the second one containing mainly the major adduct **14** (3.66 g).

Compound 10: ^{1}H NMR ($CDCl_3$): δ = 1.22 (s, 3 H, CH_3 isoprop.), 1.28 (s, 3 H, CH_3 isoprop.), 2.30 (dd, 1 H, 2-H), 3.39 (ddd, 1 H, 3-H), 3.41 (d, 1 H, OH), 3.66 (t, 1 H, 4-H_b), 3.73 (dd, 1 H, 4-H_a), 4.13 (dd, 1 H, 1-H), 4.26 and 4.34 (AB, J = 10.7, 2 H, OCH_2Ph), 6.82 (d, 1 H, 4′-H or 5′-H), 7.07 (d, 1 H, 4′-H or 5′-H), 7.11 to 7.36 (m, 20 H, CH phenyl); $J_{1,OH}$ = 10.4, $J_{1,2}$ = 1.3, $J_{2,3}$ = 3.3, $J_{3,4a}$ = 6.6, $J_{3,4b}$ = 8.1, $J_{4a,4b}$ = 8.1, $J_{4',5'}$ = 1.3.

Compound 14: ^{1}H NMR ($CDCl_3$): δ = 0.86 (d, 1 H, OH), 1.26 (s, 3 H, CH_3 isoprop.), 1.36 (s, 3 H, CH_3 isoprop.), 3.61 (d, 2 H, 4-H_a and 4-H_b), 3.96 (dd, 1 H, 1-H), 4.11 (dd, 1 H, 2-H), 4.47 (td, 1 H, 3-H), 4.44 and 4.68 (AB, J = 10.3, 2 H, OCH_2Ph), 6.76 (d, 1 H, 4′-H or 5′-H), 7.05 (d, 1 H, 4′-H or 5′-H), 7.08 to 7.28 (m, 20 H, CH phenyl); $J_{1,OH}$ = 4.5, $J_{1,2}$ = 8.1, $J_{2,3}$ = 2.2, $J_{3,4}$ = 7.3, $J_{4',5'}$ = 1.3.

Imidazolo-D-*arabino* Derivative 11: Bu_4NI (catalytic amount, ca. 15 mg) and NaH (50% in oil) in excess (480 mg, ca 10 mmol) were added at room temp under argon atmosphere to a stirred solution of the minor adduct **10** (1.90 g, ca 3.4 mmol) in anhydrous THF (35 mL). Once hydrogen formation had ceased, BnBr (485 μL, 4.10 mmol) was added, and the mixture was heated at 40 °C for 12 h. MeOH (2 mL) was then added and the resulting clear solution was evaporated to dryness in vacuum. The residue was dissolved in AcOEt (60 mL), and the solution was washed with water and brine, dried ($MgSO_4$) and filtered, and the solvents were evaporated off. The residue was purified by chromatography (AcOEt/cyclohexane, 2:8) and compound **11** (1.79 g, overall yield from the aldehyde **9**: 19%) was obtained pure. − ^{1}H NMR ($CDCl_3$): δ = 1.21 (s, 3 H,CH_3 isoprop.), 1.27 (s, 3 H, CH_3 isoprop.), 3.56 (dd, 1 H, 2-H), 3.61 (dd, 1 H, 4-H_b), 3.66 (dd, 1 H, 4-H_a), 3.80 (td, 1 H, 3-H), 3.93 and 4.13 (AB, J = 11.6, 2 H, OCH_2Ph), 4.06 (d, 1 H, 1-H), 4.43 and 4.48 (AB, J = 11.5, 2 H, OCH_2Ph), 6.91 (d, 1 H, 4′-H or 5′-H), 7.12 (d, 1 H, 4′-H or 5′-H), 7.10 to 7.30 (m, 25 H, CH phenyl); $J_{1,2}$ = 5.2, $J_{2,3}$ = 3.6, $J_{3,4a}$ = 6.7, $J_{3,4b}$ = 6.9, $J_{4a,4b}$ = 8.0, $J_{4',5'}$ = 1.4.

Imidazole-D-*ribo* Derivative 15: The same procedure as above was applied, starting from the major adduct **14** (3.66 g, ca 6.5 mmol) in THF (65 mL), Bu_4NI (ca. 30 mg), NaH (920 mg, ca 19 mmol), and BnBr (940 μL, 7.9 mmol). Workup as above, followed by chromatography, gave **15** (4.44 g, overall yield from the aldehyde **9**: ca. 48%). Compound **15** was used without any further purification in the deprotection step. − ^{1}H NMR ($CDCl_3$): δ = 1.32 (s, 3 H, CH_3 isoprop.), 1.36 (s, 3 H, CH_3 isoprop.), 3.77 (dd, 1 H, 2-H), 3.81 (t, 1 H, 4-H_b), 3.91 (dd, 1 H, 4-H_a), 3.95 and 4.31 (AB, J = 11.7, OCH_2Ph), 4.01 and 4.56 (AB, J = 11.0, OCH_2Ph), 4.25 (d, 1 H, 1-H), 5.12 (td, 1 H, 3-H), 6.80 (d, 1 H, 4′-H or 5′-H), 7.10 to 7.34 (m, 26 H, CH phenyl, and 4′-H or 5′-H); $J_{1,2}$ = 4.8, $J_{2,3}$ = 1.4, $J_{3,4a}$ = 7.0, $J_{3,4b}$ = 7.9, $J_{4a,4b}$ = 7.9, $J_{4',5'}$ = 1.3.

Imidazolo-D-*arabino* Derivative 12: A stirred solution of **11** (1.79 g, 2.76 mmol) in EtOH (20 mL) and water (20 mL), containing some Dowex® (50WX8) beads, was heated to 60 °C for 3 h. After filtration, the resin was washed several times with ether and extracted, with the aid of ultrasound, with MeOH saturated with ammonia (3 × 20 mL). The combined extracts were evaporated to dryness and the residue was purified by chromatography (ether/cyclohexane/MeOH−NH_3, 20:15:5) to provide compound **12** (702 mg, 69%) as a colourless powder. A small amount of **12** was recrystallised (CH_2Cl_2/pentane), m.p. 112−113 °C, $[\alpha]_D^{20}$ = −39 (c = 2, MeOH). − ^{1}H NMR ($CDCl_3$): δ = 3.67 (dd, 1 H, 4-H_b), 3.77 (dd, 1 H, 4-H_a), 3.81 (dd, 1 H, 2-H), 3.89 (ddd, 1 H, 3-H), 4.14 and 4.39 (AB, J = 11.0, 2 H, OCH_2Ph), 4.48 and 4.56 (AB, J = 11.6, 2 H, OCH_2Ph), 5.04 (d, 1 H, 1-H), 7.05 (s, 2 H, 4′-H and 5′-H), 7.15 to 7.33 (m, 10 H, H from phenyl); $J_{1,2}$ = 3.3, $J_{2,3}$ = 7.5, $J_{3,4a}$ = 3.6, $J_{3,4b}$ = 4.6, $J_{4a,4b}$ = 11.5. − ^{13}C NMR ($CDCl_3$): δ = 63.4 (C-4), 71.2 (C-3), 72.7 (OCH$_2$Ph), 74.2 (OCH$_2$Ph), 75.4 (C-1), 81.2 (C-2), 128.1 to 128.6 ($C_{o,m,p}$ of Ph, C-4′ and C-5′), 137.1 and 137.5 (C_s of phenyl), 146.6 (C-2′). − $C_{21}H_{24}N_2O_4$ (368.42): calcd. C 68.46, H 6.57, N 7.60; found C 68.4, H 6.5, N 7.6.

Imidazolo-D-*ribo* Derivative 16: The same procedure as above was applied, starting from **15** (4.44 g, 6.82 mmol) in EtOH (40 mL) and water (40 mL), and some Dowex® (50WX8) beads. Workup followed by chromatography as above provided **16** (1.39 g, 55%), which was crystallised (CH_2Cl_2/pentane), m.p. 109−110 °C. − $[\alpha]_D^{20}$ = +65 (c = 2, MeOH). − ^{1}H NMR ($CDCl_3$): δ = 3.31 (ddd, 1 H, 3-H), 3.59 (dd, 1 H, 4-H_b), 3.71 (dd, 1 H, 4-H_a), 4.05 (dd, 1 H, 2-H), 4.48 and 4.55 (AB, J = 11.7, 2 H, OCH_2Ph), 4.71 and 4.92 (AB, J = 11.0, 2 H, OCH_2Ph), 5.08 (d, 1 H, 1-H), 6.96 (s, 2 H, 4′-H and 5′-H), 7.28 to 7.34 (m, 10 H, H from phenyl); $J_{1,2}$ = 2.8, $J_{2,3}$ = 8.8, $J_{3,4a}$ = 3.4, $J_{3,4b}$ = 5.3, $J_{4a,4b}$ = 11.3. − ^{13}C NMR ($CDCl_3$): δ = 63.7 (C-4), 70.4 (C-3), 71.6 (OCH$_2$Ph), 75.4 (OCH$_2$Ph), 76.4 (C-1), 81.1 (C-2), 127.6 to 128.6 ($C_{o,m,p}$ of phenyl, and C-4′ and C-5′), 137.8 and 138.1 (C_s of phenyl), 145.7 (C-2′). − $C_{21}H_{24}N_2O_4$ (368.42): calcd. C 68.46, H 6.57, N 7.60; found C 68.4, H 6.6, N 7.6.

Imidazolo-D-*arabino*-piperidinose Derivative 13: DMAP (catalytic amounts, ca. 5 mg) and TsCl (355 mg, 1.86 mmol, 2.7 equiv.) were added at 0 °C to a stirred solution of **12** (254 mg, 0.69 mmol) and freshly distilled Et_3N (265 μL, 1.86 mmol, 2.7 equiv.) in CH_2Cl_2 (11 mL). After 24 h stirring at 0 °C, the reaction was quenched

with H_2O (5 mL) and the aqueous phase was extracted with CH_2Cl_2. The combined organic solutions were evaporated to give a crude mixture, which was dissolved in MeOH (9 mL) and 2 M NaOH (10 mL). The resulting solution was stirred for 12 h at room temp., and then diluted with H_2O (30 mL) and extracted with CH_2Cl_2. The combined organic solutions were dried ($MgSO_4$) and the solvents were evaporated off. The crude residue was purified by chromatography ($CHCl_3$/THF/MeOH−NH_3, 6:3.5:0.5) and provided crystalline compound **13** (110 mg, 45%), m.p. 115−117 °C (toluene). − $[\alpha]_D^{20} = -63$ (c = 2, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 2.36 (sl, 1 H, O*H*), 3.94 (dd, 1 H, 5-H_b), 4.05 (dd, 1 H, H-7), 4.14 (dd, 1 H, 5-H_a), 4.53 (ddd,1 H, 6-H), 4.54 and 4.70 (AB, J = 11.8, OCH_2Ph), 4.75 and 4.92 (AB, J = 11.9, OCH_2Ph), 4.78 (d, 1 H, 8-H), 6.84 (d, 1 H, 3-H), 7.10 (d, 1 H, 2-H), 7.20 to 7.37 (m, 10 H, C*H* phenyl); $J_{2,3}$ = 1.3, $J_{5a,5b}$ = 12.0, $J_{5a,6}$ = 5.8, $J_{5b,6}$ = 8.9, $J_{6,7}$ = 2.4, $J_{7,8}$ = 3.9. − ^{13}C NMR ($CDCl_3$): δ = 46.7 (C-5), 64.8 (C-6), 70.0 (C-8), 71.7 (O*C*H_2Ph), 72.5 (O*C*H_2Ph), 78.7 (C-7), 119.0 (C-3), 127.7 to 128.6 ($C_{o,m,p}$ of phenyl), 129.6 (C-2), 137.4 and 138.0 (C_s of phenyl), 142.4 (C-8a). − HR-MS $[M + H]^+$ ($C_{21}H_{23}N_2O_3$): calcd. 351.1709; found 351.1711.

D-*ribo*-Imidazolo-piperidinose Derivative 17: The same procedure as above was applied, starting from **16** (400 mg, 1.08 mmol), Et_3N (415 μL, 2.93 mmol, 2.7 equiv.), DMAP (ca. 15 mg) and TsCl (516 mg, 2.71 mmol, 2.5 equiv.), in CH_2Cl_2 (20 mL) under argon. The crude di-tosyl ester in MeOH (13 mL) solution was treated as above with 2 M NaOH (14 mL). Workup and separation by chromatography provided **17** (176 mg, 46%) as colourless crystals. − M.p. 128 −129 °C. − $[\alpha]_D^{20} = +115$ (c = 2, $CHCl_3$). − ^{1}H NMR (C_6D_6): δ = 2.95 (dd, 1 H, 5-H_b), 3.19 (dd, 1 H, 7-H), 3.75 (dd, 1 H, 5-H_a), 4.03 (sl, 1 H, O*H*), 4.23 and 4.41 (AB, J = 12.0, OCH_2Ph), 4.55 (m, 1 H, 6-H), 4.82 (dd, 1 H, 8-H), 4.89 and 4.98 (AB, J = 12.1, OCH_2Ph), 6.29 (d, 1 H, 3-H), 7.04 to 7.48 (m, 11 H, C*H* phenyl and 2-H); $J_{2,3}$ = 1.1, $J_{5a,5b}$ = 12.9, $J_{5a,6}$ = 2.8, $J_{5b,6}$ = 3.8, $J_{6,7}$ = 2.3, $J_{6,8}$ = 1.1, $J_{7,8}$ = 3.8. − ^{13}C NMR (C_6D_6): δ = 50.6 (C-5), 67.2 (C-6), 69.6 (C-8), 70.4 (O*C*H_2Ph), 71.3 (O*C*H_2Ph), 75.8 (C-7), 119.3 (C-3), 127.7 to 129.0 ($C_{o,m,p}$ of phenyl), 130.2 (C-2), 138.1 and 138.5 (C_s of Ph), 142.9 (C-8a). − $C_{21}H_{22}N_2O_3$ (350.40): calcd. C 71.98, H 6.33, N 8.00; found C 71.9, H 6.4, N 8.0

D-*arabino*-Imidazolo-piperidinose (3): A stirred solution of **13** (97 mg, 0.277 mmol) in AcOH (19 mL) was placed under H_2 atmosphere (1 bar) at room temp. in the presence of $Pd(OH)_2$/C ("Pearlman's catalyst", 100 mg). After 24 h the suspension was centrifuged and the catalyst was washed several times with AcOH. The solution was evaporated to dryness in vacuum, the residue was dissolved in MeOH and the resulting solution was percolated through Amberlist IRA 400 (OH^-) beads to eliminate residual AcOH. The solution was evaporated to dryness and separated by chromatography ($CHCl_3$/MeOH/NH_4OH_{aq}, 7:2.5:0.5); a second chromatographic separation (AcOEt/MeOH, 7:3) was necessary, giving compound **3** (21.5 mg, 45%) in crystalline form. − M.p.$_{dec}$ 157−158 °C. − $[\alpha]_D^{20} = -23$ (c = 1, H_2O). − CD (H_2O): Figure 1. − ^{1}H NMR (CD_3OD, 400 MHz): δ = 3.97 (dd, 1 H, 5-H_b), 4.00 (dd, 1 H, 7-H), 4.13 (dd, 1 H, 5-H_a), 4.38 (ddd, 1 H, 6-H), 4.71 (d, 1 H, 8-H), 6.98 (s, 2 H, 2-H and 3-H); $J_{5a,5b}$ = 12.3, $J_{5a,6}$ = 5, $J_{5b,6}$ = 7.7, $J_{6,7}$ = 2.1, $J_{7,8}$ = 5.1. − ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 47.8 (C-5), 66.7 (C-6), 67.8 (C-8), 74.4 (C-7), 120.2 (C-3), 129.3 (C-2), 146.4 (C-8a). − HR-MS $[M + H]^+$ ($C_7H_{11}O_3N_2$): calcd. 171.0770; found 171.0772.

D-*ribo*-Imidazolo-piperidinose (4): The same procedure as above was applied, starting from **17** (150 mg, 0.428 mmol) and $Pd(OH)_2$/C (150 mg) in AcOH (28 mL) under H_2 atmosphere (1 bar) for 15 h. Workup and separation by chromatography followed by lyophilisation gave **4** (50 mg, 69%) as a colourless crystalline powder. M.p.$_{dec}$ 190 °C. − $[\alpha]_D^{20} = -32$ (c = 1, H_2O). − CD (H_2O): Figure 1. − ^{1}H NMR (CD_3OD, 400 MHz): δ = 4.04 (dd, 1 H, 5-H_b), 4.07 (dd, 1 H, 5-H_a), 4.12 (dd, 1 H, 7-H), 4.17 (ddd, 1 H, 6-H), 4.71 (d, 1 H, 8-H), 6.97 (d, 1 H, 2-H or 3-H), 6.98 (d, 1 H, 2-H or 3-H); $J_{5a,5b}$ = 12.0, $J_{5a,6}$ = 5.3, $J_{5b,6}$ = 7.7, $J_{6,7}$ = 1.8, $J_{7,8}$ = 3.9, $J_{2,3}$ = 1.2. − ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 48.0 (C-5), 66.9 (C-8), 68.5 (C-6), 72.1 (C-7), 120.0 (C-3), 129.2 (C-2), 147.1 (C-8a). − HR-MS $[M + H]^+$ ($C_7H_{11}O_3N_2$): calcd. 171.0770; found 171.0771.

Coupling Reaction Between a Lithio-imidazole and L-Erythrose Derivative *ent*-9: (Scheme 3). − The same procedure as used for the preparation of **9** was applied, starting from *N*-trityl-imidazole (6.69 g, 21.6 mmol) in THF (300 mL) and a solution of BuLi in hexane (1.6 M, 14.7 mL, 23.5 mmol, 1.2 equiv.), under argon atmosphere. Aldehyde *ent*-**9**[11] (4.91 g, 19.6 mmol) in anhydrous THF (20 mL) was added slowly and the reaction mixture was stirred for 1 h at 0 °C. After workup and chromatography (AcOEt/ cyclohexane, 4:6, then 1:1), two fractions were obtained, the first one containing mainly adduct *ent*-**10** (minor and less polar compound, 2.23 g) and the second one adduct *ent*-**14** (major and more polar compound, 8.35 g). Each of the two fractions was used for benzylation without further purification.

The ^{1}H NMR and ^{13}C NMR spectra of *ent*-**10** and *ent*-**14** were superimposable on those of **10** and **14,** respectively.

Imidazolo L-*arabino* Derivative *ent*-11: The same procedure as for the preparation of **11** was used, starting from *ent*-**10** (2.23 g) in anhydrous THF (60 mL), a catalytic amount of Bu_4NI (10 mg) and a 50% suspension of NaH in oil (760 mg, ca. 16 mmol). After 15 min, H_2 evolution had ceased, the reaction mixture was heated at 40 °C, BnBr (1.3 mL, 11.0 mmol) was added and the solution was stirred at 40 °C for 12 h. After workup and chromatography (AcOEt/cyclohexane, 2:8), *ent*-**11** was obtained (1.98 g, 16% overall yield from aldehyde *ent*-**9**) as a solid beige foam. Its ^{1}H NMR spectrum was superimposable on that of **11.**

Imidazolo L-*ribo* Derivative *ent*-15: The same procedure as for the preparation of **11** (see above) was used, starting from impure *ent*-**14** (8.35 g) in THF (100 mL), Bu_4NI (catalytic amount), NaH (ca 50% in oil) (2.1 g, ca. 44 mmol) and BnBr (3.4 mL, 29 mmol). After workup and purification by chromatography, compound *ent*-**15** (6.85 g, 54% overall yield from aldehyde *ent*-**9**) was obtained as a solid beige foam. Its ^{1}H NMR spectrum was superimposable on that of **15.**

Imidazolo L-*arabino* Derivative *ent*-12:- The same procedure as for the preparation of **12** was used, starting from *ent*-**11** (1.98 g, 3.00 mmol) in EtOH/H_2O, 1:1 (60 mL) containing some Dowex® (50WX8) beads. After workup and chromatography ($CHCl_3$/THF/MeOH−NH_3, 6:3.5:0.5), *ent*-**12** (930 mg, 83%) was obtained as a colourless solid, which was recrystallised. M.p. 111−113 °C (toluene). − $[\alpha]_D^{20} = +38$ (c = 2, MeOH) (**12**: $[\alpha]_D^{20} = -39$, see above). Its ^{1}H NMR and ^{13}C NMR spectra were superimposable on those of **12**. − HR-MS $[M + H]^+$ ($C_{21}H_{25}N_2O_4$): calcd. 369.1816; found 369.1817.

Imidazolo L-*ribo* Derivative *ent*-16: The same procedure as above was used, starting from *ent*-**15** (6.85 g, 10.5 mmol) in EtOH/H_2O, 1:1 (140 mL), and some Dowex® (50WX8) beads. Workup provided *ent*-**16** (3.37 g, 87%) as a colourless solid, which was recrystallised. M.p. 111−112 °C (toluene). − $[\alpha]_D^{20} = -68$ (c = 2, MeOH) (**16**: $[\alpha]_D^{20} = +65$, see above). − Its ^{1}H NMR and ^{13}C NMR spectra

were superimposable on those of **16**. − HR-MS: $[M + H]^+$ ($C_{21}H_{25}N_2O_4$): calcd. 369.1816; found 369.1816.

L-*arabino*-Imidazolo-piperidinose Derivative *ent*-13: The same procedure as for **13** (see above) was used, starting from *ent*-**12** (267 mg, 0.72 mmol), freshly distilled Et_3N (400 μL, 2.88 mmol, 4.0 equiv.), DMAP (8 mg, 0.07 mmol, 0.1 equiv.) and TsCl (410 mg, 2.16 mmol, 3.0 equiv.) in anhydrous CH_2Cl_2 (15 mL), followed by treatment with 2 N aq. NaOH/MeOH, 1:1 (10 mL). Workup followed by chromatography as above for **13** provided *ent*-**13** (173 mg, 68%) as a colourless oil, which was crystallised. − M.p. 117−118 °C (toluene). − $[\alpha]_D^{20} = +63.5$ ($c = 2$, $CHCl_3$) (**13**: $[\alpha]_D^{20} = -63$, see above). − Its ^1H NMR and ^{13}C NMR spectra were superimposable on those of **13**. HR-MS: $[M + H]^+$ ($C_{21}H_{23}N_2O_3$): calcd. 351.1709; found 351.1706. − $C_{21}H_{22}N_2O_3$ (350.42): calcd. C 71.98, H 6.33, N 7.99; found C 72.1, H 6.3, N 7.9.

L-*ribo*-Imidazole-piperidinose Derivative *ent*-17: A solution of *ent*-**16** (100 mg, 0.27 mmol), Et_3N (80 μL, 0.57 mmol, 2.1 equiv.), Bu_2SnO (ca. 3 mg) as catalyst and TsCl (114 mg, 0.59 mmol, 2.2 equiv.) in anhydrous CH_2Cl_2 (6 mL) was stirred for 12 h at room temp. The mixture was diluted with CH_2Cl_2 (20 mL), washed with a saturated aq. solution of NH_4Cl (20 mL), and concentrated in vacuo without being dried. The resulting residue was added as a suspension to a 2 N NaOH/MeOH (1:1) solution (20 mL), stirred for 8 h at room temp., diluted with H_2O (30 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined organic solutions were dried ($MgSO_4$) and filtered and the solvents were evaporated off in vacuo. The crude residue was purified by chromatography (CH_2Cl_2/MeOH−NH_3, 98:2) to give *ent*-**17** (91 mg, 95%) as a colourless solid, which was recrystallised. M.p. 130 °C (toluene). − $[\alpha]_D^{20} = -123$ ($c = 2$, $CHCl_3$) (**17:** $[\alpha]_D^{20} = +115$, see above). Its ^1H NMR and ^{13}C NMR spectra were superimposable on those of **17**. − $C_{21}H_{22}N_2O_3$ (350.42): calcd. C 71.98, H 6.33, N 7.99; found C 72.0, H 6.2, N 7.8.

L-*arabino*-Imidazole-piperidinose (*ent*-3): A stirred solution of *ent*-**13** (147 mg, 0.42 mmol) in MeOH (5 mL) was placed under H_2 atmosphere (30 bar) at room temp. in the presence of moist 10% Pd/C (containing 50% water). After 8 days, the suspension was centrifuged and the catalyst was washed several times with warm MeOH. The combined organic fractions were evaporated to dryness and the residue was purified by chromatography (AcOEt/MeOH, 7:3) to give *ent*-**3** (45 mg, 63%) as a pale yellow powder after lyophilization. Recrystallisation from H_2O provided some monocrystals, one of which was used for X-ray diffraction analysis (Figure 3). − $M.p._{dec.}$ 120−125 °C. − $[\alpha]_D^{20} = +28$ ($c = 1$, H_2O). − CD (H_2O): Figure 1. − ^1H NMR and ^{13}C NMR spectra were superimposable on those of **3**. − HR-MS $[M + H]^+$ ($C_7H_{11}N_2O_3$): calcd. 171.0770; found 171.0772.

L-*ribo*-Imidazole-piperidinose (*ent*-4): The same procedure as above was used, starting from *ent*-**17** (281 mg, 0.88 mmol) and moist 10% Pd/C (containing 50% water). After 4 days at room temp., workup as above provided *ent*-**4** (92 mg, 68%) as colourless crystals. $M.p._{dec.}$ 215 °C. − $[\alpha]_D^{20} = +32$ ($c = 1$, H_2O). − CD (H_2O): Figure 1. − The ^1H NMR and ^{13}C NMR spectra were superimposable on those of **4**. − HR-MS $[M + H]^+$ ($C_7H_{11}N_2O_3$): calcd. 171. 0770; found 171.0770.

Ethyl D-Threonate Derivative 18: Tf_2O (6.43 mL, 39 mmol, 1.3 equiv.) was added slowly at −10 °C to a stirred solution of **7** (6.12 g, 30 mmol)[12,13] and anhydrous pyridine (3.63 mL, 45 mmol, 1.5 equiv.) in anhydrous CH_2Cl_2 (140 mL). After 1 h at room temp., some H_2O was added and the solution was extracted with CH_2Cl_2. The combined organic solutions were evaporated to ca. 5 mL and diluted with DMF (6 mL). Excess CH_2Cl_2 was evaporated in vacuum at room temp., $NaNO_2$ (1.02 g, 14.8 mmol, 5.0 equiv.) was added, the resulting mixture was stirred for 1 h at room temp., the salt that precipitated was filtered, the filtrate was evaporated in vacuum to dryness, and the crude residue was separated by chromatography (AcOEt/cyclohexane, 3:7). Compound **18** (4.53 g, 74%) was obtained as a pale yellow oil. − $[\alpha]_D^{20} = -21$ ($c = 2$, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 1.30 (t, $J = 7.0$, 3 H, CH_2CH_3), 1.34 (s, 3 H, CH_3 isopr.), 1.41 (s, 3 H, CH_3 isopr.), 2.98 (d, 1 H, OH), 4.00 (dd, 1 H, 4-H_b), 4.08 (dd, 1 H, 4-H_a), 4.09 (dd, 1 H, 2-H), 4.27 (q, $J = 7.0$, 1 H, $CHH'CH_3$), 4.28 (q, $J = 7.0$, 1 H, $CHH'CH_3$), 4.37 (td, 1 H, 3-H); $J_{2,OH} = 7.9$, $J_{2,3} = 2.7$, $J_{3,4a} = 6.7$, $J_{3,4b} = 7.0$, $J_{4a,4b} = 8.2$. − ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_2CH_3), 25.3 (CH_3 isopr.), 26.1 (CH_3 isopr.), 62.0 (CH_2CH_3), 65.6 (C-4), 70.3 (C-2), 76.3 (C-3), 109.9 [$C(CH_3)_2$], 172.1 (C-1). The ^1H NMR and ^{13}C NMR spectra were identical to those of the L-ethyl threonate enantiomer described in the literature.[13] − $C_9H_{16}O_5$ (204.22): calcd. C 52.93, H 7.90; found C 52.7, H 7.5.

Ethyl D-Threonate Derivative 19: A mixture of freshly prepared anhydrous Ag_2O (26.72 g, 114.9 mmol, 1.5 equiv.), powdered molecular sieves (4Å, 21 g) and KI (687 mg, 4.14 mmol, 0.05 equiv.) was heated under vacuum at 300 °C. After this had cooled to room temp., a solution of **18** (15.66 g, 76.7 mmol) in anhydrous toluene (150 mL) was added and the mixture was heated at 50 °C. BnBr (10.5 mL, 82.2 mmol, 1.15 equiv.) was added, and the stirred solution was heated to reflux for 1 h and left to cool to room temp. The suspension was filtered and the solids were washed with AcOEt (300 mL). The combined organic solutions were evaporated to dryness in vacuo and the residue was separated by chromatography (AcOEt/cyclohexane, 1:9). Compound **19** (13.32 g, 77%) was obtained as a pale yellow oil. − $[\alpha]_D^{20} = -54$ ($c = 2$, $CHCl_3$) (see also *ent*-**19**: $[\alpha]_D^{20} = +59$ ($c = 2$, $CHCl_3$), cf. ref.[11]). − ^1H NMR ($CDCl_3$): δ = 1.29 (t, $J = 7.1$, 3 H, CH_2CH_3), 1.35 (s 3 H, CH_3 isopr.), 1.39 (s, 3 H, CH_3 isopr.), 3.95 (dd, 1 H, 4-H_b), 3.98 (d, 1 H, 2-H), 4.01 (dd, 1 H, 4-H_a), 4.22 (q, $J = 7.1$, 2 H, CH_2CH_3), 4.39 (q, 1 H, 3-H), 4.52 and 4.78 (AB, $J = 11.9$, 2 H, OCH_2Ph), 7.28 to 7.38 (m, 5 H, H of phenyl); $J_{2,3} = 5.9$, $J_{3,4a} = 6.5$, $J_{3,4b} = 6.4$, $J_{4a,4b} = 8.7$. − ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH_2CH_3), 25.3 (CH_3 isopr.), 26.3 (CH_3 isopr.), 61.2 (CH_2CH_3), 65.5 (C-4), 72.8 (OCH_2Ph), 75.9 (C-3), 78.6 (C-2), 109.9 [$C(CH_3)_2$], 128.0 to 128.4 ($C_{o,m,p}$ of phenyl), 137.1 (C_s of phenyl), 170.1 (C-1).

D-Threose Derivative 20: A solution of DIBAH (1.2 M, 28.3 mL, 34.0 mmol, 2.5 equiv.) in toluene was added dropwise at −78 °C to a stirred solution of **19** (4.00 g, 13.6 mmol) in anhydrous toluene (92 mL). After ca. 1 h, excess DIBAH was slowly neutralised with MeOH (ca. 40 mL), and the solution was allowed to warm to room temperature. The solution was treated sequentially with saturated aq. Seignette salt (K and Na tartrate) solution (3 mL) and some brine (6 mL), resulting in the precipitation of aluminium salts, which were filtered and washed with AcOEt. The stirred filtrates were dried ($MgSO_4$) and filtered and the solvents were removed. The resulting syrup was dissolved in anhydrous toluene and the solution was concentrated in vacuo; this procedure was repeated three times in order to obtain the free aldehyde instead of the hydrate. The final syrup was placed under vacuum over fresh P_2O_5 in a dessicator for 20 h to yield **20** as a yellow oil (3.39 g, quant. yield). − ^1H NMR ($CDCl_3$): δ = 1.35 (s, 3 H, CH_3 isopr.), 1.43 (s, 3 H, CH_3 isopr.), 3.86 (dd, 1 H, 2-H), 3.95 (dd, 1 H, 4-H_b), 4.06 (dd, 1 H, 4-H_a), 4.38 (q, 1 H, 3-H), 4.66 and 4.79 (AB, $J = 11.9$, 2 H, OCH_2Ph), 7.34 to 7.38 (m, 5 H, H of phenyl), 9.72 (d, 1 H, 1-H); $J_{1,2} = 1.5$, $J_{2,3} = 5.4$, $J_{3,4a} = 6.6$, $J_{3,4b} = 5.9$, $J_{4a,4b} = 8.8$. − ^{13}C NMR ($CDCl_3$): δ = 25.1 (CH_3 isopr.), 26.1 (CH_3 isopr.), 65.3 C-

4), 73.3 (O*C*H$_2$Ph), 75.3 (C-3), 82.8 (C-2), 109.8 [*C*(CH$_3$)$_2$], 128.1 to 128.6 (C$_{o,m,p}$ of phenyl), 136.9 (C$_s$ of phenyl), 202.1 (C-1).

Coupling Reaction Between a Lithio-imidazole and D-Threose Derivative 20: (Scheme 4). A similar procedure to that used for the coupling reaction with aldehyde **9** (see above) was employed, starting from *N*-trityl-imidazole (5.61 g, 18.1 mmol) in anhydrous THF (225 mL) under argon atmosphere at −5 °C, with a solution of BuLi in hexane (1.6 M, 12.3 mL, 19.7 mmol, 1.2 equiv.) and aldehyde **20** (4.11 g, 16.4 mmol) in THF (10 mL). After workup and chromatography (AcOEt/cyclohexane, 7:3), an impure fraction containing mainly **21** (2.68 g) was obtained, followed by a second fraction containing **25** (2.29 g) and some *N*-trityl-imidazole. The two fractions were benzylated separately without further purification. This coupling reaction was not optimised.

Compound 21: ^{1}H NMR (CDCl$_3$): δ = 1.21 (s, 3 H, C*H*$_3$ isopr.), 1.24 (s, 3 H, C*H*$_3$ isopr.), 2.53 (dd, 1 H, 2-H), 2.88 (d, 1 H, OH), 3.08 (t, 1 H, 4-H$_b$), 3.45 (dd, 1 H, 4-H$_a$), 3.79 (q, 1 H, 3-H), 4.12 (dd, 1 H, 1-H), 4.43 and 4.49 (AB, *J* = 11.3, OC*H*$_2$Ph), 6.80 (d, 1 H, 4′-H or 5′-H), 7.08 (d, 1 H, 4′-H or 5′-H), 7.13 to 7.35 (m, 20 H, H of phenyl); $J_{1,OH}$ = 8.5, $J_{1,2}$ = 3.2, $J_{2,3}$ = 6.4, $J_{3,4a}$ = 6.4, $J_{3,4b}$ = 7.9, $J_{4a,4b}$ = 8.1, $J_{4',5'}$ = 1.4.

Compound 25: ^{1}H NMR (CDCl$_3$): δ = 0.82 (d, 1 H, OH), 1.30 (s, 6 H, 2 × C*H*$_3$ isopr.), 3.69 (dd, 1 H, 4-H$_b$), 3.86 (dd, 1 H, 4-H$_a$), 3.92 (dd, 1 H, 2-H), 4.22 (q, 1 H, 3-H), 4.24 (dd, 1 H, 1-H), 4.54 and 4.63 (AB, *J* = 10.2, OC*H*$_2$Ph), 6.82 (d, 1 H, 4′-H or 5′-H), 7.07 to 7.35 (m, 21 H, H of phenyl, and 4′-H or 5′-H); $J_{1,OH}$ = 4.2, $J_{1,2}$ = 8.3, $J_{2,3}$ = 5.9, $J_{3,4a}$ = 6.6, $J_{3,4b}$ = 7.1, $J_{4a,4b}$ = 8.7, $J_{4',5'}$ = 1.3.

Imidazolo-D-*xylo* Derivative 22: The same procedure as for the preparation of **11** was used, starting from impure adduct **21** (2.68 g) in anhydrous THF (50 mL) under argon atmosphere, with a catalytic amount of Bu$_4$NI (ca. 20 mg), NaH (ca 50% in oil, 810 mg, ca. 17 mmol), and BnBr (1.1 mL, 9.6 mmol). After workup and chromatography (AcOEt/cyclohexane, 1:9), **22** (1.53 g, overall yield from aldehyde **20**: 14%) was isolated as a beige foam. − ^{1}H NMR (CDCl$_3$): δ = 1.27 (s, 6 H, 2 × C*H*$_3$ isoprop.), 3.38 (m, 3 H, 3-H, 4-H$_a$ and 4-H$_b$), 3.74 (t, 1 H, 2-H), 3.79 and 4.22 (AB, 2 H, *J* = 11.7, 2 H, OC*H*$_2$Ph), 4.16 (d, 1 H, 1-H), 4.65 (s, 2 H, OC*H*$_2$Ph), 6.89 (d, 1 H, 4′-H or 5′-H), 7.08 to 7.27 (m, 26 H, H of phenyl, and 4′-H or 5′-H); $J_{1,2}$ = 5.8, $J_{2,3}$ = 5.8, $J_{4',5'}$ = 1.4. − ^{13}C NMR (CDCl$_3$): δ = 26.2 (*C*H$_3$ isoprop.), 26.9 (*C*H$_3$ isoprop.), 66.7 (C-4), 70.2 (O*C*H$_2$Ph), 73.7 (C-1), 73.9 (O*C*H$_2$Ph), 75.7 [*C*(Ph)$_3$], 77.2 (C-3), 80.2 (C-2), 108.5 [*C*(CH$_3$)$_3$], 123.0 (C-4′), 126.0 (C-5′), 126.7 to 130.0 (C$_{o,m,p}$ of phenyl), 139.0 (C$_s$ of phenyl), 139.1 (C$_s$ of phenyl), 142.4 (3 × C$_s$ phenyl), 146.3 (C-2′).

Imidazolo-D-*lyxo* Derivative 26: The same procedure as above was used, starting from impure adduct **25** (2.29 g), Bu$_4$NI (20 mg) in THF (40 mL), NaH (ca. 50% in oil, 680 mg, ca. 14 mmol), and BnBr (0.97 mL, 8.1 mmol). Workup as above followed by chromatography provided **26** (1.94 g, overall yield from the aldehyde **20**: 18%) as a colourless foam. − ^{1}H NMR (CDCl$_3$): δ = 1.28 (s, 3 H, C*H*$_3$ isoprop.), 1.31 (s, 3 H, C*H*$_3$ isoprop.), 3.65 (dd, 1 H, 4-H$_b$), 3.84 and 4.01 (AB, *J* = 12.5, 2 H, OC*H*$_2$Ph), 3.90 (d, 1 H, 4-H$_a$), 4.02 (dd, 1 H, 2-H), 4.25 (td, 1 H, 3-H), 4.34 (d, 1 H, 1-H), 4.45 and 4.59 (AB, *J* = 10.4, 2 H, OC*H*$_2$Ph), 6.85 (d, 1 H, 4′H or 5′-H), 7.02 to 7.32 (m, 26 H, H of phenyl, and 4′-H or 5′-H); $J_{1,2}$ = 8.1, $J_{2,3}$ = 5.0, $J_{3,4a}$ = 6.4, $J_{3,4b}$ = 7.6, $J_{4a,4b}$ = 8.2, $J_{4',5'}$ = 1.4. − ^{13}C NMR: δ = 25.8 (*C*H$_3$ isoprop.), 26.4 (*C*H$_3$ isoprop.), 66.6 (C-4), 68.9 (O*C*H$_2$Ph), 72.9 (C-1), 74.9 (O*C*H$_2$Ph), 75.8 [*C*(Ph)$_3$], 76.9 (C-3), 80.8 (C-2), 108.5 [*C*(CH$_3$)$_2$], 123.1 (C-4′), 125.4 (C-5′), 126.7 to 130.1 (C$_{o,m,p}$ of phenyl), 138.7 and 138.8 (2 × C$_s$ of phenyl), 142.4 (3 × C$_s$ of phenyl), 147.6 (C-2′).

Imidazolo-D-*xylo* Derivative 23: A stirred solution of **22** (3.30 g, 5.06 mmol) in HCl (4 N, 19 mL) was heated at reflux for 4 h. The mixture was cooled to room temp., then washed twice with Et$_2$O. The organic fractions were extracted with HCl (2 N, 30 mL). The combined acidic aqueous fractions were basified (aq. K$_2$CO$_3$) to pH = 10 and extracted with CH$_2$Cl$_2$. The combined organic fractions were dried (MgSO$_4$) and filtered, and the solvents were evaporated. The crude residue was purified by chromatography (CHCl$_3$/THF/MeOH−NH$_3$, 6:3.5:0.5) to provide **23** (1.69 g, 91%) as a crystalline compound. M.p. 103−104 °C (EtOH/H$_2$O, 7:3). − $[\alpha]_D^{20}$ = +51 (*c* = 2, MeOH). − ^{1}H NMR (CDCl$_3$): δ = 2.57 (sl, 1 H, OH), 3.51 (dd, 1 H, 4-H$_b$), 3.60 (dd, 1 H, 4-H$_a$), 3.74 (m, 1 H, 3-H), 3.77 (1 H, 2-H), 4.46 and 4.54 (AB, *J* = 11.6, 2 H, OC*H*$_2$Ph), 4.49 and 4.56 (AB, J = 11.2, 2 H, OC*H*$_2$Ph), 4.96 (d, 1 H, 1-H), 7.03 (sl, 2 H, 4′-H and 5′-H), 7.21 to 7.37 (m, 10 H, H of phenyl), 9.79 (sl, 1 H, N-H). − ^{13}C NMR: δ = 63.5 (C-4), 71.3 (C-3), 72.4 (O*C*H$_2$Ph), 74.6 (O*C*H$_2$Ph), 76.7 (C-1), 81.2 (C-2), 116.2 (C-4′ and C-5′), 128.1 to 128.6 (C$_{o,m,p}$ of phenyl), 137.1 and 137.6 (2 × C$_s$ of phenyl), 145.7 (C-2′). − C$_{21}$H$_{24}$N$_2$O$_4$ + 1/2 H$_2$O (377.44): calcd. C 66.83, H 6.68, N 7.42; found C 66.8, H 6.6, N 7.5.

Imidazolo-D-*lyxo* Derivative 27: The same procedure as above was used, starting from **26** (3.36 g, 5.17 mmol) in HCl (4 N, 20 mL) at reflux. Workup provided **27** (1.385 g, 73%) as a colourless foam, which was recrystallised. M.p.$_{dec.}$ 161 °C (EtOH/H$_2$O, 7:3). − $[\alpha]_D^{20}$ = −34 (*c* = 2, MeOH). − ^{1}H NMR (CDCl$_3$): δ = 3.53 (d, 2 H, 4-H$_a$ and 4-H$_b$), 3.66 (q, 1 H, 3-H), 4.05 (dd, 1 H, H-2), 4.47 and 4.53 (AB, *J* = 11.6, OC*H*$_2$Ph), 4.59 and 4.70 (AB, *J* = 11.2, 2 H, OC*H*$_2$Ph), 4.87 (d, 1 H, H-1), 7.01 (s, 2 H, 4′-H and 5′-H), 7.24 to 7.35 (m, 10 H, C*H* phenyl); $J_{1,2}$ = 3.3, $J_{2,3}$ = 4.8, $J_{3,4}$ =4.7. − ^{13}C NMR (CDCl$_3$): δ = 62.1 (C-4), 71.0 (C-3), 71.6 (O*C*H$_2$Ph), 74.7 (O*C*H$_2$Ph), 75.5 (C-1), 81.1 (C-2), 127.7 to 128.5 (C$_{o,m,p}$ of phenyl), 137.3 and 137.7 (2 × C$_s$ of phenyl), 145.8 (C-2′). − C$_{21}$H$_{24}$N$_2$O$_4$ (368.43): calcd. C 68.46, H 6.57, N 7.60; found C 68.6, H 6.5, N 7.7.

D-*xylo*-Imidazolo-piperidinose Derivative 24: Bu$_2$SnO (catalytic amounts, ca. 5 mg) and TsCl (194 mg, 1.02 mmol, 2.5 equiv.) were added at room temp. to a stirred solution of **23** (150 mg, 0.40 mmol) and Et$_3$N (170 µL; 1.22 mmol; 3.0 equiv.) in anhydrous CH$_2$Cl$_2$ (9 mL). After 12 h at room temp., the reaction mixture was diluted with CH$_2$Cl$_2$ (30 mL), washed with a saturated aqueous solution of NH$_4$Cl (40 mL), evaporated to near dryness in vacuum and taken up in 2 N NaOH/MeOH (1:1, 20 mL), and the resulting reaction mixture was stirred for 12 h at room temp. The solution was diluted with water (30 mL) and extracted several times with CH$_2$Cl$_2$. The organic solution was dried (MgSO$_4$) and filtered, and the solvents were removed. The crude residue was purified by chromatography (Et$_2$O/MeOH−NH$_3$, 98:2) to provide **24** (124 mg, 87%) as a crystalline solid. M.p. 101−101.5 °C (EtOH/H$_2$O, 7:3). − $[\alpha]_D^{20}$ = +31 (*c* = 2, CHCl$_3$). − ^{1}H NMR (C$_6$D$_6$): δ = 3.62 (dd, 1 H, 5-H$_b$), 3.73 (dd, 1 H, 5-H$_a$), 3.93 (dd, 1 H, H-7), 3.96 (m, 1 H, 6-H), 4.11 and 4.27 (AB, *J* = 11.9, 2 H, OC*H*$_2$Ph), 4.84 (d, 1 H, 8-H), 4.89 and 4.99 (AB, *J* = 11.9, OC*H*$_2$Ph), 6.34 (d, 1 H, 3-H), 6.97 to 7.16 (m, 8 H, C*H* phenyl), 7.26 (d, 1 H, H-2), 7.31 to 7.35 (m, 2 H, C*H* phenyl); $J_{2,3}$ = 1.1, $J_{5a,5b}$ = 12.7, $J_{5a,6}$ = 3.0, $J_{5b,6}$ = 3.0, $J_{6,7}$ = 5.1, $J_{7,8}$ = 3.4. − ^{13}C NMR (CDCl$_3$): δ = 48.8 (C-5), 66.6 (C-6), 71.0 (C-8), 71.7 (O*C*H$_2$Ph), 72.5 (O*C*H$_2$Ph), 75.8 (C-7), 119.5 (C-3), 127.8 to 128.5 (C$_{o,m,p}$ of phenyl), 129.1 (C-2), 137.1 and 137.2 (2 × C$_s$ of phenyl), 141.4 (C-8a). − C$_{21}$H$_{22}$N$_2$O$_3$ (350.42): calcd. C 71.98, H 6.33, N 7.99; found C 71.9, H 6.2, N 8.1.

D-*lyxo*-Imidazolo-piperidinose Derivative 28: The same procedure as above was used, starting from **27** (200 mg, 0.54 mmol), Et_3N (230 μL, 1.62 mmol, 3.0 equiv.), Bu_2SnO (ca. 10 mg) and TsCl (259 mg, 1.35 mmol, 2.5 equiv.) in CH_2Cl_2 (12 mL). Workup as above followed by chromatography provided **28** (169 mg, 90%) as a crystalline compound. M.p. 146−147 °C (EtOH/H_2O, 7:3). $[\alpha]_D^{20} = -191$ (c = 2, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 3.65 (dd, 1 H, 7-H), 3.72 (dd, 1 H, 5-H_b), 4.41 (dd, 1 H, 5-H_a), 4.43 and 4.65 (AB, J = 11.8, 2 H, OCH_2Ph), 4.69 (td, 1 H, 6-H), 4.70 and 4.79 (AB, J = 12.0, 2 H, OCH_2Ph), 4.83 (d, 1 H, 8-H), 6.88 (d, 1 H, H-3), 7.11 (d, 1 H, H-2), 7.30 to 7.47 (m, 10 H, CH phenyl); $J_{2,3}$ = 1.1, $J_{5a,5b}$ = 12.1, $J_{5a,6}$ = 6.6, $J_{5b,6}$ = 9.4, $J_{6,7}$ =9.7, $J_{7,8}$ = 3.5. − ^{13}C NMR ($CDCl_3$): δ = 48.4 (C-5), 64.2 (C-6), 67.2 (C-8), 70.7 (OCH$_2$Ph), 71.2 (OCH$_2$Ph), 79.5 (C-7), 119.3 (C-3), 127.7 to 128.6 ($C_{o,m,p}$ of phenyl),129.8 (C-2), 137.2 and 137.8 (2 × C_s of phenyl), 143.1 (C-8a). − $C_{21}H_{22}N_2O_3$ (350.42): calcd. C 71.98, H 6.33, N 7.99; found C 72.1, H 6.2, N 8.0.

D-*xylo*-Imidazolo-piperidinose (5): A stirred solution of **24** (233 mg, 0.66 mmol) in EtOH/AcOH, 1:1 (10 mL) was placed under H_2 atmosphere (1 bar) at room temp. in the presence of moist (20% H_2O) $Pd(OH)_2$/C ("Pearlman's catalyst", 400 mg). After 12 h the suspension was centrifuged and the catalyst was rinsed several times with hot MeOH. The combined organic solutions were evaporated to dryness in vacuo, the crude residue was taken up again in MeOH, and the resulting solution was passed through Amberlist IRA 400 (OH^-) (15 mL) beads in order to eliminate the last traces of AcOH. After evaporation of the solvent, the residue was purified by chromatography (AcOEt/MeOH, 8:2) to give **5** (75 mg, 66%) as colourless crystals. M.p.$_{dec.}$ 175 °C. − $[\alpha]_D^{20} = -56$ (c = 1, MeOH). − CD (H_2O): Figure 1. − ^{1}H NMR (CD_3OD, 400 MHz): δ = 3.91 (dd, 1 H, 7-H), 3.92 (dd, 1 H, 5-H_b), 4.07 (ddd, 1 H, 6-H), 4.27 (dd, 1 H, 5-H_a), 4.56 (d, 1 H, 8-H), 7.01 (d, 1 H, 2-H or 3-H),7.02 (d, 1 H, 2-H or 3-H); $J_{5a,5b}$ = 12.6, $J_{5a,6}$ = 4.6, $J_{5b,6}$ = 6.5, $J_{6,7}$ = 7.5, $J_{7,8}$ = 5.6, $J_{2,3}$ = 1.3. − ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 49.2 (C-5), 68.9 (C-6), 69.4 (C-8), 75.2 (C-7), 120.0 (C-3), 129.3 (C-2), 146.8 (C-8a). − $C_7H_{10}N_2O_3$ (170.17): calcd. C 49.40, H 5.92, N 16.46; found C 49.5, H 5.9, N 16.4.

D-*lyxo*-Imidazolo-piperidinose (6): The same procedure as above was used, starting from **28** (283 mg, 0.81 mmol) and moist $Pd(OH)_2$/C (400 mg), under H_2 atmosphere (1 bar). After workup as above, the crude final product was purified by chromatography ($CHCl_3$/MeOH, 8:2) to provide **6** (122 mg, 89%) as a slightly yellow, crystalline solid. M.p.$_{dec.}$ 182 °C (H_2O/EtOH); one of the monocrystals was used for X-ray diffraction analysis (Figure 2). − $[\alpha]_D^{20} = -42$ (c = 1, MeOH). − CD (H_2O): Figure 1. − ^{1}H NMR (CD_3OD, 400 MHz): δ = 3.83 (dd, 1 H, 5-H_b, 3.99 (dd, 1 H, 7-H), 4.28* and 4.29* (m, 2 H, 6-H and 5-H_a respectively), 4.85 (d, 1 H, 8-H), 6.98 (d, 1 H, 2-H or 3-H), 6.99 (d, 1 H, 2-H or 3-H); $J_{5a,5b}$ = 12.7*, $J_{5a,6}$ = 4.4*, $J_{5b,6}$ = 5.1*, $J_{6,7}$ = 6.8*, $J_{7,8}$ = 3.7*, $J_{2,3}$ = 1.3. (*These values for second order signals were calculated with the NUTS Program from Acorn NMR). − ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 48.0 (C-5), 65.4 (C-8), 67.8 (C-6), 72.2 (C-7), 120.2 (C-3), 128.7 (C-2), 147.0 (C-8a). $C_7H_{10}N_2O_3$ (170.17): calcd. C 49.40, H 5.92, N 16.46; found C 49.0, H 5.9, N 16.3.

Coupling Reaction Between a Lithiated Imidazole and L-Threose Derivative *ent*-20: (Scheme 5). A procedure similar to that for the coupling reaction with aldehyde **9** (see above) was used, starting from *N*-trityl-imidazole (6.18 g, 19.9 mmol) in anhydrous THF (250 mL) under argon atmosphere at −5 °C, with a solution of BuLi in hexane (1.6 M, 13.6 mL, 21.7 mmol, 1.2 equiv.) and aldehyde *ent*-**20** (4.53 g, 18.1 mmol)[11] in THF (20 mL). After workup, the resulting crude oil was separated by chromatography (AcOEt/cyclohexane, 3:7, then 6:4), which provided two fractions. The less polar one contained a mixture (5.18 g) of the L-*xylo* adduct *ent*-**21** and some unchanged trityl-imidazole; the more polar one contained almost pure L-*lyxo* compound *ent*-**25** (4.80 g). Both fractions were used as such for the next reaction step. The ^{1}H NMR and ^{13}C NMR spectra of *ent*-**21** and *ent*-**25** superimposable on those of **21** and **25**.

Imidazolo-L-*xylo* Derivative *ent*-22: Bu_4NI (catalytic amount, ca. 15 mg) and NaH (ca 50% in oil, 1.3 g, ca. 27 mmol) were added at room temperature under argon atmosphere to a stirred solution of the impure minor adduct *ent*-**21** (5.18 g) in anhydrous THF (80 mL). Once hydrogen formation had ceased, BnBr (2.2 mL, 18.6 mmol) was added, and the mixture was heated at 40 °C for 12 h. MeOH (2 mL) was added and the resulting clear solution was evaporated to dryness in vacuo. The residue was dissolved in AcOEt (150 mL), the solution was washed with water (80 mL) and brine, then dried ($MgSO_4$) and filtered, and the solvents were removed. The residue was purified by chromatography (AcOEt/cyclohexane, 2:8) to provide pure *ent*-**22** (2.97 g, overall yield from the aldehyde *ent*-**20**: 25%) as a beige foam. The ^{1}H NMR and ^{13}C NMR spectra were superimposable on those of **22**.

Imidazolo-L-*lyxo* Derivative *ent*-26: The same procedure as above was used, starting from *ent*-**25** (4.80 g) in THF (80 mL), Bu_4NI (ca. 20 mg), NaH (50% in oil, 1.2 g, ca. 25 mmol) and BnBr (2.0 mL, 16.9 mmol). Workup as above followed by chromatography provided compound *ent*-**26** (5.10 g, overall yield from the aldehyde *ent*-**20**: 43%). Its ^{1}H NMR and ^{13}C NMR spectra were superimposable on those of **26**.

Imidazolo-L-*xylo* Derivative *ent*-23: A solution of *ent*-**22** (2.90 g, 4.46 mmol) in aq. HCl (2 N, 70 mL) was heated at reflux for 4 h, cooled to room temp., and washed with Et_2O (2 × 50 mL). The organic fractions were extracted with HCl (2 N, 30 mL). The combined aqueous phases were basified with aq. ammonia to ca. pH 10 and extracted with AcOEt (4 × 80 mL). The combined organic fractions were dried ($MgSO_4$) and filtered, and the solvents were removed. The crude residue was purified by chromatography ($CHCl_3$/THF/MeOH−NH_3, 6:3:1) to provide *ent*-**23** (877 mg, 53%) as a colourless foam, which was recrystallised. − M.p. 99−100 °C ($CHCl_3$). − $[\alpha]_D^{20} = -53$ (c = 2, CH_3OH) (**23:** $[\alpha]_D^{20} = +51$). − The ^{1}H NMR and ^{13}C NMR spectra were superimposable on those of **23**. − HR-MS $[M + H]^+$ ($C_{21}H_{25}N_2O_4$): calcd. 369.1815; found 369.1816). − $C_{21}H_{24}N_2O_4$ + 1/2 H_2O (377.44): calcd. C 66.83, H 6.68, N 7.42; found C 66.8, H 6.6, N 7.4.

Imidazolo-L-*lyxo* Derivative *ent*-27: The same procedure as employed for the preparation of **12** was used, starting from *ent*-**26** (5.10 g, 7.84 mmol) in EtOH/H_2O (1:1, 80 mL), containing some Dowex® (50WX8) beads. After workup and chromatography ($CHCl_3$/THF/MeOH−NH_3, 6:3.5:0.5), *ent*-**27** (2.32 g, 80%) was obtained as a colourless solid, which was recrystallised. M.p.$_{dec.}$ 161 °C (toluene). − $[\alpha]_D^{20} = +33$ (c = 2, MeOH) (**27:** $[\alpha]_D^{20} = -34$, see above). − The ^{1}H NMR and ^{13}C NMR spectra were superimposable on those of **27**. − HR-MS $[M + H]^+$ ($C_{21}H_{25}N_2O_4$) calcd. 369.1815; found 369.1816. − $C_{21}H_{24}N_2O_4$ (368.43): calcd. C 68.46, H 6.57, N 7.60; found C 68.2, H 6.6, N 7.7.

L-*xylo*-Imidazolo-piperidinose Derivative *ent*-24: DMAP (catalytic amounts, ca. 10 mg) and TsCl (387 mg, 2.03 mmol, 2.5 equiv.) were added at 0 °C to a stirred solution of *ent*-**23** (300 mg, 0.81 mmol) and Et_3N (310 μL, 2.23 mmol, 2.7 equiv.) in CH_2Cl_2 (12 mL) . After 24 h the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with a saturated aqueous solution of NH_4Cl (40 mL) and evaporated to near dryness, and the residue was taken up in 2 N

NaOH/MeOH (1:1, 20 mL), the resulting suspension being stirred at room temp. for 12 h. The reaction medium was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic fractions were dried ($MgSO_4$), filtered and evaporated to dryness, and the crude residue was purified by chromatography ($CHCl_3$/THF/MeOH−NH_3, 7:2.5:0.5) to provide *ent*-**24** (142 mg) as a colourless oil that crystallised spontaneously, together with recovered *ent*-**23** (104 mg). Yield of *ent*-**24** from consumed *ent*-**23**: 69%. − M.p. 99 °C. − $[\alpha]_D^{20}$ = −33 (*c* = 2, $CHCl_3$) (**24:** $[\alpha]_D^{20}$ = +31, see above). − The ^1H NMR and ^{13}C NMR were superimposable on those of **24**. − HR-MS $[M + H]^+$ ($C_{21}H_{23}N_2O_3$): calcd. 351.1709; found 351.1710).

L-*lyxo*-Imidazolo-piperidinose Derivative *ent*-28: A procedure similar to the one employed for the synthesis of **24** was used, starting from *ent*-**27** (200 mg, 0.54 mmol), Et_3N (230 μL, 1.65 mmol), Bu_2SnO (ca 5 mg) and TsCl (260 mg, 1.36 mmol, 2.5 equiv.) in CH_2Cl_2 (12 mL) and 2 N NaOH/MeOH (1:1, 30 mL). Chromatography provided *ent*-**28** (145 mg, 76%) as a colourless solid, which was recrystallised. − M.p. 146−147 °C (toluene). − $[\alpha]_D^{20}$ = +196 (*c* = 2, $CHCl_3$) (**28:** $[\alpha]_D^{20}$ = −191, see above). − The ^1H NMR and ^{13}C NMR spectra were superimposable on those of **28**. − HR-MS $[M + H]^+$ ($C_{21}H_{23}N_2O_3$): calcd. 351.1709; found 351.1707. − $C_{21}H_{22}N_2O_3$ (350.42): calcd. C 71.98, H 6.33, N 7.99; found C 71.8, H 6.2, N 8.0.

L-*xylo*-Imidazolo-piperidinose (*ent*-5): A vigorously stirred solution of *ent*-**24** (219 mg, 0.62 mmol) in MeOH (8 mL) was placed under H_2 pressure (30 bar) in an autoclave in the presence of Pd/C (10%) (containing 50% water; 440 mg) at room temp. for 64 h. The catalyst was removed by centrifugation and washed several times with hot MeOH, and the combined organic solutions were evaporated to dryness in vacuo. The crude residue was purified by chromatography (AcOEt/MeOH, 7:3) to provide *ent*-**5** (79 mg, 75%) as a colourless oil that solidified spontaneously and was recrystallised. $M.p._{dec.}$ 192 °C (EtOH). − $[\alpha]_D^{20}$ = +55 (*c* = 1, MeOH) (**5**: $[\alpha]_D^{20}$ = −56, see above). CD (H_2O): Figure 1. − The ^1H NMR and ^{13}C NMR spectra were superimposable on those of **5**. − HR-MS $[M + H]^+$ ($C_7H_{11}N_2O_3$): calcd. 171.0770; found 171.0772.

L-*lyxo*-Imidazolo-piperidinose (*ent*-6): The same procedure as above was used, starting from *ent*-**28** (439 mg, 1.25 mmol) and Pd/C (10%) (containing 50% water; 450 mg) in MeOH (15 mL) under H_2 pressure (20 bar) at room temp. for 4 days. Workup as above followed by chromatography ($CHCl_3$/MeOH/NH_4OH, 7:3:0.5) provided *ent*-**6** (113 mg, 53%) as colourless crystals, which were recrystallised. $M.p._{dec.}$ 201−202 °C (EtOH). − $[\alpha]_D^{20}$ = +42 (*c* = 1, MeOH) (**6:** $[\alpha]_D^{20}$ = −42, see above). − CD (H_2O): Figure 1. − The ^1H NMR and ^{13}C NMR spectra were superimposable on those of **6**. − HR-MS for $[M + H]^+$ ($C_7H_{11}N_2O_3$): calcd. 171.0770; found 171.0770.

X-ray Diffraction Analysis of *ent*-3 and 6. Experimental Details

Compound *ent*-**3** crystallised with one molecule H_2O, not shown in the diagram.

Table 3. Crystal data and parameter collection for *ent*-**3** and **6**.

Table 3. Crystal data and data collection parameters for *ent*-**3** and for **6**.

	ent-**3**	**6**
formula	$C_7H_{10}H_2O_3$, H_2O	$C_7H_{10}N_2O_3$
mol. weight	188.18	170.17
crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a [Å]	6.7413(2)	6.6823(3)
b [Å]	7.9980(2)	7.3559(4)
c [Å]	15.3798(3)	15.165(1)
α [°]	90	90.000
β [°]	90	90.000
γ [°]	90	90.000
V [Å^3]	829.23	745.41
Z	4	4
F(000)	400	360
$d_{calcd.}$ [gcm^{-3}]	1.51	1.52
μ [mm^{-1}]	0.12	0.11
crystal size [mm]	0.10 × 0.14 × 0.40	0.11 × 0.14 × 0.21
T [K]	293	293
radiation	Mo-K_α (λ = 0.71073)	Mo-K_α (λ = 0.71073)
measurement method	CCD	CCD
Θ_{max} [deg]	32.03	30.03
no. of measured reflections	11063	7884
no. of independent reflections	2782	2149
no. of reflns in refinement	2586	1783
no. of variables	139	122
final *R*	0.0335	0.0388
final R_w	0.0387	0.0390
weighting scheme	Chebychev polynomial [19]	Chebychev polynomial [19]
last max/min. in difference map	0.33/−0.38	0.36/−0.40

The usual corrections were applied. The structure was solved by direct methods using the SIR92 program.[17] Anisotropic least-squares, full-matrix refinement was carried out on all non-hydrogen atoms using the program CRYSTALS.[18] Scattering factors were taken from the International Tables, Vol. IV, Table 2.2 B.

For *ent*-**3**: The positions of the hydrogen atoms were determined geometrically. The refinement of 139 parameters including 2586 reflections with $I > 2.00\ \sigma(I)$ resulted in a residual of 0.0335 (R_w = 0.0387). Chebychev polynomial weights[19] were used to complete the refinement. The density maximum in the last difference map was 0.33 e/Å^3, the last minimum was −0.38 e/Å^3

For **6**: The hydrogen atoms are in calculated positions or were located in the difference Fourier map and refined using appropriate restraints. The refinement of 122 parameters including 1783 reflections with $I > 2.00\ \sigma(I)$ resulted in a residual of 0.0388 (R_w = 0.0390). Chebychev polynomial weights[19] were used to complete the refinement. The density maximum in the last difference map was 0.36 e/Å^3, the last minimum was −0.40 e/Å^3.

Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre under the numbers CCDC 165612 for *ent*-**3** and CCDC 165613 for **6**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

We wish to thank the Fondation pour l'Ecole de Chimie de Mulhouse for a PhD grant to François Gessier. We are indebted to Estelle Dubost and to Jeffery Newsome, who worked out some of the organic synthetic steps, and to Josiane Kohler for the CD spectral measurements. And, last but not least, the support of the Centre National de la Recherche Scientifique (UPRES-A 7015) is gratefully acknowledged.

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Received April 20, 2001
[O01194]