An Examination of the Purported Reverse Anomeric Effect beyond Acetylated *N*-Xylosyl- and *N*-Glucosylimidazoles

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Syntheses of six new *N*-(pentopyranosyl)imidazoles have been achieved, and their conformations were observed with and without protonation. A decisive decrease in $J_{5',4}$, consistent with stabilization of the $^1C_4$ conformations, was clearly observed for three *N*-(pentopyranosyl)imidazoles. As well, no reverse anomeric stabilization was observed for *N*-(2,3,4-tri-*O*-acetyl-α-D-lyxopyranosyl)imidazole upon protonation. It is suggested that the previous observations of the reverse anomeric effect were due to the slight increase in steric bulk of the imidazole aglycone upon protonation, along with favorable dipolar interactions between ring substituents, and not by a reverse of the anomeric effect.

Introduction

Anomeric stabilization of axially oriented electronegative aglycones is one of the hallmarks of carbohydrate chemistry. In 1965, the paradigm of a reverse anomeric effect (RAE) was suggested in a report by Lemieux and Morgan[1] on the abnormal conformation of *N*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-4-methylpyridinium bromide, which was thought to exist in the $^1C_4$ conformation such that the aglycone was in an equatorial orientation with all of the acetoxy groups axially disposed. Subsequently it was suggested that the compound was in the $B_{2,5}$ conformation.[2] A later report by Lemieux[3] on the conformation of *N*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)imidazole demonstrated that this compound did indeed exist in the $B_{2,5}$ conformation upon protonation with trifluoroacetic acid (TFA). The most oft-quoted study of the RAE is the work of Paulsen and co-workers.[4] By observing the conformation of *N*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)imidazole in $CDCl_3$, it was noted that the proportion of the $^1C_4$ conformation increased from 65% to >95% upon protonation by TFA (Scheme 1). In the more polar solvent acetone the initial proportion of the $^1C_4$ conformation was 85%, a reflection of the role of increased solvent polarity in diminishing the electrostatic anomeric effect.[5] We have recently reported, in the cases of *N*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)imidazole and *N*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)-2-methylimidazole, that the increase in solvent polarity concomitant with TFA addition is insufficient to cause a shift to the $^1C_4$ conformation on its own.[6]

There have been reports in the literature suggesting that the RAE does not exist at all. Perrin and co-workers have reported two studies decrying the RAE. By comparison of the equilibrium between α and β anomers for a series of D-glucosylamines both protonated and unprotonated, it was determined that there was no increase in the proclivity for a cationic aglycone to assume an equatorial orientation.[7] Also, from a comparison of the pK_a's for mixtures of α and β *N*-glycopyranosylimidazoles,[8] reverse anomeric stabilization was concluded not to exist. As well, Kirby and co-workers[9] have reported an ^{1}H NMR spectroscopic and an X-ray crystallographic study of a 1,3-dioxane ring having a bulky quaternary methylated quinuclidine at C-2 which revealed no reverse anomeric stabilization. Pinto and co-workers have determined that there is no generalized reverse anomeric effect in neutral or protonated *N*-aryl-5-thioglucopyranosylamines or *N*-arylglucopyranosylamines.[10] There have also been reports that the equatorial stabilization seen in $O-C-N^+$ fragments is not manifest in the corresponding $S-C-P^+$ fragments.[11]

The physical evidence supporting the existence of an RAE is paltry at best—changes in coupling constants for acetylated *N*-(α-D-xylopyranosyl)imidazoles.[4,6] Interestingly, reverse anomeric stabilization is claimed to be documented by theoretical calculations.[12] Also, reverse

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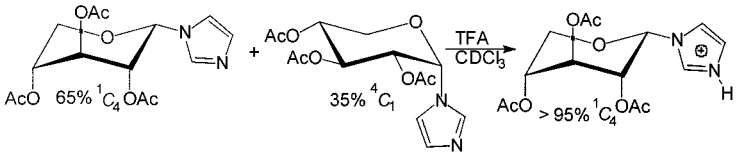
Scheme 1



anomeric stabilization of equatorially oriented cationic aglycones has been invoked to rationalize a host of phenomena, for example, in the intermediacy of nitrilium cations in glycoside synthesis,[13] in the use of ammonium[14] or sulfonium[15] cationic intermediates for controlling the stereochemical course of glycoside synthesis (the former, in particular, in the synthesis of 2′-deoxy-*β*-D-nucleosides[16]), and in the addition reactions of glycals.[17] Indeed, belief in the existence of the RAE has gone so far that the idea of a reverse-exo-anomeric effect has been proposed.[18] In light of the relatively meager physical evidence for the existence of the RAE, we felt examination beyond *N*-(D-xylopyranosyl)imidazoles was imperative. Thus, the syntheses of a variety of protected *N*-(aldopentopyranosyl)imidazoles, namely, acetylated *N*-(glycopyranosyl)imidazoles of D-arabinose, D-lyxose, and D-ribose were performed. In addition, *N*-(2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl)imidazole and *N*-(2,3,4-tri-*O*-methyl-α-D-xylopyranosyl)imidazole were synthesized to evaluate the effect of altering protecting groups on the best system for observing the RAE.

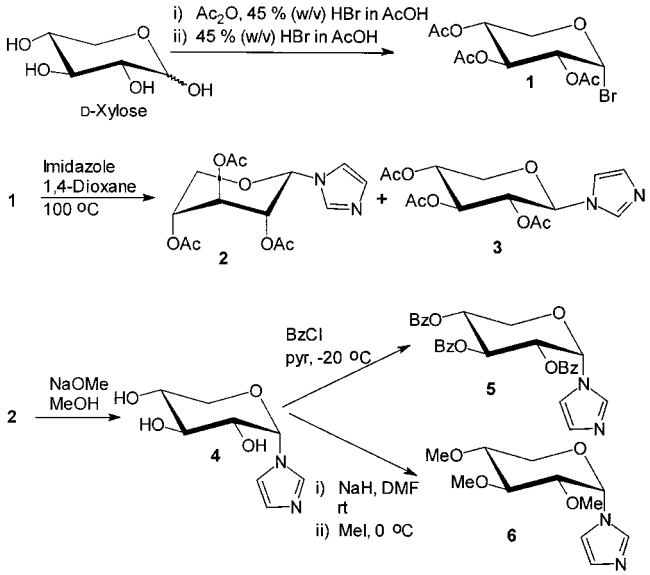
Results

N-(2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl)imidazole (**2**, Scheme 2) and *N*-(2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosyl)-imidazole (**3**) were prepared as reported by Paulsen and co-workers.[4] Separation of the two anomers was achieved by column chromatography. The syntheses of *N*-(2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl)imidazole (**5**) and *N*-(2,3,4-tri-*O*-methyl-α-D-xylopyranosyl)imidazole (**6**) were accomplished by de-*O*-acetylation of **2** to afford *N*-(α-D-xylopyranosyl)imidazole (**4**), followed by treatment with either benzoyl chloride in pyridine, or deprotonation with NaH in DMF followed by addition of MeI. Attempting the formation of **5** or **6** by routes analogous to that described for **2**, namely, treatment of either 2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl bromide or 2,3,4-tri-*O*-methyl-α-D-xylopyranosyl bromide with imidazole in 1,4-dioxane, afforded unresolvable mixtures of anomers.

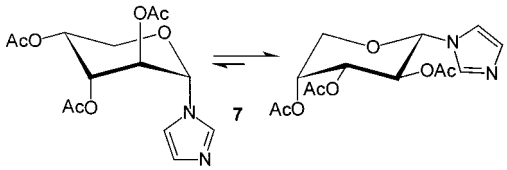
To further our understanding of the conformational equilibria of *N*-(pentopyranosyl)imidazoles, the syntheses of *N*-(2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl)imidazole (**7**), *N*-(2,3,4-tri-*O*-acetyl-α-D-lyxopyranosyl)imidazole (**8**), and *N*-(2,3,4-tri-*O*-acetyl-*β*-D-ribopyranosyl)imidazole were performed by routes analogous to that described for the synthesis of **2**.

Treatment of 2,3,4-tri-*O*-acetyl-*β*-D-arabinopyranosyl bromide with imidazole in 1,4-dioxane afforded the

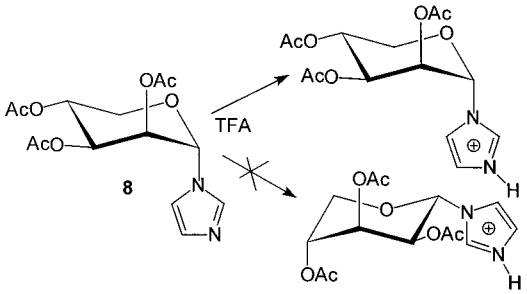
Scheme 2



Scheme 3



Scheme 4



desired *N*-(2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl)imidazole (**7**, Scheme 3). The same treatment of 2,3,4-tri-*O*-acetyl-α-D-lyxopyranosyl bromide afforded *N*-(2,3,4-tri-*O*-acetyl-α-D-lyxopyranosyl)imidazole (**8**, Scheme 4), and treatment of 2,3,4-tri-*O*-acetyl-*β*-D-ribopyranosyl bromide with imidazole, as described previously, afforded *N*-(2,3,4-tri-*O*-acetyl-*β*-D-ribopyranosyl)imidazole.

The anomeric selectivity observed for the reactions of the glycopyranosyl bromides with imidazole is puzzling given the small differences between the molecules. While 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide gave preponderantly the α imidazole, the same treatment with the corresponding *β*-D-ribosyl species, differing from the *xylo* at C-1 and C-3, gave solely the *β*. The C-2 epimer of α-D-*xylo*, namely the α-D-*lyxo* species,[19] afforded the α imidazole; the same result was noted for the *β*-D-*arabino*

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species, differing from the α-D-*xylo* at C-1 and C-2. Even compounds having the D-*xylo* configuration provide contradictory results. Reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (xylose with an acetoxymethyl group at C-6) with imidazole is known to afford a 1:1 mixture of α and *β* anomers[20] Reaction of 2,3,4-tri-*O*-acetyl-α-D-quinovopyranosyl bromide (xylose with a methyl group at C-6) with imidazole affords solely the *β*-D anomer.[21] The yields of the reactions were generally low. It is notable that significant amounts of a black tarlike substance, insoluble in organic solvents, are also produced in the course of the reactions.

There is evidence for the interaction of heteroatomic solvents with anomeric glycosyl halides resulting in the formation of intimate ion-pairs.[22] A possible explanation for the anomeric selectivity observed is as follows. Initially, an oxygen of 1,4-dioxane displaces the bromide of the glycosyl bromide to form a cationic species. There is the possibility then of reaction with imidazole or displacement by another 1,4-dioxane molecule. An equilibrium will be established wherein the most stable species will preponderate, and, thus, be more likely to react with imidazole. Factors affecting this equilibrium will include anomeric stabilization, 1,3-diaxial steric repulsions, 1,3-dipolar attractions, and 1,4-transannular attractions. As all of these effects may be operative, which one will be primarily responsible for the observed anomeric selectivity is hard to say.

Conformations in solution were determined by the method of averaging of spin−spin coupling,[23] in duplicate, as previously described.[6] ^{1}H NMR spectra were acquired at 400 MHz on a Bruker AM-400 spectrometer except for the spectra of **6**, which were acquired at 600 MHz on a Bruker AMX-600 spectrometer. All spectra were acquired at 298 K. Changes in $J_{5',4}$ (5′ refers to the axial proton at C-5 in keeping with previous work by Durette and Horton[24]) were monitored; $J_{5',4}$ was selected as it provided a clear glimpse of interactions between H-5′ and H-4 unfettered by adjacent spins. Also, the shift from a large axial−axial coupling to a smaller equatorial−equatorial coupling[25] ought to provide a more accurate manifestation of conformational changes.

Coupling constants are widely used to establish conformations in solution as they are known to vary, predictably, with dihedral angle.[26] It is important to realize that $^3J_{HH}$ also varies with solvent, with the electronegativity of other substituents, and with the orientation of the electronegative substituents.[27] Controls for extraneous changes in $J_{5',4}$ were provided by **7**, having an equatorially oriented imidazole group, and by **8**, having an axially oriented imidazole group; neither compound exhibited any significant change in $J_{5',4}$, even upon full protonation, confirming the significance of the shifts of $J_{5',4}$ for **2**, **5**, and **6**.

The decrease on protonation in $J_{5',4}$ for *N*-(2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl)imidazole (**5**) and *N*-(2,3,4-tri-*O*-methyl-α-D-xylopyranosyl)imidazole (**6**), in $CDCl_3$, upon addition of TFA was pronounced. The value measured for $J_{5',4}$ in unprotonated **5** was 5.81 Hz; after addition of 0.5 equiv of TFA, $J_{5',4}$ decreased to 4.30 Hz (coalescence of the signals for H-5′ and H-5 precluded further determination of $J_{5',4}$). For **6**, the value measured for $J_{5',4}$ was 5.12 Hz prior to protonation, and 2.6 Hz after addition of 1 equiv of TFA. For **2**, $J_{5',4}$ decreased from 5.34 to 1.90 Hz after addition of 1 equiv of TFA. In all cases, the marked decrease in $J_{5',4}$ is consistent with a substantial shift to the $^1C_4$ conformation. The limiting values for $J_{ax,ax}$ and $J_{eq,eq}$ were those obtained using peracetylated aldopentoses in $(CD_3)_2CO$.[24] While the observed changes in $J_{5',4}$ may not provide exact values for the proportion of each conformation, they clearly indicate a decisive trend toward an equatorially oriented aglycone.

Examination of the ^{1}H NMR spectrum of **7** in $CDCl_3$ revealed the compound to be entirely in the $^1C_4$ conformation prior to protonation. The $^1C_4$ conformation has been similarily observed also for 2,3,4-tri-*O*-acetyl-1-*O*-benzoyl-α-D-arabinopyranose,[28] methyl 2,3,4-tri-*O*-acetyl-α-D-arabinopyranoside,[29] and 1,2,3,4-tetra-*O*-acetyl-α-D-arabinopyranose.[39] Thus, the *arabino* compounds are not amenable to detection of reverse anomeric effects.

The ^{1}H NMR spectrum of **8** in $CDCl_3$, with $J_{5',4} = 10.3$ Hz, is consistent with >95% of the $^4C_1$ conformation prior to protonation, a result markedly different from that observed in the α-D-*xylo* case. Addition of several equivalents of TFA had no effect on $J_{5',4}$ for **8**. That the imidazole was, in fact, protonated is demonstrated by a shift for δ_{H-2Im} from 7.65 to 8.96.

Discussion

At first glance, the decrease on protonation in $J_{4,5'}$ (consistent with a shift to the $^1C_4$ conformation[30]) for *N*-(2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl)imidazole is impressive, temptingly suggestive of reverse anomeric stabilization of a seemingly sterically disfavored form; however, this observation is deceiving. For the same reason that 2,3,4-tri-*O*-benzoyl-*β*-D-xylopyranosyl chloride exists, in solution, to a greater extent in the $^1C_4$ form than does the corresponding acetylated compound, namely the greater electronegativity of benzoate vs acetate,[31] it should not be surprising that the benzoylated xyloside similarly prefers having the three benzoates axially

(19) Compound **8** was identified as having the α-D configuration based on observation of a broad singlet ($J_{1,2}$ < 1.5 Hz) for H-1 consistent with an eq−eq coupling. At 600 MHz, a sharper singlet is observed. It is noteworthy that the other signals of the spectrum of **8** were very well resolved, as were all the spectra for the other glycosylimidazoles reported herein. The ^{1}H NMR spectrum of the deacetylated **8** was insufficiently resolved to permit observation of $J_{1,2}$. Attempts to observe NOEs between H-1 and H-2 were unsuccessful, consistent with **8** having the α-D configuration; however, this does not represent positive proof of structure. The possibility exists that merely no NOE was observable between H-1 and H-2 for the *β*-D anomer. All the glycosyl imidazoles reported herein were highly amorphous, defying valient efforts at recrystallization. Had the *β* anomer been formed, a larger eq−ax coupling of 3−5 Hz would have been observed. See, for example Durette, P. L.; Horton, D. *Carbohydr. Res.* **1971**, *18*, 57. Bhacca, N. S. et al. *J. Org. Chem.* **1968**, *33*, 2484.

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(30) The only other possibility for $J_{4,5'}$ to decrease is for the molecule to adopt a $B_{1,4}$ conformation. The likelihood of this is negligible.

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oriented. The most striking examples of anomeric (and alleged reverse anomeric) effects are with carbohydrate derivatives having the α-D-*xylo* configuration; in these cases substituents at carbons 2, 3, and 4 are all equatorially oriented in the $^4C_1$ conformation and all axially oriented in the $^1C_4$ conformation. It is in the $^1C_4$ conformation that all of the dipoles for the ring substituents are antiparallel and thus in their most stable arrangement.

Examples of dipolar stabilization of seemingly unstable steric arrangements have previously been noted. In a conformational study of 3-acetoxytetrahydropyran, Anderson and Sepp[32] reported that, in solution, the molecule exists as a 1:1 mixture of axial and equatorial conformations. Favorable dipolar interactions were cited, although no further details were provided. This tendency to stabilize the axial conformation was found to increase as the electronegativity of the ring heteroatom increased.[33] 4,4-Difluorocyclohexanol was discerned to exist in solution as equatorial and axial conformations in equal proportions.[34] As the electron-withdrawing ability of the substituent at C-1 increased, upon introduction of a benzoic ester or replacement of the hydroxyl with chlorine, the axial conformation was found to preponderate. Wood and co-workers,[35] looking at the conformational equilibrium of 1*H*,4*H*-*trans*-1,4-bis(trifluoroacetoxy)-cyclohexane-d_8, have suggested that polarization of the C−X bond imparts a partial positive charge to the carbon atom, thereby creating an attractive force between C-1 and X-4 when the two substituents are in a diaxial orientation. Similarly, a stabilizing interaction between the carbonyl oxygen of an ester and either a ring carbon or a carbonyl carbon in a 1,3-diaxial disposition is plausible. Stabilization of 1,2 dipoles of six-membered rings by a diaxial orientation is similarly well-known.[36]

With three dipoles yearning to assume a mutually antiparallel orientation, the *xylo* configuration can be considered to be spring-loaded. Previous work has demonstrated that the increase in steric bulk on protonation of imidazole is insufficient to effect a shift to the $^1C_4$ conformation on its own.[37] It is suggested that the transannular dipolar stabilization described above, taken with the slight steric perturbation of an extra proton (with counterion) on the imidazole, is responsible for the observed shift to the $^1C_4$ form for acetylated *N*-xylopyranosylimidazoles. In essence, the proton acts as the "straw that breaks the camel's back".

The decrease on protonation in $J_{4,5'}$ for **6** is noteworthy. Replacing acetoxy groups with methoxy groups has been noted to bring about a change in conformation of pyranoid rings.[38] For example, while peracetylated β-D-xylose exists as 51% in the $^1C_4$ conformation,[39] only 10% of permethylated β-D-xylose is found in the $^1C_4$ conformation.[40] Further, whereas 1,2,3,4,6-penta-*O*-acetyl-α-D-idopyranose has been found to prefer in solution the all-axial $^4C_1$ conformation[41] having the acetoxy groups at C-1,2,3,4 axially oriented and hence with incumbent 1−3 diaxial interactions, the analogous permethylated compound prefers instead the $^1C_4$ conformation.[42] It appears that favorable interactions between 1,3-diaxial groups plays a significant role in the conformation of the sugar. This effect is evident in the present study in the lack of any shift for *N*-(2,3,4-tri-*O*-acetyl-α-D-lyxopyranosyl)-imidazole (**8**) upon protonation. The loss of a single axial substituent at C-2, with concomitant losses of antiparallel dipolar interactions to C-3 and C-4, is enough to prevent adoption of the $^1C_4$ conformation. That such a seemingly small difference should be of import is evident in comparing the conformations of **2** and **8** (both unprotonated) in $CDCl_3$—a difference of >60% between *N*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)imidazole and *N*-(2,3,4-tri-*O*-acetyl-α-D-lyxopyranosyl)imidazole.

Conclusions

So-called reverse anomeric stabilization has been truly noted for four analogous compounds in only one solvent, namely in the cases of *N*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)imidazole,[3] *N*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)-2-methylimidazole,[6] *N*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)imidazole,[2] and *N*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)pyridinium bromide,[1] in $CDCl_3$. The present work reaffirms the validities of the reports of Lemieux[1,2,3] and Paulsen[4] on the enhanced stabilization in the cases of equatorially oriented cationic aglycones; the enhanced stabilization of the $^1C_4$ form of *N*-(2,3,4-tri-*O*-methyl-α-D-xylopyranosyl)imidazole (**6**) is of particular significance, as it demonstrates stabilization of a more sterically more challenging form than in the initial reports of the RAE. The *arabino* and *lyxo* examples are significant in that they further point to the limited scope of the observation of any RAE.

A discernible shift to a conformation having an equatorial aglycone is indeed observed, as evidenced by marked decreases in $J_{4,5'}$ for a range of compounds, all having the α-D-*xylo* configuration. However, the lack of such a shift for the corresponding *lyxo* species points to the limited scope of this effect. Conflicting data are presented. Clear stabilization of the $^1C_4$ conformation is noted based on observation of coupling constants, yet a comparison of the pK_a's of **2** and **3** during titration with acid demonstrates the opposite,[7,8] a greater stabilization of the cationic axial imidazole, consistent with a normal anomeric effect. It is seen that the change in $J_{4,5'}$ as described by Lemieux[1,2,3] and by Paulsen[4] on systems unnaturally disposed toward an equatorial aglycone was indeed an accurate observation, but that its cause was not due to a reverse of the anomeric effect, but merely a normal anomeric effect subject to unusual dipolar interactions. Thus, we also affirm that there is no reverse anomeric effect, and that the previous observations of the "RAE" were due to normal steric effects.

Experimental Section

General Methods. 1,4-Dioxane was dried by distilling a solution in the presence of blue sodium benzyl ketyl. Methanol was dried by distilling a solution in the presence of $Mg(OMe)_2$.

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N,*N*-Dimethylformamide and pyridine were dried by distilling a solution of each in the presence of CaH_2. Trifluoroacetic acid was dried by refluxing in the presence of trifluoroacetic anhydride, followed by fractional distillation. Routine drying during processing of all compounds was accomplished over $MgSO_4$. Chemical-shift and coupling assignments were made with the aid of spin−spin decoupling experiments (COSY, HETCOR).

***N*-(2,3,4-Tri-*O*-acetyl-α-and *β*-D-xylopyranosyl)imidazoles (2 and 3).** A mixture of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide[43] (22 g, 65 mmol) and imidazole (22 g, 0.32 mol) in 1,4-dioxane (200 mL) was heated at reflux temperature for 4 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure; the residue was dissolved in CH_2Cl_2, and the solution was washed sequentially with satd $NaHCO_3$ and water, dried, filtered, and the solvent was removed under reduced pressure. Fractionation of the residue was achieved using column chromatography [4:1 (v/v) EtOAc−hexane] to afford the products as white solids. α anomer (7.3 g, 35%): R_f 0.3, 19:1 (v/v) EtOAc−MeOH; mp 180−181 °C; $[\alpha]_D$ − 45.0° (*c* 1, $CHCl_3$); {lit.[4] mp 180 °C, $[\alpha]_D$ −44.4° (*c* 1, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3 H, OAc), 2.12 (s, 3 H, OAc), 2.18 (s, 3 H, OAc), 3.79 (dd, 1 H, $J_{5',5}$ 12.9, $J_{5',4}$ 4.9 Hz, H-5′), 4.02 (dd, 1 H, $J_{5,5'}$ 12.9, $J_{5,4}$ 3.4 Hz, H-5), 4.80−5.01 (m, 1 H, H-4), 5.12 (dd, 1 H, $J_{2,3}$ 6.5, $J_{2,1}$ 3.3 Hz, H-2), 5.42 (t, 1 H, $J_{3,4}$, $J_{3,2}$ 6.5 Hz, H-3), 5.80 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 7.09 (s, 1 H, H_{Im}), 7.15 (s, 1 H, H_{Im}), 7.80 (s, 1 H, H_{Im}); ^{13}C NMR: δ 21.08 (OAc), 63.42 (C-5), 66.92, 67.02, 68.82 (C-2,3,4), 81.01 (C-1), 117.98 (C_{Im}), 128.66 (C_{Im}), 169.74, 169.23, 169.66 (OAc). *β* anomer (1.05 g, 4.8%): R_f 0.4, 19:1 (v/v) EtOAc−MeOH; mp 170−171 °C; $[\alpha]_D$ −33.1° (*c* 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.91 (s, 3 H, OAc), 2.00 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 3.47 (t, 1 H, $J_{5',5}$ 11.2, $J_{5',4}$ 11.2 Hz, H-5′), 4.22 (dd, 1 H, $J_{5,5'}$ 11.6, $J_{5,4}$ 5.7 Hz, H-5), 5.09 (m, 1 H, H-4), 5.18−5.28 (m, 3 H, H-1,2,3), 7.00 (s, 2 H, H_{Im}), 7.59 (s, 1 H, H_{Im}); ^{1}H NMR [$(CD_3)_2CO$, 400 MHz]: δ 1.81 (s, 3 H, OAc), 1.97 (2, 3 H, OAc), 2.00 (s, 3 H, OAc), 3.71 (t, 1 H, $J_{5',5}$ 10.7, $J_{5',4}$ 10.7 Hz, H-5′), 4.18 (dd, 1 H, $J_{5,5'}$ 10.2, $J_{5,4}$ 4.5 Hz, H-5), 5.13 (m, 1 H, H-4), 5.42 (m, 2 H, H-2,3), 5.64 (d, 1 H, $J_{1,2}$ 7.1 Hz, H-1), 6.92, 7.28 (2s, 2 H, H_{Im}), 7.73 (s, 1 H, H_{Im}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.13, 20.58, 20.62 (OAc), 65.49 (C-5), 68.44, 70.85, 72.41 (C-2,3,4), 84.30 (C-1), 116.65, 130.35 (C_{Im}-4,5), 136.60 (C_{Im}-2), 168.72, 169.68, 169.99 (OAc); MS (ES^+) Expected for $C_{14}H_{18}O_7N_2$ $[M + H]^+$: 327.1. Found: 327.1. Anal. Calcd for $C_{14}H_{18}O_7N_2$: C, 51.70; H, 5.58; N, 8.61. Found: C, 51.80; H, 5.75; N, 8.62.

***N*-(α-D-Xylopyranosyl)imidazole (4).** To a solution of *N*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)imidazole (**2**, 1 g, 3 mmol) in MeOH (20 mL) was added a tiny piece of sodium metal. The solution was stirred for 2 h under argon. Amberlite IR-120 (H^+) resin was added, and stirring was continued for a further 30 min. The mixture was filtered, and the solvent was removed under reduced pressure to afford the product as a white solid (500 mg, 83%): mp 166−167 °C; $[\alpha]_D$ − 4.6° (*c* 3.2, MeOH); ^{1}H NMR (400 MHz, D_2O): δ 3.60 (m, 2 H, H-5,5′), 3.82−3.95 (m, 3 H, H-2,3,4), 5.70 (br s, 1 H, H-1), 6.92 (s, 1 H, H_{Im}), 7.26 (s, 1 H, H_{Im}), 7.84 (s, 1 H, H_{Im}); ^{13}C NMR (100 MHz, D_2O): δ 66.83 (C-5), 67.91, 70.16, 70.38 (C-2,3,4), 82.54 (C-1), 119.52, 127.67 (C_{Im}); MS (EI^+): Expected for $C_8H_{12}O_4N_2$ $[M]^+$: 200.1. Found: 200.0. Anal. Calcd for $C_8H_{12}O_4N_2$: C, 48.01; H, 6.04; N, 14.00. Found: C, 47.90; H, 6.20; N, 13.84.

***N*-(2,3,4-Tri-*O*-benzoyl-α-D-xylopyranosyl)imidazole (5).** A solution of *N*-(α-D-xylopyranosyl)imidazole (**4**, 220 mg, 1.1 mmol) in pyridine (3 mL) was cooled to −20 °C. Benzoyl chloride (0.38 mL, 3.3 mmol) was added dropwise, and the mixture was stirred for 2 h. Water was added, and the mixture was extracted with CH_2Cl_2. The organic extracts were washed sequentially with 2 N H_2SO_4, satd $NaHCO_3$, and water, dried, and filtered, and the solvent was removed under reduced pressure. Fractionation of the residue was achieved by column chromatography using 2:1 (v/v) EtOAc−hexane as eluent to afford the product as a white solid (257 mg, 45%): mp 77−79 °C; $[\alpha]_D$ −10.7° (*c* 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.17 (dd, 1 H, $J_{5',5}$ 13.0, $J_{5',4}$ 4.4 Hz, H-5′), 4.34 (dd, 1 H, $J_{5,5'}$ 13.1, $J_{5,4}$ 3.1 Hz, H-5), 5.31 (m, 1 H, H-4), 5.57 (dd, 1 H, $J_{2,3}$ 5.4, $J_{2,1}$ 3.0 Hz, H-2), 5.97 (t, 1 H, $J_{3,4}$ 5.1, $J_{3,2}$ 5.1 Hz, H-3), 6.06 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1), 7.01 (s, 1 H, H_{Im}), 7.21−7.63 [m, 11 H, Bz(9), Im(2)], 7.96−8.11 (m, 6 H, Bz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 65.39 (C-6), 67.21, 68.19, 68.737 (C-2,3,4). 81.78 (C-1), 117.74 (C_{Im}), 128.41, 128.64, 128.73, 128.91, 129.59, 129.92, 130.03, 133.55, 133.85, 133.96 (Bz, Im), 164.53, 164.91, 165.45 (OBz); HRMS (EI^+): Expected for $C_{29}H_{24}O_7N_2$ $[M]^+$: 512.1575. Found: 512.1571. Anal. Calcd for $C_{29}H_{24}O_7N_2$: C, 67.97; H, 4.72; N, 5.47. Found: C, 67.60; H, 5.02; N, 5.40.

***N*-(2,3,4-Tri-*O*-methyl-α-D-xylopyranosyl)imidazole (6).** To a solution of *N*-(α-D-xylopyranosyl)imidazole (**4**, 500 mg, 2.5 mmol) in DMF (6 mL) was added NaH (60% dispersion in oil, 320 mg, 8.0 mmol), and the mixture was heated at 50 °C for 30 min. The mixture was cooled on ice, and MeI (0.47 mL, 7.5 mmol) was added dropwise. Stirring was continued for 3 h. The solvent was removed under reduced pressure, and the mixture was added to EtOAc; the solution was washed with water, dried, and filtered, and the solvent was removed under reduced pressure. Fractionation of the residue was achieved by column chromatography using EtOAc as eluent to afford the product as a clear oil (520 mg, 86%): $[\alpha]_D$ + 12.5° (*c* 0.4, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.29 (m, 1 H, H-4), 3.46 (s, 3 H, OCH_3), 3.48 (s, 3 H, OCH_3), 3.51 (dd, 1 H, $J_{2,3}$ 6.4, $J_{2,1}$ 3.4 Hz, H-2), 3.58 (dd, 1 H, $J_{5',5}$ 11.3, $J_{5',4}$ 5.2 Hz, H-5′), 3.59 (s, 3 H, OCH_3), 3.65 (t, 1 H, $J_{3,4}$, $J_{3,2}$ 6.1 Hz, H-3), 3.85 (dd, 1 H, $J_{5,5'}$ 12.4, $J_{5,4}$ 3.6 Hz, H-5), 5.64 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 7.10 (s, 1 H, H_{Im}), 7.25 (s, 1 H, H_{Im}), 7.94 (s, 1 H, H_{Im}); ^{13}C NMR(100 MHz, $CDCl_3$): δ 58.34, 59.21, 59.79 (OCH_3), 63.67 (C-5), 76.83, 78.80, 79.64 (C-2,3,4), 81.50 (C-1), 118.44, 128.98 (C_{Im}); HRMS (EI^+): Expected for $C_{11}H_{18}O_4N_2$ $[M]^+$: 242.1267. Found: 242.1272. Anal. Calcd for $C_{11}H_{18}O_4N_2 \cdot 0.25H_2O$: C, 53.54; H, 7.56; N, 11.35. Found: C, 53.40; H, 7.80; N, 11.33.

***N*-(2,3,4-Tri-*O*-acetyl-α-D-arabinopyranosyl)imidazole (7).** A mixture of 2,3,4-tri-*O*-acetyl-*β*-D-arabinopyranosyl bromide[44] (1.1 g, 3.24 mmol) and imidazole (1 g, 14.69 mmol) in 1,4-dioxane (50 mL) was maintained at reflux temperature under argon for 4 h and processed in the usual way. Fractionation of the residue was achieved by column chromatography using 4:1 (v/v) EtOAc−hexane as eluent to afford the product as a white solid (900 mg, 85%): mp 113 °C; $[\alpha]_D$ −25.73° (*c* 1.85, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92 (s, 3 H, OAc), 2.02 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 3.86 (d, 1 H, $J_{5',5}$ 13.4 Hz, H-5′), 4.15 (dd, 1 H, $J_{5,5'}$ 13.4, $J_{5,4}$ 1.9 Hz, H-5), 5.17 (dd, 1 H, $J_{3,2}$ 10.1, $J_{3,4}$ 3.5 Hz, H-3), 5.19 (d, 1 H, $J_{1,2}$ 9.1 Hz, H-1), 5.39 (br t, 1 H, $J_{4,5}$ 1.6 Hz, H-4), 5.54 (t, 1 H, $J_{2,3}$, $J_{2,1}$ 9.4 Hz, H-2), 6.99, 7.12 (2 s, 2 H, H_{Im}-4, 5), 7.67 (s, 1 H, H_{Im}-2); ^{13}C NMR (50 MHz): δ 20.13, 20.49, 20.85 (OAc), 66.97 (C-5), 67.90, 68.43, 70.76 (C-2,3,4), 84.41 (C-1), 116.90, 129.99, 136.56 (C_{Im}), 168.69, 169.85, 170.10 (OAc); MS (ES^+) Expected for $C_{14}H_{18}O_7N_2$ $[M + H]^+$: 327.1; Found: 327.2. Anal. Calcd for $C_{14}H_{18}O_7N_2$: C, 51.70; H, 5.58; N, 8.61. Found: C, 51.79; H, 5.57; N, 8.53.

***N*-(2,3,4-Tri-*O*-acetyl-α-D-lyxopyanosyl)imidazole (8).** A mixture of 2,3,4-tri-*O*-acetyl-α-D-lyxopyranosyl bromide[45] (4.5 g, 13.3 mmol), imidazole (3 g, 44.1 mmol), and 1,4-dioxane (50 mL) was maintained at reflux temperature under argon for 4 h. After cooling, the mixture was processed in the usual way to afford the product as a white solid (927 mg, 21%): mp 105−106 °C; $[\alpha]_D$ −46.3° (*c* 1.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (s, 3 H, OAc), 2.07 (s, 6 H, 2 OAc), 3.46 (t, 1 H, $J_{5',5}$, $J_{5',4}$ 10.3 Hz, H-5′), 4.34 (dd, 1 H, $J_{5,5'}$ 11.5, $J_{5,4}$ 5.5 Hz, H-5), 5.19 (dd, 1 H, $J_{3,4}$ 10.2, $J_{3,2}$ 3.1 Hz, H-3), 5.30 (m, 1 H, H-4), 5.51 (br s, 1 H, H-1), 5.53 (d, 1 H, $J_{2,3}$ 3.1 Hz, H-2), 6.96 (s, 1 H, H_{Im}), 7.13 (s, 1 H, H_{Im}), 7.62 (s, 1 H, H_{Im}); ^{13}C NMR (50 MHz): δ 20.55, 20.607, 20.73 (OAc), 65.45 (C-5), 65.64, 69.32, 70.48 (C-2,3,4), 83.16 (C-1), 116.99, 129.42, 135.64 (C_{Im}), 169.44, 169.89, 170.00 (OAc); MS (ES^+) Expected for $C_{14}H_{18}O_7N_2$

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$[M + H]^+$: 327.1. Found: 327.2. Anal. Calcd for $C_{14}H_{18}O_7N_2$: C, 51.70; H, 5.58; N, 8.61. Found: C, 51.62; H, 5.88; N, 8.51.

***N*-(2,3,4-Tri-*O*-acetyl-*β*-D-ribopyranosyl)imidazole.** A mixture of 2,3,4-tri-*O*-acetyl-*β*-D-ribopyranosyl bromide[46] (2 g, 5.9 mmol), imidazole (2 g, 29.4 mmol), and 1,4-dioxane (50 mL) was maintained at reflux temperature under argon for 4 h and processed in the usual way. Fractionation of the residue was achieved by column chromatography using 4:1 (v/v) EtOAc−hexane as eluent to afford the product as a white, amorphous, solid (700 mg, 36%): mp 107−110 °C; $[\alpha]_D$ −10.0° (*c* 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92 (s, 3 H, OAc), 2.02 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 3.91 (t, 1 H, $J_{5',5}$, $J_{5',4}$ 11.0 Hz, H-5′), 4.04 (dd, 1 H, $J_{5,5'}$ 11.0, $J_{5,4}$ 5.5 Hz, H-5), 5.14 (m, 1 H, H-4), 5.19 (dd, 1 H, $J_{2,1}$ 9.3, $J_{2,3}$ 2.9 Hz, H-2), 5.47 (d, 1 H, $J_{1,2}$ 9.4 Hz, H-1), 5.75 (br s, 1 H, H-3), 6.95, 7.02 (2s, 2 H, H_{Im}-4,5), 7.61 (s, 1 H, H_{Im}-2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.20, 20.56, 20.76 (OAc), 63.55 (C-5), 65.82, 68.14, 68.74 (C-2,3,4), 81.12 (C-1), 116.43, 130.26 (C_{Im}), 168.65, 169.03, 169.94 (OAc); MS (ES^+) Expected for $C_{14}H_{18}O_7N_2$ $[M + H]^+$: 327.1; $[M + Na]^+$: 349.1. Found: 327.2; 349.2. Anal. Calcd for $C_{14}H_{18}O_7N_2$: C, 51.70; H, 5.58; N, 8.61. Found: C, 51.70; H, 5.69; N, 8.62.

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NMR Titrations. A 1:1 mixture (12 mg) of **2** and **3** was dissolved in 0.5 mL of either $CDCl_3$, CD_3OD, $(CD_3)_2SO$, or $(CD_3)_2CO$. Aliquots of TFA (5 μL, 0.67 M) in the same solvent were added and chemical shifts recorded. All experiments were performed in duplicate at 298 K.

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