Synthesis of Chiral Polyhydroxylated Benzimidazoles by a Tandem Radical Fragmentation/Cyclization Reaction: a Straight Avenue to Fused Aromatic-Carbohydrate Hybrids

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Abstract

The synthesis of benzimidazole-fused iminosugars through a tandem β-fragmentation-intramolecular cyclization reaction is described. The use of the benzimidazole ring as the internal nucleophile as well as the use of phenyliodosophthalate (PhI(Phth)), a new metal-free and low toxic hypervalent iodine reagent, are the most remarkable novelties of this synthetic strategy. With this approach, we have demonstrated the usefulness of the fragmentation of anomeric alkoxyl radicals (ARF) promoted by the PhI(Phth)/I2 system for the preparation of new compounds with potential interest for both medicinal and synthetic chemists.
1. INTRODUCTION

The benzimidazole ring is an aromatic bicyclic heterocycle increasingly present in numerous drugs due to its ability as hydrogen-bond donor and acceptor, as well as its electron-rich aromatic platform, all of which makes it a privileged structure for supramolecular recognition and therefore, the development of new therapeutic agents.\(^1\)

*N*-Ribosyldimethyl benzimidazole (I) is the most prominent natural benzimidazole and acts as an axial ligand for cobalt in B\(_{12}\) vitamin.\(^2\) Furthermore, different bioactive hybrid heterocycles containing the benzimidazole ring have been described in the literature as shown in Figure 1.\(^3\) Strikingly, scarce examples of benzimidazoles fused to carbohydrates have been reported, with applications ranging from nucleoside surrogates for kinase inhibition to chiral ligands in metal-mediated C-C bond formation.\(^4\) Nevertheless, we believe the scope of activities of benzimidazole-containing derivatives could be further extended into the inhibition of glycosidases, thus leading to potential drugs targeting these enzymes. By virtue of the resulting structure (the position of the basic center, the hydroxylation pattern, the ring size as well as its flexibility, the sp\(^2\)-flattening of the pseudo-anomeric region of the ring and the interactions with the aglycon binding site), hybrid benzimidazole-fused iminosugars display every requirement for potential selective inhibition of glycoside-processing enzymes.\(^4\) \(^c\)-\(^j\)

![Figure 1. Bioactive benzimidazole-containing hybrid heterocycles](image)

Recently, our research group has been involved in the development of new sustainable syntheses of potentially active compounds. In this regard, synthetic strategies based on
alkoxyl radicals using metal-free promoters such as hypervalent iodine (III) reagents have been developed, featuring among them the tandem β-fragmentation of anomeric alkoxyl radicals/intramolecular cyclization.\(^5\) This methodology relies upon the initial formation of the alkoxyl radical generated by the homolysis of a transient hypoiodite intermediate, triggering a β-fragmentation of the C1-C2 bond that generates an acyclic C-2 radical. From this point on, the electronic nature at C-2 has a strong influence on the outcome of this reaction intermediate. In fact, when the substituent at C-2 is an electron-donating group, the radical is rapidly oxidized to provide an oxocarbenium ion that can be trapped either by external or internal nucleophiles (Scheme 1).\(^6\)

![Scheme 1.- Anomeric Alkoxyl Radical Fragmentation (ARF): Mechanism and Applications.](image)

Probably the most interesting application of this reaction is towards the synthesis of polyhydroxylated heterocycles. Given the potential in this field, the main goal of our research has been focused on synthetizing new classes of iminosugar derivatives
starting from carbohydrates. In order to do so, a nitrogen-containing moiety must be suitably positioned to react as the internal nucleophilic species. Following this strategy, a variety of novel polyhydroxylated heterocyclic compounds has been recently prepared.\(^7\) However, to the best of our knowledge, the benzimidazole ring has never been engaged as the nucleophilic counterpart in this kind of reaction (Scheme 1).

2. RESULTS AND DISCUSSION

The retrosynthesis of the benzimidazole-sugars is depicted below (scheme 2), where four steps are required from the corresponding starting materials. Apart from the β-fragmentation/cyclization reaction, the iodine-catalyzed condensation of the corresponding aldehydes with ortho-phenylenediamine is the key step of this strategy.\(^8\) In turn, these aldehydes would come either from the oxidation of primary alcohols or the reduction of the corresponding nitriles.

Scheme 2.- Retrosynthetic analysis.

D-Lyxose derivative 4 was prepared starting from 1 (1-\(O\)-benzoyl-2,3-\(O\)-isopropylidene-\(\alpha\)-D-mannofuranose, readily available in two steps from commercial D-mannose diacetonide).\(^9\) Oxidative cleavage of the vicinal diol with sodium periodate in a mixture of acetone/water provided the corresponding aldehyde 2, which was subsequently engaged in the condensation step to obtain compound 3 in good yield.
Then, Zemplén deprotection of compound 3 afforded the desired substrate 4 in 79% yield (Scheme 3).

![Scheme 3](image)

**Scheme 3.** Reagents and conditions: a) NaIO₄, acetone/H₂O (1:1), rt, 3.5 h, then b) o-C₆H₄(NH₂), CeCl₃·7H₂O, CuI, I₂, acetonitrile, rt, 1 h, 87% (two steps); c) MeONa, MeOH, rt, 3 h, 79%.

D-Ribose derivative 8 was synthetized starting from 5 (1-O-benzoyl-2,3-O-isopropylidene-β-D-ribofuranose, readily available in four synthetic steps from D-ribose)¹⁰ by using a similar protocol. In order to oxidize the primary alcohol into an aldehyde, a battery of reagents was tested. Chromium (VI) reagents, such as pyridinium dichromate (PDC) and pyridinium chlorochromate (PCC), afforded the corresponding aldehyde in low yields. Disappointingly, we were not able to improve the yield when Dess-Martin reagent was used. Finally, IBX¹¹ was found to be the best oxidizing agent and afforded, after condensation with the corresponding diamine, the desired benzimidazole-containing derivative 7 in 48% yield over the two steps, which was then deprotected to afford 8 following the same protocol (Scheme 4).
Scheme 4.- Reagents and conditions: a) IBX, DMSO, rt, 3 h, then b) \( \alpha\)-C\(_6\)H\(_4\)(NH\(_2\))\(_2\), CeCl\(_3\)·7H\(_2\)O, CuI, I\(_2\), acetonitrile, rt, 4.5 h, 48% (two steps); c) MeONa, MeOH, rt, 1 h, 84%.

In order to test the scope of our synthetic proposal, precursors of six-membered benzimidazole-sugars were also synthetized. The synthetic scheme used was similar to that applied before. Nitrile \( 9\)\(^{7b}\) derived from D-ribofuranose in four synthetic steps, was first reduced with DIBAL-H to generate the corresponding aldehyde \( 10\), which was then engaged in the condensation step, without further purification, to afford the benzimidazole-containing compound \( 11\) in 53% yield over the two steps. The anomeric benzyl protecting group was finally removed by catalytic hydrogenation to provide the final precursor \( 12\) (Scheme 5).

Scheme 5.- Reagents and conditions: a) DIBAL-H, toluene, \(-78^\circ\)C, 1.5 h, then b) \( \alpha\)-C\(_6\)H\(_4\)(NH\(_2\))\(_2\), CeCl\(_3\)·7H\(_2\)O, CuI, I\(_2\), acetonitrile, rt, 1.5 h, 53% (two steps); c) Pd(OH)\(_2\)/C (30%), H\(_2\) (1 atm), EtOAc, rt, 72 h, 81%.

Additionally, substrate \( 13\) (available from D-mannose diacetonide in five steps)\(^{10}\) from the hexose series in the furanose form, was used to investigate the influence of carrying a substitution at position C-5. The benzimidazole-containing glycoside \( 15\) was readily prepared by oxidation of the primary alcohol \( 13\) under Dess-Martin conditions and subsequent condensation of the resulting aldehyde (72% yield). The anomeric PMB
protecting group was finally removed by treatment with CAN, to quantitatively yield the hemiacetal 16 (Scheme 6).

Scheme 6.- Reagents and conditions: a) DMP, DCM, rt, 1.5 h, then b) \( o\)-C\(_6\)H\(_4\)(NH\(_2\))\(_2\), CeCl\(_3\) \( \cdot \) 7H\(_2\)O, CuI, I\(_2\), acetonitrile, rt, 2.5 h, 72\% (two steps); c) CAN, acetonitrile/H\(_2\)O (10:1), rt, 2 h, quant.

The purpose of precursor 20 was to test the viability of the tandem \( \beta \)-fragmentation-intramolecular cyclization onto a six-membered ring derivative; when compound 17 (prepared in five steps from D-mannose\(^7\)) was oxidized and subsequently treated with \( o \)-phenylenediamine, the corresponding benzimidazole-containing sugar 19 was obtained in 59\% yield over the two steps. Then, deprotection of the benzyl ether was performed via catalytic hydrogenation, affording the desired anomeric alcohol 20 in good yield (Scheme 7).

Scheme 7.- Reagents and conditions: a) DMP, DCM, rt, 2 h; b) \( o\)-C\(_6\)H\(_4\)(NH\(_2\))\(_2\), CeCl\(_3\) \( \cdot \) 7H\(_2\)O, CuI, I\(_2\), acetonitrile, rt, 1 h, 57\% (two steps); c) Pd(OH)\(_2\)/C (30\%), H\(_2\) (1 atm), EtOAc, rt, 48 h, 83\%. 
As an integral part of the research carried out in our group on homolytic trasnformations in carbohydrate scaffolds, the development of new synthetic strategies to generate alkoxy radicals using hypervalent iodine, mainly with DIB/I₂ or PhIO/I₂ systems has been thoroughly explored. Herein, a novel phenyliodosophtalate (PhI(Phth))/I₂ system is also presented as an alternative to prevent the nucleophilicity and acidity of DIB-derived acetic acid and to avoid the unstability of the PhIO. The synthesis of the PhI(Phth) can be readily accomplished in a two-step procedure starting from dibutyl phthalate. Saponification and cyclization with DIB afforded the desired PhI(Phth) in 89% yield over two steps.¹²

The first goal of this study was to identify the optimal conditions to carry out the β-fragmentation/intramolecular cyclization of the benzimidazole-containing sugar-hemiacetals described above. In this context, precursor 4 was first chosen to perform the study, which started by testing the same conditions reported before for the synthesis of structurally related tetrazolo-sugar.⁷b Thus, when compound 4 was treated with PhIO/I₂ in EtOAc at 80 °C under irradiation (entry 1, Table 1) a complex mixture of products was obtained, from which the benzimidazole-derivative 21 could be isolated in 29% yield. When PhIO/I₂ system was changed to DIB/I₂ (entry 2) under the same conditions, a mixture of compounds 21 (47%) and 21b (14%) was generated, the latter one originating from the trapping of the oxocarbenium ion intermediate by acetic acid released during the formation of the hypoiodite intermediate. Replacement of EtOAc by DCE minimized the formation of compound 21b to only a 4% yield. Alternatively, when the mixture was stirred at room temperature, under irradiation with two 80W visible light lamps, both compounds 21 and 21b were obtained in a similar proportion (entries 3 and 4, respectively). To our delight, when precursor 4 was treated with the less nucleophilic PhI(Phth)/I₂ system under the original conditions (EtOAc at 80°C
under irradiation), the desired cyclic compound 21 was obtained in a better yield and as a sole product (entry 5). Higher reaction temperatures (100 °C, entry 6) accelerated the overall process, albeit with a slight decrease in the yield of the cyclized product. Thus, in view of the results obtained so far, the best conditions found involved EtOAc as solvent and heating at 80 °C under irradiation, either with DIB/I₂ or PhI(Phth)/I₂ reagents (entries 2 and 5, respectively). Out of the two oxidizing reagents, PhI(Phth)/I₂ appears to be more appropriate in order to generate the cyclized compound 21.¹³

![Chemical structures](image)

**Table 1.** Optimization of the β-ARF/cyclization reaction conditions. ¹³Reaction conditions: All reactions were performed at 0.05 M in dry EtOAc under irradiation with two 80 W tungsten-filament lamps at the stated temperature containing the oxidizing hypervalent iodine reagent (2.2 mmol) and I₂ (1.2 mmol) per mmol of substrate
When compound 8 was treated with PhI(Phth)/I₂, the desired all-syn cyclic benzimidazole-sugar 22 was successfully obtained in a 53% yield. The homolysis protocol was then applied to potential precursors of six-membered fused heterocycles. Compound 12, which is also a D-ribose derivative, afforded the desired compound 23 in 48% yield, where this lower yield could be explained by the higher degree of flexibility of the molecule, thereby making the cyclization step more challenging due to unfavorable entropy. In order to study how the intramolecular cyclization is affected when functional groups are introduced at position C-5, the D-manno-furanose derivative 16 was tested next. Surprisingly, after 1 h of reaction under the same conditions, the desired cyclized compound 24 was isolated in an unsatisfactory 26% yield (entry 4, Table 2). We believe this poor reactivity might result from a hydrogen bond established between the benzimidazole amine and the neighboring methoxy group, that translates into a deactivation of the nucleophile. Then, in order to evaluate the effectiveness of the radical tandem β-fragmentation on six-membered ring derivatives, D-manno-pyranose derivative 20 was treated with PhI(Phth)/I₂ as before (entry 5, Table 2). In this case, despite the presence of a methoxy group at position C-4, compound 25 was obtained with a good yield. This could stem from the fact that the six-membered ring derivative 20 possesses a more restricted flexibility, which prevents such hydrogen-bonding and preorganizes the system into a conformation that allows the cyclization reaction to proceed more easily.

**Table 2.- Synthesis of Benzimidazolo-sugars**

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Reaction conditions: All reactions were performed at 0.05 M in dry EtOAc (20 mL) under irradiation with two 80 W tungsten-filament lamps at reflux temperature containing Phl(Phth) (2.2 mmol) and I₂ (1.2 mmol) per mmol of substrate; Isolated yield.

Finally, in order to show the applicability of our methodology to produce new sugar mimics with potential inhibitory properties, two selected examples were partially or totally deprotected. In our experience, the formate group can be easily removed under mild basic conditions, resulting in a compound with a free hydroxyl group ready for
further derivatization if so desired. For example, when compound 21 was treated under Zemplén conditions, an oil identified as the corresponding alcohol was obtained in 80% yield. Alternatively, the total elimination of all protecting groups can be carried out under standard acidic conditions, i.e. with TFA in DCM or TFA in THF/H₂O at room temperature or reflux, depending on the model. As an example, compound 25 was treated with TFA in DCM to yield an oil identified as 27 after column purification (Scheme 8).

![Scheme 8](image)

**Scheme 8**.- Reagents and conditions: a) MeONa, MeOH, rt, 80%; b) TFA, DCM, rt, 40%.

3.- CONCLUSION

In summary, the first approach to the synthesis of benzimidazole-fused iminosugars through a tandem β-fragmentation-intramolecular cyclization reaction has been presented. This key radical step was newly promoted by phenyliodosophtalate (PhI(Phth)), a metal-free hypervalent iodine (III) promoter, easily synthesized in a two-step procedure. Due to its non-nucleophilic properties, PhI(Phth) has been found to be more effective than DIB in generating the corresponding cyclic products. Furthermore, PhI(Phth) has demonstrated a greater stability compared to the well-known PhIO
reagent. By using this radical-polar crossover reaction, hybrid benzimidazole-sugars were produced in moderate to good yields starting from their corresponding hemiacetalic precursors. Arguably, the synthesis of these final compounds involves four successive reaction steps: formation of the anomeric alkoxyl radical, β-fragmentation of the alkoxyl radical, oxidation of the resulting C-radical to generate the corresponding oxocarbenium ion, and trapping of this cationic intermediate by the nucleophilic nitrogen of the benzimidazole. Thus, the overall yield for the synthesis of compounds 21 to 25 actually constitutes a combined yield of a four-step process, with up to 85% yield for each one of these individual steps. We believe the straightforward transformation of hemiacetals into the corresponding fused benzimidazole-sugars described in this study, as well as the demonstrated possibility to remove all protecting groups, can be extrapolated to other chiral substrates and will therefore be of ample interest to the synthetic scientific community.

4. EXPERIMENTAL SECTION

**General Methods.** Optical rotations were measured with a polarimeter at the sodium line at ambient temperature in CHCl₃ solutions. IR spectra were recorded CHCl₃ unless otherwise stated, with a FTIR instrument. NMR spectra were recorded with a 400 MHz spectrometer for ¹H and 100.6 MHz for ¹³C in CDCl₃ unless otherwise stated, in the presence of TMS as internal standard. Structures were confirmed by COSY, DEPT, HSQC and NOESY experiments when necessary. Mass spectra were recorded with a spectrometer by using electrospray ionization (ESI⁺-TOF). Merck silica gel 60 PF (0.063-0.2 mm) was used for column chromatography. Circular layers of 1 mm of Merck silica gel 60 PF₂₅₄ were used on a Chromatotron for centrifugally assisted chromatography. Commercially available reagents and solvents were analytical grade or were purified by standard procedures prior to use. All reactions involving air- or
moisture-sensitive materials were carried out under a nitrogen atmosphere. The staining reagents for TLC analysis were conducted with 0.5% vanillin in H$_2$SO$_4$-EtOH (1:4) and further heating until development of color.

(5R)-5-O-Benzoyl-3,4-O-isopropylidene-D-arabinodialdo-5,2-furanose (2): To a solution of 1-O-benzoyl-2,3-O-isopropylidene-α-D-mannofuranose$^9$ (1) (1620 mg, 5.00 mmol) in a (1:1) acetone/water mixture (50 mL, 10 mL/mmol) was added NaIO$_4$ (1872 mg, 8.75 mmol). The reaction mixture was stirred for 3.5 h at room temperature. The mixture was then diluted with DCM and poured into water, extracted several times with DCM, dried over sodium sulfate and concentrated under vacuum. The crude was directly engaged in the next step without further purification to prevent the potential degradation of the compound. As a consequence, all the aldehyde derivatives synthetized were directly engaged in the next step without further purifications.

1-O-Benzoyl-2,3-O-isopropylidene-β-D-ribofuranoside (6): IBX (421 mg, 1.50 mmol) was dissolved in DMSO (4 mL). The dissolution requires 5-15 minutes. 1-O-Benzoyl-2,3-O-isopropylidene-α-D-ribofuranose (5)$^{10}$ (294 mg, 1.00 mmol) was then added to the mixture. The solution was stirred at room temperature without any particular precaution (such as inert atmosphere and dry solvent) during 3 h. Then the mixture was diluted with water to give a white precipitate, filtrated, extracted with ether, and finally concentrated under vacuum to afford a pink oil. The crude was directly engaged in the next step.

Benzyl 5-deoxy-2,3-O-isopropylidene-β-D-ribo-hexodialdo-1,4-furanoside (10): A solution of the corresponding nitrile $^9$$^{12}$ (504 mg, 1.74 mmol) in dry toluene (11 mL, 2 mL/mmol) was cooled to −78 °C before addition of DIBAL-H (1M in Toluene), and stirred at this temperature for 1.5 h. Afterward, 1M HCl was added until the organic layer became clear. The reaction mixture was extracted with ice-cold Et$_2$O and the
combined organic layer was dried over sodium sulfate, filtrated and concentrated under vacuum to afford a yellow oil. The crude was directly engaged in the next step.

4-Methoxybenzyl (6S)-2-\textit{O}-methyl-4,5-\textit{O}-isopropylidene-\textit{D}-manno-dialdo-6,3-furanoside (14): A solution of 4-methoxybenzyl 5-\textit{O}-methyl-2,3-\textit{O}-isopropylidene-\textit{\alpha}-D-mannofuranoside (13)\textsuperscript{7b} (500 mg, 1.41 mmol) in dry DCM (10 mL) containing Dess-Martin periodinane (DMP) (721 mg, 1.70 mmol) was stirred at room temperature for 1.5 h. The reaction mixture was diluted with ether (30 mL) and 1.3M NaOH (10 mL) was added, stirred for 15 minutes, and extracted. The organic layer was washed with water, dried and concentrated under vacuum to afford a yellow pale oil. The crude obtained was directly engaged in the next step.

Benzyl (6S)-3-\textit{O}-methyl-4,5-\textit{O}-isopropylidene-\textit{\alpha}-D-mannodialdo-6,2-pyranoside (18):\textsuperscript{7b} A solution of benzyl 4-\textit{O}-methyl-2,3-\textit{O}-isopropylidene-\textit{\alpha}-D-glucopyranoside (17)\textsuperscript{7b} (487 mg, 1.50 mmol) in dry DCM (12 mL) containing DMP (1272 mg, 3.00 mmol) was stirred at room temperature for 2 h. The reaction mixture was diluted with ether (30 mL) and 1.3M NaOH (12 mL) was added, stirred for 15 minutes and extracted. The organic layer was washed with water, dried and concentrated under vacuum. The crude was then purified by column chromatography on silica gel (hexane/EtOAc 7:3) to afford the corresponding aldehyde (285 mg, 0.89 mmol, 59%) as a pale yellow oil.

General procedure for the synthesis of benzimidazole\textsuperscript{8} derivatives: CeCl\textsubscript{3} (0.3 mmol), CuI (0.3 mmol) and I\textsubscript{2} (2.0 mmol) were dissolved in acetonitrile (15 mL). The mixture was stirred at room temperature and under agitation during 30 minutes. Then the corresponding aldehyde (1.0 mmol) was added. The mixture was stirred during 10 minutes before addition of the diamine (1.5 mmol). Then the solution was stirred at room temperature for 1-5 h. The mixture was then extracted and washed with aqueous
sodium thiosulfate and EtOAc. The organic phase was dried and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc mixtures) to afford the desired benzimidazole derivative.

**(4R)-4-C-(1H-benzimidazol-2-yl)-1-O-benzoyl-2,3-O-isopropylidene-β-L-erythro furanoside** (3): Following the general procedure, compound 2 (1460 mg, 5.00 mmol) afforded, after 1 h, the desired compound 3 (1653 mg, 4.35 mmol, 87% two steps) as an off-white powder after silica gel chromatography (hexane/EtOAc 1:1): IR: $\nu_{\text{max}}$ 3458, 2995, 2952, 2935, 1732, 1602, 1455, 1260, 1090 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 9.63 (bs, 1H, NH), 8.05–8.03 (m, 2H, Har), 7.76 (bs, 1H, H$_{\text{ar}}$), 7.63–7.60 (m, 1H, H$_{\text{ar}}$), 7.49–7.45 (m, 3H, H$_{\text{ar}}$), 7.29–7.27 (m, 2H, H$_{\text{ar}}$), 6.58 (s, 1H, H$_1$), 5.63 (d, $J = 3.4$ Hz, 1H, H$_2$), 5.26 (dd, $J = 5.6$, 3.4 Hz, 1H, H$_3$), 5.05 (d, $J = 5.6$ Hz, 1H, H$_4$), 1.53 (s, 3H, CH$_3$), 1.35 (s, 3H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$C 164.9 (C, C=O), 148.2 (C, C=N), 142.8 (C, C$_{\text{ar}}$), 133.6 (CH, C$_{\text{ar}}$), 133.4 (C, C$_{\text{ar}}$), 129.7 (2 x CH, C$_{\text{ar}}$) 129.0 (C, C$_{\text{ar}}$), 128.4 (2 x CH, C$_{\text{ar}}$), 123.0 (CH, C$_{\text{ar}}$), 122.1 (CH, C$_{\text{ar}}$), 119.6 (CH, C$_{\text{ar}}$), 113.6 (C, isop), 111.2 (CH, C$_{\text{ar}}$), 100.9 (CH, C$_1$), 85.0 (CH, C$_4$), 80.9 (CH, C$_3$), 79.0 (CH, C$_2$), 26.0 (CH$_3$, isop), 24.4 (CH$_3$, isop); MS (ESI$^+$) $m/z$ (rel intensity) 403 [(M+Na)$^+$, 100]; HRMS (ESI-TOF) $m/z$ [M+Na]$^+$ Calcd for C$_{21}$H$_{20}$N$_2$O$_5$Na 403.1270; Found 403.1266.

**(4R)-4-C-(1H-benzimidazol-2-yl)-1-O-benzoyl-2,3-O-isopropylidene-β-D-erythro furanoside** (7): Following the general procedure, compound 6 (292 mg, 1.00 mmol) afforded, after 5 h, the desired compound 7 (182 mg, 0.48 mmol, 48% two steps) as a yellow oil after silica gel chromatography (hexane/EtOAc 80:20): [$\alpha$]$_D^{20}$ +81.9 (c 0.16, CHCl$_3$); IR: $\nu_{\text{max}}$ 2985, 2962, 1728, 1602, 1454, 1270, 1094 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 10.11 (s, 1H, NH), 7.73 (d, $J = 7.9$ Hz, 1H, H$_{\text{ar}}$), 7.30 (t, $J = 7.4$ Hz, 1H, H$_{\text{ar}}$), 7.24–7.19 (m, 3H, H$_{\text{ar}}$), 7.10 (bs, 2H, H$_{\text{ar}}$), 6.94 (t, $J = 7.8$ Hz, 2H, H$_{\text{ar}}$), 6.58 (s, 1H, H$_1$), 6.07 (d, $J = 5.8$ Hz, 1H, H$_2$), 5.66 (s, 1H, H$_4$), 4.99 (d, $J = 5.8$ Hz, 1H, H$_3$), 1.55
Benzyl 5-(1H-benzimidazol-2-yl)-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (11): Following the general procedure, compound 10 (508 mg, 1.74 mmol) afforded, after 1.5 h, the desired compound 11 (352 mg, 0.93 mmol, 53% two steps) after silica gel chromatography (gradient hexane/EtOAc from 50:50 to 0:100) as a yellow oil: IR: \( \nu_{\text{max}} \) 3436, 3034, 2958, 1614, 1515, 1456, 1376, 1252, 1083 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta H \) 9.69 (bs, 1H, NH), 7.61–7.22 (m, 9H, H\(_\text{ar}\)), 5.31 (s, 1H, H\(_1\)), 4.80 (d, \( J = 6.1 \) Hz, 1H, H\(_2\)), 4.77 (d, \( J = 6.1 \) Hz, 1H, H\(_3\)), 4.72 (t, \( J = 7.4 \) Hz, 1H, H\(_4\)), 4.71 (d, \( J = 11.9 \) Hz, 1H, AB\(_\text{syst}\)), 3.28 (d, \( J = 7.3 \) Hz, 2H, H\(_5\)), 1.49 (s, 3H, isop), 1.32 (s, 3H, isop); \(^13\)C NMR (100.6 MHz, CDCl\(_3\)): \( \delta C \) 151.3 (C, C=N), 136.9 (C, C\(_\text{ar}\)), 128.7 (2 x CH, C\(_\text{ar}\)), 128.5 (C, C\(_\text{ar}\)), 128.1 (CH, C\(_\text{ar}\)), 127.9 (C, C\(_\text{ar}\)), 127.8 (2 x CH, C\(_\text{ar}\)), 122.3 (2 x CH, C\(_\text{ar}\)), 119.1 (CH, C\(_\text{ar}\)), 112.9 (C, isop), 110.5 (CH, C\(_\text{ar}\)), 108.8 (CH, C\(_1\)), 85.4 (CH, C\(_2\)), 85.2 (CH, C\(_4\)), 83.8 (CH, C\(_3\)), 70.3 (CH\(_2\), C[Bn]), 34.7 (CH\(_2\), C\(_5\)), 26.5 (CH\(_3\), isop), 25.0 (CH\(_3\), isop); MS (ESI\(^+\)) m/z (rel intensity) 381 [(M+H\(^+\), 100]; HRMS (ESI-TOF) m/z [M+Na\(^+\)] Calcd for C\(_{22}\)H\(_{29}\)N\(_2\)O\(_4\) 381.1814; Found 381.1811.

4-Methoxybenzyl \((5R)-5-C-(1H-benzimidazol-2-yl)-5-O-methyl-2,3-O-isopropylidene-β-D-lyxofuranoside\) (15): Following the general procedure, compound 14 (496 mg, 1.41 mmol) afforded, after 2.5 h, the desired compound 15 (445 mg, 1.01 mmol, 72%
two steps) after silica gel chromatography (gradient hexane/EtOAc from 50:50 to 30:70) as a yellow oil: \([\alpha]_D^{20} -7.14 \text{ (c 0.28, CHCl}_3\); IR: \(\nu_{\text{max}}\) 3692, 3449, 3000, 2940, 1613, 1515, 1249, 1084 \text{ cm}^{-1}; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta_H\) 9.70 (bs, 1H, NH), 7.84–7.82 (m, 1H, \(H_{\text{ar}}\)), 7.48–7.47 (m, 1H, \(H_{\text{ar}}\)), 7.30–7.26 (m, 1H, \(H_{\text{ar}}\)), 7.12 (d, \(J = 8.5\) Hz, 2H, \(H_{\text{ar}}\)), 6.79 (d, \(J = 8.5\) Hz, 2H, \(H_{\text{ar}}\)), 6.73–6.71 (m, 1H, \(H_{\text{ar}}\)), 5.18 (d, \(J = 6.6\) Hz, 1H, \(H_1\)), 4.90 (d, \(J = 6.6\) Hz, 1H, \(H_2\)), 4.46 (d, \(J = 11.3\) Hz, 1H, \(H_4\)), 3.78 (s, 3H, OCH\(_3\)), 3.42 (s, 3H, OCH\(_3\)[PMB]), 1.28 (s, 3H, isop), 1.21 (s, 3H, isop); \(^{13}\)C NMR (125.7 MHz, CDCl\(_3\)): \(\delta_C\) 159.2 (C, \(C_{\text{ar}}\)), 152.2 (C, \(C=N\)), 142.8 (C, \(C_{\text{ar}}\)), 133.7 (C, \(C_{\text{ar}}\)), 129.5 (2 x CH, \(C_{\text{ar}}\)), 129.3 (C, \(C_{\text{ar}}\)), 123.1 (CH, \(C_{\text{ar}}\)), 122.0 (CH, \(C_{\text{ar}}\)), 120.3 (CH, \(C_{\text{ar}}\)), 113.8 (2 x CH, \(C_{\text{ar}}\)), 112.6 (C, isop), 110.8 (CH, \(C_{\text{ar}}\)), 105.5 (CH, \(C_1\)), 84.6 (CH, \(C_5\)), 80.9 (CH, \(C_3\)), 79.5 (CH, \(C_4\)), 75.4 (CH, \(C_2\)), 69.0 (CH\(_2\), PMB), 58.0 (CH\(_3\)), 55.2 (CH\(_3\), OMe), 25.5 (CH\(_3\), isop), 24.5 (CH\(_3\), isop); MS (ESI\(^+\)) \(m/z\) (rel intensity) 463 [(M+Na\(^+\)], 100]; HRMS (ESI-TOF) \(m/z\) [M+Na\(^+\] Calcd for C\(_{24}\)H\(_{28}\)N\(_2\)O\(_6\)Na 463.1845; Found 463.1833.

**Benzyl (5R)-5-(1H-benzimidazol-2-yl)-4-O-methyl-2,3-O-isopropylidene-\(\alpha\)-L-ribo pyranoside (19):** Following the general procedure, compound 18 (285 mg, 0.89 mmol) afforded, after 2.5 h, the desired compound 19 (379 mg, 0.86 mmol, 97%) after silica gel chromatography (gradient hexane/EtOAc from 70:30 to 30:70) as a pale yellow powder: \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta_H\) 9.47 (bs, 1H, NH), 7.85–7.83 (m, 1H, \(H_{\text{ar}}\)), 7.46–7.45 (m, 1H, \(H_{\text{ar}}\)), 7.32–7.27 (m, 7H, \(H_{\text{ar}}\)), 5.29 (s, 1H, \(H_1\)), 4.89 (d, \(J = 9.8\) Hz, 1H, \(H_2\)), 4.74 (d, \(J = 12.0\) Hz, 1H, AB\(_{\text{syst}}\)), 4.60 (d, \(J = 12.0\) Hz, 1H, AB\(_{\text{syst}}\)), 4.40 (t, \(J = 6.3\) Hz, 1H, \(H_4\)), 4.29 (d, \(J = 6.3\) Hz, 1H, \(H_5\)), 3.60 (dd, \(J = 9.8, 6.3\) Hz, 1H, \(H_3\)), 3.36 (s, 3H, OCH\(_3\)), 1.56 (s, 3H, isop), 1.39 (s, 3H, isop); \(^{13}\)C NMR (125.7 MHz, CDCl\(_3\)): \(\delta_C\) 151.2 (C, \(C=N\)), 143.1 (C, \(C_{\text{ar}}\)), 136.8 (C, \(C_{\text{ar}}\)), 133.3 (C, \(C_{\text{ar}}\)), 128.5 (2 x CH, \(C_{\text{ar}}\), 128.2
(2 x CH, C_ar), 128.0 (CH, C_ar), 123.2 (CH, C_ar), 122.2 (CH, C_ar), 120.1 (CH, C_ar), 110.7 (CH, C_ar), 109.6 (C, isop), 97.1 (CH, C_1), 80.8 (CH, C_3), 77.8 (CH, C_4), 75.5 (CH, C_5), 69.9 (CH_2, Bn), 66.0 (CH, C_2), 59.3 (CH_3, OCH_3), 27.9 (CH_3, isop), 26.1 (CH_3, isop);

MS (ESI+) m/z (rel intensity) 433 [(M+Na)^+, 100]; HRMS (ESI-TOF) m/z [M+Na]^+ Calcd for C_{23}H_{26}N_2O_5Na 433.1739; Found 433.1739.

**General procedure for the hydrolysis of anomeric benzoate:** To a solution of the corresponding protected compound (1.0 mmol) in dry methanol (5 mL) was added sodium methoxide (2.0 mmol). After 1–3 h of stirring, the reaction mixture was concentrated under vacuum. The crude was then purified by column chromatography on silica gel (hexane/EtOAc mixtures) to afford the desired anomeric alcohol.

**(4R)-4-C-(1H-benzimidazol-2-yl)-2,3-O-isopropylidene-L-erythrofuranoside** (4):

Following the general procedure, compound 3 (1210 mg, 3.21 mmol) afforded, after 3 h, the desired compound 4 (693 mg, 2.51 mmol, 79%) after silica gel chromatography (gradient hexane/EtOAc from 80:20 to 30:70) as a pale brown powder crystalline compound: m.p. (n-hexane/Ethyl acetate) 193–195 °C; IR: \( \nu_{max} \) 3691, 3602, 3408, 2990, 2934, 1602, 1457, 1380, 1231, 1165, 1069 cm\(^{-1}\); NMR showed a mixture of anomers in a 20:1 \( \alpha/\beta \) ratio. Only major compound is described. \(^1\)H NMR (400 MHz, CDCl_3): \( \delta_H \) 7.49 (d, \( J = 7.9 \) Hz, 1H, H_ar), 7.42 (d, \( J = 7.9 \) Hz, 1H, H_ar), 7.25 (td, \( J = 7.9, 1.3 \) Hz, 1H, H_ar), 7.20 (td, \( J = 7.9, 1.3 \) Hz, 1H, H_ar), 5.87 (d, \( J = 1.3 \) Hz, 1H, H_1), 5.46 (d, \( J = 2.6 \) Hz, 1H, H_4), 5.11 (dd, \( J = 6.9, 2.6 \) Hz, 1H, H_3), 5.01 (dd, \( J = 6.9, 1.4 \) Hz, 1H, H_2), 1.37 (s, 3H, CH_3), 0.95 (s, 3H, CH_3); \(^{13}\)C NMR (100.6 MHz, CDCl_3): \( \delta_C \) 151.2 (C, C=N), 140.9 (C, C_ar), 133.6 (C, C_ar), 124.0 (CH, C_ar), 123.2 (CH, C_ar), 119.1 (CH, C_ar), 109.8 (C and CH, isop and C_ar), 77.4 (CH, C_1), 77.1 (CH, C_3), 76.9 (CH, C_2), 64.6 (CH, C_4), 26.2 (CH_3, isop), 24.3 (CH_3, isop); MS (ESI^+) m/z (rel intensity) 299 [(M+Na)^+, 100]; HRMS (ESI-TOF) m/z [M+Na]^+ Calcd for C_{14}H_{16}N_2O_4Na 299.1008; Found 299.1008.
(4R)-4-\((1H\mbox{-benzimidazol-2-yl})-2,3-O\)-isopropylidene-D-erythofuranoside \((8)\): Following the general procedure, compound 7 (364 mg, 0.96 mmol) afforded, after 1 h, the desired compound 8 (222 mg, 0.80 mmol, 84%) after silica gel chromatography (gradient hexane/EtOAc from 70:30 to 30:70) as a white powder: IR: \(\nu_{max} \ 3691, 3602, 3455, 2990, 2938, 1602, 1456, 1385, 1160, 1073 \ \text{cm}^{-1};\) NMR showed a mixture of anomers in a 1:20 \(\alpha/\beta\) ratio. Only major compound is described. \(^1\)H NMR (400 MHz, CD\(_3\)OD): \(\delta_H\) 7.67 (dd, \(J = 7.2, 1.1 \ \text{Hz}, 1\text{H, H}_{\text{ar}}\)), 7.53 (d, \(J = 7.2 \ \text{Hz}, 1\text{H, H}_4\)), 7.31–7.22 (m, 2H, H\_ar), 5.96 (d, \(J = 1.3 \ \text{Hz}, 1\text{H, H}_1\)), 5.28 (d, \(J = 3.4 \ \text{Hz}, 1\text{H, H}_4\)), 4.98 (dd, \(J = 7.2, 3.4 \ \text{Hz}, 1\text{H, H}_3\)), 4.80 (dd, \(J = 7.2, 1.3 \ \text{Hz}, 1\text{H, H}_2\)), 1.33 (s, 3H, isop), 0.87 (s, 3H, isop); \(^{13}\)C NMR (100.6 MHz, CD\(_3\)OD): \(\delta_C\) 154.3 (C, C=N), 143.6 (C, C\_ar), 135.8 (C, C\_ar), 124.1 (CH, C\_ar), 123.5 (CH, C\_ar), 119.9 (CH, C\_ar), 111.4 (C, isop), 110.5 (CH, C\_ar), 79.0 (CH, C\_3), 78.4 (CH, C\_3), 77.1 (CH, C\_2), 66.5 (CH, C\_4), 26.7 (CH\_3, isop), 24.6 (CH\_3, isop); MS (ESI\(^{+}\)) \(m/z\) (rel intensity) 277 \([\text{M+H}]^+, 100]\); HRMS (ESI-TOF) \(m/z\) [M+Na]\(^+\) Calcd for C\(_{14}\)H\(_{17}\)N\(_2\)O\(_4\) 277.1188; Found 277.1181.

5-(\(1H\mbox{-benzimidazol-2-yl})\)-5-deoxy-2,3-\(O\)-isopropylidene-D-ribofuranose \((12)\): To a solution of 11 (34 mg, 0.09 mmol) in EtOAc (2 mL) was added 30% Pd(OH\(_2\))/C (10 mg, 20% w/w). Three vacuum/hydrogen cycles were performed, and the mixture was stirred at rt and under hydrogen atmosphere for 72 h. The reaction mixture was then filtered over a Celite pad, washed with EtOAc, and the filtrate was evaporated. The crude was purified by column chromatography on silica gel (hexane/EtOAc 1:1) to yield compound 12 (21 mg, 0.07 mmol, 81%) as a pale yellow oil: IR: \(\nu_{max} \ 3452, 3427, 2995, 2952, 1537, 1456, 1385, 1271, 1072 \ \text{cm}^{-1};\) NMR showed a mixture of anomers in a 1:6 \(\alpha/\beta\) ratio. Only major compound is described. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta_H\) 7.36–7.34 (m, 2H, H\_ar), 7.14–7.12 (m, 2H, H\_ar), 5.64 (s, 1H, H\_1), 4.73 (d, \(J = 5.7 \ \text{Hz}, 1\text{H, H}_2\)), 4.69 (d, \(J = 6.0 \ \text{Hz}, 1\text{H, H}_3\)), 4.60–4.57 (m, 1H, H\_4), 3.33 (dd, \(J = 15.1, 10.4 \ \text{Hz}\), 1H, H\_5).
Hz, 1H, H$_5$), 3.24 (dd, $J = 15.1, 4.1$ Hz, 1H, H$_5$), 1.46 (s, 3H, isop), 1.30 (s, 3H, isop); $^{13}$C NMR (125.7 MHz, CDCl$_3$): $\delta$C 151.6 (C, C=N), 143.5 (C, C$_{ar}$), 137.5 (C, C$_{ar}$), 122.6 (2 x CH, C$_{ar}$), 115.5 (CH, C$_{ar}$), 114.7 (CH, C$_{ar}$), 112.7 (C, isop), 103.9 (CH, C$_1$), 86.7 (CH, C$_2$), 84.7 (CH, C$_4$), 84.0 (CH, C$_3$), 34.6 (CH$_2$, C$_5$), 26.5 (CH$_3$, isop), 25.0 (CH$_3$, isop); MS (ESI$^+$) m/z (rel intensity) 313 [(M+Na)$^+$, 100]; HRMS (ESI-TOF) m/z [M+Na]$^+$ Calcd for C$_{15}$H$_{18}$N$_2$O$_4$Na 313.1164; Found 313.1158.

(5R)-5-C(1H-benzimidazol-2-yl)-5-O-methyl-2,3-O-isopropylidene-D-lyxofuranose (16): To a stirred solution of 15 (43 mg, 0.10 mmol) in acetonitrile/water mixture (1 mL, 10:1 v/v) at 0 °C was added cerium (IV) ammonium nitrate (CAN) (164 mg, 0.30 mmol) portion-wise. The reaction mixture was stirred at rt for 2 h, then concentrated under vacuum, and the crude was purified by column chromatography on silica gel (hexane/EtOAc 1:1) to afford the compound 16 (32 mg, 0.10 mmol, quant.) as a yellow oil: IR: $\nu_{max}$ 3691, 3607, 2924, 2853, 1725, 1264, 1602, 1098 cm$^{-1}$; NMR showed a mixture of anomers in a 20:1 $\alpha$/β ratio. Only major compound is described. $^1$H NMR (500 MHz, CD$_3$OD): $\delta$H 7.89 (bs, 1H, NH), 7.61–7.59 (m, 2H, H$_{ar}$), 7.31–7.29 (m, 2H, H$_{ar}$), 5.17 (s, 1H, H$_1$), 4.96 (dd, $J = 5.7$, 3.5 Hz, 1H, H$_3$), 4.82 (d, $J = 8.8$ Hz, 1H, H$_5$), 4.58 (d, $J = 5.7$ Hz, 1H, H$_2$), 4.46 (dd, $J = 8.8$, 3.5 Hz, 1H, H$_4$), 3.36 (s, 3H, OCH$_3$), 1.45 (s, 3H, isop), 1.36 (s, 3H, isop); $^{13}$C NMR (125.7 MHz, CD$_3$OD): $\delta$C 154.4 (C, C=N), 143.5 (C, C$_{ar}$), 138.1 (C, C$_{ar}$), 124.6 (2 x CH, C$_{ar}$), 116.0 (CH, C$_{ar}$), 114.1 (C, isop), 113.9 (CH, Car), 102.4 (CH, C$_1$), 87.2 (CH, C$_2$), 81.7 (CH, C$_4$), 81.2 (CH, C$_3$), 76.5 (CH, C$_5$), 58.4 (CH$_3$, OCH$_3$), 26.5 (CH$_3$, isop), 25.1(CH$_3$, isop); MS (ESI$^+$) m/z (rel intensity) 321 [(M+H)$^+$, 100]; HRMS (ESI-TOF) m/z [M+Na]$^+$ Calcd for C$_{16}$H$_{21}$N$_2$O$_5$ 321.1450; Found 321.1448.

(5R)-5-(1H-benzimidazol-2-yl)-4-O-methyl-2,3-O-isopropylidene-L-ribopyranose (20): To a solution of 19 (340 mg, 0.77 mmol) in EtOAc (15 mL) was added 30%
Pd(OH)$_2$/C (102 mg, 20% w/w). Three vacuum/hydrogen cycles were performed, and the mixture was stirred at rt and under hydrogen atmosphere for 48 h. The reaction mixture was then filtered over a Celite pad, washed with EtOAc, and the filtrate was evaporated. The crude was purified by column chromatography on silica gel (hexane/EtOAc 1:1) to yield compound 20 (205 mg, 0.64 mmol, 83%) as a pale yellow powder. IR: $\nu_{\text{max}}$ 3448, 2992, 2940, 1623, 1456, 1384, 1244, 1072 cm$^{-1}$; NMR showed a mixture of isomers in 5:1 $\alpha$/\& ratio. Only the major one is described. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$H 7.30–7.20 (m, 4H, H$_{\text{ar}}$), 5.61 (s, 1H, H$_1$), 5.29 (d, $J$ = 8.5 Hz, 1H, H$_2$), 4.49 (t, $J$ = 6.1 Hz, 1H, H$_4$), 4.34 (d, $J$ = 6.1 Hz, 1H, H$_3$), 3.78 (dd, $J$ = 8.5, 6.1 Hz, 1H, H$_3$), 3.50 (s, 3H, OCH$_3$), 1.47 (s, 3H, isop), 1.39 (s, 3H, isop); $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$C 152.4 (C, C=N), 141.5 (C, C$_{\text{ar}}$), 136.2 (C, C$_{\text{ar}}$), 123.5 (CH, C$_{\text{ar}}$), 123.0 (CH, C$_{\text{ar}}$), 119.2 (CH, C$_{\text{ar}}$), 110.1 (C, isop), 109.5 (CH, C$_{\text{ar}}$), 92.2 (CH, C$_1$), 80.2 (CH, C$_3$), 76.4 (CH, C$_5$), 76.0 (CH, C$_4$), 65.6 (CH, C$_2$), 59.0 (CH$_3$, OCH$_3$), 27.4 (CH$_3$, isop), 25.7 (CH$_3$, isop); MS (ESI$^+$) m/z (rel intensity) 343 [(M+Na)$^+$, 100]; HRMS (ESI-TOF) m/z [M+Na]$^+$ Calcd for C$_{16}$H$_{20}$N$_2$O$_5$Na 343.1270; Found 343.1283.

Phenyliodosophthalate synthesis:

Dibutylphthalate (2000 mg, 7.20 mmol) was dissolved in methanol (6 mL) before addition of potassium hydroxide (1613 mg, 28.80 mmol) and the reaction mixture was stirred for 1 h at room temperature. The mixture was then poured into water and extracted with ether. The collected aqueous layer was acidified with 6N HCl, extracted with ethyl acetate, and the organic phase was concentrated under vacuum to afford the desired phthalic acid (1195 mg, 7.20 mmol, quant.) as a white powder. Afterward, a solution of phthalic acid (1195 mg, 7.20 mmol) and DIB (2318 mg, 7.20 mmol) in chlorobenzene (50 mL) was stirred for 1 h at 50°C, and the reaction mixture was concentrated under vacuum. The solid obtained was
washed several times with hexane, and finally concentrated under vacuum to afford the desired PhI(Phth) (2358 mg, 6.41 mmol, 89%) as a white powder.

**General procedure for the synthesis of fused benzimidazole-sugars 21, 22, 23, 24 and 25 using PhI(Phth):** A solution of the corresponding hemiacetal (1.0 mmol) in dry EtOAc (20 mL) containing PhI(Phth) (2.2 mmol) and iodine (1.2 mmol) was irradiated with 80 W tungsten-filament lamps at 80°C for 1–1.7 h. The reaction mixture was then poured into aqueous sodium thiosulfate and extracted. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude was purified by column chromatography on silica gel (hexane/EtOAc mixtures) to afford the desired product.

**(1S,2S,3R)-3-O-formyl-1,2-O-isopropylidene-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-ajimidazolo-1,2,3-triol (21):** Following the general procedure, compound 4 (342 mg, 1.23 mmol) afforded, after 1.7 h, the desired compound 21 (252 mg, 0.92 mmol, 75%) after silica gel chromatography (hexane/EtOAc 70:30) as a white powder: $[\alpha]_{D}$^20 +70 (c 0.14, CHCl$_3$); IR: $\nu_{max}$ 2995, 2943, 1735, 1602, 1451, 1238, 1154, 1102 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 8.16 (s, 1H, OCOH), 7.84–7.82 (m, 1H, H$_{ar}$), 7.60–7.58 (m, 1H, H$_{ar}$), 7.37–7.34 (m, 2H, H$_{ar}$), 6.54 (d, $J = 4.5$ Hz, 1H, H$_1$), 6.21 (s, 1H, H$_3$), 5.26 (d, $J = 4.5$ Hz, 1H, H$_2$), 1.51 (s, 3H, isop), 1.12 (s, 3H, isop); $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$C 159.3 (CH, OCOH), 153.1 (C, C=N), 148.7 (C, C$_{ar}$), 127.8 (C, C$_{ar}$), 124.0 (CH, C$_{ar}$), 123.6 (CH, C$_{ar}$), 120.9 (CH, C$_{ar}$), 115.3 (C, isop), 110.8 (CH, C$_{ar}$), 88.3 (CH, C$_1$), 86.2 (CH, C$_2$), 71.3 (CH, C$_3$), 27.4 (CH$_3$, isop), 27.2 (CH$_3$, isop); MS (ESI$^+$) m/z (rel intensity) 297 [(M+Na)$^+$, 100]; HRMS (ESI-TOF) m/z [M+Na]$^+$ Calcd for C$_{14}$H$_{14}$N$_2$O$_4$Na 297.0851; Found 297.0849.

**(1S,2S,3R)-3-O-formyl-1,2-O-isopropylidene-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-ajimidazolo-1,2,3-triol (22):** Following the general procedure, compound 8 (50 mg, 0.18 mmol) afforded, after 1 h, the desired compound 22 (26 mg, 0.09 mmol, 53%) after...
silica gel chromatography (hexane/EtOAc 70:30) as a white powder: \([\alpha]_D^{20} = -87.7\) (c 0.13, CHCl₃); IR: \(\nu_{max}\) 2995, 1735, 1602, 1451, 1232, 1162, 1084 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl₃): \(\delta_H 8.26\) (s, 1H, OCOH), 7.81–7.79 (m, 1H, Hₐr), 7.59–7.57 (m, 1H, Hₐr), 7.35 (dd, \(J = 6.1, 3.2\) Hz, 2H, Hₐr), 6.38 (d, \(J = 4.5\) Hz, 1H, H₁), 6.06 (d, \(J = 5.0\) Hz, 1H, H₃), 5.60 (dd, \(J = 4.5, 5.0\) Hz, 1H, H₂), 1.51 (s, 3H, isop), 1.04 (s, 3H, isop); \(^{13}\)C NMR (100.6 MHz, CDCl₃): \(\delta_C 159.6\) (CH, OCOH), 148.8 (C, Cₐr), 123.8 (CH, Cₐr), 85.6 (CH, Cₐ), 81.7 (CH, C₂), 66.5 (CH, C₃), 27.5 (CH₃, isop), 27.1 (CH₃, isop); MS (ESI\(^+\)) \(m/z\) (rel intensity) 297 [(M+Na)\(^+\), 100]; HRMS (ESI-TOF) \(m/z\) [M+Na]\(^+\) Calcd for C₁₄H₁₄N₂O₄Na 297.0851; Found 297.0857.

\((1S,2S,3R)-3-O\text{-formyl-1,2-O-isopropylidene-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine-1,2,3-triol} (23): Following the general procedure, compound 12 (37 mg, 0.13 mmol) afforded, after 2 h, the desired compound 23 (16 mg, 0.06 mmol, 43%) after silica gel chromatography (hexane/EtOAc 70:30) as a white powder: \([\alpha]_D^{20} = -105\) (c 0.20, CHCl₃); IR: \(\nu_{max}\) 3021, 2962, 1733, 1602, 1458, 1173, 1173, 1083 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl₃): \(\delta_H 8.19\) (s, 1H, OCOH), 7.73–7.71 (m, 1H, Hₐr), 7.54–7.52 (m, 1H, Hₐr), 7.32–7.28 (m, 2H, Hₐr), 6.21 (d, \(J = 4.7\) Hz, 1H, H₁), 5.48 (ddd, \(J = 11.3, 5.7, 1.9\) Hz, 1H, H₃), 4.92 (dd, \(J = 4.7, 1.9\) Hz, 1H, H₂), 3.51 (dd, \(J = 15.5, 11.3\) Hz, 1H, H₄), 3.46 (dd, \(J = 15.5, 5.7\) Hz, 1H, H₄), 1.52 (s, 3H, isop), 1.16 (s, 3H, isop); \(^{13}\)C NMR (100.6 MHz, CDCl₃): \(\delta_C 159.7\) (CH, OCOH), 143.5 (C, Cₐr), 133.2 (C, Cₐr), 123.1 (CH, Cₐr), 119.4 (CH, Cₐr), 113.2 (C, isop), 110.4 (CH, Cₐr), 81.2 (CH, C₁), 74.1 (CH, C₂), 66.8 (CH, C₃), 27.2 (CH₃, isop), 26.6 (CH₃, isop), 25.2 (CH₂, C₄); MS (ESI\(^+\)) \(m/z\) (rel intensity) 311 [(M+Na)\(^+\), 100]; HRMS (ESI-TOF) \(m/z\) [M+Na]\(^+\) Calcd for C₁₅H₁₆N₂O₄Na 311.1008; Found 311.1008.
(1S,2S,3R,4R)-3-O-formyl-1,2-O-isopropylidene-4-O-methyl-1,2,3,4-tetrahydro benzo[4,5]imidazo[1,2-a]pyridine-1,2,3,4-tetraol (24): Following the general procedure, compound 16 (32 mg, 0.10 mmol) afforded, after 1 h, the desired compound 24 (5 mg, 0.02 mmol, 26%) after silica gel chromatography (hexane/EtOAc 70:30) as a pale yellow powder: [α]_D^{20} +17.2 (c 0.33, CHCl₃); IR: 𝜈_{max} 3050, 2996, 2928, 1730, 1694, 1539, 1456, 1377, 1226 cm⁻¹; ^1H NMR (500 MHz, CDCl₃): δ_H 8.06 (s, 1H, OCOH), 7.83–7.81 (m, 1H, H_ar), 7.59–7.57 (m, 1H, H_ar), 7.35–7.33 (m, 2H, H_ar), 6.22 (d, J = 4.7 Hz, 1H, H₁), 6.06 (ddd, J = 4.7, 3.2, 0.9 Hz, 1H, H₃), 4.93 (d, J = 3.2 Hz, 1H, H₄), 4.84 (t, J = 4.7 Hz, 1H, H₂), 3.73 (s, 3H, OCH₃), 1.53 (s, 3H, isop), 1.27 (s, 3H, isop); ^13C NMR (125.7 MHz, CDCl₃): δ_C 159.4 (CH, OCOH), 147.4 (C, C=N), 143.3 (C, C_ar), 133.8 (C, C_ar), 123.5 (CH, C_ar), 123.2 (CH, C_ar), 120.3 (CH, C_ar), 112.8 (C, isop), 110.6 (CH, C_ar), 81.0 (CH, C₁), 74.0 (CH, C₂), 72.0 (CH, C₄), 67.5 (CH, C₃), 58.8 (CH₃, OCH₃), 27.4 (CH₃, isop), 26.4 (CH₃, isop); MS (ESI⁺) m/z (rel intensity) 341 [(M+Na)^⁺, 100]; HRMS (ESI-TOF) m/z [M+Na]^⁺ Calcd for C₁₆H₁₈N₂O₅Na 341.1113; Found 341.1118.

(1S,2S,3R,4R)-4-O-formyl-1,2-O-isopropylidene-3-O-methyl-1,2,3,4-tetrahydro benzo[4,5]imidazo[1,2-a]pyridine-1,2,3,4-tetraol (25): Following the general procedure, compound 20 (41 mg, 0.12 mmol) afforded, after 1 h, the desired compound 25 (22 mg, 0.07 mmol, 58%) after silica gel chromatography (hexane/EtOAc 1:1) as a pale yellow powder: [α]_D^{20} +38.5 (c 0.54, CHCl₃); IR: 𝜈_{max} 2994, 2938, 1697, 1617, 1459, 1385, 1109 cm⁻¹; ^1H NMR (400 MHz, CDCl₃): δ_H 8.42 (s, 1H, OCOH), 7.80–7.78 (m, 1H, H_ar), 7.57–7.54 (m, 1H, H_ar), 7.32–7.30 (m, 2H, H_ar), 6.56 (d, J = 3.2 Hz, 1H, H₁), 6.19 (d, J = 4.8 Hz, 1H, H₄), 4.83 (t, J = 4.8 Hz, 1H, H₃), 4.39 (dd, J = 4.8, 3.2 Hz, 1H, H₂), 3.55 (s, 3H, OCH₃), 1.51 (s, 3H, isop), 1.22 (s, 3H, isop); ^13C NMR (125.7 MHz, CDCl₃): δ_C 160.0 (CH, OCOH), 145.6 (C, C=N), 143.1 (C, C_ar), 134.0 (C, C_ar),
(1S,2S,3R)-1,2-O-isopropylidene-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazo-1,2,3-triol (26): Following the general procedure for anomeric benzoate deprotection, compound 21 (129.5 mg, 0.47 mmol) afforded, after 1 h, the desired compound 26 (93.0 mg, 0.38 mmol, 80%) after silica gel chromatography (hexane/EtOAc 1:1) as a colorless oil: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta_H\) 7.66–7.64 (m, 1H, H\(_{\text{ar}}\)), 7.52–7.49 (m, 1H, H\(_{\text{ar}}\)), 7.28–7.24 (m, 2H, H\(_{\text{ar}}\)), 6.48 (d, \(J = 4.3\) Hz, 1H, H\(_1\)), 5.40 (s, 1H, H\(_3\)), 5.26 (d, \(J = 4.3\) Hz, 1H, H\(_2\)), 1.47 (s, 3H, isop), 1.08 (s, 3H, isop); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)): \(\delta_C\) 158.9 (C, C=N), 147.3 (C, C\(_{\text{ar}}\)), 130.2 (C, C\(_{\text{ar}}\)), 123.6 (CH, C\(_{\text{ar}}\)), 123.3 (CH, C\(_{\text{ar}}\)), 119.7 (CH, C\(_{\text{ar}}\)), 114.5 (C, isop), 110.9 (CH, C\(_{\text{ar}}\)), 90.4 (CH, C\(_1\)), 86.5 (CH, C\(_2\)), 69.5 (CH, C\(_3\)), 27.5 (CH\(_3\), isop), 27.0 (CH\(_3\), isop); MS (ESI\(^+\)) \(m/z\) (rel intensity) 247 [(M+H\(^+\), 100]; HRMS (ESI-TOF) \(m/z\) [M+H\(^+\)] Calcd for C\(_{13}\)H\(_{15}\)N\(_2\)O\(_3\) 247.1083; Found 247.1088.

(2S,3R,4R)-3-O-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine-1,2,3,4-tetraol (27): To a stirred solution of 25 (20 mg, 0.06 mmol) in DCM (0.6 mL, 10 mL/mmol) at rt was added trifluoroacetic acid (TFA) (0.6 mL, 10 mL/mmol), and the resulting reaction mixture was stirred for 24 h, then concentrated under vacuum, and the crude was purified by column chromatography on silica gel (EtOAc) to afford the compound 27 (6 mg, 0.02 mmol, 40%) as a colorless oil: MS (ESI\(^+\)) \(m/z\) (rel intensity) 273 [(M+Na\(^+\), 100]; HRMS (ESI-TOF) \(m/z\) [M+Na\(^+\)] Calcd for C\(_{12}\)H\(_{14}\)N\(_2\)O\(_3\)Na 273.0851; Found 273.0864.
SUPPORTING INFORMATION

H and 13C NMR spectra for all new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

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REFERENCES AND FOOTNOTES


(13) This protocol was repeated several times by using D-lyxose derivative 4 as a precursor, and it was observed that when PhI(Phth) was over a month old, lower yields were consistently obtained (49-57%). Hence, a freshly prepared batch of PhI(Phth) was used in order to ensure optimal reaction conditions.