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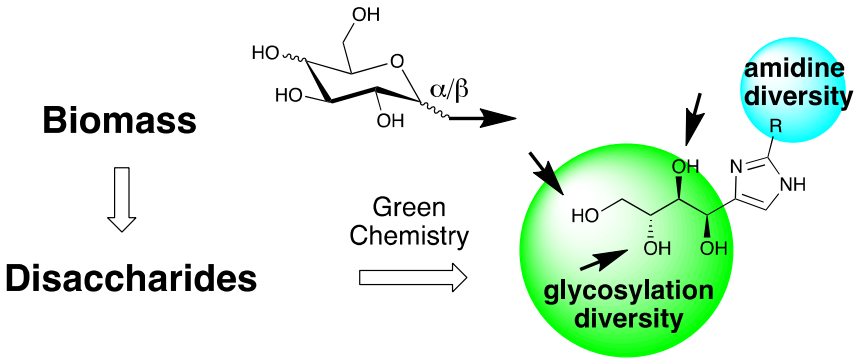
Conversion of reducing carbohydrates into hydrophilic substituted imidazoles

Andreas Brust,[a,b,*] and Eckehrd Cuny[b]

Glyco-diversity library: Disaccharide based benign green synthesis of tetrahydroxybutyl imidazole building blocks with a diverse glycosylation pattern.



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Conversion of reducing carbohydrates into hydrophilic substituted imidazoles

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Carbohydrates, as cheap mass-products, promise to be outstanding candidates as sustainable raw materials. To achieve the goal of carbohydrate utilisation as industry raw materials, environmental low impact conversions from sugars to high value products are needed. Here we present the conversion of reducing sugars into imidazole heterocycles. Imidazole formation was achieved by a one-pot conversion of reducing mono and disaccharides with amidines in a melt of ammonium carbonate. A range of disaccharides were converted into different 2-substituted imidazoles carrying a varying glycosylation pattern on the 4-tetrahydroxy butyl side chain. All conversions were performed without the need of protecting groups, using benign reagents and solvents.

Introduction

Mankind is facing the end of cheap oil, with the peak of production already passed.[1] The chemical industry is heavily reliant on oil or coal based hydrocarbons, which form the foundation of our modern lifestyle. This discrepancy creates the inevitable necessity for a progressive changeover towards renewable and hence, sustainable feedstock to fulfil the industry's raw material needs.[2] Carbohydrates are by far the most abundant organic compounds and represent the major portion of the renewable biomass. Carbohydrate utilization for the production of low cost, sustainable and eco-friendly chemicals or polymers of versatile industrial applicability is of central importance for relieving the industry reliance on petrochemical raw materials.[2-7]

The conversion of bulk scale produced sustainable carbohydrates into building blocks for fine chemical production requires entry reactions with broad applicability and reaction pathways using benign reagents and solvents. Aromatic *N*-heterocycles are key building blocks of the chemical industry and their refinement leads to drugs, pesticides, polymers, pigments, ionic liquids and other high value materials. The partial transformation of the carbon chain of sugars into *N*-heterocycles, polymers and other synthesis building blocks is of interest to release the raw material pressure and to reach a sustainable chemical industry.

The key to the utilization of carbohydrates is the ability to chemically arm the poly hydroxylated sugar framework by introducing reactive moieties like e.g. carbonyl function or amine groups suitable for follow on chemistries. The utilization of sugar derived furfurals[8, 9] as raw materials was previously demonstrated, leading to reactive 1,4-diketo compounds[10] or γ-keto-carboxylic acid analogues[11] and these were converted into *N*-heterocycles of the pyrrole-, thiophene-, pyridazine-, diazepinone-, pyridinol-, benzodiazepinone- and pyridazinone- type.[10,12,13] Furthermore, Lichtenthaler and coworkers[13-15] expanded on the utilization of sugar phenyl osazones as building blocks for the synthesis of pyrrazoles.[13-15]

Other rare examples of direct single step conversions of natural reducing sugars into aromatic *N*-heterocycles has

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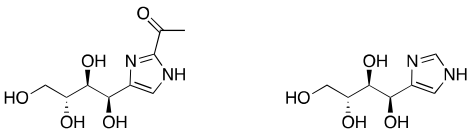
lead to quinoxalines,[16, 17] pyrazines,[18] imidazoles,[19, 20] fused ring pyrazolo[3,4-b]quinoxalines[16,21,22] and benzimidazoles.[23-25]

In this work we were particularly interested in the synthesis of imidazoles. This class of *N*-heterocycles appears widely in a range of high value products in particular in bioactive molecules like histidine, histamine and in commercial drug molecules.[26, 27] *N*-containing poly-cyclic structures have been reported to be associated with a wide range of biological activity. In particular the imidazole/benzimidazole ring system is considered as a privileged structure for the modulation of biological response. [28, 29]

Simple imidazoles are industrially produced with the Radziszewski reaction,[30] condensing 1,2-dicarbony compounds with aldehydes and ammonia. Based on *glucose* was the access to 4(5)-hydroxymethyl-imidazole possible, but only in a complicated multistep process.[20] Rather then interested in simple imidazoles, we are aiming here for imidazole products with poly-hydroxylated / glycosylated side chains introduced by the sugar building block used.

An example of carbohydrate based bioactive imidazoles is the 2-acetyl-4-tetrahydroxy-butyl imidazole **1** which has been found as a Maillard product caramel color[31] in e.g. roasted coffee[32] and is synthetically accessible from D-glucosone,[33] D-Glucoseamine[34] or 1-amino-1-deoxy-D-fructose.[35] The imidazole **1** is highly interesting due to its pharmacological properties as a potent sphingosin-1-phospahate lyase inhibitor making it herewith commercially valuable in the treatment of autoimmune diseases[36] and rheumatoid arthritis.[37]

The non acetylated parent molecule **2** is accessible in a high pressure reaction from D-*fructose* or D-*glucose* in liquid ammonia with formamidine acetate.[19] These amidine based cyclization methods incorporate the α-hydroxy-carbonyl C-2 functionality of reducing saccharides into the imidazole ring system (see scheme 2).



***Scheme 1**: D-Glucose and D-Fructose based N-heterocycles of the imidazole type*

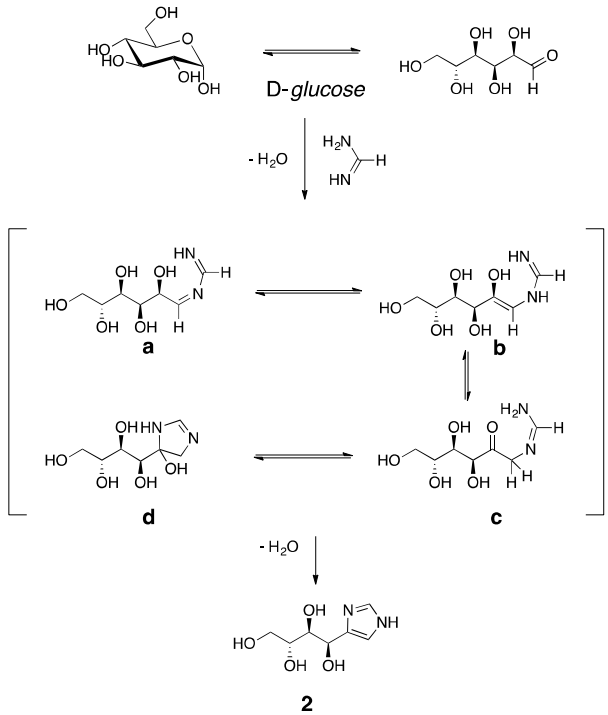
These straightforward one-pot procedures[19] caught our attention as an interesting gateway to imidazole raw materials that still contain parts of the carbohydrate skeleton. These reaction pathways may offer a bulk scale access to interesting starting materials for imidazole containing high value products.

Here we present a straightforward procedure that allows the conversion of generally all reducing disaccharides and monosaccharides into side chain poly-hydroxylated imidazoles with a varying glycosylation pattern as well as 2-substitution on the aromatic imidazole ring system.

Results

In the synthetic access of imidazole **2** developed by Streith et al[19], compressed ammonia plays the role of solvent, to set formamidine free from its salt, as well as base, assisting in tautomeric rearrangement and aromatization. While high-pressure operations in liquid ammonia are common for industrial applications we aimed to develop a more convenient methodology that would give us access to a library of molecules in a short time frame.

To accomplish this we have experimented with D-*glucose* and D-*fructose* using different ammonia sources. E.g. aqueous-ammonia solution, solutions of ammonium carbonate, ammonium hydrogen carbonate, ammonium acetate was used, employing varying temperature. The best results we finally achieved when employing melts of ammonium carbonate. A mixture of ammonium carbonate, formamidine acetate and *fructose* or *glucose* (5/1.6/1) was producing a low viscosity melt above 60°C allowing for easy magnetic steering. The ammonium carbonate decomposes during heating with the formation of ammonia, water and release of carbon dioxide to the atmosphere, resulting overall in large ammonia excess compared to the use of aqueous solutions. Under these condition the amidines, which are either released from their salts by ammonia or are formed by aminolysis of imido esters react under imine formation with the carbonyl moiety of the reducing sugar (see scheme 2; → **a**). This initial step is then followed by Amadori rearrangement[38] under formation of an adjacent carbonyl moiety (**a** → **b** → **c**), which finally allows for cyclization and tautomeric aromatization to yield the imidazole moiety **2**.



***Scheme 2**: Proposed mechanism of imidazole (2) formation from D-glucose and formamidine*

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The reactions were worked up after approximately 2h when the carbon dioxide formation had stopped.

The obtained brown syrup-like solutions were dissolved in methanol and decolorized with activated charcoal and purified by column chromatography on silica gel. The imidazole **2** was obtained in a 50% yield similar to the method described by Streith. [19]

With this facile method in hand we were interested to expand the chemistry towards bulk scale available disaccharides[5] and to herewith produce hydrophilic tetrahydroxybutyl imidazoles of type **2** with different glycosylation pattern, effectively introduced, based on the disaccharide used. Disaccharides investigated were the reducing dissacharide-pyranoses *melibiose* (α-D-Gal*p*-(1→6)-D-Glc*p*), *leucrose* (α-D-Glc*p*-(1→5)-D-Fru*p*), *maltose* (α-D-Glc*p*-(1→4)-D-Glc*p*), *cellobiose* (β-D-Glc*p*-(1→4)-D-Glc*p*) and *lactose* (β-D-Gal*p*-(1→4)-D-Glc*p*) as well as the furanose disaccharides *lactuloses* (β-D-Gal*p*-(1→4)-D-Fru*f*) and the industrial produced *isomaltulose* (α-D-Glc*p*-(1→6)-D-Fru*f*). Most of these, in particular *maltose*, *cellobiose*, *lactose, isomaltulose* and *lactulose* are mass scale produced, sustainable, low cost raw materials.[5]

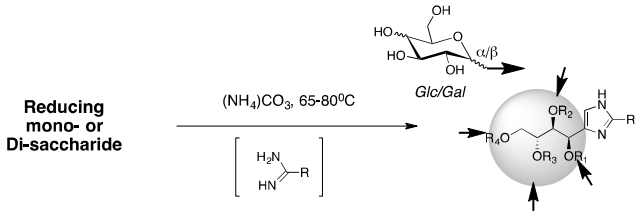
To further broaden the scope of the developed one pot procedure, (see scheme 3) different nitrogen donor molecules were investigated, to give access to ring position 2-substituted imidazoles. Other than formamidine acetate, we investigated ethylacetimidate and benzylamidine hydrochloride as cyclization partner to introduce a 2-methyl or 2-phenyl moiety into the formed imidazoles.

Due to its low cost as an industrial produced bulk sugar derived from sucrose we focused our initial efforts on *isomaltulose* (α-D-Glc*p*-(1→6)-D-Fru*f*). This model sugar was used to evaluate the stability of the glycosidic linkage under the used reaction conditions and to investigate if a dissacharide ketose is a suitable starting material for imidazole formation.

We applied the one pot imidazole formation procedure to *isomaltulose* using formamidine acetate, ethylacetimidate as well as benzylamidine hydrochloride under the same conditions used for the synthesis of **2** starting from *glucose* or *fructose*. In all cases we could obtain the envisaged imidazoles (**3**-**5**) in decreasing yields of 48%, 30%, and 5% for the 2-H (**3**), 2-Me (**4**) and 2-Ph (**5**) substituted imidazole respectively. This results show that the one pot procedure is generally suitable for the conversion of reducing dissaccharides into imidazoles but the introduction of 2-substitution into the imidazole moiety is hampered by the hydrolytic instability (R = H, < Me, < Ph) of the applied amidines, under the ammonium carbonate melt conditions. This was in particular prominent and confirmed when using benzamidine (R = Ph). In this case large quantities of benzoic acid amide were isolated as a major hydrolysis side product.

Not only *isomaltulose* (α-D-Glc*p*-(1→6)-D-Fru*f*) did successfully deliver imidazoles **3-5** but also all other used disaccharides *melibiose* (α-D-Gal*p*-(1→6)-D-Glc*p*), *leucrose* (α-D-Glc*p*-(1→5)-D-Fru*p*), *maltose* (α-D-Glc*p*-(1→4)-D-Glc*p*), *cellobiose* (β-D-Glc*p*-(1→4)-D-Glc*p*), *lactose* (β-D-Gal*p*-(1→4)-D-Glc*p*) and *lactuloses* (β-D-Gal*p*-(1→4)-D-Fru*f*) could be transformed into imidazoles **6-12** resulting in imidazole products with a variety of glycosylation patterns (scheme 3) on the tetrahydroxybutyl side chain (**3**-**12**).

All products were purified by silica gel chromatography using an ethanol / ammonia mixture as eluent. Observed yields were moderate (25-50%) most likely due to losses during chromatography, amidine hydrolysis as well as formation of unwanted Maillard products. Table 1 shows a summary of the imidazole products (**2**-**12**) obtained and related product yields. In light of the cheap availability of most reducing disaccharides, the obtained moderate yields are still satisfactory in particular for 2 position unmodified or methylated products.



Scheme 3: *One pot condensation of carbohydrates with amidines in a ammonium carbonate melt, yielding tetrahydroxybutyl substituted imidazoles with a variable α/β-D-Glc/Gal- glycosylation sphere depending on used starting disaccharide (see table 1)*

Table 1: *Product yields obtained from "one pot" transformation of sugars into imidazoles (scheme 3). Matrix shows obtained variable glycosylation pattern of the tetrahydroxyl side chain and imidazole ring substitution.*

Sugar	R	Product	R_4	R_3	R_2	R_1	Yield [%]
Fructose	H[a]	**2**	H	H	H	H	50
Glucose	H	**2**	H	H	H	H	47
Isomaltulose	H	**3**	α-D-Glc	H	H	H	49
Isomaltulose	Me[b]	**4**	α-D-Glc	H	H	H	30
Isomaltulose	Ph[c]	**5**	α-D-Glc	H	H	H	5
Melibiose	H	**6**	α-D-Glc	H	H	H	38
Melibiose	Me	**7**	α-D-Glc	H	H	H	27
Leucrose	H	**8**	H	α-D-Glc	H	H	38
Leucrose	Me	**9**	H	α-D-Glc	H	H	26
Maltose	H	**10**	H	H	α-D-Glc	H	28
Cellobiose	H	**11**	H	H	β-D-Glc	H	25
Lactose	H	**12**	H	H	β-D-Gal	H	40

Amidines introduced as: [a] formamidine acetate, [b] ethylacetimidate, [c] benzamidine hydrochloride

Conclusion

Carbohydrates provide a sustainable source of carbon, which can replace petrochemical raw materials.[2, 7] The incorporation of the carbohydrate backbone carbons into imidazoles, while maintaining the residual carbohydrate integrity was aim of this work, and delivered hybrid products with hydrophilic, poly-hydroxylated side chain substitution. The envisaged

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imidazole class of *N*-heterocycles, finds a multitude of technical applications and is known to be a privileged structure for bioactive molecules.[26, 27] Thus we ventured to find an improved and general applicable route towards imidazoles, derived from low cost, renewable sugars.

We developed a protecting group free process, employing benign solvents and reagents throughout synthesis and purification. We could show that reducing sugars in general and in particular reducing disaccharides can be cyclized to tetrahydroxybutyl substituted imidazoles (**2-12**). The reaction media of molten ammonium carbonate enabled the synthesis of 2-substituted imidazoles by employing different amidines as nitrogen source. Furthermore the process was gentle enough to allow for the use of a range of dissacharides with different glycosidic linkage resulting in a wide variety of products with a diverse glycosylation pattern. The developed synthesis can be easily transferred into large-scale production and the produced imidazoles **2- 12** may provide suitable raw materials for novel high value products with unique properties based on their carbohydrate origin. Future development of follow on chemistry for these products will show how suitable the developed entry reactions might be to provide a raw material source for novel fine chemical production strategies.

Experimental

Analytical instrumentation used: Melting points (uncorrected values) recorded on a Bock monoskop instrument. Spectral measurements were performed on: Perkin Elmer 241 (rotations), Varian MAT 311 A (MS), Bruker WM 300 instruments (^{1}H at 300, ^{13}C NMR at 75.5 MHz, respectively). Perkin-Elmer 240 elemental analyzer was used for compound microanalysis and purity confirmation. TLC on silica gel 60 F_{254} plastic sheets (Merck) was used to monitor the reactions and to ascertain the purity of the products (single point on TLC plate); eluents employed and R_f values observed are given in the appropriate experiment; detection of TLC plates was performed with UV-light or by charring with sulfuric acid. Column chromatography: silica gel 60 (63-200 mesh, Macherey-Nagel).

General Procedure for the synthesis of imidazoles (2-12): A mixture of 10 mmol of carbohydrate was heated at 65-80°C with $(NH_4)_2CO_3$ (4.8 g, 50 mmol) and 16 mmol of a amidine source of either formamidine acetate (1.7g) or ethylacetimidate hydrochloride (1.9g) or benzamidine hydrochloride hydrate (2.8g) until no further gas development could be observed. The obtained brown-red melts were dissolved in methanol and decolorized with activated charcoal. The obtained pale yellow solutions were concentrated and purified on silica gel (5 x 30 cm) employing ethanol / concentrated (25%) ammonia (3 : 1) as eluent.

4-[(1'R,2'S,3'R)-1',2',3',4'-Tetrahydroxybutyl]-imidazole (**2**): was obtained from D-*fructose* or D-*glucose* with formamidine acetate. Evaporation of fractions with R_f 0.37 [EtOH / conc. NH_3-sol. (3 : 1)] yielded product imidazole **2** (470 mg, 50 % from *fructose*; 442mg, 47% from *glucose*) as a yellowish hard foam. — $[\alpha]_D^{20}$ = - 12.2 (c 1.0, H_2O). – [Previously published data.[19]: $[\alpha]_D^{20}$ = - 12.0° (c 1.0, H_2O), 38 % employing chromatography on a ion exchange column]. (Found: C, 44.72; H, 6.50; N, 14.90% $C_7H_{12}N_2O_4$ requires C, 44.68; H, 6.43; N, 14.89%); ^{1}H NMR (300 MHz, D_2O): δ 3.60 - 3.89 (m, 4 H, 2'-H, 3'-H, 4'-H_2), 5.15 (d, 1 H, 1'-H), 7.38 (s, 1 H, 5-H), 8.44 (s, 1 H, 2-H). $J_{1',2'}$ = 1.1 Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 65.3 (C-4'), 67.4 (C-1'), 73.2 (C-3'), 75.5 (C-2'), 118.5 (C-5), 136.6 (C-2), 137.4 (C-4).

4-[(1'R,2'S,3'R)-4'-(α-D-Glucopyranosyloxy)-1',2',3'-trihydroxy-butyl]-imidazole (3) was obtained from *isomaltulose* with formamidine acetate. Evaporation of product containing chromatography fractions yielded imidazole **3** (1.75 g, 49 %) as a colourless hard foam. — R_f 0.19 [EtOH / conc. NH_3-sol. (3 : 1)]. — $[\alpha]_D^{20}$ + 77.2 (c 1.0, DMSO). (Found: C, 44.52; H, 6.30; N, 8.05% $C_{13}H_{22}N_2O_9$ requires C, 44.57; H, 6.33; N, 8.00%); ^{1}H NMR (300 MHz, D_2O): δ 3.42 (dd, 1 H, 4''-H), 3.57 (dd, 1 H, 2''-H), 3.67 (m, 1 H, 4'-Ha), 3.72 (m, 2 H, 3''-H, 5''-H), 3.78 (m, 1 H, 6''-Ha), 3.83 (m, 1 H, 6''-Hb), 3.90 (m, 1 H, 4'-Hb), 3.95 (m, 2 H, 2'-H, 3'-H), 4.93 (d, 1 H, 1''-H), 5.03 (d, 1 H, 1'-H), 7.18 (s, 1 H, 5-H), 7.82 (s, 1 H, 2-H). — $J_{1',2'}$ = 2.6, $J_{1'',2''}$ = 3.7, $J_{2'',3''}$ = 9.8, $J_{3'',4''}$ = 9.3, $J_{4'',5''}$ = 9.3 Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 63.3 (C-6''), 69.7 (C-1'), 71.1 (C-4'), 72.3 (C-3'), 72.4 (C-4''), 74.4 (C-2''), 74.6 (C-3''), 75.9 (C-2', C-5''), 100.9 (C-1''), 119.1 (C-5), 138.6 (C-2), 140.9 (C-4). MS (FD): m/z = 351 [M^++H], 373 [M^++Na].

4-[(1'R,2'S,3'R)-4'-(α-D-Glucopyranosyloxy)-1',2',3'-trihydroxybutyl]-2-methylimidazole (4) was obtained from *isomaltulose* with ethylacetimidat-hydrochlorid. Evaporation of product containing fractions, yielded 2-methyl imidazole **4** (1.05 g, 30 %) as a yellow hard foam. — R_f 0.25 [EtOH / conc. NH_3-sol. (3 : 1)]. — $[\alpha]_D^{20}$ + 75.3 (c 1.0, DMSO). (Found: C, 46.19; H, 6.68; N, 7.65% $C_{14}H_{24}N_2O_9$ requires C, 46.15; H, 6.64; N, 7.69%);
^{1}H NMR (300 MHz, D_2O): δ 2.37 (s, 3 H, 2-CH_3), 3.42 (dd, 1 H, 4''-H), 3.57 (dd, 1 H, 2''-H), 3.65 (m, 1 H, 4'-Ha), 3.72 (m, 2 H, 3''-H, 5''-H), 3.77 (m, 1 H, 6''-Ha), 3.82 (m, 1 H, 6''-Hb), 3.88 (m, 1 H, 4'-Hb), 3.92 (bs, 2 H, 2'-H, 3'-H), 4.92 (d, 1 H, 1''-H), 4.95 (d, 1 H, 1'-H), 7.02 (s, 1 H, 5-H). — $J_{1',2'}$ = 1.8, $J_{1'',2''}$ = 3.7, $J_{2'',3''}$ = 9.8, J3'',4'' = 9.3, J4'',5'' = 9.3 Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 14.6 (2-CH_3), 62.8 (C-6''), 69.0 (C-1'), 70.6 (C-4'), 71.7 (C-3'), 71.8 (C-4''), 73.8 (C-2''), 74.0 (C-3''), 75.4 (C-2', C-5''), 100.4 (C-1''), 118.1 (C-5), 139.5 (C-2), 148.0 (C-4). MS (FD): m/z = 365 [M^+], 366 [M+1$^+$].

4-[(1'R,2'S,3'R)-4'-(α-D-Glucopyranosyloxy)-1',2',3'-trihydroxybutyl]-2-phenylimidazole (5) was obtained from *isomaltulose* with benzamidine hydrochloride hydrate Evaporation of product containing fractions, yielded 2-phenyl imidazole **5** (213 mg, 5 %) as a yellow-brown hard foam — R_f 0.42 [EtOH / conc. NH_3-sol. (3 : 1)]. (Found: C, 53.62; H, 6.20; N, 6.55% $C_{19}H_{26}N_2O_9$ requires C, 53.52; H, 6.15; N, 6.57%); ^{1}H NMR (300 MHz, D_2O): δ 3.47 (dd, 1 H, 4''-H), 3.60 (dd, 1 H, 2''-H), 3.70 (m, 1 H, 4'-Ha), 3.75 (m, 2 H, 3''-H, 5''-H), 3.78 (m, 1 H, 6''-Ha), 3.84 (m, 1 H, 6''-Hb), 3.96 (m, 1 H, 4'-Hb), 3.98 (m, 1 H, 2'-H), 4.01 (m, 1 H, 3'-H), 4.98 (d, 1 H, 1''-H), 5.17 (d, 1 H, 1'-H), 7.36 (s, 1 H, 5-H); 7.52 - 7.85 (m, 5 H, C6H5). — $J_{1',2'}$ = 2.2, $J_{1'',2''}$ = 3.7, $J_{2'',3''}$ = 9.7, $J_{3'',4''}$ = 9.3, $J_{4'',5''}$ = 9.3 Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 63.4 (C-6''), 68.7 (C-1'), 71.3 (C-4'), 72.2 (C-3'), 72.4 (C-4''), 74.4 (C-2''), 74.7 (C-3''), 75.6 (C-2'), 76.0 (C-5''),

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101.0 (C-1''), 120.3 (C-5), 128.8-137.0 (C_6H_5), 140.0 (C-4), 148.6 (C-2). MS (FD): m/z = 427.2 [M^++H], 450.2 [M^++Na].

4-[(1'R,2'S,3'R)-4'-(α-D-Galactopyranosyloxy)-1',2',3'-trihydroxybutyl]-imidazole (6) from *melibiose* with formamidine acetate yielded imidazole **6** (1.33 g, 38 %) as a yellow-brown hard foam. — R_f 0.16 [EtOH / conc. NH_3-sol. (3 : 1)]. ^{1}H NMR (300 MHz, D_2O): δ 3.60 (m, 1 H, 4'-Ha), 3.74 (m, 1 H, 6''-H), 3.84 (dd, 1 H, 2''-H), 3.86 (m, 1 H, 4'-Hb), 3.88 (m, 1 H, 4''-H), 3.91 (m, 1 H, 2'-H), 3.94 (m, 1 H, 5''-H), 3.96 (m, 1 H, 3''-H), 3.98 (m, 1 H, 3'-H), 4.98 (d, 1 H, 1''-H), 5.15 (d, 1 H, 1'—H), 7.32 (s, 1 H, 5-H), 8.25 (d, 1 H, 2-H). — $J_{1',2'}$ = 2.3, $J_{1'',2''}$ = 3.3, $J_{2'',3''}$ = 7.5, $J_{3'',4''}$ = 3.4, $J_{4'',5''}$ =3.4, J_{gem}, 6''-H_2 = 14.5 Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 64.0 (C-6''), 68.4 (C-1'), 71.4 (C-4', C-2''), 72.1 (C-3'), 72.2 (C-3''), 72.3 (C-4''), 73.8 (C-5''), 75.7 (C-2'), 101.2 (C-1''), 119.0 (C-5), 137.6 (C-2), 138.9 (C-4). MS (FD): m/z = 351 [M^++H], 373 [M^++Na].

4-[(1'R,2'S,3'R)-4'-(α-D-Galactopyranosyloxy)-1',2',3'-trihydroxybutyl]-2-methylimidazole (7) from *melibiose* with ethylacetimidate hydrochloride yielded 2-methyl-imidazole **7** (979 mg, 27 %) as a yellow-brown hard foam. — R_f 0.20 [EtOH / conc. NH_3-sol. (3 : 1)]. (Found: C, 44.62; H, 6.35; N, 8.10% $C_{13}H_{22}N_2O_9$ requires C, 44.57; H, 6.33; N, 8.00%); ^{1}H NMR (300 MHz, D_2O): δ 2.62 (s, 3 H, 2-CH_3), 3.75 (m, 1 H, 4''-H), 3.76 (m, 2 H, 6''-H), 3.82 (m, 1 H, 2'-H), 3.82 - 3.89 (m, 2 H, 2''-H, 4''-H), 3.95 - 3.99 (m, 3 H, 3'-H, 3''-H, 5''-H), 5.00 (d, 1 H, 1''-H), 5.17 (d, 1 H, 1'-H), 7.26 (s, 1 H, 5-H). — $J_{1',2'}$ = 1.5, $J_{1'',2''}$ = 3.5, $J_{2'',3''}$ = 8.1, $J_{3'',4''}$ = 3.5, $J_{4'',5''}$ = 3.5 Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 13.5 (2-CH_3), 64.0 (C-6''), 67.1 (C-1'), 71.4 (C-4', C-2''), 71.9, 72.1 (C-3', C-3''), 72.4 (C-4''), 73.8 (C-5''), 75.4 (C-2'), 101.2 (C-1''), 118.0 (C-5), 135.9 (C-2), 148.2 (C-4). MS (FD): m/z = 365 [M^+], 366 [M+1$^+$].

4-[(1'R,2'S,3'R)-3'-(α-D-Glucopyranosyloxy)-1',2',4'-trihydroxybutyl]-imidazole (8) from *leucrose* with formamidine acetate yielded imidazole **8** (1.7 g, 38 %) as a yellow-brown hard foam. — R_f 0.21 [EtOH / conc. NH_3-sol. (3 : 1)]. ^{1}H NMR (300 MHz, D_2O): δ 3.44 (dd, 1 H, 4''-H), 3.61 (dd, 1 H, 2''-H), 3.75-3.79 (m, 2 H, 4'-Ha ,6''-Ha), 3.80-3.86 (m, 4 H, 3'-H, 2''-H, 3''-H, 5''-H), 3.90-3.93 (m, 2 H, 4'-Hb, 6''-Hb), 4.00 (dd, 1 H, 2'-H), 5.13 (d, 1 H, 1''-H), 5.23 (d, 1 H, 1'-H), 7.42 (s, 1 H, 5-H), 8.52 (s, 1 H, 2-H). — $J_{2,5}$ = 1.0, $J_{1',2'}$ = 2.3, $J_{2',3'}$ = 7.9, $J_{1'',2''}$ = 3.9, $J_{3'',4''}$ = 9.6, $J_{4'',5''}$ = 9.6 Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 63.3 (C-6''), 63.9 (C-4'), 67.4 (C-1'), 72.4 (C-4''), 74.2 (C-2'), 74.4 (C-2''), 75.0 (C-3''), 75.6 (C-5''), 82.0 (C-3') 102.5 (C-1''), 119.0 (C-5), 136.9 (C-2), 137.5 (C-4). MS (FD): m/z = 351 [M^++H], 373 [M^++Na].

4-[(1'R,2'S,3'R)-3'-(α-D-Glucopyranosyloxy)-1',2',4'-trihydroxybutyl]-2-methyl-imidazole (9) from *leucrose* with ethylacetimidate hydrochloride yielded imidazole **9** (940 mg, 26 %) as a yellow-brown hard foam. — R_f 0.27 [EtOH / conc. NH_3-Sol. (3 : 1)]. ^{1}H NMR (300 MHz, D_2O): δ 2.62 (s, 3 H, 2-CH_3), 3.44 (t, 1 H, 4''-H), 3.62 (dd, 1 H, 2''-H), 3.75 - 3.80 (m, 2 H, 4'-Ha, 6''-Ha), 3.80 - 3-86 (m, 4 H, 3'-H, 2''-H, 3''-H, 5''-H), 3.90 - 3.93 (m, 2 H, 4'-Hb, 6''-Hb), 4.00 (dd, 1 H, 2'-H), 5.13 (d, 1 H, 1''-H), 5.24 (d, 1 H, 1'-H), 7.28 (s, 1 H, 5-H). — $J_{1',2'}$ = 2.2, $J_{2',3'}$ = 7.9, $J_{1'',2''}$ = 3.8, $J_{2'',3''}$ = 10.0, $J_{3'',4''}$ = $J_{4'',5''}$ = 9.6 Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 13.0 (2-CH_3), 62.7 (C-6''), 63.3 (C-4'), 66.3 (C-1'), 71.9 (C-4''), 73.4 (C-2'), 73.8 (C-2''), 74.5 (C-3''), 75.0 (C-5''), 81.6 (C-3'), 102.1 (C-1''), 117.6 (C-5), 135.3 (C-2), 147.0 (C-4). MS (FD): m/z = 365 [M^+], 366 [M+1$^+$].

4-[(1'R,2'S,3'R)-2'-(α-D-Glucopyranosyloxy)-1',3',4'-trihydroxybutyl]-imidazole (10) from *maltose* with formamidine acetate yielded imidazole **10** (1.3 g, 28 %) as a yellow-brown hard foam. — R_f 0.24 [EtOH / conc. NH_3-sol. (3 : 1)]. (Found: C, 44.59; H, 6.29; N, 8.08% $C_{13}H_{22}N_2O_9$ requires C, 44.57; H, 6.33; N, 8.00%); ^{1}H NMR (300 MHz, D_2O): δ 3.43 (dd, 1 H, 4''-H), 3.61 (dd, 1 H, 2''-H), 3.55 - 3.61 (m, 1 H, 4'-Ha), 3.67 - 3.79 (m, 2 H; 4'-Hb , 6''-Ha), 3.80 - 3.84 (m, 3 H, 3'-H, 3''-H, 5''-H), 3.89 - 3.92 (m, 1 H, 6''-Hb), 4.19 (dd, 1 H, 2'-H), 5.10 (d, 1 H, 1''-H), 5.21 (d, 1 H, 1'-H), 7.24 (s, 1 H, 5-H), 8.00 (s, 1 H, 2-H). — $J_{1',2'}$ = 3.8, $J_{2',3'}$ = 5.4, $J_{1'',2''}$ = 3.9, $J_{2'',3''}$ = 10.0, $J_{3'',4''}$ = 9.6, $J_{4'',5''}$ = 9.3 Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 63.2 (C-6''), 63.7 (C-4'), 69.1 (C-1'), 72.4 (C-4''), 74.3 (C-3'), 74.6 (C-2''), 74.9 (C-3''), 75.5 (C-5''), 85.1 (C-2') 101.8 (C-1''), 119.0 (C-5), 136.7 (C-2), 137.3 (C-4). MS (FD): m/z =351 [M^++H], 373 [M^++Na].

4-[(1'R,2'S,3'R)-2'-(β-D-Glucopyranosyloxy)-1',3',4'-trihydroxybutyl]-imidazole (11) from *cellobiose* with formamidine acetate yielded imidazole **11** (875 mg, 25 %) as a yellow-brown hard foam. — R_f 0.20 [EtOH / conc. NH_3-sol. (3 : 1)]. ^{1}H NMR (300 MHz, D_2O): δ 3.30 - 3.35 (m, 3 H, 2''-H, 5''-H, 4''-H), 3.44 - 3.50 (m, 1 H, 3''-H), 3.68 - 3.77 (m, 4 H, 6''-H2, 4'-H2), 3.78 - 3.86 (m, 1 H, 3'-H), 4.11 (dd, 1 H, 2'-H), 4.51 (d, 1 H, 1''-H), 5.10 (d, 1 H, 1'-H), 7.33 (s, 1 H, 5-H), 8.27 (s, 1 H, 2-H). — $J_{2,5}$ = 1.3, $J_{1',2'}$ = 4.1, $J_{2',3'}$ = 6.4, $J_{1'',2''}$ = 8.2 Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 63.4 (C-4'), 64.7 (C-6''), 68.4 (C-1'), 71.8 (C-4''), 74.0 (C-3'), 76.1 (C-5''), 78.3 (C-2'', C-3''), 84.0 (C-2') 105.2 (C-1''), 119.3 (C-5), 137.3 (C-2), 137.9 (C-4). MS (FD): m/z = 351 [M^++H], 373 [M^++Na].

4-[(1'R,2'S,3'R)-2'-(β-D-Galactopyranosyloxy)-1',3',4'-trihydroxybutyl]-imidazole (12) from *lactose* with formamidine acetate yielded imidazole **12** (1.40 g, 40 %) as a yellow-brown hard foam. — R_f 0.13 EtOH / conc. NH_3-sol. (3 : 1). ^{1}H NMR (300 MHz, D_2O): δ 3.55 - 3.61 (m, 2 H, 4'-Ha, 6''-Ha), 3.63 - 3.65 (m, 2 H, 2''-H, 3''-H), 3.65 - 3.67 (m, 1 H, 5''-H), 3.67 - 3.70 (m, 2 H; 4'-Hb , 6''-Hb), 3.77 - 3.86 (m, 1 H, 3'-H), 3.91 (dd, 1 H, 4''-H), 4.17 (dd, 1 H, 2'-H), 4.51 (d, 1 H, 1''-H), 5.07 (d, 1 H, 1'-H), 7.27 (s, 1 H, 5-H), 8.05 (s, 1 H, 2-H). — $J_{2,5}$ = 0.8, $J_{1',2'}$ = 5.4, $J_{2',3'}$ = 5.4, $J_{1'',2''}$ = 7.6, $J_{3'',4''}$ = $J_{4'',5''}$ = 3.4 Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 63.6 (C-4'), 64.6 (C-6''), 69.0 (C-1'), 71.3 (C-4''), 73.9 (C-4'), 74.4 (C-3'), 75.4 (C-5''), 77.7 (C-2''), 85.0 (C-2') 105.9 (C-1''), 119.6 (C-5), 138.1 (C-2), 138.5 (C-4).
MS (FD): m/z = 351 [M+1$^+$], 373 [M+Na$^+$].

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