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Improved preparation of 4(5)-aryl-2-(β-D-glucopyranosyl)-imidazoles, the most efficient glucose analogue inhibitors of glycogen phosphorylase

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Abstract

The synthesis of 4(5)-aryl-2-(β-D-glucopyranosyl)-imidazoles, the currently most efficient glucose derived inhibitors of glycogen phosphorylase enzymes was amended and extended by using *O*-perbenzylated β-D-glucopyranosyl cyanide as the starting material. This compound and its derivatives *C*-(β-D-glucopyranosyl)formimidate and formamidine were obtained in large scale reactions to give the products in ~20 grams amounts. Ring closing reactions of the formimidate and formamidine by α-amino- and α-bromoketones, respectively, produced the *O*-perbenzylated imidazoles which were deprotected by catalytic hydrogenation or by $EtSH/BF_3 \cdot OEt_2$. Newly prepared 4(5)-(4-nitro- and -aminophenyl)-2-(β-D-glucopyranosyl)-imidazoles proved less efficient inhibitors (K_i values of 1141 and 411 nM, respectively) than their unsubstituted counterpart (K_i = 280 nM).

Keywords

C-Glycosyl-compounds; cyanide; amidine; imidate; imidazole; glycogen phosphorylase; inhibitor.

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Introduction

The imidazole ring is a frequent heterocyclic motif in essential biomolecules and other natural products. It has emerged as an attractive building block in drug design because of its good biocompatibility and multifaceted ability to make favourable interactions (e.g. hydrogen bonds, van der Waals interactions, π-π stackings, ionic contacts and coordination to metal ions) in various biological environments.[1] A large array of compounds with an imidazole scaffold are marketed drugs for the medication of prevalent diseases (e.g. cancer, viral, fungal, bacterial and parasitic infections, neurodegenerative disorders, hypertension, allergy, gastric ulcers, obesity etc.), and further representatives are under investigation not only in therapeutic but also in diagnostic and pathologic fields.[1]

Among the bioactive imidazole derivatives some carbohydrate based conjugates, first of all *N*- and *C*-nucleoside analogues can also be found with existing (e.g. AICAR and Mizoribine)[2] or possible pharmaceutical utilizations (e.g. imidazofurin).[3] A 2-*C*-glycopyranosylated imidazole was reported to inhibit some glycosidase enzymes.[4]

In our recent studies it has been shown that 4(5)-aryl-2-(β-D-glucopyranosyl)-imidazoles (**7**, Scheme 1) exhibit nanomolar inhibitory activities towards glycogen phosphorylase enzymes (GPs), and the very low K_i values (156 and 26 nM against human liver GPa, 280 and 31 nM against rabbit muscle GPb, 226 and 65 nM against rabbit muscle GPa for **7a** and **7b**, respectively) render these derivatives to be the best known glucose analogue inhibitors of GPs.[5,6] Based on these findings this type of compounds may have the potential to be applied in diseased states wherein the action of GPs is essential (e.g. type 2 diabetes,[7] ischemic injuries,[8,9] tumor growth[10]).

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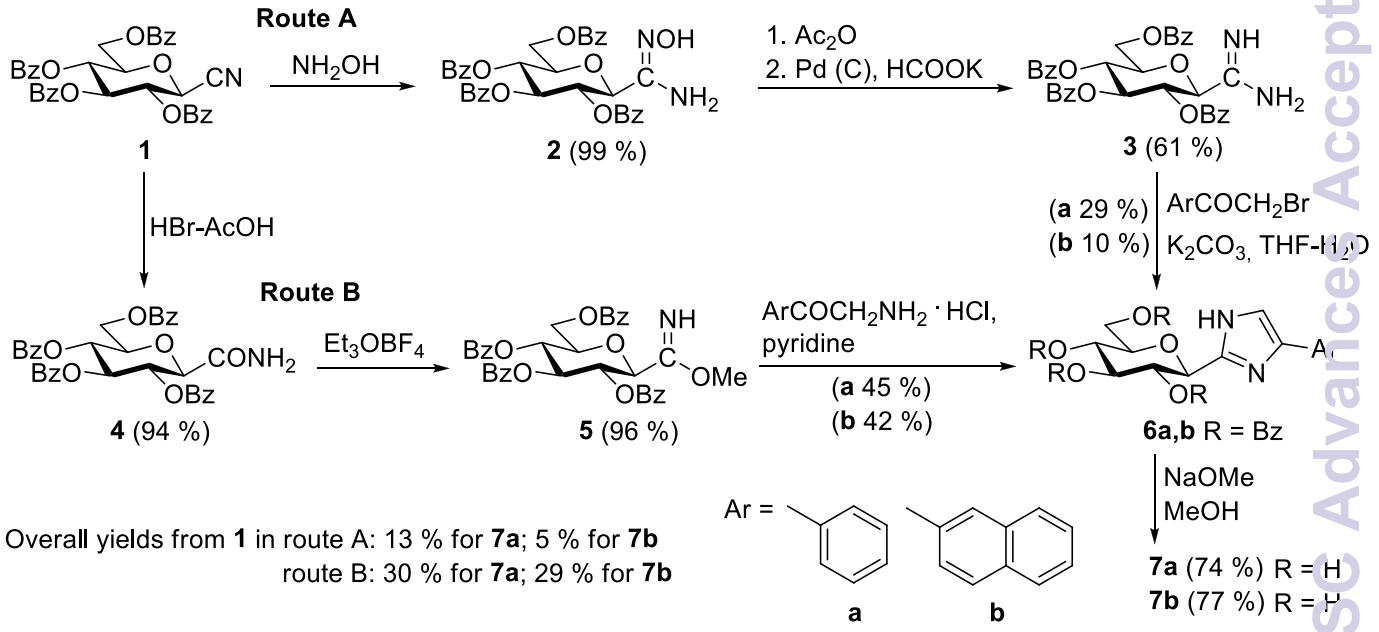
The first syntheses of **7** were worked out starting from *O*-perbenzoylated glucopyranosyl cyanide[11] **1** as outlined in Scheme 1.[5,6] The cyclisation of amidine[12] **3**, prepared from **1** via amidoxime[13,14] **2**, with α-bromo-ketones gave imidazoles **6** only in very low yields (route A) primarily due to the lability of the benzoyl-protecting groups under the necessarily applied basic conditions.[5] In route B the transformation of amide[11] **4** to imidate[15] **5** and the subsequent ring closure with α-amino-ketones required less basic conditions. Although this resulted in somewhat better yields of **6**,[6] the overall yields for **7** seemed still unsatisfactory. Therefore, we set out to find a more efficient route for the preparation of this promising class of compounds first of all by changing the *O*-protecting groups to base stable benzyl ethers.



Scheme 1. Previous syntheses of 4(5)-aryl-2-(β-D-glucopyranosyl)-imidazoles

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Results and discussion

O-Perbenzylated D-glucopyranosyl cyanides both in α- and β-configurations are known from the literature.[16-19] While the pure α-configured cyanide could be obtained from glucosyl trichloroacetimidate and TMSCN in a 1 gram scale reaction,[17] no practicable, large scale preparation of the β-anomer has yet been described. Small quantities of this compound (up to 300-400 mg) were achieved upon reaction of 1-*O*-acetate[16] or 1-*O*-phosphate[18] of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with TMSCN followed by preparative layer or flash column chromatographic separation from the concomitant α-anomeric pair. Another method applying debenzoylation of *O*-perbenzoylated β-D-glucopyranosyl cyanide[11] followed by standard *O*-perbenzylation was also reported.[20]

For the planned syntheses of the target *C*-glucosyl imidazoles several grams of the *O*-perbenzylated β-D-glucopyranosyl cyanide were needed. To this end, the preparation of this compound was effected by modifying the procedure of Garcia-Lopez et al.[16] (Scheme 2). Acetylation of commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**8**) followed by $BF_3{\cdot}Et_2O$ promoted substitution of the resulting 1-*O*-acetyl-D-glucopyranose **9αβ** with TMSCN furnished an anomeric mixture of glucosyl cyanides **10αβ** (α:β ~1.25:1) in high yield. From the worked-up reaction mixture the pure cyanide **10β** was separated by crystallisation from EtOH. In this way ~18 g of **10β** could be obtained from 50 g of **8** without chromatographic purification.

Next, transformations of cyanide **10β** into the corresponding amidine **11** and imidate **12** were investigated (Scheme 2). Amidine hydrochloride **11** was prepared in excellent yield in a *one-pot* two-step procedure from **10β** by the addition[21] of MeO^- ion to the nitrile group (to give the unisolated **12**) followed by treatment[22] with NH_4Cl. Imidate **12** was also isolated in high

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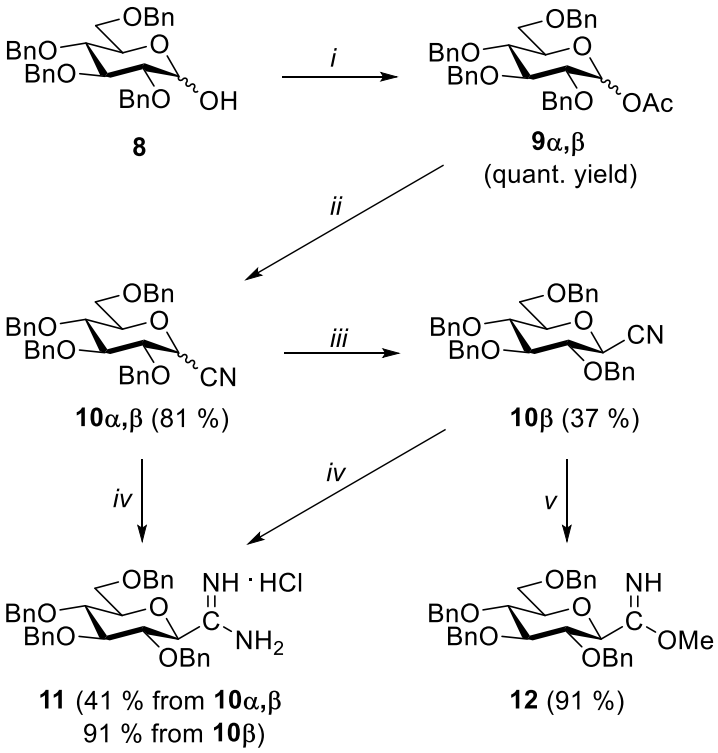
yield by trituration of the worked-up mixture of the first reaction step (**10β→12**) with hexane. Amidine **11** could also be obtained directly from **10αβ** due to the poorer reactivity of **10α** under the applied conditions. Thus, addition of Et_2O to the reaction mixture, obtained in a consecutive treatment of **10αβ** by NaOMe and NH_4Cl containing **10α** and **11**, allowed amidine salt **11** to crystallize and be isolated in 41 % yield. Finally, a large scale preparation of **11** (~20 g pure product) was accomplished by a multistep reaction sequence **8→9αβ→10αβ→11** in 40 % overall yield without isolation of the intermediates.



Scheme 2. Reaction conditions: *i*) Ac_2O, dry pyridine, rt; *ii*) TMSCN, $BF_3{\cdot}Et_2O$, dry CH_3CN, rt; *iii*) crystallization from EtOH; i*v*) 1. NaOMe in MeOH, $CHCl_3$, rt, 2. NH_4Cl, rt; *v*) NaOMe in MeOH, $CHCl_3$, rt.

Treatment of amidine **11** with α-bromo-ketones (Table 1, conditions *i*) afforded the desired *O*-perbenzylated *C*-glucosyl imidazoles **13** in good yields accompanied by small amounts of *N*-aroylmethyl imidazoles **14**. The latter by-products were obviously formed by the reactions of

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13 with the α-bromo-ketones under the basic reaction conditions. Compounds **14a,b** could be separated by column chromatography, and HMBC NMR measurements (Fig. 1) proved the depicted structures.

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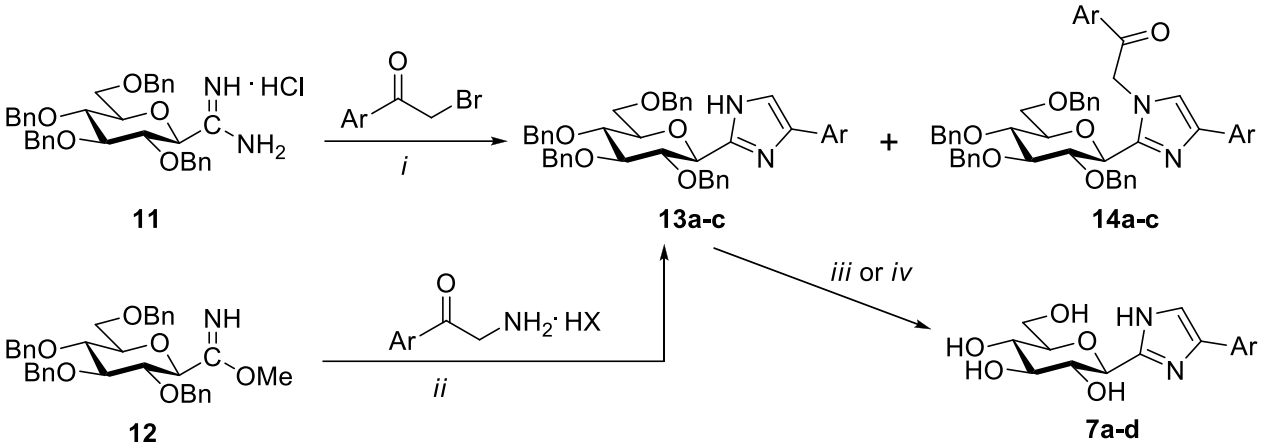
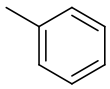
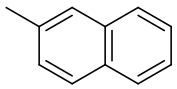
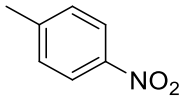
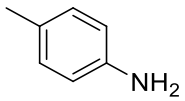
Table 1. Synthetic routes towards *C*-glucosyl imidazoles **7**



i) THF-H_2O 8:1, K_2CO_3, rt; *ii*) dry pyridine, rt; *iii*) $Pd(OH)_2/C$, H_2, ccHCl, EtOAc, EtOH, rt; *iv*) $BF_3{\cdot}Et_2O$, EtSH, CH_2Cl_2, rt.

	Ar	Conditions and yields (%)				
			13	**14**		**7**
a		*i*	72	7		
		ii	33	–	*iii*	89
b		*i*	69	8	*iii*	inseparable
		ii	47	–	*iv*	82
c		*i*	36	traces	*iv*	45
d		–	–	–	*iii* (from **13c**)	66

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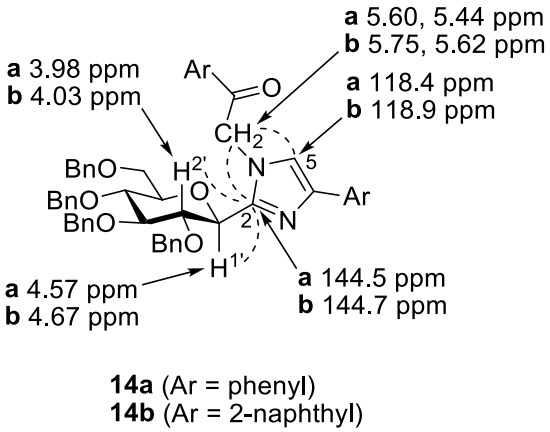

14a (Ar = phenyl)
14b (Ar = 2-naphthyl)

Figure 1. Structure elucidation of compounds **14a,b** by 2D ^{1}H-^{13}C HMBC measurements (dashed lines indicate the observed cross peaks)

Extension of the above reaction to the synthesis of 4(5)-(4-nitrophenyl)imidazole **13c** gave the expected compound in acceptable yield. It is to be noted that under these conditions the *O*-perbenzoylated counterpart of **13c** could not be obtained from the corresponding amidine.

In order to exclude the possibility of the formation of by-products **14** the synthesis of imidazoles **13a,b** was also tried by cyclisation of imidate **12** with the corresponding α-amino-ketones (Table 1, conditions *ii*), however, these reactions provided the desirable heterocycles in significantly lower yields.

Finally, removal of the *O*-benzyl protecting groups of compounds **13** were studied. Catalytic hydrogenation of **13a** and **13c** with $Pd(OH)_2/C$ in the presence of hydrochloric acid (to avoid poisoning of the catalyst by protonation of the imidazole) was smoothly accomplished to provide the phenyl and 4-aminophenyl derivatives **7a** and **7d**, respectively, in good yields (Table 1, conditions *iii*). However, the same reaction of 2-naphthyl-imidazole **13b** afforded the expected deprotected derivative **7b** together with inseparable by-products. The ^{1}H-NMR and MS measurements of this mixture revealed that beside *O*-debenzylation partial saturation

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of the naphthalene ring also took place. Further attempts to selectively cleave the benzyl groups of **13b** under reductive ($Pd(OH)_2$/C, $HCOONH_4$, MeOH), oxidative (CrO_3, AcOH; DDQ, CH_2Cl_2, H_2O or MeOH) or other (TMSI, CH_3CN; BBr_3 or $BBr_3 \cdot SMe_2$, CH_2Cl_2) conditions failed. Finally, the treatment of **13b** with ethanethiol in the presence of $BF_3 \cdot OEt_2$ (Table 1, conditions *iv*) proved suitable to get **7b** in high yield. By applying this method for the deprotection of **13c** the 4-nitrophenyl derivative **7c** was also obtained, albeit in lower yield.

The 4(5)-(4-nitro- and -aminophenyl)imidazoles **7c** and **7d** were assayed against rabbit muscle GPb as described earlier[23] to show K_i values of 1141 and 411 nM, respectively. This finding revealed that substitution of the phenyl ring in the 4-position resulted in a weakening of the inhibition (K_i = 280 nM for **7a**), and this effect was smaller for the amino substituent in comparison to that of the nitro group.

Conclusion

In conclusion, an improved method was elaborated for the synthesis of 4(5)-aryl-2-β-D-glucopyranosyl imidazoles **7** from *O*-perbenzylated β-D-glucopyranosyl cyanide **10β**. Cyanide **10β** and its more reactive derivatives amidine **11** and imidate **12** were prepared in ~20 grams scales. Ring closures of **11** and **12** by α-bromoketones or α-aminoketones, respectively, gave the expected *O*-protected imidazoles **13** which were debenzylated by usual catalytic hydrogenation (**7a,d**) or EtSH/$BF_3 \cdot OEt_2$ (**7b,c**). Overall yields for **7a** and **7b** were raised to 58 and 51 %, respectively, based on the starting **10β**. Substitution of the phenyl ring of **7a** in the 4-position by a nitro (**7c**) or an amino group (**7d**) resulted in somewhat less efficient inhibitors of rabbit muscle glycogen phosphorylase b.

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Experimental

General Methods

Melting points were measured on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at rt. NMR spectra were recorded with Bruker 360 (360/90 MHz for $^{1}H/^{13}C$) or Bruker 400 (400/100 MHz for $^{1}H/^{13}C$) or Avance II 500 (500/125 MHz for $^{1}H/^{13}C$) spectrometers. Chemical shifts are referenced to the internal TMS (^{1}H), or to the residual solvent signals (^{13}C). Proton-signal assigments for compounds **9-14** are based on COSY correlations. Microanalyses were performed on an Elementar Vario Micro cube instrument. Mass spectra were obtained by a Thermo Scientific LTQ XL instrument. TLC was performed on DC-Alurolle Kieselgel 60 F_{254} (Merck), and the plates were visualised under UV light and by gentle heating (generally no spray reagent was used but, if more intense charring was necessary, the plate was sprayed with the following solution: abs. EtOH (95 mL), ccH_2SO_4 (5 mL) anisaldehyde (1 mL)). For column chromatography Kieselgel 60 (Merck, particle size 0.063-0.200 mm) was used. MeCN, $CHCl_3$ and CH_2Cl_2 were distilled from P_4O_{10} and stored over 4 Å molecular sieves. Pyridine was distilled from KOH and stored over KOH pellets. MeOH was purified by distillation after refluxing for a couple of hours with magnesium turnings and iodine. Organic solutions were dried over anhydrous $MgSO_4$ and concentrated under diminished pressure at 40-60 ºC (water bath). 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranose (Carbosynth), TMSCN (ACROS), EtSH (TCI), $Pd(OH)_2/C$ (Sigma Aldrich) and $BF_3{\cdot}Et_2O$ (Merck) were purchased from the indicated suppliers. 2-Amino-1-arylethanones were synthesized according to literature procedures.[6,24]

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General procedure I for the synthesis of 4(5)-aryl-2-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl)-imidazoles (13a-c) from *C*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)formamidine hydrochloride (11)

C-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)formamidine hydrochloride (**11**, 0.20 g, 0.33 mmol) and K_2CO_3 (0.09 g, 0.66 mmol, 2 equiv.) were stirred in a THF-H_2O solvent mixture (8 mL and 1 mL, respectively) at rt for 15 min. After that, 2-bromo-1-arylethanone (0.33 mmol, 1 equiv.) was added to the reaction mixture and the stirring was continued at rt. When TLC (9:1 $CHCl_3$-MeOH and 1:1 hexane-EtOAc) indicated total consumption of the starting material (2 d) the mixture was diluted with EtOAc (20 mL) and extracted with water (2 × 10 mL). The organic phase was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (2:1 hexane-EtOAc).

General procedure II for the synthesis of 4(5)-aryl-2-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl)-imidazoles (13a,b) from methyl *C*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)formimidate (12)

Methyl *C*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)formimidate (**12,** 0.20 g, 0.34 mmol) and the hydrochloride or hydrobromide salt of the corresponding 2-amino-1-arylethanone (0.69 mmol, 2 equiv.) were dissolved in anhydrous pyridine (5 mL). The mixture was stirred at rt and the reaction was monitored by TLC (2:1 hexane-acetone). After completion of the reaction (2 d) the solution was diluted with EtOAc (20 mL) and extracted with water (3 × 10 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated, then the residue was purified by column chromatography (3:1 hexane-EtOAc).

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General procedure III for the removal of *O*-benzyl protecting groups by catalytic hydrogenation

A degassed, vigorously stirred suspension of 20 % $Pd(OH)_2/C$ (50 weight % of substrate) in a mixture of EtOAc (3 mL) and EtOH (15 mL) was saturated with H_2 (3 ×), and a solution of the corresponding *O*-perbenzylated β-D-glucopyranosyl imidazole **13** (0.42 mmol) in EtOAc (3 mL) and a drop of concentrated HCl were added. After stirring the reaction mixture under H_2 atmosphere at rt for overnight it was neutralized with $NaHCO_3$. The catalyst and the inorganic precipitates were filtered off through a pad of celite and washed thoroughly with MeOH (3 × 3 mL). The filtrate was then concentrated under reduced pressure and the residual crude product was purified by column chromatography (5:1 $CHCl_3$-MeOH).

General procedure IV for the removal of *O*-benzyl protecting groups by using EtSH/BF_3·OEt_2

To a solution of the corresponding *O*-perbenzylated β-D-glucopyranosyl imidazole **13** (0.54 mmol) in anhydrous CH_2Cl_2 (10 mL) EtSH (1.6 mL, 21.46 mmol, 40 equiv.) and BF_3·OEt_2 (1.35 mL, 10.88 mmol, 20 equiv.) were added, and the reaction mixture was stirred at rt. After completion of the reaction (3 d) monitored by TLC (1:1 hexane-EtOAc and 3:1 $CHCl_3$-MeOH) the mixture was diluted with EtOAc (10 mL) and extracted with water (3 × 3 mL). The combined aqueous phases were concentrated under diminished pressure and the residue was purified by column chromatography (19:1 → 9:1 $CHCl_3$-MeOH).

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Syntheses and characterization of the compounds

2-(β-D-Glucopyranosyl)-4(5)-phenyl-imidazole (7a)

Prepared from compound **13a** (0.24 g, 0.36 mmol) according to General procedure III. Purification by column chromatography yielded 0.10 g (89 %) colourless syrup. Physical and spectroscopic data were identical to those reported previously.[5]

2-(β-D-Glucopyranosyl)-4(5)-(2-naphthyl)-imidazole (7b)

Prepared from compound **13b** (0.39 g, 0.54 mmol) according to General procedure IV. Purification by column chromatography yielded 0.16 g (82 %) colourless syrup. Physical and spectroscopic data were identical to those reported previously.[5]

2-(β-D-Glucopyranosyl)-4(5)-(4-nitrophenyl)-imidazole (7c)

Prepared from compound **13c** (0.20 g, 0.28 mmol) according to General procedure IV. Purification by column chromatography yielded 0.05 g (45 %) yellow syrup. R_f = 0.50 (7:3 $CHCl_3$-MeOH); $[\alpha]_D$ = +10 (c 0.50, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.22 (2H, d, *J* = 8.9 Hz, aromatics), 7.94 (2H, d, *J* = 8.9 Hz, aromatics), 7.67 (1H, s, imidazole CH), 4.39 (1H, d, *J* = 9.6 Hz, H-1'), 3.90 (1H, dd, *J* = 12.0, 1.6 Hz, H-6'a), 3.74 (1H, dd, *J* = 12.0, 5.0 Hz, H-6'b), 3.66 (1H, pseudo t, *J* = 9.4, 9.0 Hz, H-2' or H-3' or H-4'), 3.55-3.46 (3H, m, H-2' and/or H-3' and/or H-4', H-5'); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 149.4 (PhC_4-NO_2), 147.5, 141.5 (imidazole C-2, C-4), 126.1, 125.1 (aromatics), 118.5 (imidazole C-5), 82.2, 79.3, 76.9, 74.6, 71.3 (C-1' – C-5'), 62.8 (C-6'). ESI-MS positive mode (m/z): calcd for $C_{15}H_{18}N_3O_7^+$ $[M+H]^+$: 352.11. Found: 352.33.

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4(5)-(4-Aminophenyl)-2-(β-D-glucopyranosyl)-imidazole (7d)

Prepared from compound **13c** (0.30 g, 0.42 mmol) according to General procedure III. Purification by column chromatography yielded 0.10 g (66 %) pale yellow amorphous solid. R_f = 0.37 (1:1 $CHCl_3$-MeOH); $[\alpha]_D$ = +2 (c 0.30, MeOH); ^{1}H NMR (360 MHz, D_2O) δ (ppm): 7.49 (2H, d, *J* = 8.2 Hz, aromatics), 7.31 (1H, s, imidazole CH), 6.89 (2H, d, *J* = 8.2 Hz, aromatics), 4.52 (1H, d, *J* = 9.5 Hz, H-1'), 3.95 (1H, dd, *J* = 12.5, 1.8 Hz, H-6'a), 3.83 (1H, dd, *J* = 12.5, 4.2 Hz, H-6'b), 3.75 (1H, pseudo t, *J* = 9.4, 9.0 Hz, H-2' or H-3' or H-4') 3.70-3.60 (3H, m, H-2' and/or H-3' and/or H-4', H-5'); ^{13}C NMR (90 MHz, D_2O) δ (ppm): 145.9 (PhC_4-NH_2), 144.9, 137.5 (imidazole C-2, C-4), 126.2 (2), 122.4, 116.7 (2) (aromatics), 115.3 (imidazole C-5), 80.0, 77.1, 74.7, 72.8, 69.5 (C-1' – C-5'), 60.9 (C-6'). ESI-MS positive mode (m/z): calcd for $C_{15}H_{20}N_3O_5^+$ $[M+H]^+$: 322.14. Found: 322.33.

1-*O*-Acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose[25,26] (9α,β)

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranose (**8**, 5.00 g, 9.25 mmol) was dissolved in anhydrous pyridine (15 mL) and cooled in an ice bath. To this stirred solution Ac_2O (1.31 mL, 13.87 mmol; 1.5 equiv.) was added. The mixture was allowed to warm up to room temperature while stirred, and the transformation was monitored by TLC (1:4 EtOAc-hexane). When the reaction was complete (2 d) the mixture was poured into ice-water and extracted with $CHCl_3$ (3 × 25 mL). The combined organic phase was washed with 10 % aq HCl solution (2 × 20 mL), satd aq $NaHCO_3$ solution (20 mL) and brine (20 mL). The separated organic layer was dried and concentrated to give the title compound as a colourless oil in quantitative yield. This crude anomeric mixture was sufficiently pure for the next step. R_f: 0.36 (1:4 EtOAc-hexane); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.35-7.12 (aromatics), 6.36 (d, *J* = 3.5 Hz, α-H-1), 5.61 (d, *J* = 8.1 Hz, β-H-1), 4.97-4.46 (Ph*CH*$_2$), 3.97-3.55 (sugar protons), 2.12 (s, α-CH_3), 2.03 (s, β-CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 169.5 (α-C=O), 169.3 (β-C=O), 138.7, 138.5, 138.2, 138.1 (2),

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138.0, 137.9, 137.7, 128.6-127.7 (aromatics), 94.1, 84.9, 81.1, 77.3, 75.6 (β-C-1 – β-C-5), 90.1, 81.8, 79.0, 77.0, 72.9 (α-C-1 – α-C-5), 68.2 (β-C-6, α-C-6), 75.8, 75.1 (2), 73.6 (4 × β-Ph*C*H$_2$), 75.8, 75.4, 73.6, 73.3 (4 × α-Ph*C*H$_2$), 21.2 (α-CH$_3$), 21.1 (β-CH$_3$).

2,3,4,6-Tetra-*O*-benzyl-α- and -β-D-glucopyranosyl cyanides (10αβ)

A: Trimethylsilyl cyanide (2.68 mL, 21.45 mmol, 2.5 equiv.) and BF$_3$·Et$_2$O (53 μL, 0.43 mmol, 0.05 equiv.) were added to a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**9α,β**, 5 g, 8.58 mmol) in anhydrous CH$_3$CN (15 mL), and the reaction mixture was stirred at room temperature. After disappearance of the starting material (~15 min, TLC, 1:5 EtOAc-hexane) the solvent was removed, and a solution of the resulting oil in EtOAc (50 mL) was extracted with satd aq NaHCO$_3$ solution (2 × 20 mL) and brine (20 mL). The organic phase was dried, concentrated, and column chromatography (1:7 EtOAc-hexane) yielded **10αβ** (3.82 g, 81 %) as a colourless oil. R$_f$: 0.3 (1:5 EtOAc-hexane); ^{1}H NMR (CDCl$_3$) δ (ppm) 7.35-7.12 (aromatics), 4.96-4.42 (Ph*C*H$_2$), 4.61 (d, *J* = 6.2 Hz, α-H-1), 4.03 (d, *J* = 10.0 Hz, β-H-1), 3.89 (pseudo t, *J* = 9.3, 9.2 Hz, α-H-3), 3.82 (ddd, *J* = 9.4, 3.1, 2.3 Hz α-H-5), 3.78-3.63 (α,β-H-2, α,β-H-4, α,β-H-6, α,β-H-6'), 3.58 (pseudo t, *J* = 9.3, 8.8 Hz, β-H-3), 3.40 (ddd, *J* = 9.5, 3.5, 2.3 Hz, β-H-5). ^{13}C NMR (CDCl$_3$) δ (ppm) 138.3, 138.1, 138.0, 137.8, 137.7, 137.6, 137.3, 136.9, 128.8-127.8 (aromatics), 116.9 (β-C≡N), 115.5 (α-C≡N), 85.6, 83.2, 80.0, 79.7, 77.2, 77.0, 76.4, 76.2, 67.6, 67.0 (α,β-C-1 – α,β-C-5), 68.3, 67.9 (α,β-C-6), 76.0, 75.9 (2), 75.3 (2), 74.0, 73.7, 73.6 (8 × Ph*C*H$_2$).

Analytically pure **10β** could be obtained by crystallisation: an ethanolic solution of **10αβ** (5 mL EtOH/1 g mixture) was kept at 5 °C for 30 min followed by sonication for 5-10 min and this cycle was repeated 5 times. Then, the mixture was kept at rt for 2 days whereupon the crystalline **10β** (1.75 g, 37 %) was obtained. Mp: 85-87 °C (lit.[16] mp: 76-78 °C); [α]$_D$ = +27 (c 1.00, CHCl$_3$) (lit. [α]$_D$ = +29 (c 1, CHCl$_3$);[16] +16.7 (c 1.3, CHCl$_3$);[18] +25 (c 1.5, CHCl$_3$)[20]); ^{1}H

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NMR ($CDCl_3$) δ (ppm): 7.33-7.12 (20H, m, aromatics), 4.93, 4.84 (2 × 1H, 2d, *J* = 10.2 Hz, Ph*CH*$_2$), 4.87, 4.84 (2 × 1H, 2d, *J* = 10.5 Hz, Ph*CH*$_2$), 4.79, 4.54 (2 × 1H, 2d, *J* = 10.7 Hz, Ph*CH*$_2$), 4.60, 4.53 (2 × 1H, 2d, *J* = 12.1 Hz, Ph*CH*$_2$), 4.06 (1H, d, *J* = 9.9 Hz, H-1), 3.77 (1H, pseudo t, *J* = 9.9, 9.2 Hz, H-2), 3.73-3.68 (2H, m, H-6, H-6'), 3.65 (1H, pseudo t, *J* = 9.9, 9.2 Hz, H-4), 3.59 (1H, pseudo t, *J* = 9.2, 9.2 Hz, H-3) 3.42 (1H, ddd, *J* = 9.9, 4.6, 2.6 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ (ppm): 138.1, 137.8, 137.7, 136.9, 128.6-127.8 (aromatics), 116.9 (C≡N), 85.6, 80.0, 79.8, 77.0, 67.6 (C-1 – C-5), 75.9 (2), 75.3, 73.7 (4 × Ph*C*H$_2$), 68.3 (C-6). Anal. Calcd for $C_{35}H_{35}NO_5$ (549.66): C, 76.48; H, 6.42; N, 2.55. Found: C, 76.67; H, 6.46; N, 2.49.

B: To a stirred solution of **8** (50 g, 92.47 mmol) in anhydrous pyridine (150 mL) Ac_2O (13.1 mL, 138.71 mmol; 1.5 equiv.) was added at 0 ^{0}C. The mixture was allowed to warm up to room temperature and stirred until TLC (1:4 EtOAc-hexane) showed total consumption of the starting material (2 d). The reaction mixture was then poured into ice-water and extracted with $CHCl_3$ (3 × 250 mL). The combined organic phase was extracted with 10 % aq HCl solution (2 × 200 mL), satd aq $NaHCO_3$ solution (200 mL) and brine (200 mL), respectively. The separated organic layer was dried over $MgSO_4$, filtered and concentrated to give compound **9α,β**. Traces of pyridine were removed by repeated co-evaporations with toluene. The obtained syrup was dissolved in anhydrous CH_3CN (150 mL) and trimethylsilyl cyanide (28.9 mL, 231.18 mol, 2.5 equiv.) and $BF_3{\cdot}Et_2O$ (571 µL, 4.62 mmol, 0.05 equiv.) were added, and the stirrring was continued at rt. After disappearance of the starting material (~15 min, TLC 1:5 EtOAc-hexane) the solvent was removed. The resulting oil was diluted with EtOAc (500 mL) and extracted with satd aq $NaHCO_3$ solution (2 × 200 mL) and brine (200 mL). The organic phase was dried and concentrated to a syrup from which 18.73 g (37 %) of **10β** was obtained by crystallisation from EtOH as described above.

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_C_-(2,3,4,6-Tetra-_O_-benzyl-β-D-glucopyranosyl)formamidine hydrochloride (11)

A: To a solution of cyanide **10β** (1 g, 1.82 mmol) in a mixture of anhydrous MeOH (5 mL) and $CHCl_3$ (1.5 mL) was added a 1M solution of NaOMe in MeOH (2.73 mL, 2.73 mmol, 1.5 equiv.). The mixture was stirred at rt and monitored by TLC (1:5 EtOAc–hexane). After disappearance of the starting material (1 d) NH_4Cl (0.24 g, 4.55 mmol, 2.5 equiv.) was added, and when TLC (1:1 EtOAc-hexane and 9:1 $CHCl_3$-MeOH) showed complete conversion (1 d) of the intermediate formimidate **12** (R_f = 0.4 in 1:1 EtOAc-hexane) into a product (baseline, 1:1 EtOAc-hexane, R_f = 0.5 in 9:1 $CHCl_3$-MeOH), the solvents were removed. The residue was dissolved in EtOAc (10 mL), extracted with water (2 × 5 mL), dried, and concentrated. The obtained syrup was triturated with Et_2O to give **11** (1.00 g, 91 %) as a white crystalline solid. Mp: 110-112 °C; $[\alpha]_D$ = +35 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 9.84 (2H, s, NH_2), 7.52 (2H, s, NH_2), 7.35-7.14 (20H, m, aromatics), 4.89, 4.84 (2 × 1H, 2d, *J* = 10.8 Hz, Ph*CH*$_2$), 4.86, 4.54 (2 × 1H, 2d, *J* = 10.5 Hz, Ph*CH*$_2$), 4.78, 4.54 (2 × 1H, 2d, *J* = 11.0 Hz, Ph*CH*$_2$), 4.52, 4.44 (2 × 1H, 2d, *J* = 11.8 Hz, Ph*CH*$_2$), 4.27 (1H, d, *J* = 9.4 Hz, H-1), 3.76 (1H, pseudo t, *J* = 8.6, 8.6 Hz, H-3), 3.72 (1H, dd, *J* = 11.7, 3.1 Hz, H-6), 3.66-3.56 (3H, m, H-4, H-5, H-6'), 3.47 (1H, pseudo t, *J* = 9.4, 8.6 Hz, H-2). ^{13}C NMR ($CDCl_3$) δ (ppm): 167.9 (C=N), 137.8, 137.6, 137.3, 136.3, 128.8-127.6 (aromatics), 86.0, 79.4, 78.4, 77.1, 73.3 (C-1 – C-5), 75.5 (2), 75.0, 73.6 (4 × Ph*C*H$_2$), 68.6 (C-6). MS-ESI (*m/z*, positive mode): Calcd. for $C_{35}H_{39}N_2O_5^+$ $[M + H]^+$: 567.29. Found: 567.75. Anal. Calcd for $C_{35}H_{39}ClN_2O_5$ (603.15): C, 69.70; H, 6.52; N, 4.64. Found: C, 69.00; H, 6.68; N, 4.60.

B: 1M NaOMe in MeOH (4.09 mL, 4.09 mmol, 0.75 equiv.) was added to a solution of cyanides **10αβ** (3 g, 5.46 mmol) in a mixture of anhydrous MeOH (15 mL) and $CHCl_3$ (4.5 mL), and the reaction mixture was stirred at rt for 1 d (TLC, 1:5 EtOAc-hexane, R_f = 0.3 and 0.1 for **10α** and **12**, respectively, indicating the significantly poorer reactivity of **10α**). NH_4Cl

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(0.36 g, 6.82 mmol, 1.25 equiv.) was added, and the stirring was continued for an additional 24 h at rt, when TLC (1:1 EtOAc–hexane and 9:1 $CHCl_3$–MeOH) indicated complete conversion of the intermediate formimidate **12** (R_f = 0.4, 1:1 EtOAc–hexane) into a more polar product (baseline in 1:1 EtOAc–hexane, R_f = 0.5 in 9:1 $CHCl_3$–MeOH). The solvents were removed, the residue was dissolved in EtOAc (30 mL) and extracted with water (2 × 15 mL). The organic phase was dried and concentrated to an oil, which on trituration by Et_2O gave a solid which was filtered off and rinsed by Et_2O to remove traces of unreacted **10α**. Yield of the title compound, identical with the material desribed above, was 1.35 g (41 %).

C: Starting from compound **8** (46.4 g, 85.81 mmol) the crude mixture of **10α,β** was obtained as described above. It was then dissolved in a mixture of anhydrous MeOH (250 mL) and $CHCl_3$ (75 mL), a 1M solution of NaOMe in MeOH (64.4 mL, 64.36 mmol, 0.75 equiv.) was added, and the mixture was stirred at rt for 1 d. After that, NH_4Cl (5.74 g, 107.26 mmol, 1.25 equiv.) was added to the reaction mixture, and stirred at rt for additional 24 h. The final product **11** was obtained from this reaction mixture after work-up and crystallization steps identical to those described above to give 20.7 g (40 %) white solid.

Methyl *C*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)formimidate (12)

To a solution of cyanide **10β** (3 g, 5.46 mmol) in a mixture of anhydrous MeOH (15 mL) and $CHCl_3$ (5 mL) was added a 1M solution of NaOMe in MeOH (2.73 mL, 2.73 mmol, 0.5 equiv.). The mixture was stirred at rt and monitored by TLC (1:5 EtOAc-hexane). After total conversion of the starting material (1 d) the mixture was neutralized with a cation exchange resin Amberlyst 15 (H^+ form), then the resin was filtered off and the solvent was removed. The residual syrup was triturated with hexane and the precipitate was filtered off. The obtained white amorphous solid (2.89 g, 91 %) was pure enough for further transformation. R_f = 0.4 (1:1 EtOAc-hexane); $[\alpha]_D$ = +12 (c 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):

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7.72 (1H, broad s, NH), 7.34-7.15 (20H, m, aromatics), 4.90, 4.84 (2 × 1H, 2d, J = 11.1 Hz, PhCH_2), 4.81, 4.56 (2 × 1H, 2d, J = 10.8 Hz, PhCH_2), 4.68, 4.54 (2 × 1H, 2d, J = 10.6 Hz, PhCH_2), 4.59, 4.54 (2 × 1H, 2d, J = 12.3 Hz, PhCH_2), 3.78 (1H, d, J = 9.1 Hz, H-1'), 3.78 (3H, s, OCH_3), 3.72-3.68 (3H, m, H-3', H-6'a, H-6'b), 3.64 (1H, pseudo t, J = 9.4, 9.0 Hz, H-4'), 3.53-3.49 (2H, m, H-2', H-5'); ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm): 170.7 (C=N), 138.5, 138.1, 138.0, 137.8, 128.5-127.7 (aromatics), 86.3, 81.7, 78.9, 77.7, 77.5 (C-1' – C-5'), 75.7, 75.1(2), 73.5 (4 × PhCH_2), 68.8 (C-6'), 53.3 (OCH_3). MS-ESI (*m/z*, positive mode): Calcd. for $C_{36}H_{40}NO_6^+$ $[M + H]^+$: 582.29. Found: 582.58.

4(5)-Phenyl-2-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl)-imidazole (13a) and 1-(2-oxo-2-phenylethyl)-4-phenyl-2-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl)-imidazole (14a)

A: From amidine **11** (0.20 g, 0.33 mmol) and 2-bromo-1-phenylethanone (0.07 g, 0.33 mmol) according to General procedure I. Purification by column chromatography yielded **14a** as the first and **13a** as the second fraction.

Compound **13a**: Yield: 0.16 g (72 %), colourless syrup. R_f = 0.47 (1:1 hexane-EtOAc); $[\alpha]_D$ = +6 (c 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.19 (1H, broad s, NH), 7.64-7.01 (26H, m, aromatics, imidazole CH), 4.97, 4.86 (2 × 1H, 2d, J = 11.1 Hz, PhCH_2), 4.85, 4.50 (2 × 1H, 2d, J = 10.9 Hz, PhCH_2), 4.56 (1H, d, J = 9.3 Hz, H-1'), 4.50, 4.29 (2 × 1H, 2d, J = 10.5 Hz, PhCH_2), 4.47, 4.41 (2 × 1H, 2d, J = 12.1 Hz, PhCH_2), 3.88 (1H, pseudo t, J = 9.3, 9.2 Hz, H-2'), 3.80 (1H, pseudo t, J = 9.2, 9.1 Hz, H-3'), 3.70 (1H, pseudo t, J = 9.3, 9.1 Hz, H-4'), 3.69 (1H, dd, J = 10.4, 2.2 Hz, H-6'a), 3.64 (1H, dd, J = 10.4, 4.4 Hz, H-6'b), 3.57 (1H, ddd, J = 9.3, 4.4, 2.2 Hz, H-5'); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 145.4, 141.4 (imidazole C-2, C-4), 138.7, 138.1, 137.9, 137.6, 135.7, 128.7-125.0 (aromatics), 114.4 (imidazole C-5), 86.5, 81.7, 78.9, 77.8, 75.4 (C-1' – C-5'), 75.7, 75.2, 74.9, 73.5 (4 × PhCH_2),

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69.0 (C-6'). ESI-MS positive mode (m/z): calcd for $C_{43}H_{43}N_2O_5^+$ $[M+H]^+$: 667.32. Found: 667.44.

Compound **14a**: Yield: 19 mg (7 %), colourless syrup. R_f = 0.55 (3:2 hexane-EtOAc); $[\alpha]_D$ = –2 (c 0.50, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm): 7.89, 7.82 (2 × 2H, 2d, *J* = 7.3 Hz in each, aromatics), 7.57 (1H, t, *J* = 7.4 Hz, aromatic), 7.39-7.11 (26H, m, aromatics), 5.60, 5.44 (2 × 1H, 2d, *J* = 18.1 Hz, CO*CH*$_2$), 4.96, 4.84 (2 × 1H, 2d, *J* = 10.9 Hz, Ph*CH*$_2$), 4.81, 4.48 (2 × 1H, 2d, *J* = 10.8 Hz, Ph*CH*$_2$), 4.71, 4.62 (2 × 1H, 2d, *J* = 10.2 Hz, Ph*CH*$_2$), 4.57 (1H, d, *J* = 9.8 Hz, H-1'), 4.37, 4.32 (2 × 1H, 2d, *J* = 12.1 Hz, Ph*CH*$_2$), 3.98 (1H, pseudo t, *J* = 9.8, 9.0 Hz, H-2'), 3.77 (1H, pseudo t, *J* = 9.2, 9.0 Hz, H-3'), 3.64 (1H, pseudo t, *J* = 9.4, 9.2 Hz, H-4'), 3.63 (1H, dd, *J* = 10.4, 2.0 Hz, H-6'a), 3.58 (1H, dd, *J* = 10.4, 4.2 Hz, H-6'b), 3.52 (1H, ddd, *J* = 9.4, 4.2, 2.0 Hz, H-5'); ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm): 192.3 (CO), 144.5, 140.7 (imidazole C-2, C-4), 138.7, 138.3, 138.1 (2), 134.5, 134.3, 134.2-125.1 (aromatics), 118.4 (imidazole C-5), 86.8, 80.7, 79.1, 77.7, 75.6 (C-1' – C-5'), 75.9, 75.2, 74.9, 73.4 (4 × Ph*C*H$_2$), 69.1 (C-6'), 52.3(*C*H$_2$CO). ESI-MS positive mode (m/z): calcd for $C_{51}H_{49}N_2O_6^+$ $[M+H]^+$: 785.36. Found: 785.50.

B: Imidate **12** (0.20 g, 0.34 mmol) and 2-amino-1-phenylethanone hydrochloride (0.12 g, 0.69 mmol) gave 0.08 g of **13a** (33 %) according to General procedure II.

4(5)-(2-Naphthyl)-2-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl)-imidazole (13b) and 1-(2-(2-naphthyl)-2-oxoethyl)-4-phenyl-2-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl)-imidazole (14b)

A: From amidine **11** (0.20 g, 0.33 mmol) and 2-bromo-1-(naphthalen-2-yl)ethanone (0.08 g, 0.33 mmol) according to General procedure I. Purification by column chromatography yielded **14b** as the first and **13b** as the second fraction.

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Compound **13b**: Yield: 0.16 g (69 %), white solid after trituration of the resulting syrup with EtOH. Mp = 150-151 °C; R_f = 0.46 (1:1 hexane-EtOAc), $[\alpha]_D$ = +23 (c 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.43 (1H, br s, NH), 8.21 (1H, s, aromatic), 7.78-7.02 (27H, m, aromatics, imidazole CH), 4.99, 4.87 (2 × 1H, 2d, *J* = 11.0 Hz, Ph*CH*$_2$), 4.86, 4.54 (2 × 1H, 2d, *J* = 10.9 Hz, Ph*CH*$_2$), 4.60 (1H, d, *J* = 9.4 Hz, H-1'), 4.52, 4.30 (2 × 1H, 2d, *J* = 10.3 Hz, Ph*CH*$_2$), 4.46, 4.40 (2 × 1H, 2d, *J* = 12.1 Hz, Ph*CH*$_2$), 3.91 (1H, pseudo t, *J* = 9.4, 9.1 Hz, H-2'), 3.83 (1H, pseudo t, *J* = 9.1, 9.0 Hz, H-3'), 3.71 (1H, pseudo t, *J* = 9.4, 9.0 Hz, H-4'), 3.70 (1H, dd, *J* = 10.4, 2.2 Hz, H-6'a), 3.68 (1H, dd, *J* = 10.4, 4.4 Hz, H-6'b), 3.61 (1H, ddd, *J* = 9.4, 4.4, 2.2 Hz, H-5'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 145.4, 141.5 (imidazole C-2, C-4), 138.7, 138.1, 137.9, 137.6, 133.9, 132.7, 131.9, 128.6-127.7, 126.1, 125.3, 124.1, 123.2 (aromatics), 112.7 (imidazole C-5), 86.6, 81.6, 79.1, 77.9, 75.4 (C-1' – C-5'), 75.8, 75.2, 75.0, 73.5 (4 × Ph*C*H$_2$), 69.1 (C-6'). ESI-MS positive mode (m/z): calcd for $C_{47}H_{45}N_2O_5^+$ $[M+H]^+$: 717.33. Found: 717.42.

Compound **14b**: Yield: 23 mg (8 %), colourless syrup. R_f = 0.49 (3:2 hexane-EtOAc); $[\alpha]_D$ = +7 (c 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.47 (1H, s, aromatic), 8.36 (1H, s, aromatic), 7.99-7.10 (32H, m, aromatics), 5.75, 5.62 (2 × 1H, 2d, *J* = 17.8 Hz, CO*CH*$_2$), 4.98, 4.86 (2 × 1H, 2d, *J* = 11.0 Hz, Ph*CH*$_2$), 4.79, 4.47 (2 × 1H, 2d, *J* = 10.8 Hz, Ph*CH*$_2$), 4.72, 4.66 (2 × 1H, 2d, *J* = 10.3 Hz, Ph*CH*$_2$), 4.67 (1H, d, *J* = 9.8 Hz, H-1'), 4.33, 4.29 (2 × 1H, d, *J* = 12.3 Hz, Ph*CH*$_2$), 4.03 (1H, pseudo t, *J* = 9.8, 9.1 Hz, H-2'), 3.80 (1H, pseudo t, *J* = 9.1, 9.0 Hz, H-3'), 3.66 (1H, pseudo t, *J* = 9.5, 9.0 Hz, H-4'), 3.64 (1H, dd, *J* = 10.2, 2.0 Hz, H-6'b), 3.58 (1H, dd, *J* = 10.2, 4.3 Hz, H-6'a), 3.55 (1H, ddd, *J* = 9.5, 4.3, 2.0 Hz, H-5'); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 192.3 (CO), 144.7, 140.8 (imidazole C-2, C-4), 138.7, 138.2, 138.1, 138.0, 136.1, 134.0, 132.7, 132.6, 131.9, 131.7, 130.1-123.2 (aromatics), 118.9 (imidazole C-5), 86.8, 80.7, 79.2, 77.8, 75.8 (C-1' – C-5'), 75.9, 75.2, 75.0, 73.4 (4 × Ph*C*H$_2$),

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69.1 (C-6'), 52.5 (CH_2CO). ESI-MS positive mode (m/z): calcd for $C_{59}H_{53}N_2O_6^+$ $[M+H]^+$: 885.39. Found: 885.58.

B: Imidate **12** (0.20 g, 0.34 mmol) and 2-amino-1-(naphthalen-2-yl)ethanone hydrobromide (0.18 g, 0.69 mmol) gave 0.12 g of **13b** (47 %) according to General procedure II.

4(5)-(4-Nitrophenyl)-2-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl)-imidazole (13c)

Prepared from amidine **11** (0.20 g, 0.33 mmol) and 2-bromo-1-(4-nitrophenyl)ethanone (0.08 g, 0.33 mmol) according to General procedure I. Purification by column chromatography yielded 0.09 g (36 %) yellow syrup. R_f = 0.42 (1:1 hexane-EtOAc); $[\alpha]_D$ = +34 (c 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.41 (1H, s, NH), 8.14, 7.79 (2 × 2H, d, *J* = 8.7 Hz in each, aromatics), 7.35-6.98 (21H, m, aromatics, imdazole CH), 4.97, 4.89 (2 × 1H, 2d, *J* = 11.0 Hz, Ph*CH*$_2$), 4.87, 4.56 (2 × 1H, 2d, *J* = 10.9 Hz, Ph*CH*$_2$), 4.58 (1H, d, *J* = 9.3 Hz, H-1'), 4.53, 4.32 (2 × 1H, 2d, *J* = 10.5 Hz, Ph*CH*$_2$), 4.45, 4.41 (2 × 1H, 2d, *J* = 12.1 Hz, Ph*CH*$_2$), 3.89 (1H, pseudo t, *J* = 9.3, 9.0 Hz, H-2'), 3.81 (1H, pseudo t, *J* = 9.0, 8.9 Hz, H-3'), 3.71 (1H, pseudo t, *J* = 9.3, 8.9 Hz, H-4') 3.69-3.63 (3H, m, H-5', H-6'a, H-6'b); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 146.2 (2), 140.9 (Ph*C*$_4$-NO_2, imidazole C-2, C-4), 139.3 138.5, 138.0, 137.8, 137.4, 128.6-124.2 (aromatics), 114.8 (imidazole C-5), 86.5, 81.4, 79.0, 77.8, 75.1 (C-1' – C-5'), 75.8, 75.2, 75.0, 73.5 (4 × Ph*C*H$_2$), 69.1 (C-6'). ESI-MS positive mode (m/z): calcd for $C_{43}H_{42}N_3O_7^+$ $[M+H]^+$: 712.30. Found: 712.25.

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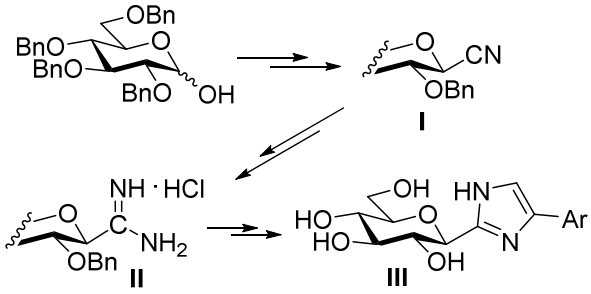

Large scale (up up to 20 g) preparation of **I** and **II** allowed the best inhibitors of glycogen phosphorylase **III** to be synthesized in close to 60 % overall yields from **I**.

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