One pot $InCl_3$-catalyzed synthesis of 1-glycosylmethyl-1H-imidazoles

Mária Petrušová,[a] Hana Smrtičová,[a] Božena Pribulová,[a] Silvia Vlčková,[a]
Iveta Uhliariková,[a] Tibor Docsa,[b] László Somsák,[c] Ladislav Petruš [a,*]

[a] Institute of Chemistry, Center for Glycomics, Slovak Academy of Sciences, 84538 Bratislava, Slovakia
[b] Department of Medical Chemistry, Faculty of Medicine, University of Debrecen, Egyetem square 1, H-4032 Debrecen, Hungary
[c] Department of Organic Chemistry, University of Debrecen, POB 20, 4010 Debrecen, Hungary

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ABSTRACT

A series of 1-glycosylmethyl-4,5-diphenyl-1H-imidazoles with six different glycosyls were obtained in 48–55% yields from the multicomponent reaction of the corresponding C-glycosyl methylamines, formaldehyde, benzil, and ammonium acetate under catalysis with indium(III) chloride in methanol at ambient temperature. Starting with C-β-D-glucopyranosyl or C-β-D-galactopyranosyl methylamines, the procedure also was examined with phenylglyoxal or glyoxal instead of benzil, and the pertinent 1-β-D-glycopyranosylmethyl-4-phenyl-1H-imidazole and -5-phenyl-1H-imidazole or 1-β-D-glycopyranosylmethyl-1H-imidazole derivatives were prepared and isolated. Of four differently 4- and 5-substituted 1-(β-D-glucopyranosylmethyl)-1H-imidazoles, only the 5-phenyl derivative exhibited a weak inhibition of rabbit muscle glycogen phosphorylase b (IC_{50} = 125 μM).

Keywords:
1-Glycosylmethyl-1H-imidazoles
Multicomponent reaction

* Corresponding author. Tel.: +421-2-59410-232; fax: +421-2-59410-232; e-mail address: ladislav.petrus@savba.sk

Indium(III) chloride catalysis
C-Glycosyl methylamines
Rabbit muscle glycogen phosphorylase inhibition

1. Introduction

Imidazoles are important heterocycles occurring in natural compounds,[1] antifungal drugs [2] and many other artificial substances with a variety of other biological activities, applicable in medicinal chemistry and pharmacology,[3,4,5,6] as well as in material science,[7,8,9] catalysis [9,10,11] or the preparation of ionic liquids.[12] Numerous methods for the synthesis of imidazoles have been designed, starting from the first Debus [13] and Radzisewski [14] syntheses up to their latest convergent annulations,[15,16] and several pertinent reviews have appeared.[17,18,19,20] Recently, a photochemical one-pot three-component synthesis of tetrasubstituted imidazoles has appeared.[21] The multicomponent Debus-Radzisewski imidazole synthesis is still attracting strong interest in view of improving and simplifying the procedure, including its catalysis.[22,23,24,25,26,27] In particular, $InCl_3$, due to its non-toxic nature, low heterophilicity and compatibility with both organic and aqueous media, has emerged as a prominent Lewis acid catalyst in organic synthesis, including multicomponent reactions at room temperature.[28] As such, a one-pot, four component synthesis of 1,2,4,5-tetrasubstituted imidazoles catalyzed by $InCl_3 \cdot 3H_2O$ has been shown to work efficiently in methanol at room temperature with 1,2-dicarbonyl compounds of the benzil type, primary amines, ammonium acetate and aromatic aldehydes.[24] This contribution evaluates the convenience of using the published procedure for the synthesis of 1-glycosylmethylated imidazoles as a novel group of carbohydrate mimetics from stable sugar primary amines, formaldehyde, ammonium acetate and also from 1,2-dicarbonyl compounds other than those of the benzil type.

2. Results and discussion

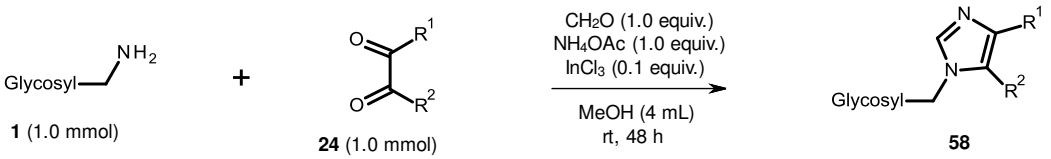
Optimized conditions for the four component one pot reaction concerning the reaction solvent and the amount of catalyst [24] were chosen for all the synthetic experiments here. The starting C-glycosyl methylamines are available in three steps from the parent aldoses via nitromethane addition, followed by thermally induced eliminative anhydrization of the obtained 1-deoxy-1-nitroalditols,[29,30] and final electron-transfer reduction of the resulting glycosyl nitromethanes.[31,32,33] Stirring a methanolic solution of equimolar amounts of sugar

amine **1a**, benzil (**2**, $R^1 = R^2 = Ph$), formaldehyde, and ammonium acetate, with addition of a 0.1 molar equivalent of $InCl_3$, at rt for 48 h, followed by purification of the reaction mixture by flash chromatography, afforded the expected 1,4,5-trisubstituted imidazole **5a** in 50% yield (Table 1). 1,4,5-Trisubstituted imidazoles **5b**–**5f** were prepared similarly, using the corresponding sugar amines **1b**–**1f**, and were isolated in 48–55% yields. In addition to these products and unreacted benzil, the reaction mixtures also contained some more polar compounds on TLC. Apparently, formaldehyde and glycosyl methylamines as the most reactive species in the reaction mixture produced 1,3-oxazinane and/or 1,3,5-triazine side products, analogous to those produced from formaldehyde and simpler aminoalcohols.[34,35,36] This was supported by the detection of the $[(\beta\text{-D-GlcpCH}_2\text{NH}_2) + (\text{CH}_2\text{O}) - \text{H}_2\text{O} + \text{H}]^+$ and $[2(\beta\text{-D-GlcpCH}_2\text{NH}_2) + (\text{CH}_2\text{O}) - 2\text{H}_2\text{O} + 2\text{Na}]^{2+}$ ions with the respective m/z = 206.10235 (found) vs. 206.10230 (calcd) and m/z = 228.08429 (found) vs. 228.08424 (calcd) in the HRMS spectrum of the normal multicomponent reaction mixture with benzil and β-D-$\text{GlcpCH}_2\text{NH}_2$ even after 7 days. In addition, there was also the $[M + H]^+$ ion of the non-glycosylmethylated 4,5-diphenylimidazole at m/z = 221.10736 (found) vs. 221.10732 (calcd), which also contributed to the decreased yields of the expected 1-glycosylmethylated imidazoles. Comparable yields of imidazoles, when formaldehyde or another aliphatic aldehyde was the reaction component, have also been reported in the pilot paper.[24]

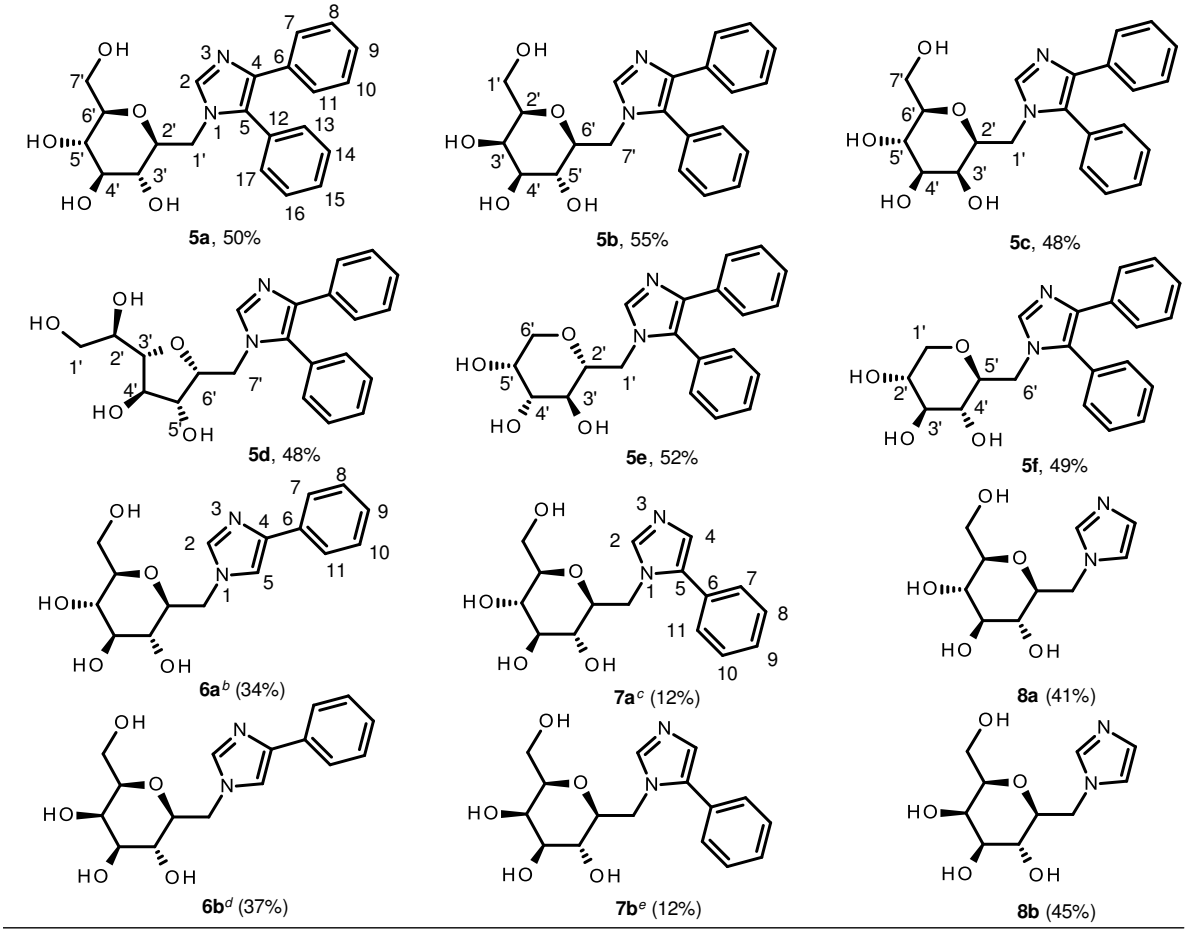
Further, phenylglyoxal (**3**, $R^1 = Ph$, $R^2 = H$, Table 1) instead of benzil, the same other reaction components and conditions as above were used in this multicomponent reaction with carbohydrate amines **1a** and **1b.** In both cases, both possible 4-phenyl and 5-phenyl gluco derivatives **6a** and **7a**, and galacto derivatives **6b** and **7b** were isolated. Less sterically hindered 1,4-disubstituted imidazoles **6a** and **6b** were the major products, significantly prevailing over 1,5-disubstituted imidazoles **7a** and **7b**.

Finally, glyoxal (**4**, $R^1 = R^2 = H$, Table 1) as the simplest 1,2-dicarbonyl compound was examined in place of benzil in this $InCl_3$ catalyzed multicomponent synthesis of imidazoles. Thus, again with carbohydrate amines **1a** and **1b,** the respective 1-glycosylmethyl-1H-imidazoles **8a** and **8b** were isolated in 41% and 45% yields. Moreover, among all the glycosylmethylated imidazoles obtained here, compounds **8a** and **8b** most closely mimic normal disaccharides and are promising candidates to modulate activity of sugar processing enzymes. The other glycosylated imidazoles known from the literature contain glycosyl moieties linked directly to the nitrogen or carbon atoms of the imidazole ring and mimic nucleosides rather than disaccharides.[23,37,38,39]

Table 1. $InCl_3$ catalyzed one-pot preparation of 1-glycosylmethylated imidazoles from C-glycosylmethylamines (**1**), formaldehyde, ammonium acetate, and benzil (**2**, $R^1 = R^2 = Ph$) or phenylglyoxal (**3**, $R^1 = Ph$, $R^2 = H$) or glyoxal (**4**, $R^1 = R^2 = H$) in methanol.



product, yield (%)[a]



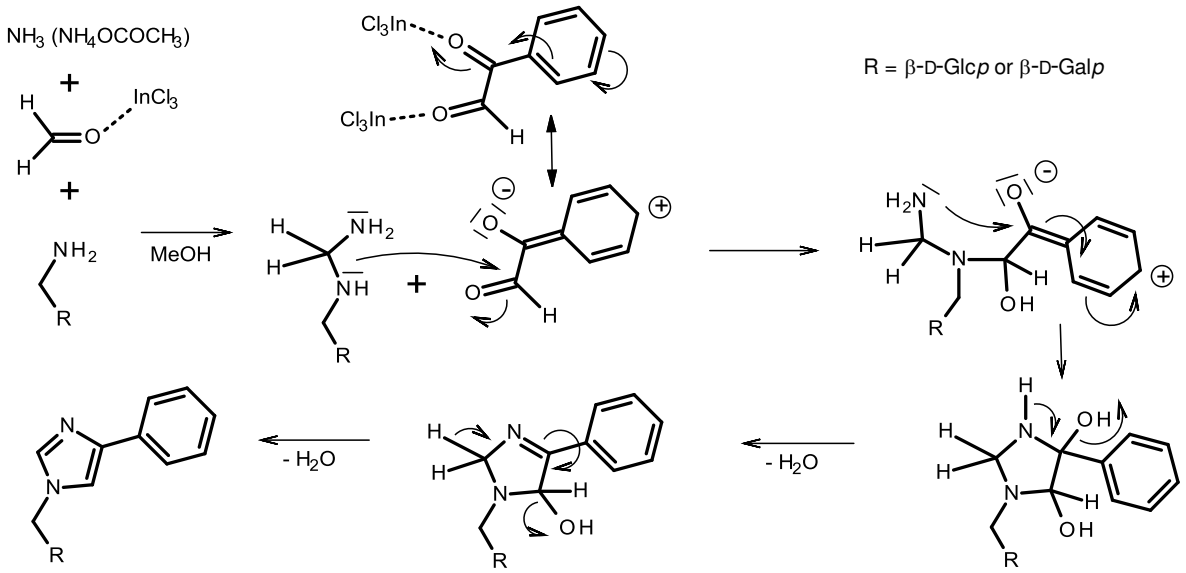
[a] isolated yield. [b] major product, in addition to the minor **7a**. [c] minor product, in addition to the major **6a**. [d] major product, in addition to the minor **7b**. [e] minor product, in addition to the major **6b**.

The structures of all 1-glycosylmethylated imidazoles were proved by their characteristic ^{1}H- and ^{13}C-NMR spectra. The chemical shift of the only hydrogen atom of the 1,4,5-trisubstituted ring of imidazoles **5a**–**5e** was observed at $\delta_{H\text{-}2} = 7.93 \pm 0.06$, essentially at the same values as those observed for the 1,5-disubstituted ring of imidazoles **7a** and **7b**; $\delta_{H\text{-}2}$ = 7.95 and 7.92, respectively. On the other side, the chemical shifts of the same hydrogen atom of the 1,4-disubstituted ring of imidazoles **6a** and **6b** were recorded at the respective values of $\delta_{H\text{-}2}$ = 7.74 and 7.72, which are almost identical with those observed at $\delta_{H\text{-}2}$ = 7.69 and 7.64

for the respective 1-monosubstituted imidazoles **8a** and **8b**. The apparent reason for the similar behaviour of the first two and the second two groups of imidazoles is cross-conjugation. While the (C-2)=(N-3) double bond in imidazoles **5a**–**5f**, **7a** and **7b** is normally conjugated via the (C-4)=(C-5) double bond with their 5-phenyl group, at the same time it is only cross-conjugated with their 4-phenyl group in imidazoles **6a** and **6b** or without any interaction with no substituent in position 4 of imidazoles **8a** and **8b**.

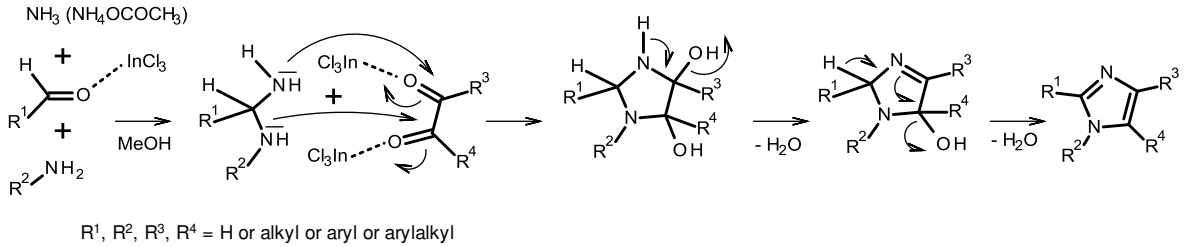
The distinction of the mono-phenylated imidazoles was done using classic ^{1}H NMR NOE experiments as well and the space spin interaction between the sugar CH_2N and phenyl CH protons was observed for imidazoles **7a** and **7b** with their 5-phenyl substitution only. The values of the sugar vicinal proton-proton coupling constants proved that the configurations of the 1-glycosylmethyl moieties on the imidazole ring remained unchanged. Similarly as for the signals of imidazole ring protons, the ^{13}C chemical shifts of the individual imidazole ring carbon atoms were also found in narrow intervals, as, e.g., for the most populated series of 1,4,5-trisubstituted imidazoles **5a**–**5f** at $\delta_{C\text{-}2}$ = 138.15 ± 0.29, $\delta_{C\text{-}4}$ = 136.96 ± 0.35 and $\delta_{C\text{-}5}$ = 129.01 ± 0.30.

The mechanism of the multicomponent synthesis of trisubstituted and tetrasubstituted imidazoles catalyzed by $InCl_3$ has been proposed in two different respective versions.[24] However, the plausible mechanism of this multicomponent synthesis of imidazoles should be universal and encompassing all its peculiarities. Therefore, the specification of the mechanism postulated here was first examined for the multicomponent reaction with phenylglyoxal (Scheme 1). Indeed, the most nucleophilic secondary amino group of the intermediary adduct of C-glycosyl methylamine and ammonia to formaldehyde, preferentially should attack the most activated, aldehydic carbonyl of phenylglyoxal, leaving the remaining two counter reaction centres to close the next intermediate, imidazolidine ring. The subsequent aromatization acompanied with 3,4- and 2,5-eliminations of two molecules of water stabilizes the reaction product, the structure of which is in accordance with the observed prevalence of the 1,4-disubstituted imidazoles **6a** and **6b** over 1,5-disubstituted imidazoles **7a** and **7b**.



Scheme 1. Plausible reaction pathway of the $InCl_3$ catalyzed multicomponent synthesis of imidazoles with glycosylmethylamines, formaldehyde, ammonia and phenylglyoxal favouring the major 4-phenyl derivative over the 5-phenyl isomer.

The results obtained in this study also allowed postulating the general addition-elimination mechanism of the multicomponent synthesis of imidazoles (Scheme 2). Thus, the mechanism proposed here is plausible for the synthesis of unsubstituted up to tetrasubstituted imidazoles.



Scheme 2. General addition-elimination mechanism of the $InCl_3$ catalyzed multicomponent synthesis of imidazoles.

Imidazoles **5a**–**8a**, each of them containing both *β*-D-glucopyranosyl and aromatic moieties, linked together by the methylene group, were tested for inhibition of rabbit muscle glycogen phosphorylase (RMGP) b. Compounds **5a**, **6a**, and **8a** did not inhibit the enzyme up to 625 μM concentration, while **7a** showed weak inhibition characterized by an IC_{50} = 125 μM value (calculated K_i = 68 μM). Taking into account previous observations and structure-activity relationships of RMGP b inhibitors,[40,41,42] it is thought that the presence of the tetrahedral centre between the sugar and the aglycon may be responsible for the weak effect.

This moiety may lend the molecules high flexibility resulting in considerable loss of entropy upon binding.

3. Conclusion

In summary, this study has extended a one pot, multicomponent synthesis of aromatically trisubstituted and tetrasubstituted imidazoles catalyzed by $InCl_3$ to the preparation of 1-glycosylmethylated imidazoles as a novel group of carbohydrate mimetics. The largely non-aromatic character of the reaction components results in moderate yields of the target compounds, which may be on account of the competitive, non-aromatic side products, as indicated by the HRMS analysis of reaction mixtures.

4. Experimental

4.1. General information

Melting points were measured on a Kofler stage. Optical rotations were measured with a Jasco P2000 polarimeter at 20 °C. High resolution mass determination was performed by ESI-MS on a Thermo Scientific Orbitrap Exactive instrument operating in positive mode. ^{1}H- and ^{13}C-NMR spectra were recorded at 295 K on VNMRS 400 MHz Varian spectrometer equipped with 5 mm ^{1}H–^{19} F/^{15} N–^{31}P PFG AutoX DB NB probe head and on VNMRS 600MHz Varian spectrometer equipped with HCN ^{13}C enhanced salt tolerant cold probe. Chemical shifts are referenced to either CD_3OD (δ 3.31 for ^{1}H, δ 47.57 for ^{13}C) or $(CD_3)_2SO$ (δ 2.50 for ^{1}H, δ 39.97 for ^{13}C). Full spectral assignment was done using the COSY, NOESY, HSQC, HMBC and H2BC NMR experiments. Fourier-transform infra red (FTIR) spectra were measured with Thermo Fisher Scientific Nicolet 6700 spectrometer equipped with DTGS detector and Omnic 8.0 software. The spectra were collected in the middle region from 4,000 to 400 cm^{-1} at a resolution of 4 cm^{-1}, the number of scans was 128. Diamond Smart Orbit ATR accessory was applied for measurement in solid state. TLC was run on Merck 60 F254 silica gel precoated aluminium plates; visualisation was effected by briefly immersing the plates into 10% ethanolic sulfuric acid and charring them with a hot air gun, or alternatively, by developing the plates with alkaline silver nitrate. Flash chromatography was performed using Acros silica gel (37–75 μm) and the S_1 solvent mixture EtOAc–n-BuOH–MeOH–H_2O 18:9:7:3 (v/v). Additional flash chromatographic purification of product

imidazoles was done with the S_2 solvent mixture PhMe–MeOH 2:1 (v/v) for the benzil-based imidazoles and with the S_3 solvent mixture EtOAc –MeOH 1:1 (v/v) for the phenylglyoxal and glyoxal-based imidazoles.

4.2. Enzyme assay

Glycogen phosphorylase b was prepared from rabbit skeletal muscle according to the method of Fischer and Krebs,[43] using dithiothreitol instead of L-cysteine, and recrystallized at least three times before use with a specific activity of 55 U/mg protein. Kinetic experiments were performed in the direction of glycogen synthesis as described previously.[44] Kinetic data for the inhibition of rabbit skeletal muscle glycogen phosphorylase were collected using 4 mM of α-D-glucose-1-phosphate 1% w/v of glycogen and 1 mM AMP, and various concentrations of inhibitor. Inhibitor was dissolved in DMSO and diluted in the assay buffer (final concentrations between 6.25 and 625 μM) (50 mM triethanolamine, 100 mM KCl, 1 mM EDTA and 1 mM dithiothreitol) so that the DMSO concentration in the assay should be lower than 1%. IC_{50} values, when possible, were determined using the previous conditions and the K_i was calculated using the BotDB IC_{50}-to-K_i converter.[45]

4.3. General procedure for synthesis of 1-glycosylmethyl-4,5-diphenyl-1H-imidazoles

A mixture of starting C-glycosyl methylamine [31,32,33] [1 mmol, 193 mg of β-D-glucopyranosylmethylamine (**1a**) or β-D-galactopyranosylmethylamine (**1b**) or β-D-mannopyranosylmethylamine (**1c**) or β-D-galactofuranosylmethylamine (**1d**) or 163 mg of α-D-arabinopyranosylmethylamine (**1e**) or β-D-xylopyranosylmethylamine (**1f**)], benzil (**2**, 210 mg, 1 mmol), ammonium acetate (77 mg, 1 mmol), paraformaldehyde (30 mg) and $InCl_3$ (22 mg, 0.1 mmol) in methanol (4 mL) was stirred at rt for 48 h. A white turbid matter (ca 10%), not containing the product imidazole [R_f ~0.5 (S_1)] was removed by paper filtration and the filtrate was concentrated at reduced pressure. The evaporation residue was fractionated by flash chromatography first with eluant S_1 and then S_2.

1-(2,6-Anhydro-1-deoxy-D-glycero-D-gulo-heptitol-1-yl)-4,5-diphenylimidazole (1-β-D-glucopyranosyl-4,5-diphenylimidazole, **5a**). Yield 0.20 g (50%); mp 208–209 °C; $[\alpha]_D^{20}$ –40.0 (c 1.0, MeOH); ν_{max}(diamond anvil) 3235, 3061, 2866, 1660, 1595, 1444, 1070 cm^{-1}; δ_H (400 MHz, CD_3OD) 7.99 (s, 1H, H-2), 7.41–7.46 (m, 3H, H-14–16), 7.28–7.36 (m, 4H, H-7,

H-11, H-13, H-17), 7.08–7.17 (m, 3H, H-8–10), 4.27 (dd, $J_{1'a,1'b}$ 14.6, $J_{1'a,2'}$ 1.7 Hz, 1H, H-1'a), 3.89 (dd, $J_{1'b,2'}$ 8.3 Hz, 1H, H-1'b), 3.81 (dd, $J_{7'a,7'b}$ 11.9, $J_{6',7'a}$ 2.3 Hz, 1H, H-7'a), 3.66 (dd, $J_{6',7'b}$ 5.2 Hz, 1H, H-7'b), 3.31–3.37 (m, 1H, H-2'), 3.23–3.31 (m, 2H, H-4', H-5'), 3.19 (ddd, $J_{5',6'}$ 9.5 Hz, 1H, H-6'), 3.00–3.06 (m, 1H, H-3'); δ_C (100.6 MHz, CD_3OD) 138.25 (C-2), 136.82 (C-4), 134.10 (C-6), 131.07 (C-13, C-17), 130.01 (C-12), 128.87 (C-5), 128.62 (C-14, C-16), 128.45 (C-15), 127.65 (C-8, C-10), 126.64 (C-7, C-11), 126.11 (C-9), 80.05 (C-6'), 78.66 (C-2'), 78.04 (C-4'), 71.60 (C-3'), 70.02 (C-5'), 61.22 (C-7'), 46.21 (C-1'); HRMS (ESI): MH^+, found 397.1756, $C_{22}H_{24}N_2O_5H^+$ requires 397.1758.

1-(2,6-Anhydro-7-deoxy-L-glycero-L-galacto-heptitol-7-yl)-4,5-diphenylimidazole (1-β-D-galactopyranosyl-4,5-diphenylimidazole, **5b**). Yield 0.22 g (55%); mp 203–204 °C; $[\alpha]_D^{20}$ –38.0 (c 1.0, MeOH); ν_{max}(diamond anvil) 3340, 3059, 2858, 1603, 1504, 1441, 1090 cm^{-1}; δ_H (600 MHz, CD_3OD) 7.99 (s, 1H, H-2), 7.40–7.46 (m, 3H, H-14–16), 7.30–7.36 (m, 4H, H-7, H-11, H-13, H-17), 7.09–7.17 (m, 3H, H-8–10), 4.29 (dd, $J_{7'a,7'b}$ 14.6, $J_{6',7'a}$ 1.8 Hz, 1H, H-7'a), 3.93 (dd, $J_{6',7'b}$ 8.5 Hz, 1H, H-7'b), 3.87 (d, $J_{2',3'}$, $J_{3',4'}$ 1.4 Hz, 1H, H-3'), 3.73 (dd, $J_{1'a,1'b}$ 11.3, $J_{1'a,2'}$ 6.6 Hz, 1H, H-1'a), 3.70 (dd, $J_{1'b,2'}$ 5.5 Hz, 1H, H-1'b), 3.43–3.47 (m, 1H, H-2'), 3.38–3.43 (m, 2H, H-5', H-4'), 3.31–3.36 (m, 1H, H-6'); δ_C (150.8 MHz, CD_3OD) 138.08 (C-2), 136.67 (C-4), 133.99 (C-6), 131.04 (C-13, C-17), 129.92 (C-12), 128.97 (C-5), 128.60 (C-14, C-16), 128.44 (C-15), 127.65 (C-8, C-10), 126.62 (C-7, C-11), 126.13 (C-9), 79.22 (C-6'), 78.60 (C-2'), 74.62 (C-4'), 69.17 (C-3'), 68.68 (C-5'), 61.13 (C-1'), 46.28 (C-7'); HRMS (ESI): MH^+, found 397.1755, $C_{22}H_{24}N_2O_5H^+$ requires 397.1758.

1-(2,6-Anhydro-1-deoxy-D-glycero-D-galacto-heptitol-1-yl)-4,5-diphenylimidazole (1-β-D-mannopyranosyl-4,5-diphenylimidazole, **5c**). Yield 0.19 g (48%); mp 234–236 °C; $[\alpha]_D^{20}$ –22.0 (c 1.0, MeOH); ν_{max}(diamond anvil) 3279, 3143, 2854, 1599, 1504, 1441, 1074 cm^{-1}; δ_H (600 MHz, CD_3OD) 7.90 (s, 1H, H-2), 7.43–7.55 (m, 3H, H-14–16), 7.30–7.37 (m, 4H, H-7, H-11, H-13, H-17), 7.10–7.17 (m, 3H, H-8–10), 4.14 (dd, $J_{1'a,1'b}$ 14.7, $J_{1'a,2'}$ 8.5 Hz, 1H, H-1'a), 4.01 (dd, $J_{1'b,2'}$ 4.2 Hz, 1H, H-1'b), 3.80 (dd, $J_{7'a,7'b}$ 11.8, $J_{6',7'a}$ 2.3 Hz, 1H, H-7'a), 3.67 (dd, $J_{6',7'b}$ 5.5 Hz, 1H, H-7'b), 3.50–3.61 (m, 3H, H-2', H-3', H-5'), 3.34 (dd, $J_{4',5'}$ 9.5 Hz, $J_{3',4'}$ 3.4 Hz, 1H, H-4'), 3.08 (ddd, $J_{5',6'}$ 9.5 Hz, 1H, H-6'); δ_C (150.8 MHz, CD_3OD) 137.97 (C-2), 137.31 (C-4), 134.02 (C-6), 130.85 (C-13, C-17), 130.19 (C-12), 129.31 (C-5), 128.84 (C-14, C-16), 128.64 (C-15), 127.67 (C-8, C-10), 126.57 (C-7, C-11), 126.18 (C-9), 80.51 (C-6'), 76.73 (C-2'), 74.64(C-4'), 69.68 (C-3'), 67.03 (C-5'), 61.37 (C-7'), 46.07 (C-1'); HRMS (ESI): MH^+, found 397.1760, $C_{22}H_{24}N_2O_5H^+$ requires 397.1758.

1-(3,6-Anhydro-7-deoxy-D-glycero-L-galacto-heptitol-7-yl)-4,5-diphenylimidazole (1-α-D-galactofuranosyl-4,5-diphenylimidazole, **5d**). Yield 0.19 g (48%); mp 157–160 °C; $[\alpha]_D^{20}$ +2.0 (c 1.0, MeOH); ν_{max}(diamond anvil) 3299, 3057, 2924, 1601, 1504, 1441, 1038 cm^{-1}; δ_H (600 MHz, CD_3OD) 7.93 (s, 1H, H-2), 7.44–7.49 (m, 3H, H-14–16), 7.31–7.38 (m, 4H, H-7, H-11, H-13, H-17), 7.10–7.18 (m, 3H, H-8–10), 4.14 (dd, 1H, $J_{6',7'a}$ 4.5, $J_{7'a,7'b}$ 14.4 Hz, H-7'a), 4.06–4.12 (m, 2H, H-5', H-7'b), 4.00–4.06 (m, 1H, H-6'), 3.83 (t, $J_{2',3'}$, $J_{3',4'}$ 2.7 Hz, 1H, H-3'), 3.72–3.79 (m, 2H, H-2', H-4'), 3.62 (dd, 1H, $J_{1'a,2'}$ 6.2, $J_{1'a,1'b}$ 11.0 Hz, H-1'a), 3.58 (dd, 1H, $J_{1'b,2'}$ 6.7 Hz, H-1'b); δ_C (150.8 MHz, CD_3OD) 137.86 (C-2), 137.21 (C-4), 133.99 (C-6), 131.02 (C-12), 130.84 (C-13, C-17), 128.79 (C-14, C-16), 128.71 (C-5), 128.59 (C-15), 127.68 (C-8, C-10), 126.60 (C-7, C-11), 126.19 (C-9), 85.32 (C-3'), 79.71 (C-6'), 78.87 (C-5'), 76.63 (C-4'), 71.42 (C-2'), 62.79 (C-1'), 44.43 (C-7'); HRMS (ESI): MH^+, found 397.1758, $C_{22}H_{24}N_2O_5H^+$ requires 397.1758.

1-(2,6-Anhydro-1-deoxy-D-manno-hexitol-1-yl)-4,5-diphenylimidazole (1-α-D-arabinopyranosyl-4,5-diphenylimidazole, **5e**). Yield 0.19 g (52%); mp 195–197 °C; $[\alpha]_D^{20}$ +21.0 (c 1.0, MeOH); ν_{max}(diamond anvil) 3371, 3051, 2897, 1601, 1502, 1439, 1065 cm^{-1}; δ_H (600 MHz, CD_3OD) 7.87 (s, 1H, H-2), 7.42–7.47 (m, 3H, H-14–16), 7.31–7.36 (m, 4H, H-7, H-11, H-13, H-17), 7.13– 7.18 (m, 2H, H-8, H-10), 7.10–7.13 (m, 1H, H-9), 4.31 (dd, $J_{1'a,1'b}$ 14.6, $J_{1'a,2'}$ 1.6 Hz, 1H, H-1'a), 3.92 (dd, $J_{1'b,2'}$ 8.9 Hz, 1H, H-1'b), 3.89 (dd, $J_{6'a,6'b}$ 12.6, $J_{5',6'a}$ 2.0 Hz, 1H, H-6'a), 3.80–3.82 (m, 1H, H-5'), 3.47 (dd, $J_{5',6'b}$ 0.9 Hz, 1H, H-6'b), 3.38–3.43 (m, 2H, H-3', H-4'), 3.18–3.23 (m, 1H, H-2'); δ_C (150.8 MHz, CD_3OD) 138.05 (C-2), 136.97 (C-4), 134.16 (C-6), 130.99 (C-13, C-17), 130.03 (C-12), 128.83 (C-5), 128.61 (C-14, C-16), 128.43 (C-15), 127.64 (C-8, C-10), 126.66 (C-7, C-11), 126.10 (C-9), 79.43 (C-2'), 73.97 (C-3'), 69.88 (C-6'), 69.26 (C-5'), 68.97 (C-4'), 46.39 (C-1'); HRMS (ESI): MH^+, found 367.1651, $C_{21}H_{22}N_2O_4H^+$ requires 367.1652.

1-(2,6-Anhydro-1-deoxy-L-gluco-hexitol-6-yl)-4,5-diphenylimidazole (1-β-D-xylopyranosyl-4,5-diphenylimidazole, **5f**). Yield 0.18 g (49%); mp 197–199 °C; $[\alpha]_D^{20}$ –26.0 (c 1.0, DMSO); ν_{max}(diamond anvil) 3354, 3115, 2848, 1601, 1504, 1414, 1093 cm^{-1}; δ_H (400 MHz, $(CD_3)_2SO$) 7.75 (s, 1H, H-2), 7.45–7.51 (m, 3H, H-14–16), 7.31–7.38 (m, 4H, H-7, H-11, H-13, H-17), 7.14–7.19 (m, 2H, H-8, H-10), 7.06–7.11 (m, 1H, H-9), 4.12 (dd, $J_{6'a,6'b}$ 14.6, $J_{5',6'a}$ 1.9 Hz, 1H, H-6'a), 3.75 (dd, $J_{5',6'b}$ 9.0 Hz, 1H, H-6'b), 3.71 (dd, $J_{1'a,1'b}$ 11.0, $J_{1'a,2'}$ 5.3 Hz, 1H, H-1'a), 3.20–3.29 (m, 1H, H-2'), 3.16 (ddd, $J_{4',5'}$ 9.2, Hz, 1H, H-5'), 3.03 (dd, $J_{2',3'}$ 8.7 Hz, 1H, H-3'), 2.95 (dd, $J_{1'b,2'}$ 10.8 Hz, 1H, H-1'b), 2.86 (dd, $J_{3',4'}$ 9.0 Hz, 1H, H-4'); δ_C (100.6 MHz, $(CD_3)_2SO$) 138.43 (C-2), 136.76 (C-4), 135.41 (C-6), 131.45 (C-13, C-17),

130.93 (C-12), 129.36 (C-14, C-16), 129.08 (C-15), 128.94 (C-5), 128.43 (C-8, C-10), 126.34 (C-7, C-9, C-11), 79.27 (C-5'), 78.36 (C-3'), 72.23 (C-4'), 70.07 (C-1', C-2'), (46.82 (C-6'); HRMS (ESI): MH^+, found 367.1650, $C_{21}H_{22}N_2O_4H^+$ requires 367.1652.

4.4. General procedure for synthesis of 1-glycosylmethyl-4- and -5-phenyl-1H-imidazoles

A mixture of starting C-glycosyl methylamine [1 mmol, 193 mg of *β*-D-glucopyranosylmethylamine (**1a**) or *β*-D-galactopyranosylmethylamine (**1b**)], phenylglyoxal hydrate (**3**, 152 mg, 1 mmol), ammonium acetate (77 mg, 1 mmol), paraformaldehyde (30 mg) and $InCl_3$ (22 mg, 0.1 mmol) in methanol (4 mL) was stirred at rt for 48 h. Further work-up was continued according to the above General methods. In both cases, this procedure gave the major 4-phenyl derivatives [R_f ~0.32 (S_1)] and minor 5-phenyl derivatives [R_f ~0.25 (S_1)].

1-(2,6-Anhydro-1-deoxy-D-glycero-D-gulo-heptitol-1-yl)-4-phenylimidazole (1-*β*-D-glucopyranosyl-4-phenylimidazole, **6a**). Yield 0.11 g (34%); syrup; $[\alpha]_D^{20}$ +11.0 (c 1.0, MeOH); ν_{max}(diamond anvil) 3272, 2922, 2858, 1601, 1483, 1369, 1068 cm^{-1}; δ_H (400 MHz, CD_3OD) 7.74 (d, J 1.3 Hz, 1H, H-2), 7.68–7.72 (m, 2H, H-7, H-11), 7.55 (d, J 1.3 Hz, 1H, H-5), 7.30–7.36 (m, 2H, H-8, H-10), 7.18–7.23 (m, 1H, H-9), 4.40 (dd, $J_{1'a,1'b}$ 14.5, $J_{1'a,2'}$ 2.1 Hz, 1H, H-1'a), 4.21 (dd, $J_{1'b,2'}$ 6.1 Hz, 1H, H-1'b), 3.85 (dd, $J_{7'a,7'b}$ 12.0, $J_{6',7'a}$ 2.3 Hz, 1H, H-7'a), 3.64 (dd, $J_{6',7'b}$ 5.8 Hz, 1H, H-7'b), 3,47 (ddd, $J_{2',3'}$ 9.6 Hz, 1H, H-2'), 3.33–3.38 (m, 1H, H-4'), 3.27 (ddd, $J_{5',6'}$ 9.6 Hz, 1H, H-6'), 3.19 (dd, $J_{4',5'}$ 8.8 Hz, 1H, H-5'), 2.99 (dd, $J_{3',4'}$ 9.1 Hz, 1H, H-3'); δ_C (100.6 MHz, CD_3OD) 140.81 (C-4), 138.66 (C-2), 133.88 (C-6), 128.14 (C-8, C-10), 126.34 (C-9), 124.42 (C-7, C-11), 116.80 (C-5), 80.34 (C-6'), 78.35 (C-2'), 78.21 (C-4'), 70.70 (C-3'), 70.25 (C-5'), 61.50 (C-7'), 47.57 (C-1'); HRMS (ESI): MH^+, found 321.1443, $C_{16}H_{20}N_2O_5H^+$ requires 321.1445.

1-(2,6-Anhydro-7-deoxy-L-glycero-L-galacto-heptitol-7-yl)-4-phenylimidazole (1-*β*-D-galactopyranosyl-4-phenylimidazole, **6b**). Yield 0.12 g (37%); syrup; $[\alpha]_D^{20}$ –6.0 (c 1.0, MeOH); ν_{max}(diamond anvil) 3275, 2921, 2858, 1600, 1481, 1371, 1049 cm^{-1}; δ_H (400 MHz, CD_3OD) 7.72 (d, J 0.9 Hz, 1H, H-2), 7.66–7.70 (m, 2H, H-7, H-11), 7.55 (d, J 1.0, 1H, H-5), 7.28–7.36 (m, 2H, H-8, H-10), 7.15–7.21 (m, 1H, H-9), 4.42 (dd, $J_{7'a,7'b}$ 14.7, $J_{6',7'a}$ 1.1 Hz, 1H, H-7'a), 4.13–4.19 (m, 1H, H-7'b), 3.85 (dd, $J_{2',3'}$ 3.0, $J_{3',4'}$ 0.8 Hz, 1H, H-3'), 3.73 (dd, $J_{1'a,1'b}$ 11.4, $J_{1'a,2'}$ 6.9 Hz, 1H, H-1'a), 3.68 (dd, $J_{1'b,2'}$ 5.0 Hz, 1H, H-1'b), 3.38–3.51 (m, 4H, H-2', H-4'–6'); δ_C (100.6 MHz, CD_3OD) 140.80 (C-4), 138.46 (C-2), 133.90 (C-6), 128.12

(C-8, C-10), 126.30 (C-9), 124.41 (C-7, C-11), 116.61 (C-5), 79.26 (C-6'), 78.81 (C-2'), 74.83 (C-4'), 69.38 (C-3'), 68.13 (C-5'), 61.39 (C-1'), 48.12 (C-7'); HRMS (ESI): MH^+, found 321.1443, $C_{16}H_{20}N_2O_5H^+$ requires 321.1445.

1-(2,6-Anhydro-1-deoxy-D-glycero-D-gulo-heptitol-1-yl)-5-phenylimidazole (1-*β*-D-glucopyranosyl-5-phenylimidazole, **7a**). Yield 0.04 g (12%); syrup; $[\alpha]_D^{20}$ –21.0 (c 1.0, MeOH); ν_{max}(diamond anvil) 3255, 2920, 2854, 1585, 1483, 1373, 1072 cm^{-1}; δ_H (400 MHz, CD_3OD) 7.95 (s, 1H, H-2), 7.41–7.48 (m, 4H, H-7, H-8, H-10, H-11), 7.36–7.41 (m, 1H, H-9), 6.97 (s, 1H, H-4), 4.51 (dd, $J_{1'a,1'b}$ 14.7, $J_{1'a,2'}$ 1.8 Hz, 1H, H-1'a), 4.03 (dd, $J_{1'b,2'}$ 8.3Hz, 1H, H-1'b), 3.80 (dd, $J_{7'a,7'b}$ 11.9, $J_{6',7'a}$ 2.3 Hz, 1H, H-7'a), 3.65 (dd, $J_{6',7'b}$ 5.2 Hz, 1H, H-7'b), 3,40 (ddd, $J_{2',3'}$ 9.9, 1H, H-2'), 3.26–3.36 (buried m, 2H, H-4', H-5'), 3.15–3.20 (m, 1H, H-6'), 3.03–3.09 (m, 1H, H-3'); NOE contacts: H-1'a, 7 (11), H-1'a, 8 (10); δ_C (100.6 MHz, CD_3OD) 139.38 (C-2), 133.66 (C-5), 129.41 (C-6), 129.00 (C-7, C-11), 128.37 (C-8, C-10), 127.81 (C-9), 125.59 (C-4), 80.05 (C-6'), 78.86 (C-2'), 78.07 (C-4'), 71.61 (C-3'), 70.04 (C-5'), 61.23 (C-7'), 46.28 (C-1'); HRMS (ESI): MH^+, found 321.1443, $C_{16}H_{20}N_2O_5H^+$ requires 321.1445.

1-(2,6-Anhydro-7-deoxy-L-glycero-L-galacto-heptitol-7-yl)-5-phenylimidazole (1-*β*-D-galactopyranosyl-5-phenylimidazole, **7b**). Yield 0.04 g (12%); syrup; $[\alpha]_D^{20}$ –29.0 (c 1.0, MeOH); ν_{max}(diamond anvil) 3262, 2918, 2858, 1562, 1483, 1404, 1051 cm^{-1}; δ_H (400 MHz, CD_3OD) 7.92 (s, 1H, H-2), 7.32–7.48 (m, 5H, H-7–11), 6.96 (s, 1H, H-4), 4.52 (dd, $J_{7'a,7'b}$ 14.6, $J_{6',7'a}$ 1.5 Hz, 1H, H-7'a), 4.04 (dd, $J_{6',7'b}$ 8.4 Hz, 1H, H-7'b), 3.86–3.90 (dd, 1H, H-3'), 3.65–3.72 (m, 2H, H-1'a, H-1'b), 3.33–3.51 (m, 4H, H-2', H-4'–6'); NOE contacts: H-7'a, 7 (11), H-7'a, 8 (10); δ_C (100.6 MHz, CD_3OD) 139.23 (C-2), 133.59 (C-5), 129.40 (C-6), 128.98 (C-7, C-11), 128.35 (C-8, C-10), 127.78 (C-9), 125.61 (C-4), 79.48 (C-6'), 78.57 (C-2'), 74.64 (C-4'), 69.17 (C-3'), 68.76 (C-5'), 61.07 (C-1'), 46.32 (C-7'); HRMS (ESI): MH^+, found 321.1443, $C_{16}H_{20}N_2O_5H^+$ requires 321.1445.

4.5. General procedure for synthesis of 1-glycosylmethyl-1H-imidazoles

A mixture of starting C-glycosyl methylamine [1 mmol, 193 mg of *β*-D-glucopyranosylmethylamine (**1a**) or *β*-D-galactopyranosylmethylamine (**1b**)], glyoxal trimer dihydrate (**3**, 70 mg, 1/3 mmol), ammonium acetate (77 mg, 1 mmol), paraformaldehyde (30 mg) and $InCl_3$ (22 mg, 0.1 mmol) in methanol (4 mL) was stirred at rt for 48 h. Further work-

up was continued according to the above General methods. Both product imidazoles obtained by this procedure had R_f ~0.16 (S_1).

1-(2,6-anhydro-1-deoxy-D-glycero-D-gulo-heptitol-1-yl)-imidazole (1-β-D-glucopyranosylimidazole, **8a**). Yield 0.10 g (41%); syrup; $[\alpha]_D^{20}$ +16.0 (c 1.0, MeOH); ν_{max}(diamond anvil) 3261, 3120, 2895, 1582, 1514, 1372, 1074 cm^{-1}; δ_H (400 MHz, CD_3OD) 7.69 (s, 1H, H-2), 7.20 (s, 1H, H-5), 6.93 (s, 1H, H-4), 4.37 (dd, $J_{1'a,1'b}$ 14.5, $J_{1'a,2}$ 2.1 Hz, 1H, H-1'a), 4.19 (dd, $J_{1'b,2}$ 6.1 Hz, 1H, H-1'b), 3.83 (dd, $J_{7'a,7'b}$ 12.0, $J_{6',7'a}$ 2.2 Hz, 1H, H-7'a), 3.63 (dd, $J_{6',7'b}$ 5.6 Hz, 1H, H-7'b), 3.32–3.46 (m, 2H, H-2', H-4'), 3.08–3.27 (m, 2H, H-5', H-6'), 2.94 (dd, $J_{2',3'}$ 9.2, $J_{3',4'}$ 9.4 Hz, 1H, H-3'); δ_C (100.6 MHz, CD_3OD) 138.09 (C-2), 126.89 (C-4), 120.67 (C-5), 80.31 (C-6'), 78.38 (C-2'), 78.17 (C-4'), 70.65 (C-3'), 70.20 (C-5'), 61.47 (C-7'), 47.36 (C-1'); HRMS (ESI): MH^+, found 245.1130, $C_{10}H_{16}N_2O_5H^+$ requires 245.1132.

1-(2,6-Anhydro-7-deoxy-L-glycero-L-galacto-heptitol-7-yl)-imidazole (1-β-D-galactopyranosylimidazole, **8b**). Yield 0.11 g (45%); syrup; $[\alpha]_D^{20}$ –12.0 (c 1.0, MeOH); ν_{max}(diamond anvil) 3244, 3120, 2890, 1579, 1514, 1373, 1049 cm^{-1}; δ_H (400 MHz, CD_3OD) 7.64 (s, 1H, H-2), 7.10 (s, 1H, H-5), 6.86 (s, 1H, H-4), 4.32 (dd, $J_{7'a,7'b}$ 14.4, $J_{6',7'a}$ 1.2 Hz, 1H, H-7'a), 4.05 (dd, $J_{6',7'b}$ 6.7 Hz, 1H, H-7'b), 3.77 (dd, $J_{2',3'}$ 3.1, $J_{3',4'}$ 0.6 Hz, 1H, H-3'), 3.62 (dd, $J_{1'a,1'b}$ 11.4, $J_{1'a,2'}$ 6.8 Hz, 1H, H-1'a), 3.58 (dd, $J_{1'b,2'}$ 5.3 Hz, 1H, H-1'b), 3.34–3.39 (m, 2H, H-2', H-4'), 3.26–3.32 (m, 2H, H-5', H-6'); δ_C (100.6 MHz, CD_3OD) 137.75 (C-2), 126.66 (C-4), 120.49 (C-5), 79.26 (C-6'), 78.73 (C-2'), 74.77 (C-4'), 69.28 (C-3'), 68.13 (C-5'), 61.26 (C-1'), 47.96 (C-7'); HRMS (ESI): MH^+, found 245.1124, $C_{10}H_{16}N_2O_5H^+$ requires 245.1132.

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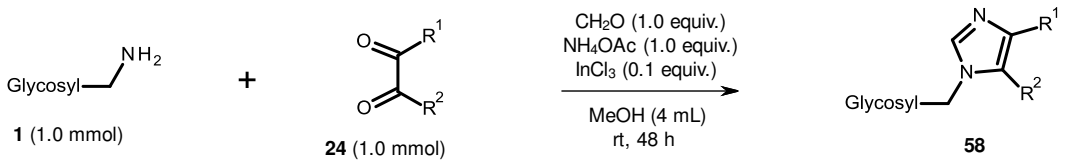
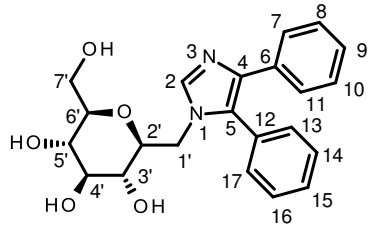
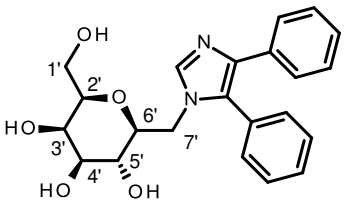
Table(s)



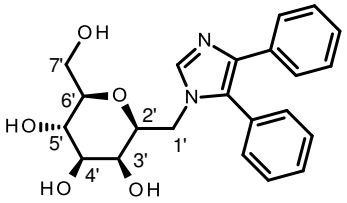
product, yield (%)[a]



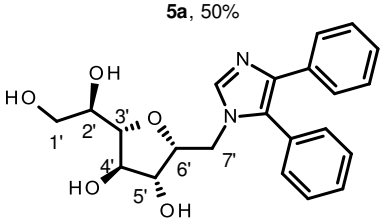
5a, 50%



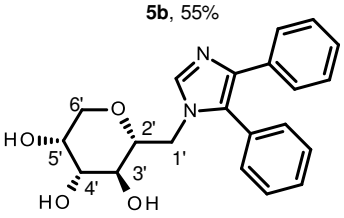
5b, 55%



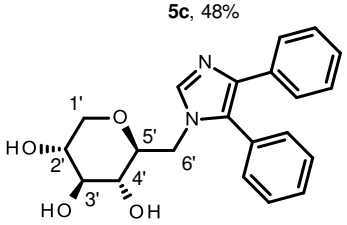
5c, 48%



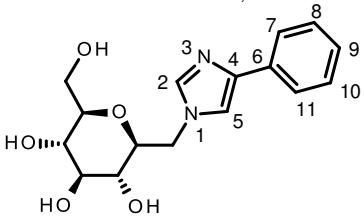
5d, 48%



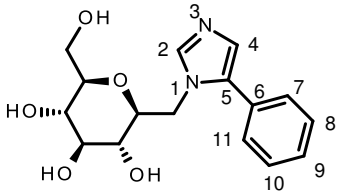
5e, 52%



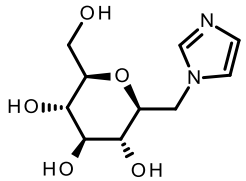
5f, 49%



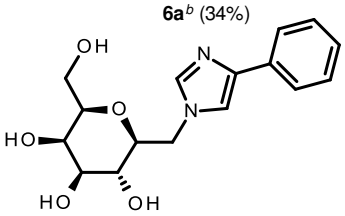
6a[b] (34%)



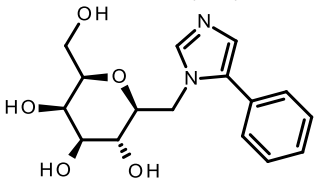
7a[c] (12%)



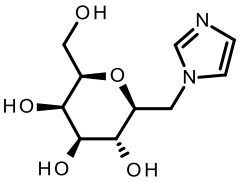
8a (41%)



6b[d] (37%)



7b[e] (12%)



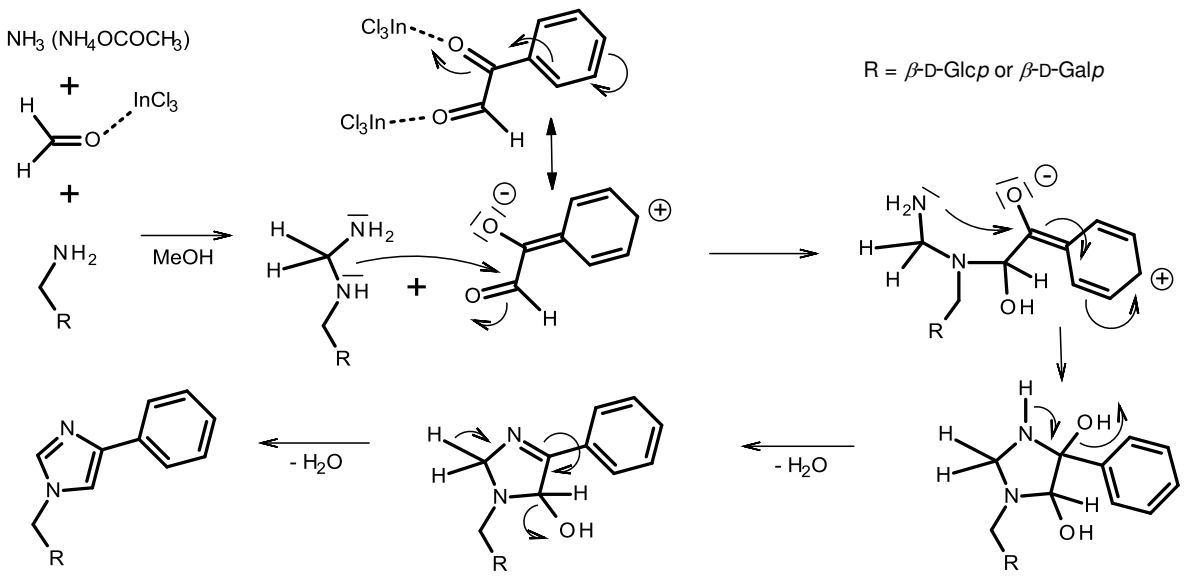
8b (45%)

Table(s)

Table 1. $InCl_3$ catalyzed one-pot preparation of 1-glycosylmethylated imidazoles from C-glycosylmethylamines (**1**), formaldehyde, ammonium acetate, and benzil (**2**, $R^1 = R^2 = Ph$) or phenylglyoxal (**3**, $R^1 = Ph$, $R^2 = H$) or glyoxal (**4**, $R^1 = R^2 = H$) in methanol.

[a] isolated yield. [b] major product, in addition to the minor **7a**. [c] minor product, in addition to the major **6a**. [d] major product, in addition to the minor **7b**. [e] minor product, in addition to the major **6b**.

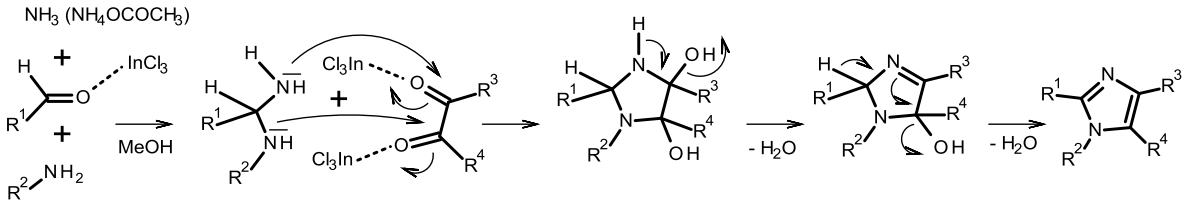
Figure(s)



Figure(s)

Scheme 1. Plausible reaction pathway of the $InCl_3$ catalyzed multicomponent synthesis of imidazoles with glycosylmethylamines, formaldehyde, ammonia and phenylglyoxal favouring the major 4-phenyl derivative over the 5-phenyl isomer.

Figure(s)

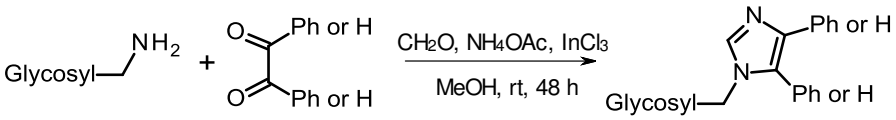


R^1, R^2, R^3, R^4 = H or alkyl or aryl or arylalkyl

Figure(s)

Scheme 2. General addition-elimination mechanism of the $InCl_3$ catalyzed multicomponent synthesis of imidazoles.

***Graphical Abstract (for review)**



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