Stereomeric Pyrrolidinopentoses Bearing an Imidazole Ring − Synthesis, Chiroptical Properties, and Evaluation as Potential Sugar-Mimic Glycosidase Inhibitors

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The syntheses of the imidazolo-pyrrolidino-pentoses *ent*-**2** (L-*arabino*), **3** (D-*xylo*), **4** (D-*lyxo*), *ent*-**4** (L-*lyxo*), and **5** (D-*ribo*) are reported, completing the series of all eight possible stereomers. The corresponding five linear imidazolo sugar precursors were prepared by nucleophilic addition of C(4)-metallated imidazole derivatives to the appropriately configured and protected aldotetroses. Cyclisation of the resulting linear imidazolo-carbohydrates was performed by means of intramolecular Walden inversion processes, followed by deprotection to afford the five target imidazolo-sugars. Three of the four D-configured stereomers proved to be good to moderate glycosidase inhibitors, as determined by Michaelis–Menten kinetics.

Introduction

Polyhydroxylated alkaloids that mimic the structures of monosaccharides are now believed to be widespread in plants and in microorganisms. These sugar mimics inhibit glycosidases by virtue of their structural resemblance to the sugar moiety of the natural substrates. In 1988, the polyhydroxypyrroline nectrisine (**1**) was isolated as an immunomodulator from the culture broth of the fungus *Nectria lucida*[1] and later shown to be a powerful inhibitor of α-glucosidase and, to a lesser extent, of α-mannosidase.[2,3] Naturally occurring five-membered glycosidase inhibitors, comprising several dozen polyhydroxylated pyrrolidines (i.e., pyrrolidines, indolizidines, and pyrrolizidines[4]), are, as a rule, saturated heterocycles. To the best of our knowledge, nectrisine (**1**), which bears an imine functionality in a five-membered azasugar ring, is the only exception so far found in nature. The pyrroline double bond, which brings about a flattening of the envelope conformation of that ring, in azasugar **1** would seem to mimic the transition state of the sugar moiety of the enzyme−substrate complex. Therefore, one may surmise that its 3D structure is in agreement with Pauling's prediction of close complementarity between the structure of the substrate (or, alternately, of its pyrroline mimic) − in its flattened transition state − and the enzyme's active site.[5,6]

In a recent article dealing with glycosidase-catalyzed hydrolysis mechanisms of polysaccharides − their building blocks being piperidinoses − Zechel and Withers reviewed the finely tuned action of these enzymes and postulated that polysaccharide hydrolases give rise to transition states possessing pronounced oxocarbonium character − and therefore flattened half-chair conformations − both with retaining and with inverting glycosidases.[7]

In 1989 we set out to incorporate an imidazole ring into a furano-pentose, the azole moiety being intended to induce a flattening of the envelope conformation of the attached pyrrolidinose moiety. The natural product nectrisine (**1**) was the reference and model compound for this research project. The first substance we synthesized along these lines was the L-*xylo*-imidazolo sugar *ent*-**3**, the 3D structure and absolute configuration of which had been ascertained by NMR spectroscopy and by single-crystal X-ray diffraction analysis.[8] Tested against a dozen human liver glycosidases, *ent*-**3** proved to be inactive as a glycosidase inhibitor.[9] Nevertheless, having previously established that some imidazolo-*piperidino*-pentoses of type **30** − which are structural isomers of *pyrrolidino*-pentose *ent*-**3** (see below: Scheme 6) − were selective and sometimes quite potent glycosidase inhibitors,[10] we surmised that some stereomers of *ent*-**3** might show similar inhibitory properties. This assumption turned out to be true, as demonstrated here for some of the eight possible stereomers, the syntheses of which are described below.

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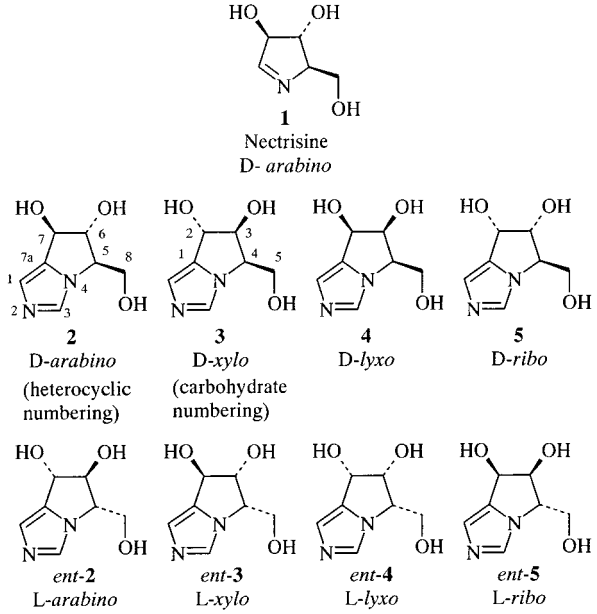
In a preceding publication we reported the synthesis of the D-*arabino* (**2**) and the L-*ribo* (*ent*-**5**) stereomers, as well as a second and more efficient synthesis of *ent*-**3**.[11] Here we describe the detailed syntheses of the five remaining stereomers (Scheme 1). ^{1}H and ^{13}C NMR spectra, as well as CD spectra corroborated the expected absolute configurations for all eight stereomers. Finally, inhibition assays of these imidazolo-sugars − **2** to **5** and *ent*-**2** to *ent*-**5** − against six commonly encountered glycosidases are reported.



Scheme 1. Nectrisine (**1**) and imidazolopyrrolidinoses **2** to **5** and *ent*-**2** to *ent*-**5**

Results

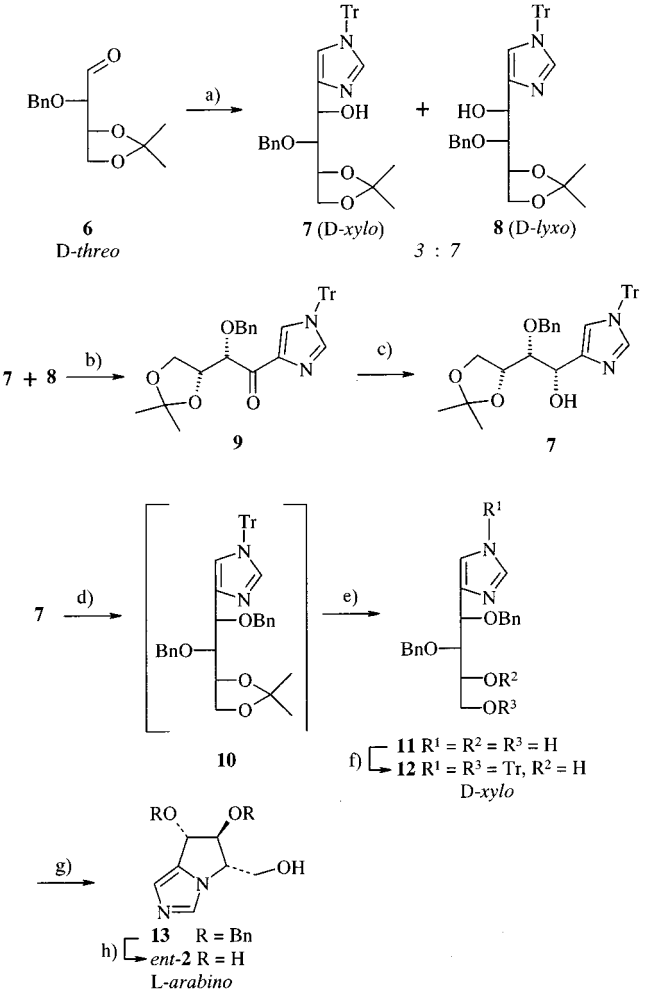
Synthesis of Imidazolo-Pyrrolidinoses

Arabinose Series 2/*ent*-2

Synthesis of the D-*arabino*-pyrrolidinose stereomer **2** had already been described by us in a preceding publication.[11] Retrosynthetic analysis of its enantiomer *ent*-**2** (Scheme 2) required the D-*threo* derivative **6** − a compound that we had prepared previously[12] − as the chiral starting material and an imidazol-4-yl anion, the preparation of which had been described and discussed in detail elsewhere.[13−15] Suffice it to say that a solution of EtMgBr in diethyl ether had to be added to 4-iodo-1-tritylimidazole in dry CH_2Cl_2 to give the C(4)-metallated imidazole building block, which was not isolated. Treatment of this with **6** provided the diastereomeric D-*xylo* (**7**; 30%) and D-*lyxo* (**8**; 70%) adducts (overall yield: 89%), which were not separated. Since it was the minor adduct **7** that was needed for the preparation of target molecule *ent*-**2**, the mixture of adducts **7** and **8** was oxidized (activated MnO_2, CH_2Cl_2, room temp.) to the corresponding ketone **9** (87%), reduction of which (L-Selectride, THF, −50 °C) afforded the desired **7** as the major compound (97%), together with small amounts of **8** (3%), in 97% overall yield. *O*-Benzylation of **7** gave **10**, acid-induced deprotection of which (HCl/THF) provided the crystalline compound **11**. Bis(tritylation) of this yielded **12**, which was treated with Tf_2O (in pyridine/CH_2Cl_2), resulting in immediate intramolecular Walden inversion. The resulting bicyclic bis(trityl)imidazolium ion intermediate, which was neither isolated nor characterized, was treated with acid (HCl) to remove the trityl protecting groups, which provided **13**. Debenzylation of this gave the desired L-*arabino* compound *ent*-**2**, the ^{1}H and ^{13}C NMR spectra of which proved to be identical to and superimposable on those of **2**. Furthermore, the chiroptical properties of *ent*-**2** and of the known D-*arabino* product **2** proved their 3D mirror image structures (Table 1; Figure 1).

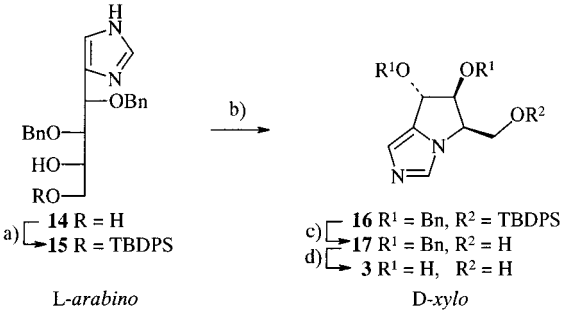
Xylose Series 3/*ent*-3

Retrosynthetic analysis of the D-*xylo* stereomer **3** required the linear imidazolo-L-*arabino* derivative **14** as the



Scheme 2. Reagents and conditions: a) 1) 4-iodo-1-tritylimidazole, EtMgBr/Et_2O, CH_2Cl_2, 2) + **6** in CH_2Cl_2; b) MnO_2, CH_2Cl_2; c) L-Selectride, THF, −50 °C; d) NaH, BnBr, TBAI, THF, 40 °C; e) 4 M HCl/THF (1:3), reflux, 6 h; f) TrCl, NEt_3, DMAP cat., CH_2Cl_2, reflux, 4 h; g) 1) Tf_2O, CH_2Cl_2, −70 °C to 0 °C, then MeOH and concentration, 2) 6 M HCl, dioxane, 55 °C, 3 h; h) H_2, $Pd(OH)_2$/C, EtOH/AcOH (3:2)

chiral precursor (Scheme 3). The synthesis of this compound had already been described in a previous publication.[10] The primary alcohol of **14** was selectively silylated (TBDPSCl/imidazole/DMF) to provide **15**. Walden inversion occurred at once when Tf_2O was added to **15** in pyridine, the secondary triflate intermediate undergoing spontaneous intramolecular nucleophilic attack by the nearest imidazole nitrogen atom to give **16**. After the standard workup, D-*xylo* derivative **16** was isolated and partly deprotected by fluoride ion (TBAF/THF) to give **17**, which was debenzylated by catalytic hydrogenolysis to yield the desired D-*xylo* target molecule **3**.

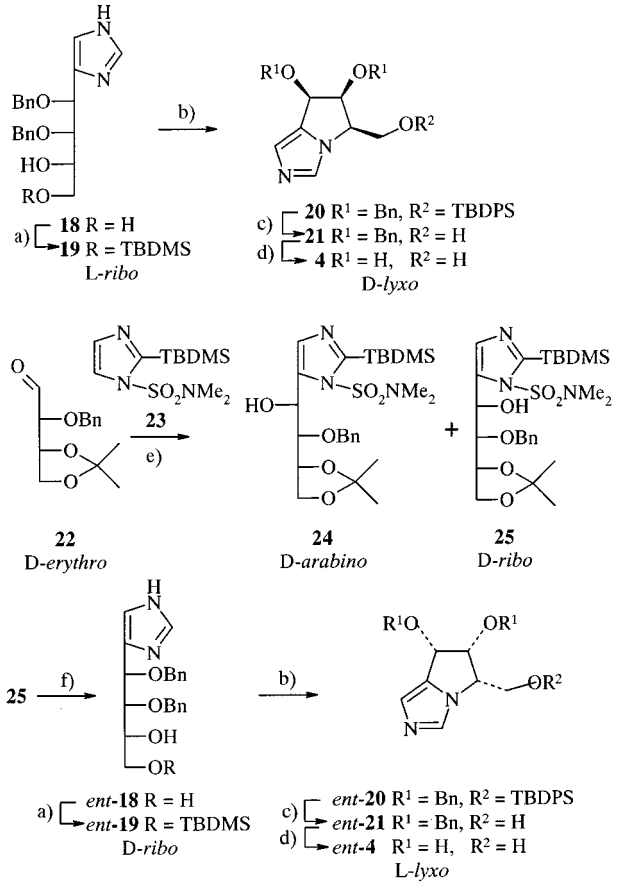


Scheme 3. Reagents and conditions: a) 1) imidazole, DMF, TBDPSCl, 2) + **14** in DMF, room temp., 14 h; b) Tf_2O, pyridine, CH_2Cl_2, −78 °C, to room temp.; c) TBAF, THF, room temp.; d) H_2 (30 bar), $Pd(OH)_2$/C, MeOH/AcOH

The synthesis of the L-*xylo* enantiomer *ent*-**3** had already been described previously[8,11] and its 3D structure demonstrated by single-crystal X-ray diffraction analysis.[8] The ^1H and ^{13}C NMR spectra of **3** proved to be identical to, and therefore superimposable on, those of *ent*-**3**. Furthermore, the chiroptical properties were in perfect agreement with the expected 3D mirror image relationship of the enantiomeric pair **3**/*ent*-**3** (Table 1, Figure 1).

Lyxose Series 4/*ent*-4

Retrosynthetic analysis of the D-*lyxo* stereomer required the linear imidazolo-L-*ribo* derivative precursor **18**, the synthesis of which we had already described in a previous publication.[10] The linear synthetic sequence was very similar to the one that we used for the preparation of the D-*xylo* compound **3**. The primary alcohol of **18** was selectively silylated (TBDPSCl/imidazole/DMF) to afford **19**. Intramolecular Walden inversion occurred at once when Tf_2O was added to **19** in pyridine, the intermediate secondary triflate undergoing nucleophilic attack by the nearest nitrogen atom of the imidazole moiety. After the standard workup, D-*lyxo* derivative **20** was isolated and treated with TBAF to give **21**, which was debenzylated by hydrogenolysis to yield the D-*lyxo* stereomer **4** (Scheme 4).



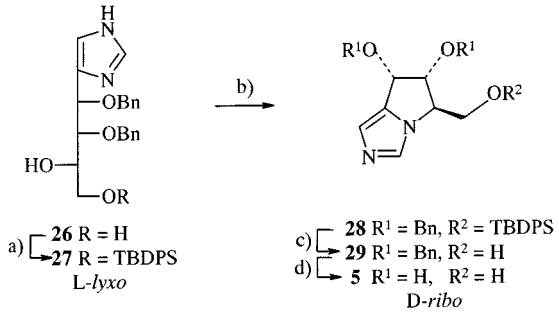
Scheme 4. Reagents and conditions: a) 1) imidazole, TBDPSCl, DMF, 2) + **18** in DMF; b) Tf_2O, CH_2Cl_2, −78 °C to room temp.; c) TBAF, THF, room temp.; d) H_2 (30 bar), $Pd(OH)_2$/C, MeOH/AcOH; e) 1) **15**, *n*BuLi, THF, −78 °C, 15 min, 2) + **22** in THF, −78 °C to room temp.; f) 1) NaH, THF, TBAI cat, BnBr, 40 °C, 2) + 6 M HCl at room temp., then 45 °C, 14 h

The retrosynthetic analysis of the L-*lyxo* stereomer *ent*-**4** was identical to the preceding one, albeit obviously in the enantiomeric series (Scheme 4). The starting material was the D-*erythro* compound **22**, a known and easily prepared product.[16,17] Nucleophilic addition of the known lithio derivative of imidazole **23**[18] to **22** provided the minor D-*arabino* product **24** (25%) and the major D-*ribo* diastereomer **25** (75%) in 88% overall yield. Adduct **25** was *O*-benzylated and the acid-sensitive protection groups of the ensuing (fully protected) intermediate were removed with HCl, to afford *ent*-**18**. From this, *ent*-**19** was formed, and eventually the pyrrolidinose derivatives *ent*-**20** and *ent*-**21** were obtained. Standard deprotection of the latter gave the L-*lyxo* derivative *ent*-**4**, the chiroptical properties of which demonstrated its mirror image relationship with the D-*lyxo* stereomer **4** (Table 1, Figure 1).

Ribose Series 5/*ent*-5

Retrosynthetic analysis of the D-*ribo* stereomer **5** required the linear imidazolo-L-*lyxo*-diol derivative **26** as the chiral precursor (Scheme 5). This diol, the synthesis of which had

already been described in a previous publication,[10] was selectively silylated (TBDPSCl/imidazole/DMF) at the primary alcohol to provide **27**. Intramolecular Walden inversion occurred spontaneously when Tf_2O was added to **27** in pyridine, the intermediate secondary triflate spontaneously undergoing S_N2 attack by the nearest N atom. After the standard workup, D-*ribo* derivative **28** was isolated. Treatment of the latter with fluoride ion (TBAF/THF) gave **29**, which was debenzylated by catalytic hydrogenolysis to give the D-*ribo* **5** target molecule (Scheme 5).



Scheme 5. Reagents and conditions: a) 1) imidazole, TBDPSCl, CH_2Cl_2, NEt_3, DMAP cat, 2) + **26** in DMF; b) Tf_2O, pyridine, CH_2Cl_2, −25 °C; c) TBAF, THF, room temp.; d) H_2, $Pd(OH)_2$/C, AcOH

The synthesis of the L-*ribo* enantiomer *ent*-**5** had already been described by us in a previous publication.[11] The ^1H and ^{13}C NMR spectra of **5** and *ent*-**5** proved to be identical and superimposable. Furthermore, their chiroptical properties permitted their 3D mirror image relationship to be demonstrated unambiguously (Table 1 and Figure 1).

Spectral Properties and Structure Analyses

The structural and configurational assignments of all eight imidazolo-pyrrolidinopentoses **2** to **5** and *ent*-**2** to *ent*-**5** could be achieved without ambiguity thanks to the combination of $^1H/^{13}C$ NMR spectroscopy, circular dichroism (CD spectra: Figure 1), and rotatory power data ($[\alpha]_D^{20}$ values: Table 1).

The D-*arabino*-configured imidazolo-pyrrolidino-pentose **2** had already been synthesized.[11] That **2** occurs in the D-*arabino* configuration is due to the fact that it had been obtained from L-sorbose, in which the configurations of carbon atoms C(3) and C(4) had been retained,[19] whereas C(5) had undergone a Walden inversion during the intramolecular cyclisation step.[11] These three consecutive asymmetric carbon atoms of L-sorbose correspond to carbon atoms C(7), C(6), and C(5), respectively, in compound **2**;[11] as for carbon atom C(2) of L-sorbose, it had been incorporated into the imidazole ring of **2** as described in a previous publication.[19] Since the newly synthesized stereomer *ent*-**2** had ^1H and ^{13}C NMR spectra identical to and superimposable on those of **2**, and since furthermore the chiroptical data of *ent*-**2** were the mirror image of those of **2** (Table 1 and Figure 1), it followed that *ent*-**2** and **2** were enantiomeric entities.

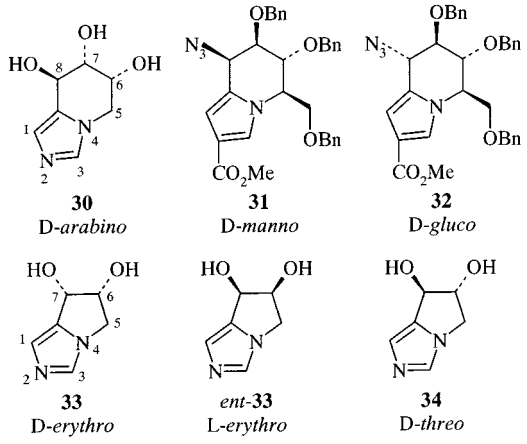
Similar arguments could be put forward to demonstrate the absolute configuration of the newly synthesized imidazolo-sugar **3**: i) compound **3** had ^1H and ^{13}C NMR spectra identical to and superimposable on those of the known stereomer *ent*-**3**,[8,11] ii) the chiroptical data of **3** were of opposite sign to and the mirror image of those of *ent*-**3** ($[\alpha]_D$ values: Table 1; CD spectra: Figure 1). It followed that **3** and *ent*-**3** were enantiomeric entities. Note furthermore that the absolute configuration of *ent*-**3** had already been ascertained in a previous publication, by a single-crystal X-ray diffraction analysis.[8]

Analogously, NMR and chiroptical arguments permitted the absolute D-*ribo* configuration of **5** to be demonstrated by comparison with the known L-*ribo* configuration of *ent*-**5**.[11]

As to the opposite enantiomers in the *lyxo* series, neither of which was known, their ^1H and ^{13}C NMR spectra proved to be identical and superimposable; furthermore they appeared to be quite different from those of the other three pairs of enantiomers. In addition, the synthetic flow sheet of **4** (D-*lyxo*) was straightforward (Scheme 4); since starting material **18** had been demonstrated to be L-*ribo*-configured (see above and Scheme 3), it followed that the target molecule **4** existed in the D-*lyxo* configuration after the intramolecular Walden inversion; hence, the L-*lyxo* configuration for *ent*-**4**, as deduced i) from its ^1H and ^{13}C NMR spectra, which proved to be identical to and superimposable on those of **4**, ii) from its CD spectrum, which was the mirror image of that of *ent*-**4** (Figure 1), and iii) from its rotatory power, which was of the same magnitude as, but of opposite sign to, that of *ent*-**4** (Table 1).

Chiroptical data, particularly circular dichroism (CD) spectra, proved to be of great help, since they enabled mirror image relationships to be demonstrated between opposite enantiomers, as described above (Figure 1). The sign of the long-wavelength Cotton effect (CE), which appeared at 210−212 nm, seemed to be determined by the absolute configuration of the asymmetric center C(7), connected directly to the imidazole chromophore, the (7*R*) configuration giving rise to a positive CE and the (7*S*) form to a negative one, as observed in all instances (Figure 1). The same correlation between the sign of the long-wavelength CE and the absolute configuration of carbon atom C(8) − also directly connected to the imidazole chromophore − had also been observed with the analogous and isomeric imidazolo-*piperidino*-pentose isomers of type **30** (Scheme 6), the (8*R*) configuration producing a positive CE and (8*S*) a negative one.[10] Similarly, Vasella and co-workers published some CD data for pyrrolo-*piperidino*-hexose derivatives, and showed that the D-*manno*-pyrrolo-piperidino-hexose **31**, which is (8*R*)-configured, appeared with a pronounced positive CE, whereas its (8*S*)-configured D-*gluco* diastereomer **32** appeared with a negative CE (Scheme 6).[20]

Furthermore, the imidazolo-*pyrrolidino*-tetroses **33** (D-*erythro*), *ent*-**33** (L-*erythro*), and **34** (D-*threo*), the syntheses of which we had described previously (the L-*threo* enantiomer



Scheme 6. Imidazolopiperidinose **30**, pyrrolopiperidinoses **31** and **32**, and imidazolopyrrolidinoses **33**, *ent*-**33**, and **34**

ent-**34** has not been prepared),[11] showed similar CD spectra, a (7*R*) configuration giving rise to a positive long-wavelength CE and (7*S*) to a negative one. Their C(5) carbon atoms being devoid of hydroxymethylene groups, these three imidazolo-*pyrrolidino*-tetroses represent reference compounds when it comes to comparative CD spectral interpretations with respect to the pentose homologues described here (those of Figure 1). To illustrate that point, let us compare the CD spectra of D-*threo*-tetrose **34** and of D-*arabino*-pentose **2**. Each had a pronounced positive CE (**34**: $\Delta\varepsilon = +4.45$ at 212 nm; **2**: $\Delta\varepsilon = +4.10$ at 210.5 nm), most probably as a consequence of their (8*R*) and (7*R*) configurations, respectively. Furthermore, each showed a negative CE at shorter wavelength (**34**: $\Delta\varepsilon = -3.90$ at 198 nm; **2**: $\Delta\varepsilon = -2.23$ at 197 nm). Last but not least, an additional negative CE appeared at higher wavelength, but only for imidazolo-pentose **2** ($\Delta\varepsilon = -0.75$ at 225.5 nm), the CD spectrum of imidazolo-tetrose **34** being devoid of such an analogous long-wavelength CE. It is reasonable to assume that this long-wavelength CE band appearing with **2** is due to the asymmetric carbon atom C(5*R*), which bears the CH_2OH group. We note that the two longest-wavelength CE bands of imidazolo-pyrrolidino-pentoses − i.e., at $\lambda = 210-212$ nm (strong band) and $\lambda = 225-226$ nm (weak band) − can clearly be distinguished in the CD spectra when of opposite sign [i.e., when C(5) and C(7) have the same CIP notation], as observed in D- and L-*arabino* and in D- and L-*lyxo* azasugar derivatives (Figure 1).

Let us now compare the CD spectra of D-*erythro*-tetrose **33** and of D-*ribo*-pentose **5**. Each had a pronounced negative long-wavelength CE at 214 nm (and a very pronounced positive CE at 199 nm). The 214-nm band of **5** was slightly broadened when compared to the corresponding band of **33**, the broadening effect obviously being due to the superposition of two CEs with different amplitudes but the same sign. That is to say that stereomeric imidazolo-pyrrolidino-pentoses with opposite CIP notations for C(5) and C(7) produce two CEs with the same sign in their CD spectra. As a consequence, the longest-wavelength and less pronounced CE (with an estimated $\lambda_{max} = 226$ nm) is hidden beneath the stronger band, the λ_{max} of which appears at 213−214 nm, this being observed with D-*xylo* (**3**) and with D-*ribo* (**5**) stereomers, as well as with their respective enantiomers (Figure 1).

Enzymatic Assays

All eight imidazolo-pyrrolidino-pentoses in Scheme 1 have been evaluated as potential inhibitors of six commercially available glycosidases, and the results compiled in Table 2. All imidazolo sugars that were active proved to be competitive inhibitors.

The D-*arabino* stereomer **2** was a good and selective inhibitor of Jack bean α-D-mannosidase ($K_i = 5$ μM). The D-*xylo* stereomer **3** proved to be an even better inhibitor of *Escherichia coli* β-D-galactosidase ($K_i = 0.2$ μM determined by Morrisson treatment),[21] albeit the association occurred at a rather reduced rate. Nevertheless, **3** turned out to be nonselective, since it also inhibited baker's yeast α-D-glucosidase and green coffee bean α-D-galactosidase (see Table 2). Similarly, D-*lyxo* stereomer **4** was a nonselective and generally a poor inhibitor of the same three glycosidases. The D-*ribo* stereomer **5** was totally inactive with any of the six glycosidases.

As to the four stereomers of the L-series, these were inactive with the exception of *ent*-**3**, which was a poor inhibitor of Jack bean α-D-mannosidase.

Imidazolo-pyrrolidino-tetroses **33** (D-*erythro*), *ent*-**33** (L-*erythro*), and **34** (D-*threo*) had already been evaluated as potential inhibitors with the same six glycosidases. They had turned out to be inactive, with only D-*threo* derivative **34** showing poor inhibition with an α-mannosidase.[11]

Within the rather limited scope of only six glycosidases, it is fair to say that the (*R*) configuration at C(5) seems to be mandatory for some inhibition to be attained; this

Table 1. Rotatory power data ($[\alpha]_D^{20}$ values) for the eight stereomers **2** to **5** and *ent*-**2** to *ent*-**5**

2 (D-*arabino*)	**3** (D-*xylo*)	**4** (D-*lyxo*)	**5** (D-*ribo*)
+9	+41	+12	+70
($c = 1.0$, H_2O)	($c = 0.6$, EtOH)	($c = 0.6$, MeOH)	($c = 1.0$, MeOH)
ent-**2** (L-*arabino*)	*ent*-**3** (L-*xylo*)	*ent*-**4** (L-*lyxo*)	*ent*-**5** (L-*ribo*)
−8	−41	−12	−58
($c = 1.0$, H_2O)	($c = 0.75$, EtOH)	($c = 0.75$, MeOH)	($c = 1.0$, MeOH)

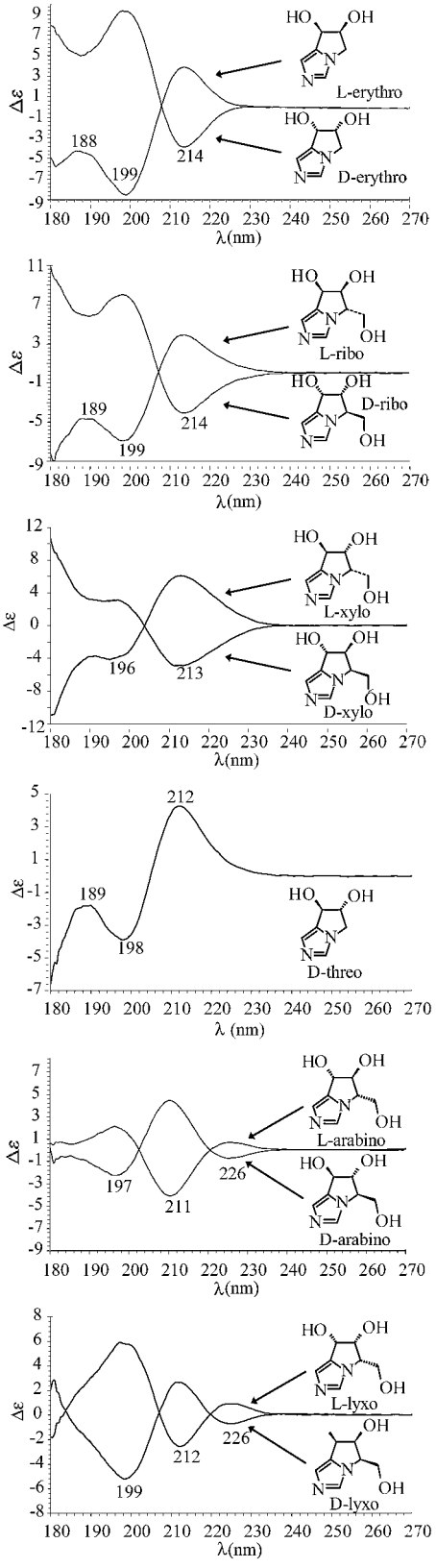


Figure 1. Circular dichroism of the imidazolopyrrolidinoses

observation goes along with the second prerequisite, that the $-CH_2OH$ handle must be present in these D-series compounds in order to obtain a proper docking into the enzymes' active sites. Beyond that, it would seem to be rather risky to deduce any rational interpretation in terms of configuration and functional complementarity between the imidazolo sugars described here and the chiral 3D structures of the enzymes' active sites.

Table 2. Inhibition constants (IC_{50}) in μM measured at 22 °C; NI = no inhibition at [I] = 1 mM; ([S] = K_M); %: percentage of inhibition at 1 mM; (1) slow association; (2) slow association, K_i with Morrisson treatment

	D-*arabino* **2**	D-*xylo* **3**	D-*lyxo* **4**	D-*ribo* **5**
α-D-Glucosidase Baker's Yeast EC 3.2.1.20	NI	IC_{50} = 40 μM (1)	IC_{50} = 730 μM	NI
β-D-Glucosidase almonds EC 3.2.1.21	NI	NI	57%	NI
α-D-Galactosidase green coffee beans EC 3.2.1.22	NI	IC_{50} = 110 μM	IC_{50} = 225 μM	NI
β-D-Galactosidase (VI) *Escherichia coli* EC 3.2.1.23	NI	IC_{50} = 10 μM K_i = 0.2 μM (2)	IC_{50} = 620 μM	NI
α-D-Mannosidase Jack beans EC 3.2.1.24	IC_{50} = 10 μM K_i = 5 μM	NI	NI	NI
β-D-Mannosidase snail acetone powder EC 3.2.1.25	NI	NI	NI	NI
	L-*arabino* *ent*-**2**	L-*xylo* *ent*-**3**	L-*lyxo* *ent*-**4**	L-*ribo* *ent*-**5**
α-D-Glucosidase baker's Yeast EC 3.2.1.20	NI	NI	NI	NI
β-D-Glucosidase almonds EC 3.2.1.21	NI	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	NI	NI	15%	NI
α-D-Mannosidase Jack beans EC 3.2.1.24	NI	IC_{50} = 150 μM	NI	NI
β-D-Mannosidase snail acetone powder EC 3.2.1.25	NI	NI	NI	NI

Experimental Section

General: Flash chromatography (FC): silica gel (Merck 60; 230−400 mesh). TLC: silica gel on aluminium sheets (Merck 60 HF_{254}); the spots were viewed under 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 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 Dichrograph (Δε values) at the research center of the Roche pharmaceutical division in Basel, Switzerland. ^{1}H and ^{13}C NMR spectra: 250 MHz and 62.9 MHz, respectively; Bruker ACF 250 spectrometer at 300 K. Internal references for ^{1}H NMR: $SiMe_4$ (δ = 0.00), $CDCl_3$ (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 were measured with an 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. "MeOH + NH_3" stands for a solution of pure MeOH saturated at room temp with NH_3 (ex gas form).

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 baker's yeast, β-glucosidase (EC 3.2.1.21) from almonds, α-galactosidase (EC 3.2.1.22) from green coffee beans, β-galactosidase from *Escherichia 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,[22] 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), *p*-nitrophenyl-β-D-glucopyranoside for β-glucosidase (K_m = 2 mM, pH = 5.0), and *p*-nitrophenyl-β-D-galactoside (K_m = 0.3 mM, pH = 7) 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 were performed at 25 °C and the reaction was started by the 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 the Dixon graphical procedure.[23,24]

Coupling Reaction between an Imidazole Grignard Reagent and the D-Threose Derivative 6: A solution of EtMgBr in Et_2O (3 M, 12.6 mL, 37.9 mmol) was added under argon at room temp. to a stirred solution of 4-iodo-1-tritylimidazole (15.16 g, 34.8 mmol)[14] in anhydrous CH_2Cl_2. After 15 min, a solution of aldehyde **6** (7.90 g, 31.6 mmol)[13–15] in anhydrous CH_2Cl_2 (45 mL) was added to the stirred mixture and left to react at room temp., the reaction being monitored by TLC (EtOAc/cyclohexane, 7:3). After 2 h, the reaction was quenched with a saturated aq. solution of NH_4Cl (100 mL) and the organic phase was separated, dried ($MgSO_4$), filtered, and concentrated to dryness in vacuo. The crude residue was purified by chromatography (EtOAc/cyclohexane, 7:3, then 8:2), the two diastereomers **7** and **8** as well as trace amounts of imidazole not being separated (all together: 15.83 g, ca. 81% of **7** + **8**).

Imidazolo Ketone Derivative 9: Precipitated activated MnO_2 (20 g) was added under argon at room temp. to a stirred solution of the above mixture of **7** + **8** (4.00 g, 7.13 mmol) in CH_2Cl_2 (45 mL). After 90 min, the reaction mixture was filtered through a small column of silica gel and the column was washed several times with EtOAc. The mixed organic phases were concentrated to dryness and the crude residue was purified by chromatography (EtOAc/cyclohexane, 4:6), to provide ketone **9** as a colorless foam (3.45 g, 87%), which was recrystallised. M.p. 126 °C (EtOAc/cyclohexane). $[\alpha]_D^{20}$ = −50 (*c* = 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.27 and 1.30 [2s, 6 H, 2 C*H*$_3$ *acetonide*], 3.94 [dd, 1 H, C(4)-H$_a$], 4.00 [dd, 1 H, C(4)-H$_b$], 4.50 and 4.70 [*AB*, 2 H, *J* = 11.7, C*H*$_2$Ph], 4.55 [td, 1 H, C(3)-H], 4.72 [d, 1 H, C(2)-H], 7.04–7.12 and 7.22–7.38 [20 H, H-*arom*], 7.46 [d, 1 H, C(4′)-H], 7.82 [d, 1 H, C(2′)-H], $J_{2',4'}$ = 1.3, $J_{2,3}$ = 5.0, $J_{3,4a}$ = 6.7, $J_{3,4b}$ = 6.7. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 25.2 and 25.8 [2 × *C*H$_3$ *acetonide*], 65.4 [C(4)], 72.4 [*C*H$_2$Ph], 75.9 [*C*Ph$_3$], 76.1 [C(3)], 81.8 [C(2)], 109.4 [*C*(CH$_3$)$_2$], 127.4–129.3 [C-*arom*], 137.2 and 138.5 (*C*$_s$ of Ph], 139.3 [C(2′)], 141.3 [*C*$_s$ of C*Ph*$_3$), 192.9 [C(1)]. $C_{36}H_{34}N_2O_4$ (558.65): C 77.39, H 6.13, N 5.01; found C 77.2, H 6.1, N 5.2.

Imidazolo-D-*xylo* Derivative 7: A solution of L-Selectride (1 M, 12.8 mL, 12.8 mmol) in THF was added dropwise at −78 °C to a stirred solution of **9** (4.75 g, 8.50 mmol) in anhydrous THF (80 mL). The reaction was monitored by TLC (EtOAc/cyclohexane, 1:1). After 1 h at −50 °C, the solution was quenched with MeOH (20 mL), and then allowed to warm up to room temp. and concentrated to near dryness in vacuum. The residue was taken up in CH_2Cl_2 (50 mL). The organic solution was washed with a saturated solution of NH_4Cl (100 mL) and the aq. phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated to dryness, and purified by chromatography (EtOAc/cyclohexane, 1:1) to give a mixture of **7** + **8** (4.61 g, 97%) in a 97:3 ratio, as determined by reverse phase HPLC (Chiracel OD-R column, eluent: MeOH/H_2O, 95:5). ^{1}H NMR ($CDCl_3$, 250 MHz) of **7**: δ = 1.30 and 1.41 [2 s, 6 H, 2 × C*H*$_3$ *acetonide*], 2.8 [s$_{large}$, OH], 3.74 [t, 1 H, H$_a$–C(4)], 3.93 [dd, 1 H, H$_b$–C(4)], 3.95 [dd, 1 H, H–C(2)], 4.27 [dt, 1 H, H–C(3)], 4.51 and 4.68 [*AB*, 2 H, *J* = 11.4, C*H*$_2$Ph], 4.73 [d, 1 H, H–C(1)], 6.89 [s, 1 H, H–C(4′)], 7.07–7.34 [m, 20 H, H-*arom*], 7.45 [s, 1 H, H–C(2′)], $J_{1,2}$ = 3.5, $J_{2,3}$ = 6.2, $J_{3,4a}$ = 6.3, $J_{3,4b}$ = 7.7, $J_{4a,4b}$ = 8.2. HR-MS: $[M + H]^+$ ion 561.2747 ($C_{36}H_{37}N_2O_4$, calcd. 561.2753).

Imidazolo-D-*xylo* Derivative 11: A suspension of NaH in oil (50%, 1.15 g, excess) was added at 0 °C to a stirred solution of almost pure **7** (as obtained above: 4.54 g, 8.10 mmol) in anhydrous THF (80 mL) under argon. When the evolution of H_2 had ceased, Bu_4NI (ca. 30 mg) and BnBr (1.16 mL, 1.67 g, 9.72 mmol) were added, the vigorously stirred solution was heated at 40 °C for 12 h and allowed to cool to room temp., and MeOH (5 mL) was added slowly. The solution was concentrated to dryness, the residue was taken up in EtOAc (80 mL), and the resulting solution was washed with H_2O and then with brine and concentrated to dryness, to afford **10** as a crude product that was neither purified nor characterized. Crude product **10** was dissolved in 4 M HCl/THF, 1:3 (40 mL) and heated at reflux for 6 h. THF was evaporated in vacuum, the aqueous phase was extracted with Et_2O (2 × 50 mL), and the organic phase was washed with 2 M HCl (2 × 50 mL). The combined aqueous phases were basified with some solid K_2CO_3 and extracted with CH_2Cl_2. The resulting organic solution was dried ($MgSO_4$), filtered, and concentrated to dryness, and the crude residue was purified by chromatography (CH_2Cl_2/MeOH + NH_3, 9:1) to afford **11** as a crystalline compound (890 mg, 30%). M.p. 114 °C (EtOAc). $[\alpha]_D^{20}$ = +47 (*c* = 2, MeOH). ^{1}H NMR (CD_3OD, 250 MHz): δ = 3.33 [td, 1 H, C(3)-H], 3.49–3.56 [m, 2 H, 2 × C(4)-H], 3.96 [dd, 1 H, C(2)-H], 4.36 and 4.47 [*AB*, 2 H, *J* = 11.6, C*H*$_2$Ph], 4.67 and 4.94 [*AB*, 2 H, *J* = 11.0, C*H*$_2$Ph], 4.83 [d, 1 H, C(1)-H], 7.10 [s, 1 H, C(2′)-H], 7.19–7.37 [m, 10 H, H-*arom*], 7.73 [s, 1 H, C(4′)-H], $J_{1,2}$ = 8.2, $J_{2,3}$ = 2.0, $J_{3,4}$ = 6.3. ^{13}C NMR (CD_3OD, 62.9 MHz): δ = 64.5 [C(4)], 71.9 [*C*H$_2$Ph], 72.8 [C(3)], 76.6 [*C*H$_2$Ph], 78.0 [C(1)], 82.5 [C(2)], 128.5–129.4 [*C-arom and C-imidazole*], 137.1 [*C-arom*], 140.3 [*C-imidazole*].

Imidazolo-D-*xylo* Derivative 12: DMAP (ca. 10 mg), anhydrous Et_3N (920 μL, 6.51 mmol, 3 equiv.), and TrCl (1.51 g, 5.43 mmol, 2.5 equiv.) were added under argon to a stirred solution of **11** (800 mg, 2.17 mmol) in CH_2Cl_2 (24 mL). This solution was heated at reflux for 4 h, allowed to cool to room temp., and washed with

brine, and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic solutions were dried ($MgSO_4$), filtered, and concentrated to dryness, and the crude residue was purified by chromatography (EtOAc/cyclohexane, 2:8) to provide compound **12** (1.044 g, 56%) as a colorless oil. $[\alpha]_D^{20} = +25$ ($c = 2$, MeOH). The ^1H NMR ($CDCl_3$, 250 MHz) and ^{13}C NMR ($CDCl_3$) spectra of **12** proved to be identical to, and therefore superimposable on, those of the known product *ent*-**12**.[11]

L-*arabino*-Imidazolo-Pyrrolidinose Derivative 13: Tf_2O (570 μL, 3.45 mmol, 3 equiv.) was added dropwise at −70 °C to a stirred solution of **12** (978 mg, 1.15 mmol) and pyridine (370 μL, 4.63 mmol, 4 equiv.) in anhydrous CH_2Cl_2 (25 mL), the temperature slowly rising to 0 °C. After 2 h, MeOH was added, the solution was concentrated in vacuo, the residue was taken up in dioxane (40 mL), some 6 M HCl (ca. 3.5 mL) was added slowly at room temp., and the resulting solution was stirred at 55 °C for 3 h and basified at room temp. with solid Na_2CO_3 (ca. 4 g). The resulting mixture was filtered, concentrated to dryness and purified by chromatography ($CHCl_3$/EtOH, 9.5:0.5) to give **13** (330 mg, 82%) as a colorless oil. $[\alpha]_D^{20} = +24$ ($c = 0.6$, $CHCl_3$). The ^1H ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) spectra of **13** proved to be identical to, and therefore superimposable on, those of the known *ent*-**13**.[11]

L-*arabino*-Imidazolo-Pyrrolidinose *ent*-2: A stirred solution of **13** (300 mg, 0.86 mmol) in EtOH/AcOH, 3:2 (10 mL) was put under H_2 for 3 d in the presence of $Pd(OH)_2/C$ (350 mg) at room temp. The suspension was filtered through Clarcel, the solution was concentrated to near dryness in vacuum, the residue was taken up in MeOH, and the resulting solution was percolated over Amberlite IRA-400 (OH^-) beads and concentrated to dryness. The residue was purified by chromatography (Et_2O/MeOH + NH_3, 7:3) to afford *ent*-**2** (72 mg, 49%) as colorless crystals. M.p.$_{dec}$ 220−221 °C (MeOH). $[\alpha]_D^{20} = -8$ ($c = 1$, H_2O) {**2**: $[\alpha]_D^{20} = +9$ ($c = 1$, H_2O)[11]} (see Table 1). CD spectra for **2** and *ent*-**2**: Figure 1. The ^1H and ^{13}C NMR spectra of *ent*-**2** were identical to, and therefore superimposable on, those of the known D-*arabino* stereomer **2**.[11] $C_7H_{10}N_2O_3$ (170.17): C 49.40, H 5.92, N 16.46; found C 49.7, H 6.0, N 16.3.

Imidazolo-L-*arabino* Derivative 15: A solution of imidazole (125 mg, 1.7 mmol) in anhydrous DMF (4 mL) was treated with *tert*-butyldiphenylsilyl chloride (310 μL, 1.1 mmol) at room temp. for 15 min. To this solution was added a solution of **14** (310 mg, 0.85 mmol)[10] in DMF (8 mL). After 14 h at room temp., conversion was complete as determined by TLC (Et_2O/MeOH + NH_3, 98:2). Water (10 mL) was added, and the aq. phase was extracted with Et_2O. The organic solution was washed with a saturated aqueous solution of NH_4Cl (15 mL) to remove imidazole and DMF, dried ($MgSO_4$), filtered, and concentrated to dryness, and the resulting crude foam was purified by chromatography (Et_2O/MeOH + NH_3, 98:2, then 95:5) to give **15** (360 mg, 70%) as a colorless resin. ^1H NMR ($CDCl_3$): δ = 1.06 [s, 9 H, $-OSiPh_2C(CH_3)_3$], 3.76 [dd, 1 H, C(4)-H_b], 3.80 [dd, 1 H, C(2)-H], 3.82 [dd, 1 H, C(4)-H_a], 3.95 [dt, 1 H, C(3)-H], 4.24 and 4.45 [*AB*, 2 H, $J = 11.9$, OCH_2Ph], 4.25 and 4.47 [*AB*, 2 H, $J = 11.2$, OCH_2Ph], 4.82 [d, 1 H, C(1)-H], 7.03 [s, 1 H, C(4′)-H], 7.05−7.12 [m, 2 H, H-*arom*], 7.18−7.50 [m, 14 H, H-*arom*], 7.58 [s, 1 H, C(2′)-H], 7.58−7.66 [m, 4 H, H-*arom*], $J_{1,2} = 3.0$, $J_{2,3} = 6.6$, $J_{3,4a} = J_{3,4b} = 4.8$, $J_{4a,4b} = 10.4$.

D-*xylo*-Imidazolo-Pyrrolidinose Derivative 16: Tf_2O (250 μL, 1.5 mmol, 2.5 equiv.) was added at −78 °C to a solution of **15** (360 mg, 0.59 mmol) and anhydrous pyridine (250 μL, 3 mmol, 5 equiv.) in anhydrous CH_2Cl_2 (7 mL). After 15 min, the reaction mixture was allowed to warm to room temp. and became deep red. After 6 h, conversion seemed to be complete according to TLC (Et_2O/MeOH + NH_3, 98:2). Some H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2, and the organic phase was washed with a saturated NH_4Cl solution to remove pyridine. It was then dried ($MgSO_4$), filtered, and concentrated to dryness, and the resulting slightly yellow oil was purified by chromatography (Et_2O/MeOH + NH_3, 99:1, then 98:2) to give **16** (178 mg, 51%) as a colorless foam. $[\alpha]_D^{20} = +20$ ($c = 0.85$, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 0.98 [s, 9 H, $-OSiPh_2C(CH_3)_3$], 3.82 [dd, 1 H, C(8)-H_b], 3.94 [dd, 1 H, C(8)-H_a], 4.57 [td, 1 H, C(5)-H], 4.61 [dd, 1 H, C(6)-H], 4.51 and 4.66 [*AB*, 2 H, $J = 11.8$, $-OCH_2Ph$], 4.61 and 4.74 [*AB*, 2 H, $J = 11.6$, $-OCH_2Ph$], 4.95 [dd, 1 H, C(7)-H], 6.99 [s, 1 H, C(1)-H], 7.19−7.66 [m, 21 H, H-*arom* and C(3)-H], $J_{1,7} = 0.5$, $J_{5,6} = 6.4$, $J_{5,8a} = 6.2$, $J_{5,8b} = 3.3$, $J_{6,7} = 3.4$, $J_{8a,8b} = 11.0$. HR-MS: $[M + H]^+$ ion 589.2881 ($C_{37}H_{41}N_2SiO_3$, calcd. 589.2886).

D-*xylo*-Imidazolo-Pyrrolidinose Derivative 17: A solution of TBAF in THF (1 M, 0.75 mL, 0.75 mmol) was added at room temp. under argon to a stirred solution of **16** (170 mg, 0.29 mmol) in anhydrous THF (3 mL). After 4 h, conversion was complete according to TLC (CH_2Cl_2/MeOH + NH_3, 9:1). Some H_2O (5 mL) was added and the aqueous solution was extracted with CH_2Cl_2. The organic phase was washed with a saturated aq. solution of Na_2SO_4 to remove the tetrabutylammonium salts, dried ($MgSO_4$), and concentrated to dryness, and the resulting viscous yellow oil was purified by chromatography (CH_2Cl_2/MeOH + NH_3, 95:5, then 90:10) to yield **17** (98 mg, 97%) as a colorless foam. ^1H NMR ($CDCl_3$): δ = 3.86 [dd, 1 H, C(8)-H_b], 3.97 [dd, 1 H, C(8)-H_a], 4.55 [td, 1 H, C(5)-H], 4.66 [dd, 1 H, C(6)-H], 4.56 and 4.68 [*AB*, 2 H, $J = 11.5$, OCH_2Ph], 4.59 and 4.71 [*AB*, 2 H, $J = 11.9$, OCH_2Ph], 4.90 [d, 1 H, C(7)-H], 6.86 [*br* s, 1 H, C(1)-H], 7.25−7.38 [m, 10 H, H-*arom*], 7.55 [*br* s, 1 H, C(3)-H], $J_{5,6} = 6.4$, $J_{5,8a} = 4.0$, $J_{5,8b} = 6.6$, $J_{6,7} = 3.3$, $J_{8a,8b} = 11.9$. ^{13}C NMR ($CDCl_3$): δ = 59.9 [C(5)], 60.9 [C(8)], 71.1 [OCH_2Ph], 72.7 [OCH_2Ph], 76.5 [C(7)], 88.5 [C(6)], 122.2 [C(1)], 127.8−128.5 [10 C, C-*arom*], 131.3 and 133.2 [C(3) and C(7a)], 137.0 and 137.3 [2 C's-*arom*].

D-*xylo*-Imidazolo-Pyrrolidinose 3: A stirred solution of **17** (98 mg, 0.28 mmol) in MeOH (2 mL) and AcOH (1 mL) was put under H_2 pressure (30 bar) in the presence of 20% $Pd(OH)_2/C$ (75 mg) at room temp. After 4 d, the suspension was centrifuged and the catalyst was rinsed several times with hot MeOH under sonication. The combined organic solutions were concentrated in vacuum, sequentially percolated over Clarcel and Amberlite IRA-400 (OH^-) beads to remove acetic acid, and concentrated to dryness, and the resulting crude oil was purified by chromatography ($CHCl_3$/MeOH/MeOH + NH_3, 8:1:1, then 7:2:1) to give **3** (32 mg, 67%) as a colorless powder. $[\alpha]_D^{20} = +41$ ($c = 0.60$, EtOH) (see Table 1). CD spectra of **3** and *ent*-**3**: Figure 1. The ^1H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) spectra proved to be identical to, and therefore superimposable on, those of the known L-*xylo* enantiomer *ent*-**3**.[8,11] HR-MS: $[M + H]^+$ ion 171.0775 ($C_7H_{11}N_2O_3$, calcd. 171.0770).

Imidazolo-L-*ribo* Derivative 19: A solution of imidazole (120 mg, 1.76 mmol) in anhydrous DMF (4 mL) was treated with *tert*-butyldiphenylsilyl chloride (300 μL, 1.08 mmol) at room temp. for 15 min. To this solution was added a solution of the known compound **18** (300 mg, 0.88 mmol)[10] in DMF (8 mL). After 14 h at room temp., conversion was complete as determined by TLC (Et_2O/MeOH + NH_3, 98:2). Water (20 mL) was added, and the reaction mixture was extracted with Et_2O. The organic solution was washed with a saturated aqueous solution of NH_4Cl (30 mL) to remove imidazole and DMF, dried ($MgSO_4$), filtered, and concentrated to dryness, and the resulting crude foam was purified by chromatography (Et_2O/MeOH + NH_3, 98:2, then 95:5) to give **19** (392 mg, 77%) as a colorless resin. ^1H NMR ($CDCl_3$): δ = 1.06 [s, 9 H,

$OSiPh_2C(CH_3)_3$], 3.43 [m, 1 H, C(3)-H], 3.72 [dd, 1 H, C(4)-H_b], 3.80 [dd, 1 H, C(4)-H_a], 3.99 [dd, 1 H, C(2)-H], 4.38 and 4.50 [*AB*, 2 H, J = 11.9, OCH_2Ph], 4.53 and 4.85 [*AB*, 2 H, J = 10.9, OCH_2Ph], 4.91 [d, 1 H, C(1)-H], 7.08 [s, 1 H, C(4′)-H], 7.10−7.50 [m, 16 H, H-*arom*], 7.54 [s, 1 H, C(2′)-H], 7.57−7.66 [m, 4 H, H-*arom*], $J_{1,2}$ = 2.6, $J_{2,3}$ = 8.7, $J_{3,4a}$ = 3.4, $J_{3,4b}$ = 5.2, $J_{4a,4b}$ = 10.4.

D-*lyxo*-Imidazolo-Pyrrolidinose Derivative 20: Tf_2O (300 μL, 1.48 mmol, 2.5 equiv.) was added at −78 °C to a solution of **19** (380 mg, 0.64 mmol) and anhydrous pyridine (300 μL, 3.2 mmol) in anhydrous CH_2Cl_2 (8 mL). After 15 min, the reaction mixture was allowed to warm to room temp. and became deep red. After 6 h, conversion seemed to be complete according to TLC (Et_2O/MeOH + NH_3, 98:2). Water (15 mL) was added, the mixture was extracted with CH_2Cl_2, and the organic phase was washed with a saturated NH_4Cl solution to remove pyridine. It was then dried ($MgSO_4$), filtered, and concentrated to dryness, and the resulting slightly yellow oil was purified by chromatography (Et_2O/MeOH + NH_3, 99:1, then 98:2) to give **20** (220 mg, 58%) as a colorless foam. $[\alpha]_D^{20}$ = −56 (c = 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.02 [s, 9 H, $OSiPh_2C(CH_3)_3$], 3.92−4.02 [m, 2 H, C(8)-H_a and C(8)-H_b], 4.47 [dd, 1 H, C(6)-H], 4.44 and 4.49 [*AB*, 2 H, J = 9.6, OCH_2Ph], 4.37 and 4.59 [*AB*, 2 H, J = 11.7, OCH_2Ph], 4.68 [ddd, 1 H, C(5)-H], 4.73 [d, 1 H, C(7)-H], 7.06 [*br* s, 1 H, C(1)-H], 7.09−7.40 [m, 16 H, H-*arom*], 7.55−7.62 [m, 2 H, H-*arom*], 7.75 [*br* s, 1 H, C(3)-H], $J_{5,6}$ = 7.1, $J_{5,8a}$ = 5.4, $J_{5,8b}$ = 8.6, $J_{6,7}$ = 5.0. ^{13}C NMR (CD_3OD): δ = 61.3 [C(5)], 65.3 [C(8)], 70.5 [C(7)], 71.3 [OCH_2Ph], 73.1 [OCH_2Ph], 83.2 [C(6)], 124.0 [C(1)], 128.7−129.5 [16 C, C-*arom*], 130.9 and 131.1 [2 C, C-*arom*], 133.8 [*br* s, C(7a)], 134.1 [2 C, C's-*arom*], 134.3 [*br* s, C(3)], 136.5 and 136.7 [2 C, C-*arom*], 138.7 and 139.0 [2 C, C's-*arom*]. HR-MS: $[M + H]^+$ ion 589.2885 ($C_{37}H_{41}N_2SiO_3$, calcd. 589.2886).

D-*lyxo*-Imidazolo-Pyrrolidinose Derivative 21: A solution of TBAF in THF (1 M, 2.8 mL, 2.8 mmol, 2.5 equiv.) was added at room temp. under argon to a stirred solution of **20** (630 mg, 1.07 mmol) in anhydrous THF (9 mL). After 4 h, conversion was complete according to TLC (CH_2Cl_2/MeOH + NH_3, 9:1). Some H_2O (5 mL) was added and the reaction mixture was extracted with CH_2Cl_2. The organic phase was washed with a saturated aq. solution of Na_2SO_4 to remove the tetrabutylammonium salts, dried ($MgSO_4$), and concentrated to dryness, and the resulting viscous yellow oil was purified by chromatography (CH_2Cl_2/MeOH + NH_3, 95:5) to yield **21** (355 mg, 95%) as a colorless foam. ^{1}H NMR ($CDCl_3$): δ = 3.95 [dd, 1 H, C(8)-H_b], 4.01 [dd, 1 H, C(8)-H_a], 4.37 [dd, 1 H, C(6)-H], 4.46 [td, 1 H, C(5)-H], 4.42 and 4.65 [*AB*, 2 H, J = 12.5, OCH_2Ph], 4.65 [d, 1 H, C(7)-H], 4.53 and 4.72 [*AB*, 2 H, J = 12.0, OCH_2Ph], 6.88 [*br* s, 1 H, C(1)-H], 7.23−7.38 [m, 10 H, H-*arom*], 7.55 [*br* s, 1 H, C(3)-H], $J_{5,6}$ = 7.3, $J_{5,8a}$ = 4.2, $J_{5,8b}$ = 7.2, $J_{6,7}$ = 5.0, $J_{8a,8b}$ = 11.9. ^{13}C NMR ($CDCl_3$): δ = 59.6 [C(5)], 61.2 [C(8)], 68.0 [C(7)], 69.7 [OCH_2Ph], 71.6 [OCH_2Ph], 81.0 [C(6)], 123.2 [C(1)], 127.6−128.3 [10 C, C-*phenyl*], 131.2 [C(7a)], 132.5 [C(3)], 136.8 [1 C, C's-*phenyl*], 136.9 [1 C, C's-*phenyl*].

D-*lyxo*-Imidazolo-Pyrrolidinose 4: A stirred solution of **21** (355 mg, 1.01 mmol) in MeOH (4 mL) and AcOH (2 mL) was put under H_2 pressure (30 bar) in the presence of 20% $Pd(OH)_2$/C (+ 30% H_2O) at room temp., the reaction being monitored by TLC (CH_2Cl_2/MeOH + NH_3, 2:1). After 7 d, conversion seemed to be complete. The suspension was centrifuged and the catalyst was rinsed several times with hot MeOH under sonication. The combined organic solutions were concentrated in vacuum, sequentially percolated over Clarcel and Amberlite IRA-400 (OH^-) beads to remove acetic acid, and then concentrated to dryness. The resulting crude oil was purified by chromatography ($CHCl_3$/MeOH/MeOH + NH_3, 8:1:1, then 7:2:1) to give **4** (95 mg, 55%) as a slightly gray powder that could not be crystallized. $[\alpha]_D^{20}$ = +12 (c = 0.6, MeOH) (see Table 1). CD spectrum: Figure 1. ^{1}H NMR (CD_3OD, 250 MHz): δ = 3.83 [dd, 1 H, C(8)-H_b], 3.95 [dd, 1 H, C(8)-H_a], 4.48 [*br* m, 1 H, C(5)-H], 4.72 [dd, 1 H, C(6)-H], 4.90 [d, 1 H, C(7)-H], 6.97 [*br* s, 1 H, C(1)-H], 7.71 [*br* s, 1 H, C(3)-H], $J_{5,6}$ = 6.3, $J_{5,8a}$ = 2.8, $J_{5,8b}$ = 6.4, $J_{6,7}$ = 5.1, $J_{8a,8b}$ = 11.6. ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 61.5 [C(8)], 62.3 [C(5)], 65.9 [C(7)], 76.9 [C(6)], 122.2 [C(1)], 133.0 [C(3)], 137.6 [C(7a)]. HR-MS: $[M + H]^+$ ion 171.0771 ($C_7H_{11}N_2O_3$, calcd. 171.0770).

Coupling Reaction between the C(4)-Lithio Derivative of Imidazole 23 and D-*erythro*-Aldehyde 22: A solution of *n*BuLi in hexane (1.6 M, 11.8 mL, 18.9 mmol, 1.1 equiv.) was added under argon at −78 °C to a stirred solution of imidazole **23** (6.05 g, 20.9 mmol) in anhydrous THF (50 mL), whereupon the solution became red. After 15 min, a solution of the known compound **22** (4.25 g, 17.0 mmol)[17,18,21] in anhydrous THF (40 mL) was added dropwise, and the reaction mixture was monitored by TLC (EtOAc/cyclohexane, 3:7). After 90 min, the solution was allowed to warm to room temp., H_2O (30 mL) was added, the reaction mixture was extracted with CH_2Cl_2, and the organic phase was dried ($MgSO_4$), filtered, and concentrated to dryness to afford an orange-colored syrup that consisted of the two diastereomers **24** (minor product) and **25** (major product) in a 1:3 ratio. These two compounds were separated by careful chromatography (EtOAc/cyclohexane, 2:8, then 3:7) to provide the D-*arabino* (**24**; 2.02 g) and the D-*ribo* diastereomer (**25**; 6.03 g) (total yield of **24** + **25**: 88%).

D-*arabino* Stereomer 24: Its ^{1}H and ^{13}C NMR spectra ($CDCl_3$) proved to be identical to and therefore superimposable on those of *ent*-**24**, the synthesis and spectral properties of which had already been described in a previous publication.[10]

D-*ribo* Stereomer 25: Its ^{1}H and ^{13}C NMR spectra proved to be identical to and therefore superimposable on those of *ent*-**25**, the synthesis and spectral properties of which had also been described in the same publication.[10]

Imidazolo-D-*ribo* Derivative *ent*-18: A suspension of NaH in oil (60%, 1.34 g, ca. 33 mmol, 3 equiv.), and a catalytic amount of Bu_4NI (50 mg) were added under argon at room temp. to a stirred solution of **25** (6.00 g, 11.1 mmol) in anhydrous THF (150 mL). The mixture was heated at 35 °C for 30 min, whereupon it turned red. BnBr (1.6 mL, 13.5 mmol, 1.2 equiv.) was added to this stirred solution, and the solution was heated at 40 °C for 15 h. The fully protected intermediate formed according to TLC (EtOAc/cyclohexane, 3:7), was neither isolated nor characterized. After the reaction mixture had cooled to room temp., H_2O (15 mL) and 6 M HCl (30 mL) were added and the solution was heated at 45 °C for 14 h. Having been allowed to cool to room temp., the reaction mixture was extracted with CH_2Cl_2 in order to remove polar impurities. The aq. phase was neutralized with ammonia and extracted with CH_2Cl_2, the organic phase was dried ($MgSO_4$), filtered, and concentrated to dryness, and the crude residue was purified by chromatography (CH_2Cl_2/MeOH + NH_3, 98:2, then 95:5, and eventually 90:10) to provide *ent*-**18** (1.74 g, 47%) as a colorless resin. $[\alpha]_D^{20}$ = +48 (c = 0.6, MeOH). The ^{1}H ($CDCl_3$) and ^{13}C NMR (CD_3OD) spectra proved to be identical to, and therefore superimposable on, those of **18**.[10] HR-MS: $[M + Na]^+$ ion 391.1636 ($C_{21}H_{24}N_2O_4Na$, calcd. 391.1634).

Imidazolo-D-*ribo* Derivative *ent*-19: This compound was produced by the same procedure as for **19**, starting from imidazole (600 mg, 8.84 mmol) in anhydrous DMF (30 mL), *tert*-butyldiphenylsilyl chloride (1.70 g, 6.2 mmol, 1.4 equiv.), and *ent*-**18** (1.63 g, 4.42

mmol). Workup followed by chromatography gave *ent*-**19** (1.53 g, 57%) as a colorless foam. The ^1H and ^{13}C NMR spectra proved to be identical to, and therefore superimposable on, those of **19** (see above).

L-*lyxo*-Imidazolo-Pyrrolidinose Derivative *ent*-20: This compound was produced by the same procedure as above for the preparation of **20**, starting from *ent*-**19** (1.53 g, 2.51 mmol), pyridine (1.1 mL, 6.7 mmol, 5 equiv.), CH_2Cl_2 (32 mL), and Tf_2O (1.1 mL, 6.7 mmol, 2.5 equiv.). Workup followed by chromatography gave *ent*-**20** (683 mg, 46%) as a colorless foam. $[\alpha]_D^{20} = +63$ ($c = 1.1$, CH_2Cl_2). The ^1H and ^{13}C NMR were identical to, and therefore superimposable on, those of **20** (see above).

L-*lyxo*-Imidazolo-Pyrrolidinose Derivative *ent*-21: This compound was produced by the same procedure as above for the preparation of **21**, starting from *ent*-**20** (680 mg, 1.15 mmol), THF (10 mL) under argon, and TBAF in THF (1 M, 2.9 mL). Workup followed by chromatography gave *ent*-**21** (365 mg, 91%) as a colorless oil. The ^1H and ^{13}C NMR spectra were identical to, and therefore superimposable on, those of **21** (see above).

L-*lyxo*-Imidazolo-Pyrrolidinose *ent*-4: This compound was produced by the same procedure as above for the preparation of **4**, starting from *ent*-**21** (150 mg, 0.43 mmol) in MeOH (4 mL) and AcOH (2 mL) under H_2 pressure (30 bar) in the presence of 20% $Pd(OH)_2/C$. After 4 d, workup and chromatography afforded *ent*-**4** (46 mg, 63%) as a colorless powder. $[\alpha]_D^{20} = -12$ ($c = 0.75$, MeOH) (see Table 1). CD spectra of **4** and *ent*-**4**: see Figure 1. The ^1H NMR and ^{13}C NMR spectra were identical to those of **4** (see above). HR-MS: $[M + H]^+$ ion 171.0770 ($C_7H_{11}N_2O_3$, calcd. 171.0770).

Imidazolo-L-*lyxo* Derivative 27: A solution of imidazole (135 mg, 1.98 mmol) in anhydrous CH_2Cl_2 (15 mL) was treated with TBDPSCl (430 μL, 1.65 mmol) in the presence of Et_3N (250 μL, 1.8 mmol) and catalytic amounts of DMAP (6 mg) for 15 min at room temp. To this solution was added a solution of the known compound **26** (501 mg, 1.36 mmol)[10] in CH_2Cl_2 (5 mL). After 3 h at room temp., conversion was complete, as monitored by TLC (Et_2O/MeOH + NH_3, 95:5). Water (10 mL) was added and the aq. phase was extracted with CH_2Cl_2, and the organic phase was washed with a saturated aq. solution of NH_4Cl (20 mL) to remove imidazole, dried ($MgSO_4$), filtered, and concentrated to dryness, and the resulting crude foam was purified by chromatography (Et_2O/MeOH + NH_3, 98:2, then 95:5) to afford **27** (715 mg, 87%) as a colorless, viscous foam. ^1H NMR (CD_3OD): δ = 1.04 [s, 9 H, $OSiPh_2C(CH_3)_3$], 3.60−3.75 [m, 2 H, C(4)-H_a and C(4)-H_b], 4.05−4.20 [m, 2 H, C(2)-H and C(3)-H], 4.07 and 4.32 [*AB*, 2 H, $J = 11.0$, OCH_2Ph], 4.36 and 4.47 [*AB*, 2 H, $J = 11.5$, OCH_2Ph], 4.73 [d, 1 H, C(1)-H], 6.95−7.00 [m, 2 H, H-*arom*], 7.09 [s, 1 H, C(4′)-H], 7.15−7.41 [m, 14 H, H-*arom*], 7.62−7.66 [m, 4 H, H-*arom*], 7.72 [s, 1 H, C(2′)-H], $J_{1,2} = 8.2$.

D-*ribo*-Imidazolo-Pyrrolidinose Derivative 28: Tf_2O (205 μL, 1.24 mmol, 3 equiv.) was added at −25 °C to a solution of **27** (250 mg, 0.41 mmol) and anhydrous pyridine (200 μL, 2.5 mmol, 6 equiv.) in anhydrous CH_2Cl_2 (10 mL). After 30 min, the solution was allowed to warm to room temp., the reaction being monitored by TLC (Et_2O/MeOH + NH_3, 98:2). After 1 h, the mixture was treated with saturated aq. $NaHCO_3$ (5 mL) and the resulting medium was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), filtered, and concentrated to dryness, and the crude residue was purified by chromatography (Et_2O/MeOH + NH_3, 98:2), to afford **28** (173 mg, 71%) as a colorless foam. ^1H NMR (CD_3OD): δ = 1.02 [s, 9 H, $OSiPh_2C(CH_3)_3$], 3.95 [dd, 1 H, C(8)-H_b], 4.21 [dd, 1 H, C(8)-H_a], 4.40 [ddd, 1 H, C(5)-H], 4.47 [dd, 1 H, C(6)-H], 4.52 and 4.64 [*AB*, 2 H, $J = 12.1$, OCH_2Ph], 4.45 and 4.69 [*AB*, 2 H, $J = 11.8$, OCH_2Ph], 4.95 [d, 1 H, C(7)-H], 7.06 [s, 1 H, C(1)-H], 7.26−7.57 [m, 20 H, H-*arom*], 7.62 [s, 1 H, C(3)-H], $J_{5,6} = 7.3$, $J_{5,8a} = 2.4$, $J_{5,8b} = 4.3$, $J_{6,7} = 4.8$, $J_{8a,8b} = 11.6$.

D-*ribo*-Imidazolo-Pyrrolidinose Derivative 29: This compound was produced by the same procedure as for *ent*-**21** in Scheme 4, starting from **28** (270 mg, 0.46 mmol) in THF (15 mL) under argon and a solution of TBAF in THF (1 M, 1.6 mL, 1.6 mmol). Standard workup followed by chromatography (Et_2O/MeOH + NH_3, 95:5, then 90:10) provided **29** (158 mg, 95%) as a foam, which crystallized. M.p. 148 °C (EtOAc). $[\alpha]_D^{20} = +151$ ($c = 1.0$, MeOH). ^1H NMR (CD_3OD): δ = 3.74 [dd, 1 H, C(8)-H_b], 4.18 [dd, 1 H, C(8)-H_a], 4.30−4.42 [m, 2 H, C(5)-H and C(6)-H], 4.51 and 4.64 [*AB*, 2 H, $J = 11.2$, OCH_2Ph], 4.60 and 4.75 [*AB*, 2 H, $J = 11.6$, OCH_2Ph], 4.91 [d, 1 H, C(7)-H], 7.02 [*br* s, 1 H, C(1)-H], 7.25−7.42 [m, 10 H, H-*arom*], 7.77 [br. s, 1 H, C(3)-H], $J_{5,8a} = 2.4$, $J_{5,8b} = 6.0$, $J_{6,7} = 4.5$, $J_{8a,8b} = 11.8$. ^{13}C NMR (CD_3OD): δ = 61.8 [C(5)], 63.2 [C(8)], 70.4 [O*C*H_2Ph], 71.4 [O*C*H_2Ph], 73.3 [C(7)], 83.8 [C(6)], 123.9 [C(1)], 129.0, 129.3, 129.5 [10 C, C-*arom*], 132.9 [C(3)], 134.7 [C(7a)], 138.9 [C's-*phenyl*], 139.0 [C's-*phenyl*]. HR-MS: $[M]^+$ ion 350.1645 ($C_{21}H_{22}N_2O_3$, calcd. 350.1630). $C_{21}H_{22}N_2O_3$ (350.40): C 71.98, H 6.33, N 8.00; found C 71.9, H 6.1, N 8.2.

D-*ribo*-Imidazolo-Pyrrolidinose 5: This compound was produced by a procedure similar to that used for **4** and *ent*-**4** (see above), starting from **29** (212 mg, 0.61 mmol) in AcOH (20 mL) under H_2 pressure (1 bar, though) in the presence of 20% $Pd(OH)_2/C$ (+ 30% H_2O). After 28 h, the reaction seemed to be complete, as monitored by TLC (Et_2O/MeOH + NH_3, 6:4). Workup followed by chromatography (Et_2O/MeOH + NH_3, 70:30) provided **5** (84 mg, 82%) as colorless crystals. M.p.$_{dec}$ 198−199 °C (MeOH). $[\alpha]_D^{20} = +70$ ($c = 1.0$, MeOH) (see also Table 1). CD spectrum: see Figure 1. The ^1H (D_2O) and ^{13}C NMR (CD_3OD) spectra were identical to, and therefore superimposable on, those of *ent*-**5**, the synthesis and spectral properties of which had already been described in a previous publication.[11] $C_7H_{10}N_2O_3$ (170.17): C 49.40, H 5.92, N 16.46; found C 49.6, H 6.0, N 16.5.

L-*ribo*-Imidazolo-Pyrrolidinose *ent*-5: This compound has already been described.[11] Rotatory power: Table 1. CD spectrum: Figure 1.

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