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Carbohydrate Transition State Mimics: Synthesis of Imidazolo-Pyrrolidinoses as Potential Nectrisine Surrogates

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Abstract—The syntheses of four glyco-imidazoles, which are pentose-derivatives belonging to the D-series, as well as the syntheses of their L-enantiomers, are reported. Starting from the known linear *xylo*, *lyxo*, *arabino*, and *ribo* imidazolo-pentoses in both the L- and the D-series, intramolecular Walden inversion led to the corresponding *arabino*, *ribo*, *xylo*, and *lyxo* pyrrolidinopentoses in the D- and the L-series, respectively, protection and deprotection steps being unavoidable prerequisites. The structures and configurations of all eight pyrrolidinopentoses were determined unambiguously, by a combination of $^{1}H/^{13}C$ NMR spectroscopy, circular dichroism and $[\alpha]_D$ values, in conjunction with single-crystal X-ray diffraction analysis of the L-*xylo* stereoisomer. Examination of the inhibitory properties of these imidazolo-pyrrolidinoses against six commonly encountered glycosidases led to the conclusion that by and large the L-stereoisomers are inactive, whereas three out the four D-stereoisomers proved to be poor to moderate inhibitors. It appears therefore that the most basic N(1) atom is not located in an optimal topology to be protonated easily inside the enzyme's active site.

Introduction

Both retaining and inverting polysaccharide glycosidases are thought to lead to transition states (TS) with a pronounced oxocarbenium character during the 'induced fit' step.[1,2] Since most natural oligo- and polysaccharides are chair conformed pyranoses, the ensuing oxocarbenium type TS's appear as flattened, that is half-chair, conformations. In 1992, Aoyagi, Aoyama and their collaborators published the structure of the natural product nagstatine **1**, and showed this imidazole-sugar to be a very potent inhibitor of some glucosaminidases, with a $K_i = 4$ nM for the bovine *N*-acetyl-β-D-glucosaminidase kidney enzyme.[3,4] The flattened half-chair conformation of the piperidinose ring of **1** is worth to be noticed: once protonated by the enzyme at the site of its most basic N(1) atom, (the positively charged) nagstatine mimics rather well the above postulated cyclic oxocarbenium type TS. In 1995, Tatsuta and his group synthesised the de-branched and at C(8) hydroxylated analogue **2** of nagstatine as well as a series of stereomers of **2**.[5] The inhibitory properties of **2** proved to be very pronounced indeed with β-D-galactosidase (*Escherichia coli*): $K_i = 2$ nM![6] More recently, we published the synthesis of the L-*arabino* analogue azasugar **3** which showed a $K_i = 1$ μM for the same β-galactosidase.[7] These two K_i values of manmade imidazolo-sugars **2** and **3** proved without any ambiguity: (i) the good binding properties of the (protonated) imidazole moiety, the basic N(1) atom occupying the pseudoanomeric position which leads to (lateral) protonation;[8,9] (ii) the importance of a well defined configuration; (iii) the importance of the hydroxymethyl group for an optimal binding (docking) of the imidazole-sugar into the enzyme's active site.

In 1988, the natural product nectrisine **4** had been isolated as an immunomodulator from the culture broth of the fungus *Nectria lucida*[10] and further shown to be a powerful inhibitor of yeast α-glucosidase.[11] The somewhat flattened conformation of nectrisine **4**—as compared to the envelope conformation of a saturated

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pyrrolidinose—once again could be considered as mimicking the TS geometry of an oligo- or polysaccharide in the enzyme's active site. We surmised that by replacing the imine double bond of **4** by an imidazole moiety, we should be able to obtain potent glycosidase inhibitors by analogy with the manmade nagstatine series, albeit to the best of our knowledge no naturally occurring imidazolo-pyrrolidinoses have been isolated so far.

In a first approach, we turned our attention to type **5** imidazolo-pyrrolidinoses (actually, their carbohydrate rings are pyrrolines)[12]—all eight stereomers have been synthesised—[13] in the hope that some of them would show inhibitory activity of glycosidases, albeit the most basic N(2) atom is located one bond farther away with respect to the N(1) atom of the reference model compound **1**. It turned out that the D-*arabino*, D-*xylo*, and D-*lyxo* stereoisomers did show some activity, the D-*arabino* stereoisomer **5** being the strongest inhibitor ($K_i = 5\ \mu M$ with α-D-mannosidase of Jack beans). On the other hand, the D-*ribo* and the four L stereoisomers in the type **5** series proved to be either inactive or only weakly active, at least with the six glycosidases we tested (Fig. 1).[13]

Like in the type **2** and type **3** piperidinose series, it seemed of interest to have the basic N atom located in the pseudoanomeric N(1) position in the pyrrolidinose series, rather than one bond farther away. These considerations led us to synthesise all eight N(1) type **6** imidazolo-pyrrolidinoses (Fig. 2) and to determine their inhibitory properties with a series of six glycosidases. The experimental results we obtained along these lines are described and discussed below.

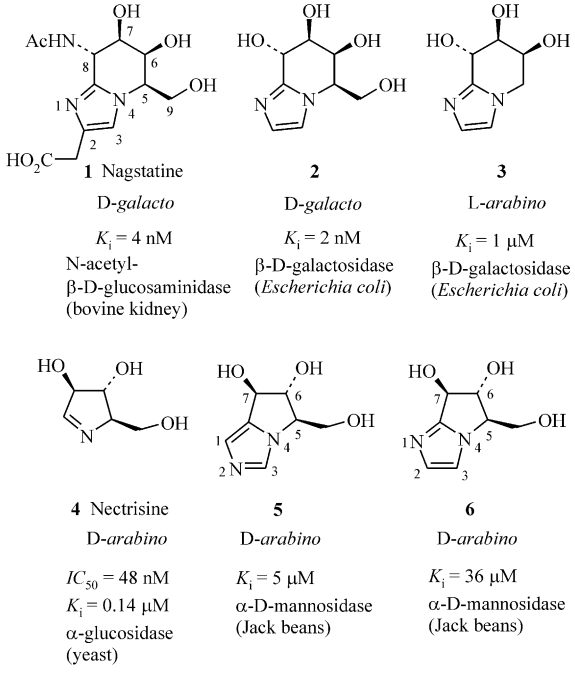


Figure 1. Various imidazolosugar inhibitors of glycosidases.

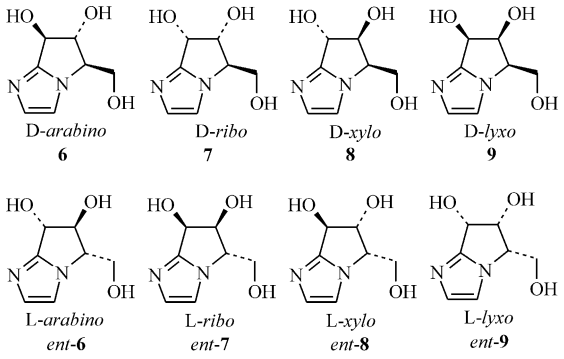


Figure 2. The eight imidazolo-[1,2]-pyrrolidinoses.

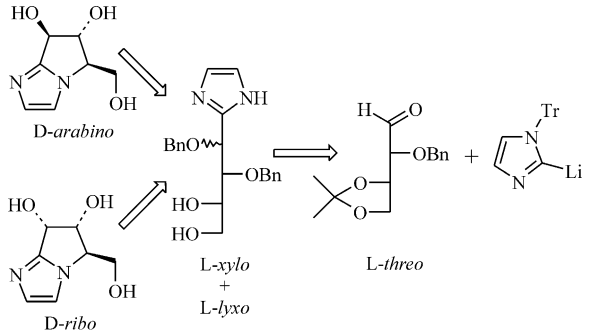
Results and Discussion

Retrosynthetic analysis (Scheme 1)

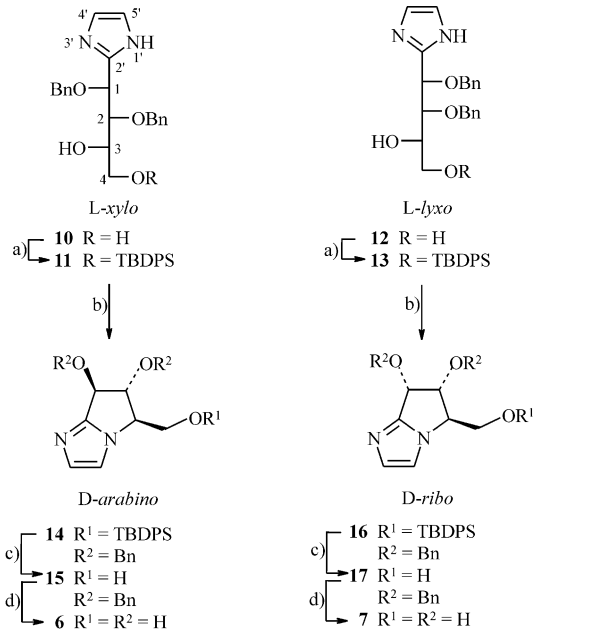
Taking but one sequence to illustrate our approach, the retrosynthetic analysis of both D-*arabino* and D-*ribo* imidazolo-pyrrolidino-pentoses from an L-*threose* precursor is represented in Scheme 1. We had already shown that nucleophilic addition of a C(2)-lithiated imidazole to a protected L-threose led to a mixture of the crystalline linear L-*xylo* and L-*lyxo* derivatives.[7] We expected the intramolecular cyclisation of these latter two compounds—properly protected and activated—to give the D-*arabino* and the D-*ribo* target molecules, respectively. As will be described below, these retrosynthetic assumptions could be translated into reality.

Arabinose and ribose series (Scheme 2)

D-Series. Reaction of the known L-*xylo* derivative **10**[7] with TBDPSCl in the presence of Et_3N and catalytic amounts of DMAP in methylene chloride led to selective silylation of the primary alcohol, affording thereby compound **11**. Reaction of triflic anhydride with **11** in the presence of pyridine at low temperature gave at once bicyclic compound **14**, obviously via a Walden inversion of the short-lived triflic ester intermediate of **11**. That latter triflate, being too active, could not be isolated. Treatment of **14** with fluoride ion (TBAF in THF) gave **15**. Hydrogenolysis (H_2/Pd/C) of the two *O*-benzyl bonds of **15** led to the expected D-*arabino* target molecule **6**. The same reaction conditions when applied to the known L-*lyxo* derivative **12** led to D-*ribo* diastereomer **7**,



Scheme 1. Retrosynthetic pathway for both the D-*arabino*- and D-*ribo*-imidazolo-[1,2]-pyrrolidinoses.



Scheme 2. Reagents and conditions for the synthesis of the D-*arabino*- and D-*ribo*-imidazolo-[1,2]-pyrrolidinoses and their enantiomers: (a) CH_2Cl_2 or DMF, NEt_3, TBDPSCl, DMAP cat; (b) CH_2Cl_2, pyridine, Tf_2O, −15 °C to rt; (c) THF, TBAF; (d) Pd catalyst, H_2 gas.

sequentially via compound **13**, the short-lived triflate of **13**, thence via intermediates **16** and **17**.

L-Series. The syntheses of the *ent*-**6** and *ent*-**7** enantiomers were performed using the same sequence of reactions as in Scheme 2, in the enantiomeric series though. In other words, the known enantiomers *ent*-**10** and *ent*-**11**[7] were the starting materials for the synthesis of the L-*arabino ent*-**6** and L-*ribo ent*-**7** enantiomers, respectively.

The experimental results showed the final target molecules to have the expected physical properties. In particular, the chiroptical data clearly demonstrated the mirror-image relationship between **6** and *ent*-**6**, and between **7** and *ent*-**7** (see Table 1 for $[\alpha]_D$ values, and the Experimental for CD spectra).

Table 1. $[\alpha]_D^{20}$ values measured in MeOH ($c = 1$)

D-*arabino* **6**	D-*ribo* **7**	D-*xylo* **8**	D-*lyxo* **9**
+23	+57	+51	+36
L-*arabino* *ent*-**6**	L-*ribo* *ent*-**7**	L-*xylo* *ent*-**8**	L-*lyxo* *ent*-**9**
−23	−53	−55	−35

Xylose and lyxose series (Scheme 3)

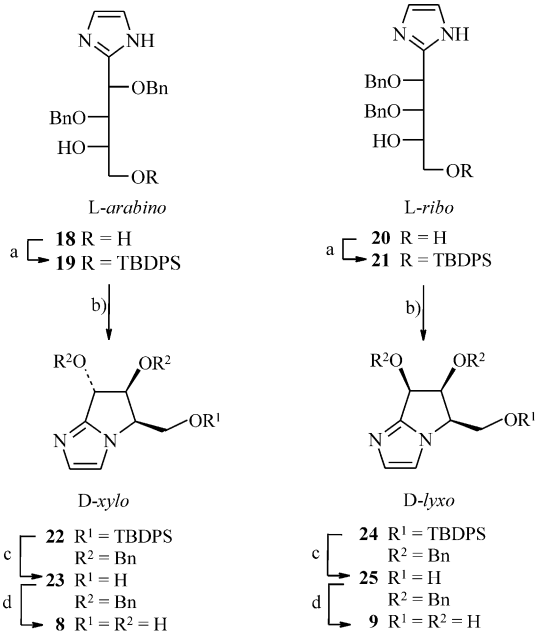
The synthetic schemes for the *xylo* and *lyxo* series parallel those we have described above for the *arabino* and *ribo* series (for the details, see Experimental).

D-Series. Reaction of the known L-*arabino* derivative **18**[7] with TBDPS gave **19** whose triflate spontaneously cyclised to give bicyclic compound **22**. Sequential removal of the three protecting groups gave the target D-*xylo* imidazolo-sugar **8**, the mono-alcohol di-*O*-benzyl derivative **23** being the result of the first step. A similar sequence of reactions starting from the known L-*ribo* derivative **20** gave the D-*lyxo* imidazolo-sugar **9**, sequentially via intermediate **21**, the short-lived triflate of **21**, and thence via intermediates **24** and **25**.

L-Series. Reaction of the known D-*arabino* derivative *ent*-**18**,[7] again with TBDPS, gave *ent*-**19** whose cyclisation led to *ent*-**22**. Removal of the protecting groups of the latter compound gave the target L-*xylo* imidazolo-sugar *ent*-**8**. A similar reaction sequence starting from the known D-*ribo* derivative *ent*-**20**[7] gave the L-*lyxo* imidazolo-sugar *ent*-**9** (see Experimental).

Spectral properties and structure analysis

Structures and absolute configuration of the eight stereisomers **6**–**9** and *ent*-**6**-*ent*-**9** (Fig. 2) could be determined unambiguously, thanks to a combination of $^1H/^{13}C$ NMR and chiroptical data analyses. These structural assignments are also due to the fact that the absolute 3-D structures of the corresponding eight linear imidazolo-pentose precursors (i.e., **10**/*ent*-**10**, **12**/*ent*-**12**, **18**/*ent*-**18**, and **20**/*ent*-**20**) had been determined previously without any ambiguity, thanks to a combination



Scheme 3. Reagents and conditions for the synthesis of the D-*xylo*- and D-*lyxo*-imidazolo-[1,2]-pyrrolidinoses and their enantiomers: (a) CH_2Cl_2 or DMF, NEt_3, TBDPSCl, DMAP cat; (b) CH_2Cl_2, pyridine, Tf_2O, −15 °C to rt; (c) THF, TBAF; (d) Pd catalyst, H_2 gas.

of $^{1}H/^{13}C$ NMR spectroscopy, circular dichroism (CD) and rotatory power data, in conjunction with two single-crystal X-ray diffraction analyses.[7] Furthermore single crystal X-ray diffraction analysis of *ent*-**8** confirmed its L-*xylo* configuration, proving thereby the Walden inversion of its D-*arabino* precursor (Fig. 3). During the key reaction step—that is, the intramolecular cyclisation—a Walden inversion occurs which brings about a configurational change from the D- to the L-series, or vice versa from the L- to the D-series. For example, the linear L-*arabino* precursor **18** leads to the bicyclic imidazolo D-*xylo* target azasugar **8** (Scheme 3); which in the enantiomeric series reads as follows: the linear D-*arabino* precursor *ent*-**18** leads to the bicyclic imidazolo L-*xylo* target azasugar *ent*-**8**.

Chiroptical properties proved to be of great help and interest. The optical rotatory power data agree rather well with the mirror image relationship between opposite enantiomers (Table 1). In terms of $[\alpha]_D$ values, it is worth noting that all D-configured imidazolosugars are dextrorotatory, the L-stereomers being levorotatory. The sign of these $[\alpha]_D$ values seems to be largely determined by the absolute configuration of carbon atom C(5), a (5*R*) configuration leading to a positive sign, a (5*S*) configuration to a negative one. In a previous publication we observed similar chiroptical properties with all type **5** stereomers [in these isomers the basic N(2) atom is one bond farther away with respect to type **6** isomers]: type **5** D-stereomers proved to be dextroratatory, their L-enantiomers levorotatory.[13]

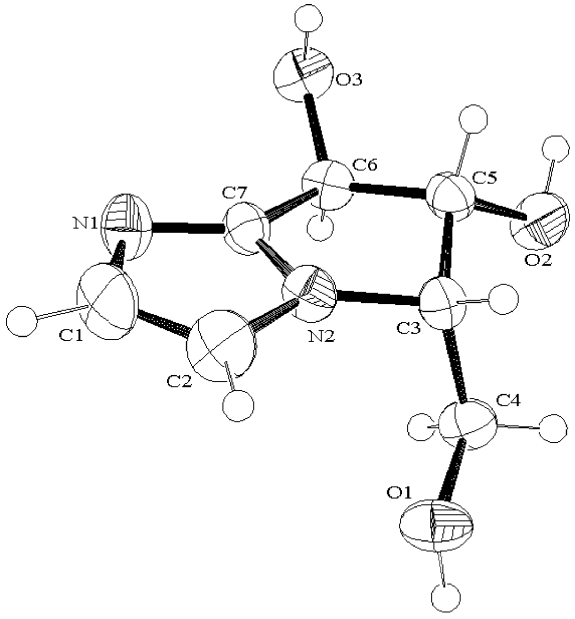


Figure 3. ORTEP plot of the structure of *ent*-8 (50% probability ellipsoïds).

As to the CD spectra of the eight type **6** target azasugars, they are definite testimony to the mirror image relationship between pairs of opposite enantiomers **6**/*ent*-**6**, **7**/*ent*-**7**, **8**/*ent*-**8** and **9**/*ent*-**9** (see Experimental).

Enzymatic assays

The eight imidazolo-pyrrolidino-pentoses (Fig. 2) have been evaluated as potential inhibitors of six commercially available glycosidases, and the results compiled in Table 2. In the D-series, those imidazolo sugars which do show some activity proved to be competitive inhibitors, but only moderate inhibitions could be measured. Both the D-*arabino* **6** and the D-*ribo* **7** stereomers inhibit α-D-mannosidase (Jack beans), with K_i values of 36 and 90 μM, respectively. Notice that in stereomer **6** all three configurations C(7), C(6) and C(5) are identical with respect to those of the corresponding asymmetric centres C(3), C(4) and C(5) of D-mannose. D-Stereomer **6** inhibits also α-D-glucosidase (baker's yeast), though only poorly ($K_i = 160$ μM), albeit in that instance too we notice a perfect configurational fit with respect to the asymmetric centres C(3), C(4) and C(5) of D-glucose. The four stereomers of the L-series are essentially inactive, at least with the six glycosidases which were tested.

It appears therefore that the eight imidazolo-pyrrazolo-pentoses of Figure 2 are poor inhibitors, if at all, of hexose-glycosidases. Obviously, the most basic N(1) atom is not located in an optimal topology—to be protonated easily in the enzyme's active site—whatever the degree of induced fit, or stated differently, whatever the degree of configurational complementarity inside the old 'lock and key' model. One may also reach the conclusion that the above postulated structural analogy between nectrisine and the eight azasugars of Figure 2 is a bit far-fetched, the most basic N(1) atom of the herein described imidazolosugars being located in quite a different position when compared to the one of nectrisine's N atom.

Table 2. Inhibition values of the imidazolo-[1,2]-pyrrolidinoses against six commercially available glycosidases

	6 D-*arabino*	**7** D-*ribo*	**8** D-*xylo*	**9** D-*lyxo*	*ent*-**6** L-*arabino*	*ent*-**7** L-*ribo*	*ent*-**8** L-*xylo*	*ent*-**9** L-*lyxo*
α-D-Glucosidase (baker's yeast)	$K_i = 160$ μM	NI	NI	NI	NI	NI	NI	NI
β-D-Glucosidase (almonds)	NI	NI	$K_i = 64$ μM	NI	NI	$K_i = 100$ μM	NI	NI
α-D-Galactosidase (green coffee beans)	NI	NI	NI	NI	NI	NI	NI	NI
β-D-Galactosidase (*Escherichia coli*)	NI	NI	NI	NI	NI	NI	NI	NI
α-D-Mannosidase (Jack beans)	$K_i = 36$ μM	$K_i = 90$ μM	NI	NI	NI	NI	NI	60% inhibition
β-D-Mannosidase (acetone snail powder)	NI	NI	NI	NI	NI	NI	NI	NI

Experimental

General

Flash chromatography (FC): silica gel (Merck 60; 230–400 mesh). TLC: silica gel on aluminium sheets (Merck 60HF_{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). Mp: Kofler hot-bench or Büchi-SMP apparatus; corrected values. Optical rotations were measured at +20 °C: Schmidt-Haensch Polartronic Universal polarimeter. CD spectra were measured in H_2O solution between 180 and 400 nm under nitrogen with a Jobin Yvon CD6 Dichrograph ($\Delta\varepsilon$ values) at the research centre of the Roche pharmaceutical division in Basel, Switzerland. ^1H and ^{13}C NMR spectra: 250 and 62.9 MHz, respectively (Bruker ACF-250 spectrometer at 300 K) or 400 and 100.6 MHz, respectively (Bruker DSX-400 spectrometer at 300 K). Internal references for ^1H NMR: $SiMe_4$ ($\delta = 0.00$), $CDCl_3$ ($\delta = 7.26$), CD_3OD ($\delta = 3.30$), [D_4]TSP for spectra in D_2O ($\delta = 0.00$); for ^{13}C NMR: $CDCl_3$ ($\delta = 77.03$), CD_3OD ($\delta = 49.02$); δ in ppm and J in Hz. HR-MS were measured with ESI mode in the departments of spectroscopy of Novartis in Basle and of the Faculté de Chimie, Université Louis Pasteur at Strasbourg. 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). Four different recipes were used, each one eight times. Each recipe is described, only once in full detail, along with its work up and chromatographic methodologies, the entire procedure being called either **Procedure A**, **Procedure B**, **Procedure C**, or **Procedure D**. In some instances, minor modifications were used; they are indicated explicitly.

Enzymatic assays

Glycosidases [α-mannosidase (EC 3.2.1.24) from Jack beans (Sigma M 7257), β-mannosidase (EC 3.2.1.25) from snail acetone powder (Sigma M 9400), α-glucosidase (EC 3.2.1.20) from baker's yeast (Sigma G-5003), β-glucosidase (EC 3.2.1.21) from almonds (Sigma G-4511), α-galactosidase (EC 3.2.1.22) from green coffee beans (Sigma G-8507), β-galactosidase (EC 3.2.1.23) from *E. coli* (Sigma G-4155)], 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 ($K_m = 1.33$ 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 ($K_m = 1.3$ mM, pH = 5.0), *p*-nitrophenyl-α-D-galactopyranoside for α-D-galactosidase ($K_m = 0.25$ mM, pH = 6.5) and *p*-nitrophenyl-β-D-galactopyranoside for β-D-galactosidase ($K_m = 0.4$ mM, pH = 7). 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.[15,16]

1,2-di-*O*-Benzyl-4-*O*-TBDPS L-*xylo* derivative 11. What follows shall be called **Procedure A**: A solution of **10**, mp = 99–100 °C[7] (214 mg, 0.58 mmol), DMAP (7 mg, 60 μmol)), anhydrous Et_3N (100 μL, 0.7 mmol) and TBDPSCl (166 μL, 0.64 mmol) in anhydrous CH_2Cl_2 (5 mL) was stirred at room temp. After 48 h, the solution was diluted with CH_2Cl_2 (20 mL), and washed with a saturated solution of NH_4Cl (20 mL). The aqueous solution was separated, extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic fractions were dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was purified by chromatography (AcOEt/cyclohexane 1:1) to give **11** (186 mg, 53%) as a colourless foam. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.95$ [s, 9H, $(CH_3)_3C$], 3.58 [d, 2H, C(4)–H_a and C(4)–H_b], 3.80 [td, 1H, C(3)–H], 3.87 [dd, 1H, C(2)–H], 4.28 and 4.37 [*AB*, 2H, $J = 11.6$, OCH_2Ph], 4.44 and 4.48 [*AB*, 2H, $J = 11.2$, OCH_2Ph], 4.87 [d, 1H, C(1)–H], 6.91 [s_{large}, 1H, C(2′)–H or C(3′)–H], 7.06 (s_{large}, 1H, C(3′)–H or C(2′)–H], 7.10–7.33 and 7.49–7.57 [m, 20H, H–*arom phenyl*], $J_{1,2} = 6.0$, $J_{2,3} = 2.4$, $J_{3,4} = 6.4$. ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 19.0$ [$SiC(CH_3)_3$], 26.8 [$SiC(CH_3)_3$], 64.3 [C(4)], 70.8 [C(3)], 71.7 [CH_2Ph], 74.4 [CH_2Ph], 76.5 [C(1)], 79.3 [C(2)], 126.9 [large hump, C(2′) and C(3′)], 127.6–128.2 (C–*arom phenyl*)], 129.6, 133.0 and 133.1 [C_s *phenyl*)], 135.39–135.41 [C–*arom phenyl*], 137.4 and 137.9 [C_s *phenyl*], 145.5 [C(2′)]

1,2-di-*O*-Benzyl-4-*O*-TBDPS D-*xylo* derivative *ent*-11. **Procedure A** as described above, starting from *ent*-**10**, mp = 103–104 °C[7] (200 mg, 0.54 mmol), DMAP (ca. 6 mg), anhydrous Et_3N (114 μL), in DMF (7 mL), and TBDPSCl (114 μL, 0.65 mmol). After 48 h, workup as above using CH_2Cl_2 (30 mL), NH_4Cl (30 mL), ($MgSO_4$), and chromatography to give *ent*-**11** (177 mg, 54%) as a colourless foam. ^1H ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100.6 MHz) spectra of *ent*-**11** proved to be identical to, and superimposable on, those of the L-*xylo* enantiomer **11**.

1,2-di-*O*-Benzyl-4-*O*-TBDPS L-*lyxo* derivative 13. **Procedure A** starting from **12**, $mp_{dec} = 161$ °C[7] (500 mg, 1.36 mmol), DMAP (ca. 7 mg, 60 μmol), anhydrous Et_3N (245 μL, 1.77 mmol), TBDPSCl (425 μL, 1.63 mmol) in anhydrous CH_2Cl_2 (15 mL). After 24 h workup and purification by chromatography as above to give **13** (719 mg, 87%) as a colourless foam. ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 1.05$ [s, 9H, $(CH_3)_3C$], 3.69 [m, 3H, C(3)-H, C(4)-H_a and C(4)-H_b], 4.23 [t, 1H, C(2)-H], 4.51 [s, 2H, OCH_2Ph], 4.60 and 4.70 [*AB*, 2H, $J = 11.0$, OCH_2Ph], 4.81 [d, 1H, C(1)-H], 6.95 [s_{large}, 1H, C(4′)-H or C(5′)-H], 7.05 (s_{large}, 1H, C(5′)-H or C(4′)-H], 7.23–7.65 [m, 22H, H-*arom phenyl*], 9.54 [s_{large}, 1H, N–H]; $J_{1,2} = 3.7$, $J_{2,3} = 3.7$ (n.b.: the other J values could not be determined, due to the fact that C(3)-H, C(4)-H_a and C(4)-H_b appear as a complex multiplet).

1,2-di-*O*-Benzyl-4-*O*-TBDPS D-*lyxo* derivative *ent*-13. Procedure A, starting from *ent*-**12**, $mp_{dec} = 161\,^{\circ}C$[7] (400 mg, 1.08 mmol), DMAP (catalytic amount), anhydrous Et_3N (227 μL, 1.63 mmol), TBDPSCl (229 μL, 1.30 mmol) in anhydrous CH_2Cl_2 (15 mL). After 24 h at rt, workup and chromatography led to *ent*-**13** (564 mg, 87%) as a colourless foam. ^1H NMR ($CDCl_3$, 250 MHz) spectrum was identical to, and superimposable on, the one of its enantiomer **13**.

6,7-di-*O*-Benzyl-8-OTBDPS D-*arabino* derivative 14 and 6,7-di-*O*-benzyl D-*arabino* derivative 15. What follows shall be called **Procedure B** for the preparation of **14**, and **Procedure C** for the preparation of **15**.

Procedure B. To a stirred solution of **11** (180 mg, 0.30 mmol) and anhydrous pyridine (95 μL, 1.2 mmol) in anhydrous CH_2Cl_2 (5 mL) at −15 °C under argon atmosphere was added dropwise Tf_2O (150 μL, 0.90 mmol). The reaction mixture was stirred at −15 °C for 15 min, and finally 12 h at rt. The resulting mixture was diluted with CH_2Cl_2 (30 mL), and the organic phase washed with a saturated solution of NH_4Cl (30 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic fractions were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by chromatagraphy (AcOEt/cyclohexane 1:1) to give **14** (93 mg, 53%) as a colourless foam which was used as such for the next reaction step. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.97 [s, 9H, $(CH_3)_3C$], 3.73 [dd, 1H, C(8)-H_b], 3.81 [dd, 1H, C(8)-H_a], 4.14 [ddd, 1H, C(5)-H], 4.26 [dd, 1H, C(6)-H], 4.42 and 4.51 (*AB*, 2H, $J = 11.6$, OCH_2Ph], 4.71 and 4.93 [*AB*, 2H, $J = 11.6$, OCH_2Ph], 4.76 [d, 1H, C(7)-H], 6.90 [d, 1H, C(3)–H], 7.08 [d, 1H, C(2)-H], 7.11–7.60 [m, 20H, H–*arom phenyl*], $J_{1,2} = 1.2$, $J_{Ha,Hb} = 10.7$, $J_{Ha,5} = 4.6$, $J_{Hb,5} = 7.3$, $J_{5,6} = 3.4$, $J_{6,7} = 2.1$.

Procedure C. To a stirred solution of the preceding compound **14** (136 mg, 0.23 mmol) in anhydrous THF (3 mL) was added dropwise a 1 M solution of TBAF in THF (600 μL; 0.58 mmol). The reaction mixture was stirred at room temp for 2 h, concentrated to dryness, the residue dissolved in CH_2Cl_2 (30 mL) and the resulting solution was washed with a saturated solution of NH_4Cl (40 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic fractions were dried ($MgSO_4$), filtered and evaporated to dryness. The resulting residue was purified by chromatogaphy (Et_2O/MeOH–NH_3 97:3) to give **15** (65 mg, 43%) as a colourless oil. $[\alpha]_D^{20} = -40$ (*c* 2, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz): δ = 3.80 (dd, 1H, C(8)-H_b], 3.93 [dd, 1H, C(8)-H_a], 4.24 [ddd, 1H, C(5)-H], 4.37 [t, 1H, C(6)-H], 4.57 and 4.65 [*AB*, 2H, $J = 11.7$, OCH_2Ph], 4.79 and 5.00 [*AB*, 2H, $J = 11.9$, OCH_2Ph], 4.83 [d, 1H, C(7)-H], 7.01 [d, 1H, C(3)-H], 7.15 [d, 1H, C(2)-H], 7.27–7.42 [m, 10H, H–*arom phenyl*]. $J_{2,3} = 1.1$, $J_{Ha,Hb} = 11.4$, $J_{5,Ha} = 4.4$, $J_{5,Hb} = 6.4$, $J_{5,6} = 2.9$, $J_{6,7} = 2.1$. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 63.2 [C(8)], 63.9 [C(5)], 71.3 [OCH_2Ph], 72.1 [OCH_2Ph], 76.4 [C(7)], 88.3 [C(6)], 114.8 [C(3)], 127.9–128.6 [C–*arom phenyl*], 133.7 [C(2)], 137.1 and 137.4 [C_s *phenyl*], 150.7 [C(7a)]. HR-MS: $[M+H]^+$ ion 351.1703 ($C_{21}H_{23}N_2O_3$, calcd 351.1709).

6,7-di-*O*-Benzyl-8-OTBDPS L-*arabino* derivative *ent*-14 and 6,7-di-*O*-benzyl L-*arabino* derivative *ent*-15. Procedure B starting from *ent*-**11** (113 mg, 0.19 mmol), and anhyd pyridine (45 μM, 0.56 mmol) in anhyd CH_2Cl_2 (3 mL) at −15 °C to which Tf_2O (77 μL, 0.46 mmol) was added. After 12 h at rt workup and purification by chromatography gave *ent*-**14** (88 mg, 80%) as a colourless foam which was used for the next reaction step. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.97 [s, 9H, $(CH_3)_3C$], 3.73 [dd, 1H, C(8)-H_b], 3.80 [dd, 1H, C(8)-H_a], 4.14 [ddd, 1H, C(5)-H], 4.26 [dd, 1H, C(6)-H], 4.42 and 4.51 [*AB*, 2H, $J = 11.7$, OCH_2Ph], 4.71 and 4.93 [*AB*, 2H, $J = 11.7$, OCH_2Ph], 4.76 [d, 1H, C(7)-H], 6.91 [d, 1H, C(3)-H], 7.09 [d, 1H, C(2)-H], 7.12–7.55 [m, 20H, H-*arom phenyl*], $J_{2,3} = 1.1$, $J_{Ha,Hb} = 10.8$, $J_{Ha,5} = 4.8$, $J_{Hb,5} = 7.6$, $J_{5,6} = 3.3$, $J_{6,7} = 2.4$. That ^1H NMR spectrum matched the one of compound **14**. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 19.14 [$SiC(CH_3)_3$], 26.75 [$SiC(CH_3)_3$], 63.8 [C(5)], 64.6 [C(8)], 71.2 [OCH_2Ph], 71.9 [OCH_2Ph], 77.0 [C(7)], 87.9 [C(6)], 114.9 [C(3)], 127.6-128.5 [C–*arom phenyl*], 129.7 [C–*arom phenyl*], 130.0 [C–*arom phenyl*], 132.7 and 132.6 [C_s *phenyl*], 133.4 [C(2)], 135.5 and 137.6 [C–*arom phenyl*], 137.1 and 137.7 [C_s *phenyl*], 150.6 [C(7a)].

Procedure C. A solution of *ent*-**14** (144 mg, 0.24 mmol) in anhydrous THF (3.8 mL) was treated with a 1 M solution of TBAF in THF (370 μL, 0.37 mmol) as above. Workup and purification with chromatography as above led to *ent*-**15** (83 mg, 97%) as a colourless oil. $[\alpha]_D^{20} = +35$ (*c* 2, $CHCl_3$). ^1H NMR ($CDCl_3$), 400 MHz): δ = 3.70 [dd, 1H, C(8)-Hb], 3.84 [dd, 1H, C(8)-H_a], 4.15 [ddd, 1H, C(5)-H], 4.28 [t, 1H, C(6)-H], 4.49 and 4.56 [*AB*, 2H, $J = 11.8$, OCH_2Ph], 4.61 and 4.89 [*AB*, 2H, $J = 11.6$, OCH_2Ph], 4.74 [d, 1H, C(7)-H], 6.92 [d, 1H, C(2)-H], 7.03 [d, 1H, C(3)-H], 7.18–7.30 [m, 10H, H–*arom phenyl*], $J_{2,3} = 1.1$, $J_{Ha,Hb} = 11.6$, $J_{5,Ha} = 4.5$, $J_{5,Hb} = 6.8$, $J_{5,6} = 2.4$, $J_{6,7} = 2.1$. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 62.8 [C(8)], 64.0 [C(5)], 71.3 [OCH_2Ph], 71.9 [OCH_2Ph], 76.6 [C(7)], 88.1 [C(6)], 115.0 [C(3)], 127.8–128.5 [C–*arom*], 133.1 [C(2)], 137.0 and 137.3 [C_s *phenyl*], 150.35 [C(7a)]. These ^1H and ^{13}C NMR spectra matched the ones of compound **15**. HR-MS: $[M+H]^+$ ion: 351.1715 ($C_{21}H_{23}N_2O_3$), calcd 351.1709.

6,7-di-*O*-Benzyl-8-OTBDPS D-*ribo* derivative 16 and 6,7-di-*O*-benzyl D-*ribo* derivative 17. Procedure B, starting from **13** (710 mg, 1.17 mmol), anhyd pyridine (370 μL) in anhyd CH_2Cl_2 (15 mL) at −15 °C to which Tf_2O (590 μL, 3.51 mmol) was added dropwise. After 12 h at rt workup as above followed by chromatography to give **16** as a colourless foam which was used as such for the next step. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.98 [s, 9H, $(CH_3)_3C$], 3.82 [dd, 1H, C(8)-H_b], 4.05 [dd, 1H, C(8)-H_a], 4.22 [dd, 1H, C(6)-H], 4.39 and 4.71 [*AB*, 2H, $J = 11.7$, OCH_2Ph], 4.44 [ddd, 1H, C(5)-H], 4.71 and 4.86 [*AB*, 2H, $J = 11.9$, OCH_2Ph], 4.74 [d, 1H, C(7)-H], 7.00 [d, 1H, C(2)-H or C(3)-H], 7.16 [d, 1H, C(3)-H or

C(2)-H], 7.20–7.59 [m, 20H, H–*arom phenyl*], $J_{2,3}=1.0$, $J_{Ha,Hb}=11.2$, $J_{5,Ha}=2.5$, $J_{5,Hb}=5.9$, $J_{5,6}=7.1$, $J_{6,7}=5.5$.

Procedure C. To a stirred solution of the preceding product **16** in anhydrous THF (20 mL) was added dropwise a 1 M solution of TBAF in THF (2 mL, 2.0 mmol). After 12 h at rt workup as above followed by chromatography (Et_2O/MeOH–NH_3 97:3) gave **17** (340 mg, 83%) as colourless crystals. Mp = 115–116 °C. $[\alpha]_D^{20} = +202$ (*c* 2, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.90 [s_{large}, OH], 3.77 [dd, 1H, C(8)-H_b], 4.13 [dd, 1H, C(8)-H_a], 4.23 [dd, 1H, C(6)-H], 4.40 [ddd, 1H, C(5)-H], 4.47 and 4.76 [*AB*, 2H, *J* = 11.5, OCH_2Ph], 4.65 and 4.82 [*AB*, 2H, *J* = 11.8, OCH_2Ph], 4.70 [d, 1H, C(7)-H], 7.06 [d, 1H, C(2)-H or C(3)-H], 7.11 [d, 1H, C(3)-H or C(2)-H], 7.28–7.45 [m, 10H, H–*arom phenyl*], $J_{2,3}=1.1$, $J_{Ha,Hb}=11.8$, $J_{5,Ha}=2.8$, $J_{5,Hb}=5.8$, $J_{5,6}=7.1$, $J_{6,7}=5.4$. ^{13}C NMR ($CDCl_3$, 62.9): δ = 61.6 [C(8)], 62.0 [C(5)], 69.1 [C(7)], 70.3 [O*C*H_2Ph], 72.2 [O*C*H_2Ph], 80.4 [C(6)], 114.5 [C(3)], 127.8–128.5 [C–*arom phenyl*], 132.6 [C(2)], 137.1 and 137.6 [C_s *phenyl*], 150.2 [C(7a)]. $C_{21}H_{22}N_2O_3$ (350.4): C 71.98, H 6.33, N 7.99; found: C 71.7, H 6.3, N 7.9.

6,7-di-*O*-Benzyl-8-OTBDPS L-*ribo* derivative ent-16 and 6,7-di-*O*-benzyl L-*ribo* derivative ent-17. Preparation of *ent*-16. **Procedure B**, starting from *ent*-**13** (546 mg, 0.90 mmol), anhydrous pyridine (218 μL) in anhydrous CH_2Cl_2 (15 mL) and Tf_2O (367 μL). After 12 h at rt workup followed by chromatogaphy gave *ent*-**16** (389 mg, 73%) as a colourless foam which was used as such in the following step. ^1H NMR ($CDCl_3$, 250 MHz): spectrum identical to, and superimposable on, that of **16**. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 19.0 [Si*C*$(CH_3)_3$], 26.5–26.8 [SiC(*C*$H_3)_3$], 62.0 [C(8)], 62.7 [C(5)], 68.8 [C(7)], 70.1 [O*C*H_2Ph], 71.9 [O*C*H_2Ph], 80.0 [C(6)], 114.6 [C(3)], 127.7–129.9 [C–*arom phenyl*], 132.3 and 132.4 [C_s *phenyl*], 132.7 [C(2)], 135.4–135.5 [C–*arom phenyl*], 137.0 and 137.5 [C_s *phenyl*], 150.0 [C(7a)].

Preparation of *ent*-17. **Procedure C**, starting from *ent*-**16** (385 mg, 0.65 mmol) in anhydrous THF (10 mL), containing a 1 M solution of TBAF in THF (0.98 mL, 0.98 mmol). After 5 h at rt, workup as above, followed by chromatography gave *ent*-**17** (220 mg, 96%) as a colourless solid. Mp = 116–116.5 °C. $[\alpha]_D^{20} = -192$ (*c* = 2, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz) and ^{13}C NMR ($CDCl_3$, 62.9 MHz) spectra identical to, and superimposable on, those of compound **17**. $C_{21}H_{22}O_3N_2$ (350.4): C 71.98, H 6.33, N 7.99; found: C 72.2, H 6.3, N 8.1.

D-*arabino*-Imidazolo-pyrrolidinose 6. What follows shall be called **Procedure D**: A stirred solution of **15** (190 mg, 0.54 mmol) in MeOH (5 mL) was put under H_2 pressure (30 bar) in the presence of 20% $Pd(OH)_2$/C (+30% H_2O) at rt, the reaction being monitored by TLC (CH_2Cl_2/MeOH–NH_3 2:1). After 7 days, the conversion seemed to be complete. The suspension was centrifuged and the catalyst was rinsed several times with hot MeOH. The combined organic solutions were evaporated to dryness in vacuum, and the residue purified by chromatography (AcOEt/MeOH 7:3) to give **6** after lyophilisation (74 mg, 80%) as colourless hygroscopic microcrystals. Mp_{dec} = 172–174 °C. $[\alpha]_D^{20} = +23$ (*c* 1, MeOH). CD (H_2O): recording starts at 180.0 (+8.27), 195 (0.00), 199.5 (−1.25), 205.0 (0.00), 210.5 (+0.68), 222 (0.00), 230 (−0.33), tailing out at ca. 245 (−0.10). ^1H NMR (D_2O, 250 MHz): δ = 3.91 [dd, 1H, C(8)-H_b], 4.13 [dd, 1H, C(8)-H_a], 4.20 [q, 1H, C(5)-H], 4.51 [t, 1H, C(6)-H], 4.95 [d, 1H, C(7)-H], 7.17 [s_{broad}, 1H, C(2)-H], 7.22 [s, 1H, C(3)-H], $J_{Ha,Hb}=12.2$, $J_{Ha,5}=3.7$, $J_{Hb,5}=5.2$, $J_{5,6}=4.1$, $J_{6,7}=3.9$. ^{13}C NMR (CD_3OD, 62.9 MHz): δ = 63.0 [C(8)], 66.8 [C(5)], 74.2 [C(7)], 84.0 [C(6)], 116.1 [C(3)] and 132.8 [C(2)], 153.4 [C(7a)]. HR-MS: $[M+H]^+$ ion 171.0770 ($C_7H_{11}N_2O_3$, calcd 171.0770).

L-*arabino*-Imidazolo-pyrrolidinose *ent*-6. Procedure D, starting from *ent*-**15** (141 mg, 0.40 mmol), 20% $Pd(OH)_2$/C (+ 30% H_2O) in EtOH (3 mL) and AcOH (3 mL) under H_2 pressure (ca. 1.5 bar). After 16 h workup as above. The clear organic solution was concentrated in vacuum and AcOH was almost entirely removed via three azeotropic distillations with toluene. Last traces of AcOH were removed with basified IRA 400 (OH^-) resin. The crude residue was purified by chromatography (CH_2Cl_2/MeOH 8:2) to give *ent*-**6** (65 mg, 95%) as a colourless solid. Mp_{dec} = 175–176 °C (MeOH). $[\alpha]_D^{20} = -23$ (*c* 1, MeOH). CD (H_2O): recording starts at 180.0 (−8.70), 182 (−8.83), 195 (0.00), 200.5 (+0.80), 205 (0.00), 210 (−1.07), 222 (0.00), 229 (+0.20), tailing out at ca. 248 (0.0). ^1H NMR (CD_3OD, 400 MHz): δ = 3.75 [dd, 1H, C(8)-H_b], 4.00 [m, 2H, C(8)-H_a and C(5)-H], 4.31 [t, 1H, C(6)-H], 4.72 [d, 1H, C(7)-H], 7.02 [d, 1H, C(2)-H], 7.12 [d, 1H, C(3)-H]; $J_{2,3}=1.3$, $J_{Ha,Hb}=11.3$, $J_{Ha,5}=4.0$, $J_{Hb,5}=6.1$, $J_{5,6}=3.5$, $J_{6,7}=3.3$. ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 63.0 [C(8)], 66.9 [C(5)], 74.2 [C(7)], 84.1 [C(6)], 116.1 [C(3)], 132.8 [C(2)], 153.5 [C(7a)]. These two NMR spectra matched those of enantiomer **6**. HR-MS: $[M+H]^+$ ion 171.0768 ($C_7H_{11}N_2O_3$, calcd 171.0770).

D-*ribo*-Imidazolo-pyrrolidinose 7. Procedure D. A stirred solution of **17** (164 mg, 0.47 mmol) in AcOH (5 mL) containing 20% $Pd(OH)_2$/C (+ 30% H_2O)(150 mg) was put under H_2 pressure (20 bar) at rt. After 2 days, workup as above and purification of the crude residue by chromatography (AcOEt/MeOH 7:3) which gave **7** (61 mg, 76%) as a colourless oil which was put in H_2O solution and deep-freezed. After lyophilisation it led to **7** (61 mg, 76%) a colourless powder which turned slightly pink. Mp_{dec} = 105–107 °C. $[\alpha]_D^{20} = +57$ (*c* 1, MeOH). CD (H_2O): recording starts at 180.00 (−0.71), 184.5 (−4.40), 195 (0.00), 205.5 (+2.11), tailing out at ca. 246 (−0.15). ^1H NMR (CD_3OD, 400 MHz): δ = 3.77 (dd, 1H, C(8)-H_b], 4.08 [dd, 1H, C(8)-H_a], 4.15 [td, 1H, C(5)-H], 4.43 [t, 1H, C(6)-H], 4.82 [d, 1H, C(7)-H], 7.03 [d, 1H, C(2)-H], 7.14 [d, 1H, C(3)-H], $J_{Ha,Hb}=11.9$, $J_{Ha,5}=2.9$, $J_{Hb,5}=5.8$, $J_{5,6}=5.6$, $J_{6,7}=5.8$, $J_{2,3}=1.0$. ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 62.2 [C(8)], 65.7 [C(5)], 66.9 [C(7)],76.5 [C(6)], 115.9 [C(3)], 132.4 [C(2)], 153.6 [C(7a)]. HR-MS: $[M+H]^+$ ion 171.0770 ($C_7H_{11}N_2O_3$, calcd 171.0770).

L-*ribo*-Imidazolo-pyrrolidinose *ent*-7. Procedure D, starting from a solution of *ent*-**17** (271 mg, 0.77 mmol), in EtOH (6 mL) and AcOH (6 mL) containing 20% $Pd(OH)_2/C$ (+50% H_2O) under H_2 pressure (ca. 1.5 bar) at rt. After 12 h, workup and purification via chromatography as above gave *ent*-**7** (92 mg, 70%) as a colourless oil. $[\alpha]_D^{20} = -53$ (*c* 0.55, MeOH). CD (H_2O): recording starts at 180.0 (ca. 0.0), 185.5 (+2.40), 195 (0.00), 206.5 (−1.61), tailing out at ca. 245 (+0.05). ^1H NMR (CD_3OD, 400 MHz): δ = 3.77 [dd, 1H, C(8)-H_b], 4.07 [dd, 1H, C(8)-H_a], 4.14 [td, 1H, C(5)-H], 4.42 [t, 1H, C(6)-H], 4.82 [d, 1H, C(7)-H], 7.02 [d, 1H, C(2)-H], 7.14 [d, 1H, C(3)-H], $J_{Ha,Hb} = 11.8$, $J_{Ha,5} = 2.8$, $J_{Hb,5} = 5.8$, $J_{5,6} = 5.7$, $J_{6,7} = 5.5$, $J_{2,3} = 1.3$. ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 62.1 [C(8)], 65.8 [C(5)], 67.0 [C(7)], 76.4 [C(6)], 116.0 [C(3)] 132.2 [C(2)], 153.3 [C(7a)]. These two NMR spectra proved to be identical to, and superimposable on, those of **7**. HR-MS: $[M+H]^+$ ion 171.0768 ($C_7H_{11}N_2O_3$, calcd 171.0770).

1,2-di-*O*-Benzyl-4-*O*-TBDPS L-*arabino* derivative 19. Procedure A, starting from a solution of **18**, mp = 111–113 °C[7] (350 mg, 0.95 mmol), DMAP (7 mg, 60 μmol), anhydrous Et_3N (170 μL, 1.0 mmol), and TBDPSCl (295 μL, 1.14 mmol) in anhydrous CH_2Cl_2 (10 mL). Workup and chromatographic purification led to **19** (405 mg, 70%) as a colourless foam. ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.07 [s, 9H, $(CH_3)_3C$], 2.87 [d, 1H, OH], 3.77 [dd, 1H, C(4)-H_b], 3.82 [dd, 1H, C(4)-H_a], 3.84 [dd, 1H, C(2)-H], 3.93 and 4.27 [*AB*, 2H, *J* = 10.8, OCH_2Ph], 3.96 [m, 1H, C(3)-H], 4.47 [s, 2H, OCH_2Ph], 5.07 [d, 1H, C(1)-H], 6.98–7.66 [m, 22H, H–*arom phenyl*, C(4′)-H and C(5′)-H], 9.53 (s_{large}, 1H, NH], $J_{1,2} = 2.7$, $J_{2,3} = 7.6$, $J_{3,4a} = 3.5$, $J_{3,4b} = 4.7$, $J_{3,OH} = 6.3$, $J_{4a,4b} = 10.1$.

1,2-di-*O*-Benzyl-4-*O*-TBDPS D-*arabino* derivative *ent*-19. Procedure A, starting from a solution of *ent*-**18**, mp = 112–113 °C[7] (379 mg, 1.03 mmol), imidazole (100 mg), DMAP (4.7 mg), Et_3N (194 μL) and TBDPSCl (325 μL, 1.21 mmol) in CH_2Cl_2 (12 mL). After 48 h, workup and chromatographic purification led to *ent*-**19** (647 mg, 75%) as a colourless foam. ^1H NMR ($CDCl_3$, 250 MHz) spectrum identical to, and superimposable on, that of **19**.

1,2-di-*O*-Benzyl-4-*O*-TBDPS L-*ribo* derivative 21. Procedure A as above, starting from **20**, mp = 111–112 °C[7] (525 mg, 1.42 mmol), imidazole (150 mg), DMAP (8 mg), Et_3N (270 μL) and TBDPSCl (470 μL, 1.75 mol) in CH_2Cl_2 (15 mL). After 48 h, workup and chromatographic purification led to **21** (736 mg, 85%) as a colourless foam. ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.05 [s, 9H, $(CH_3)_3C$], 3.40 [s_{large}, OH], 3.42 [ddd, 1H, C(3)-H], 3.71 [dd, 1H, C(4)-H_b], 3.78 [dd, 1H, C(4)-H_a], 4.08 [dd, 1H, C(2)-H], 4.46 and 4.55 [*AB*, 2H, *J* = 11.8, OCH_2Ph], 4.56 and 4.88 [*AB*, 2H, *J* = 10.9, OCH_2Ph], 5.11 [d, 1H, C(1)-H], 6.93 [s_{large}, 1H, C(4′)-H or C(5′)-H], 7.02 [s_{large}, 1H, C(5′)-H or C(4′)-H], 7.13–7.45 and 7.62–7.65 [m, 20H, H–*arom phenyl*], 9.63 [s_{large}, NH], $J_{1,2} = 2.3$, $J_{2,3} = 8.7$, $J_{3,4a} = 3.5$, $J_{3,4b} = 5.1$, $J_{4a,4b} = 10.4$.

1,2-di-*O*-Benzyl-4-*O*-TBDPS D-*ribo* derivative *ent*-21. Procedure A as above, starting from *ent*-**20**, mp = 109–110 °C[7] (530 mg, 1.44 mmol), imidazole (140 mg), DMAP (10 mg), Et_3N (265 μL) and TBDPSiCl (454 μL, 1.73 mmol) in CH_2Cl_2 (16 mL). After 48 h, workup and purification by chromatography led to *ent*-**21** (647 mg, 74%) as a colourless foam. ^1H NMR (CD_3OD, 250 MHz) spectrum identical to, and superimposable on, that of **21**.

6,7-di-*O*-Benzyl-8-OTBDPS D-*xylo* derivative 22 and 6,7-di-*O*-benzyl D-*xylo* derivative 23. Procedure B. To a stirred solution of **19** (399 mg, 0.66 mmol) and anhydrous pyridine (210 μL, 2.64 mmol) in anhydrous CH_2Cl_2 (10 mL) at −15 °C under argon atmosphere was added dropwise Tf_2O (330 mL, 1.98 mmol). The reaction mixture was stirred for 30 min at 0 °C, then overnight at rt. Workup as for **14**, but without chromatographic purification, led to crude compound **22** (477 mg) as an orange solid. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.96 [s, 9H, $(CH_3)_3C$], 3.81 [dd, 1H, C(8)-H_b], 3.93 [dd, 1H, C(8)-H_a], 4.50 [ddd, 1H, C(5)-H], 4.57 and 4.72 [*AB*, 2H, *J* = 11.7, OCH_2Ph], 4.65 [dd, 1H, C(6)-H], 4.93 and 5.15 [*AB*, 2H, *J* = 11.8, OCH_2Ph], 5.03 [d, 1H, C(7)-H], 7.02 [d, 1H, C(2)-H or C(3)-H], 7.23–7.61 [m, 21H, H–*arom phenyl*, C(2)-H or C(3)-H]; $J_{2,3} = 1.0$, $J_{Ha,Hb} = 10.9$, $J_{Ha,5} = 5.4$, $J_{Hb,5} = 3.2$, $J_{5,6} = 6.8$, $J_{6,7} = 4.3$.

Procedure C. To a stirred solution of crude **22** (477 mg) in anhydrous THF (10 mL) under argon was added dropwise a 1 M solution of TBAF in THF (1.5 mL, 2 equiv). The reaction mixture was stirred overnight at rt. Workup and chromatography gave **23** (196 mg, 84%) as a colourless solid. Mp_{dec} = 126–127 °C (toluene). $[\alpha]_D^{20} = +60$ (*c* 2, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.97 [s_{large}, 1H, OH], 3.90 [dd, 1H, C(8)-H_b], 3.97 [dd, 1H, C(8)-H_a], 4.51 [dt, 1H, C(5)-H], 4.60 and 4.73 [*AB*, 2H, *J* = 11.7, OCH_2Ph], 4.72 [dd, 1H, C(6)-H], 4.83 and 5.07 [*AB*, 2H, *J* = 11.6, OCH_2Ph], 4.91 [d, 1H, C(7)-H], 6.97 [d, 1H, C(2)-H or C(3)-H], 7.14 [d, 1H, C(3)-H or C(2)-H], 7.27–7.46 [m, 10H, H–*arom phenyl*]; $J_{2,3} = 0.9$, $J_{Ha,Hb} = 12.2$, $J_{Ha,5} = 4.3$, $J_{Hb,5} = 4.3$, $J_{5,6} = 6.8$, $J_{6,7} = 3.4$. ^{13}C NMR ($CDCl_3$, 62.9 MHz]: δ = 59.3 [C(5)], 61.7 [CH_2OH], 71.4 [OCH_2Ph], 72.8 [OCH_2Ph], 76.8 [C(7)], 87.4 [C(6)], 114.1 [C(3)], 127.9–128.7 [C–*arom phenyl*], 133.6 [C(2)], 136.8 and 137.6 [C_s *phenyl*], 150.4 [C(7a)]. $C_{21}H_{22}N_2O_3$ (350.4): calcd C 71.98, H 6.33, N 7.99; found C 72.1, H 6.2, N 7.9.

6,7-di-*O*-Benzyl-8-OTBDPS L-*xylo* derivative *ent*-22 and 6,7-di-*O*-benzyl-L-*xylo* derivative *ent*-23. Procedure B as above, starting from a solution of *ent*-**19** (469 mg, 0.77 mmol), pyridine (245 μL, 3.09 mmol), in CH_2Cl_2 (12 mL) at −10 °C to which Tf_2O (390 μL, 2.32 mmol) was added. After 12 h at rt workup and purification by chromatography (AcOEt/cyclohexane 1:1) as above led to *ent*-**22** (330 mg) which was used as such in the next step. ^1H NMR ($CDCl_3$, 250 MHz) spectrum of *ent*-**22** identical to, and superimposable on, that of compound **22**.

Procedure C. A solution of compound *ent*-**22** (330 mg) in THF (10 mL) was desilylated as above with a 1 M

solution of TBAF in THF (1.7 mL, 1.7 mmol). Workup and purification by chromatography led to *ent*-**23** (95 mg, 49%; overall yield from *ent*-**19**: 29%) as a colourless solid. Mp = 123 °C. $[\alpha]_D^{20} = -58$ (*c* 2, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz) and ^{13}C NMR ($CDCl_3$, 62.9 MHz) spectra of *ent*-**23** identical to, and superimposable on, those of **23**. HR-MS $[M+H]^+$ ion 351.1706 ($C_{21}H_{23}N_2O_3$, calcd 351.1709).

6,7-di-*O*-Benzyl-8-OTBDPS D-*lyxo* derivative 24 and 6,7-di-*O*-benzyl D-*lyxo* derivative 25. Procedure B as above starting from a solution of **21** (730 mg, 1.2 mmol), pyridine (380 μL), in CH_2Cl_2 (15 mL) at −10° C to which Tf_2O (610 μL, 36 mmol) was added. After 12 h, workup and purification by chromatography led to **24** (550 mg, 75%) which was used as such in the next step. ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.07 [s, 9H, $(CH_3)_3C$], 4.01 [dd, 1H, C(4)-H_b], 4.13 [dd, 1H, C(4)-H_a], 4.31 [dd, 1H, C(6)-H], 4.39 and 4.58 [*AB*, 2H, *J* = 12.2, OCH_2Ph], 4.43 [ddd, 1H, C(5)-H], 4.57 [d, 1H, C(7)-H], 4.64 and 4.74 [*AB*, 2H, *J* = 12.1, OCH_2Ph], 7.13–7.17, 7.25–7.49 and 7.62–7.67 [m, 22H, H–*arom phenyl* and *imidazole*]; $J_{Ha,Hb} = 10.9$, $J_{Ha,5} = 3.5$, $J_{Hb,5} = 10.1$, $J_{5,6} = 7.1$, $J_{6,7} = 5.2$.

Procedure C. A solution of **24** (550 mg, 10.9 mmol) in THF (5 mL) was desilylated as above with a 1 M solution of TBAF in THF (2 mL, 2.0 mmol). After 2 h, standard workup and purification by chromatography led to **25** (268 mg, 63% overall yield from **21**) as a colourless solid. Mp_{dec} = 104 °C (toluene). $[\alpha]_D^{20} = -140$ (*c* 2; $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz): δ = 3.02 [dd, 1H, OH], 3.92 [ddd, 1H, C(8)-H_b], 4.02 [dt, 1H, C(8)-H_a], 4.48 [ddd, 1H, C(5)-H] 4.52 and 4.79 [*AB*, 2H, *J* = 11.5, OCH_2Ph], 4.55 [dd, 1H, C(6)-H], 4.73 [d, 1H, C(7)-H], 4.76 and 4.92 [*AB*, 2H, *J* = 11.7, OCH_2Ph], 7.02 [d, 1H, C(3)-H], 7.19 [d, 1H, C(2)-H], 7.27–7.44 [m, 10H, H–*arom phenyl*], $J_{2,3} = 0.8$, $J_{Ha,OH} = 3.7$, $J_{Hb,OH} = 8.8$, $J_{Ha,Hb} = 12.0$, $J_{Ha,5} = 2.9$, $J_{Hb,5} = 4.1$, $J_{5,6} = 7.3$, $J_{6,7} = 5.2$. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 59.9 [C(5)], 61.1 [C(8)], 68.0 [C(7)], 70.5 [OCH_2Ph], 71.8 [OCH_2Ph], 79.3 [C(6)], 115.0 [C(3)], 127.9-128.6 [C–*arom phenyl*], 133.1 [C(2)], 136.8 and 136.9 [C_s *phenyl*], 149.5 [C(7a)]. $C_{21}H_{22}N_2O_3$ (350.4): calcd C 71.98, H 6.33, N 7.99; found C 71.9, H 6.2, N 7.9.

6,7-di-*O*-Benzyl-8-OTBDPS L-*lyxo* derivative *ent*-24 and 6,7-di-*O*-benzyl-L-*lyxo* derivative *ent*-25. Procedure B. To a stirred solution of *ent*-**21** (400 mg, 0.66 mmol), and anhydrous pyridine (208 μL, 2.6 mmol) in CH_2Cl_2 (10 mL) at −10 °C under argon was added dropwise Tf_2O (350 μL, 2.0 mmol). The reaction mixture was stirred for 30 min at −10 °C, then at rt. Workup led to crude compound *ent*-**24** (428 mg) which was used as such for the next step. ^1H NMR ($CDCl_3$, 250 MHz) spectrum of *ent*-**24** identical to, and superimposable on that of **24**.

Procedure C. To a stirred solution of crude *ent*-**24** (428 mg) in anhydrous THF (11 mL) under argon was added dropwise a 1 M solution of TBAF in THF (1.32 mL, 2 equiv). The reaction mixture was stirred for 2 h at rt. Workup as above followed by chromatography led to *ent*-**25** as a colourless solid (91 mg, 39% from *ent*-**21**). Mp = 99.5 °C (toluene). $[\alpha]_D^{20} = +135$ (*c* 2; $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz) and ^{13}C NMR ($CDCl_3$, 62.9 MHz) spectra identical to, and superimposable on, those of **25**. HR-MS $[M+H]^+$ ion 351.1708 ($C_{21}H_{23}N_2O_3$, calcd 351.1709).

D-*xylo*-Imidazolo-pyrrolidinose 8. Procedure D, starting from **23** (190 mg, 0.54 mmol) in MeOH (5 mL) under H_2 pressure (30 bar) in the presence of 10% Pd/C containing 50% H_2O (380 mg). After 3 days workup and chromatography led to **8** as a hygroscopic colourless powder after lyophilisation (74 mg, 80%). Mp_{dec} = 173–174 °C. $[\alpha]_D^{20} = +51$ (*c* 1, MeOH). CD (H_2O): recording starts at 180.0 (−9.80), 182.0 (−11.50), 195.0 (0.00), 206.0 (+4.29), tailing out at 240.0 (0.0). ^1H NMR (CD_3OD, 400 MHz): δ = 3.85 [dd, 1H, C(8)-H_b], 3.94 [dd, 1H, C(8)-H_a], 4.45 [td, 1H, C(5)-H], 4.61 [dd, 1H, C(6)-H], 4.82 [d, 1H, C(7)-H], 7.02 [d, 1H, C(2)-H], 7.12 [d, 1H, C(3)-H], $J_{Ha,Hb} = 11.8$, $J_{Ha,5} = 3.6$, $J_{Hb,5} = 6.2$, $J_{5,6} = 6.2$, $J_{6,7} = 4.0$, $J_{2,3} = 1.3$. ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 61.6 [CH_2OH], 62.4 [C(5)], 73.9 [C(7)], 82.9 [C(6)], 116.3 [C(3)], 132.5 [C(2)], 153.5 [C(7a)]. HR-MS: $[M+H]^+$ ion 171.0771 ($C_7H_{11}N_2O_3$, calcd 171.0770).

L-*xylo*-Imidazolo-pyrrolidinose *ent*-8. Procedure D, starting from a solution of *ent*-**23** (95 mg, 0.27 mmol) in MeOH (1.5 mL) and AcOH (1.5 mL) under H_2 pressure (1.5 bar) in the presence of 20% $Pd(OH)_2/C$ (95 mg). After 1 day workup and chromatography led to *ent*-**8** after lyophilisation (36 mg, 78%) as a colourless powder. Mp_{dec} = 163 °C (MeOH); one of the monocrystals was used for X-ray diffraction analysis (Fig. 2). $[\alpha]_D^{20} = -55$ (*c* 1, MeOH). CD (H_2O): recording starts at 180.0 (+9.30), 182.0 (+11.37), 196.5 (0.00), 206.5 (−4.83), tailing out at 245.0 (0.0). ^1H NMR (CD_3OD, 250 MHz): δ = 3.84 [dd, 1H, C(8)-H_a], 3.93 [dd, 1H, C(8)-H_b], 4.44 [td, 1H, C(5)-H], 4.61 [dd, 1H, C(6)-H], 4.82 [d, 1H, C(7)-H], 7.02 [d, 1H, C(2)-H], 7.12 [d, 1H, C(3)-H], $J_{Ha,Hb} = 11.8$, $J_{Ha,5} = 3.6$, $J_{Hb,5} = 6.0$, $J_{6,7} = 4.0$, $J_{5,6} = 6.3$, $J_{2,3} = 1.1$. ^{13}C NMR [CD_3OD, 62.9 MHz): δ = 61.6 [C(8)], 62.3 [C(5)], 73.9 [C(7)], 82.9 [C(6)], 116.2 [C(3)], 132.5 [C(2)], 153.50 [C(7a)]. These two NMR spectra match those of compound **8**. HR-MS: $[M+H]^+$ ion 171.0771 ($C_7H_{11}N_2O_3$, calcd 171.0770).

D-*lyxo*-Imidazolo-pyrrolidinose 9. *Procedure D*, starting from **25** (250 mg, 0.71 mmol) in EtOH (10 mL) under H_2 pressure (30 bar) in the presence of 10% Pd/C. After 5 days, standard workup, chromatography and lyophilisation led to **9** (90 mg, 74%) as a colourless solid. Mp_{dec} 167–168 °C. $[\alpha]_D^{20} = +36$ (*c* 1, MeOH). CD (H_2O): recording starts at 180.0 (+5.89), 182.5 (+7.92), 193.5 (0.00), 198.0 (−1.85), 203.0 (0.00), 210.0 (+2.27), 224.0 (0.00), 230.0 (−0.30), tailing out at 245.0 (0.0). ^1H NMR (CD_3OD, 400 MHz): δ = 3.81 [dd, 1H, C(8)-H_b], 3.93 [dd, 1H, C(8)-H_a], 4.40 [ddd, 1H, C(5)-H], 4.73 [dd, 1H, C(6)], 4.76 [d, 1H, C(7)-H], 7.02 [d, 1H, C(2)-H], 7.12 [d, 1H, C(3)-H], $J_{Ha,Hb} = 11.7$, $J_{Ha,5} = 3.4$, $J_{Hb,5} = 5.6$, $J_{5,6} = 6.3$, $J_{6,7} = 5.7$, $J_{2,3} = 1.3$. ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 61.2 [CH_2OH], 62.8 [C(5)], 66.5 [C(7)],

75.2 [C(6)], 116.4 [C(3)], 132.4 [C(2)], 153.7 [C(7a)]. HR-MS: $[M+H]^+$ ion 171.0771 ($C_7H_{11}N_2O_3$, calcd 171.0770).

L-*lyxo*-Imidazolo-pyrrolidinose *ent*-9. Procedure D, starting from *ent*-**25** (91 mg, 0.26 mmol) in MeOH (1.5 mL) and AcOH (1.5 mL) under H_2 atmosphere (ca. 1.2 bar) in the presence of $Pd(OH)_2/C$ (90 mg). After 20 h, workup and chromatography led to *ent*-**9** after lyophilisation (25 mg, 57%) as a colourless solid. $Mp_{dec} = 136\,^{\circ}C$. $[\alpha]_D^{20} = -35$ (*c* 1, MeOH). CD (H_2O): recording starts at 180.0 (−5.57), 182.0 (−7.03), 193.5 (0.00), 198.0 (+1.23), 204.0 (0.00), 210.0 (−2.19), 227.0 (0.00), 231.5 (+0.11), tailing out at 243.0 (−0.10). ^1H NMR (CD_3OD, 250 MHz): $\delta = 3.81$ [dd, 1H, C(8)-H_b], 3.93 [dd, 1H, C(8)-H_a], 4.40 [ddd, 1H, C(5)-H], 4.70 [dd, 1H, C(6)-H], 4.76 [d, 1H, C(7)-H], 7.02 [d, 1H, C(2)-H], 7.12 [d, 1H, C(3)-H], $J_{Ha,Hb} = 11.7$, $J_{Ha,5} = 3.4$, $J_{Hb,5} = 5.6$, $J_{5,6} = 5.7$, $J_{6,7} = 5.6$, $J_{2,3} = 1.1$. ^{13}C NMR (CD_3OD, 62.9 MHz): $\delta = 61.1$ [CH_2OH], 62.7 [C(5)], 66.4 [C(7)], 75.1 [C(6)], 116.4 [C(3)], 132.3 [C(2)], 153.6 [C(7a)]. These two NMR spectra match those of compound **9**. HR-MS: $[M+H]^+$ ion 171.0766 ($C_7H_{11}N_2O_3$, calcd 171.0770).

X-ray diffraction analysis of *ent*-8

Single crystals of *ent*-**8**, suitable for X-ray crystallography, were grown by crystallization from methanol. Data were collected at 293 K on a Bruker-Nonius KappaCCD area detector using Mo-K_α radiation ($\lambda = 0.71073$). The compound with the chemical formula of $C_7H_{10}N_2O_3$ crystallized in the orthorhombic space group $P2_12_12_1$. The dimensions of the unit-cell are: $a = 4.8564(6)$, $b = 12.661(3)$, $c = 12.840(4)$, $\alpha = \beta = \gamma = 90°$. The usual corrections were applied. The structure was solved using the program SIR 92.[17] Anisotropic refinement on all non-hydrogen atoms was carried out using the program CRYSTALS.[18] Scattering factors were taken from the International Tables Vol. IV table 2.2B. The plots were created using ORTEP-3 for Windows.[19]

CCDC 196227 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit @ccdc.cam.ac.uk).

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