


 Cite this: *RSC Adv.*, 2016, 6, 94787

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

 Eszter Szennyés,^a Éva Bokor,^a Gyula Batta,^a Tibor Docsa,^b Pál Gergely^b and László Somsák^{*a}

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/BF₃·OEt₂. 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).

 Received 31st August 2016
Accepted 28th September 2016

DOI: 10.1039/c6ra21839c

www.rsc.org/advances

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 GP_a, 280 and 31 nM against rabbit muscle GP_b, 226 and 65 nM against rabbit muscle GP_a 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 growth¹⁰).

The first syntheses of 7 were worked out starting from *O*-perbenzoylated glucopyranosyl cyanide¹¹ 1 as outlined in Scheme 1.^{5,6} The cyclisation of amidine¹² 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 amide¹¹ 4 to imidate¹⁵ 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.

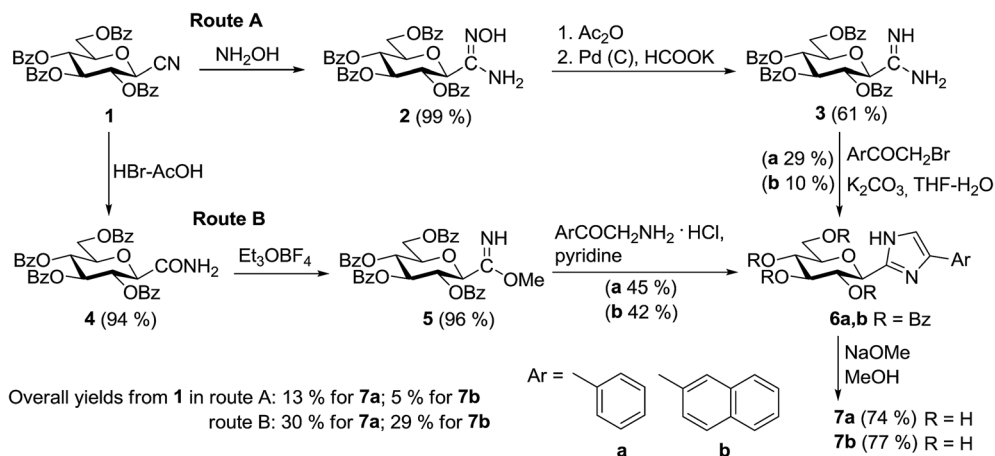
Results and discussion

O-Perbenzylated D-glucopyranosyl cyanides both in α - and β -configurations are known from the literature.¹⁶⁻¹⁹ While the

^aDepartment of Organic Chemistry, University of Debrecen, POB 400, H-4002 Debrecen, Hungary. E-mail: somsak.laszlo@science.unideb.hu; Fax: +36 52512744; Tel: +36 52512900 ext. 22348

^bDepartment of Medical Chemistry, Faculty of Medicine, University of Debrecen, Egyetem tér 1, H-4032 Debrecen, Hungary

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ra21839c



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

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*-acetate¹⁶ or 1-*O*-phosphate¹⁸ 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 cyanide¹¹ followed by standard *O*-perbenzoylation was also reported.²⁰

For the planned syntheses of the target *C*-glucosyl imidazoles several grams of the *O*-perbenzoylated 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 Acetylation of commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**8**) followed by

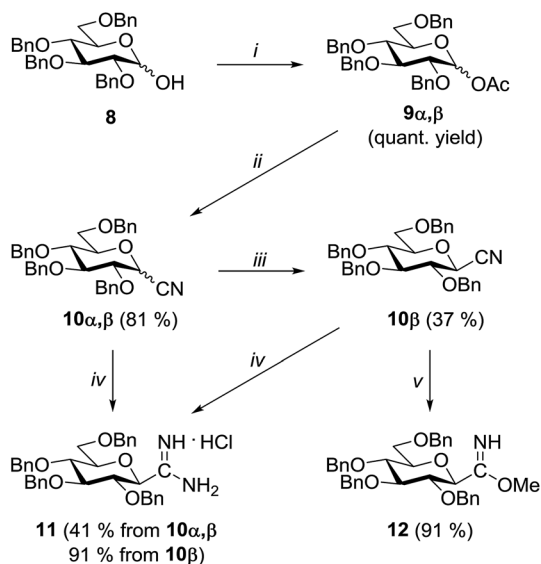
$\text{BF}_3 \cdot \text{OEt}_2$ promoted substitution of the resulting 1-*O*-acetyl-D-glucopyranose **9 $\alpha\beta$** with TMSCN furnished an anomeric mixture of glucosyl cyanides **10 $\alpha\beta$** (α : β ~ 1.25 : 1) in high yield. From the worked-up reaction mixture the pure cyanide **10 β** was separated by crystallisation from EtOH. In this way ~18 g of **10 β** could be obtained from 50 g of **8** without chromatographic purification.

Next, transformations of cyanide **10 β** 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 **10 β** by the addition²¹ of MeO^- ion to the nitrile group (to give the unisolated **12**) followed by treatment²² with NH_4Cl . Imidate **12** was also isolated in high yield by trituration of the worked-up mixture of the first reaction step (**10 β** \rightarrow **12**) with hexane. Amidine **11** could also be obtained directly from **10 $\alpha\beta$** due to the poorer reactivity of **10 α** under the applied conditions. Thus, addition of Et_2O to the reaction mixture, obtained in a consecutive treatment of **10 $\alpha\beta$** by NaOMe and NH_4Cl containing **10 α** 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** \rightarrow **9 $\alpha\beta$** \rightarrow **10 $\alpha\beta$** \rightarrow **11** in 40% overall yield without isolation of the intermediates.

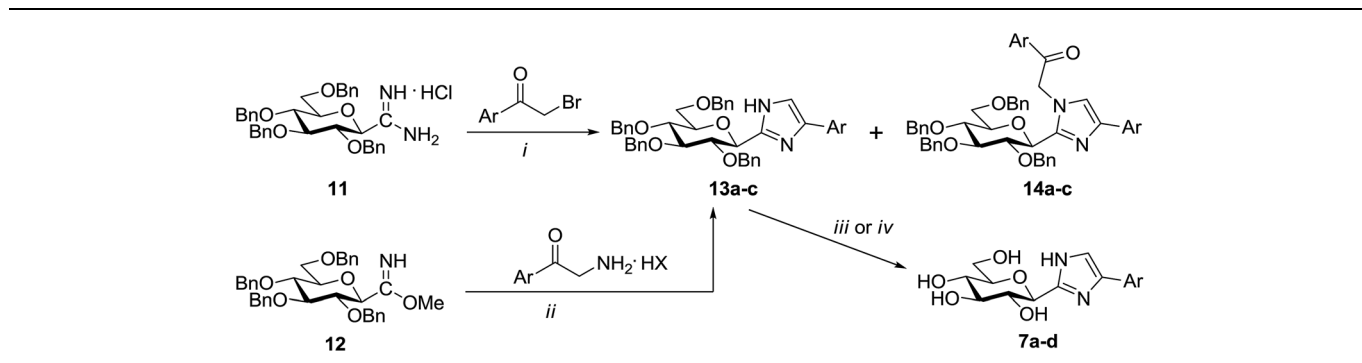
Treatment of amidine **11** with α -bromo-ketones (Table 1, conditions (i)) afforded the desired *O*-perbenzoylated *C*-glucosyl imidazoles **13** in good yields accompanied by small amounts of *N*-aroylmethyl imidazoles **14**. The latter by-products were obviously formed by the reactions of **13**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

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



Scheme 2 Reaction conditions: (i) Ac_2O , dry pyridine, rt; (ii) TMSCN, $\text{BF}_3 \cdot \text{OEt}_2$, dry CH_3CN , rt; (iii) crystallization from EtOH; (iv) 1: NaOMe in MeOH, CHCl_3 , rt, 2: NH_4Cl , rt; (v) NaOMe in MeOH, CHCl_3 , rt.

Table 1 Synthetic routes towards C-glucosyl imidazoles 7^a

		Conditions and yields (%)				
Ar		13	14		7	
a		i	72	7	iii	89
		ii	33	—		
b		i	69	8	iii	Inseparable ^b
		ii	47	—		
c		i	36	Traces	iv	45
d		—	—	—	iii (from 13c)	66

^a (i) THF–H₂O 8 : 1, K₂CO₃, rt; (ii) dry pyridine, rt; (iii) Pd(OH)₂/C, H₂, ccHCl, EtOAc, EtOH, rt; (iv) BF₃·OEt₂, EtSH, CH₂Cl₂, rt. ^b Inseparable from the partially saturated by-product (see text).

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 ¹H-NMR and MS measurements of this mixture revealed that beside *O*-debenzylation partial saturation of the naphthalene ring also took place. Further attempts to selectively cleave the benzyl groups of **13b** under reductive (Pd(OH)₂/C, HCOONH₄, MeOH), oxidative (CrO₃, AcOH; DDQ, CH₂Cl₂, H₂O or MeOH) or other (TMSI, CH₃CN; BBr₃ or BBr₃·SMe₂, CH₂Cl₂) conditions failed. Finally, the treatment of **13b** with ethanethiol in the presence of BF₃·OEt₂ (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 earlier²³ 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 **10b**. Cyanide **10b** and

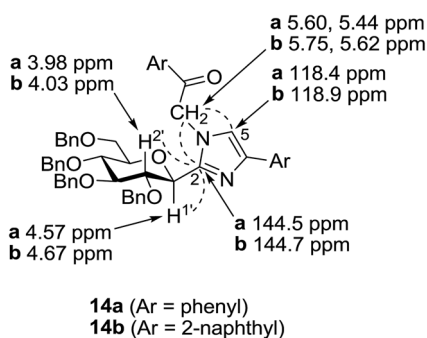


Fig. 1 Structure elucidation of compounds **14a,b** by 2D ¹H–¹³C HMBC measurements (dashed lines indicate the observed cross peaks).

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/BF₃·OEt₂ (**7b,c**). Overall yields for **7a** and **7b** were raised to 58 and 51%, respectively, based on the starting **10b**. 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 in comparison to **7a**.

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 ¹H/¹³C) or Bruker 400 (400/100 MHz for ¹H/¹³C) or Avance II 500 (500/125 MHz for ¹H/¹³C) spectrometers. Chemical shifts are referenced to the internal TMS (¹H), or to the residual solvent signals (¹³C). Proton-signal assignments 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 F₂₅₄ (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), ccH₂SO₄ (5 mL) anisaldehyde (1 mL)). For column chromatography Kieselgel 60 (Merck, particle size 0.063–0.200 mm) was used. MeCN, CHCl₃ and CH₂Cl₂ were distilled from P₄O₁₀ 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 MgSO₄ and concentrated under diminished pressure at 40–60 °C (water bath). 2,3,4,6-Tetra-*O*-benzyl- β -D-glucopyranose (Carbosynth), TMSCN (ACROS), EtSH (TCI), Pd(OH)₂/C (Sigma Aldrich) and BF₃·OEt₂ (Merck) were purchased from the indicated suppliers. 2-Amino-1-arylethanones were synthesized according to literature procedures.^{6,24}

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 K₂CO₃ (0.09 g, 0.66 mmol, 2 equiv.) were stirred in a THF–H₂O 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 CHCl₃–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 MgSO₄, 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 MgSO₄, filtered and the solvent was evaporated, then the residue was purified by column chromatography (3 : 1 hexane–EtOAc).

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 H₂ (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 H₂ atmosphere at rt for overnight it was neutralized with NaHCO₃. 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 CHCl₃–MeOH).

General procedure IV for the removal of *O*-benzyl protecting groups by using EtSH/BF₃·OEt₂

To a solution of the corresponding *O*-perbenzylated β -D-glucopyranosyl imidazole **13** (0.54 mmol) in anhydrous CH₂Cl₂ (10 mL) EtSH (1.6 mL, 21.46 mmol, 40 equiv.) and BF₃·OEt₂ (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 CHCl₃–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 CHCl₃–MeOH).

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 CHCl₃-MeOH); $[\alpha]_D^{25} = +10$ (c 0.50, MeOH); ¹H NMR (400 MHz, CD₃OD) 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'); ¹³C NMR (100 MHz, CD₃OD) δ (ppm): 149.4 (PhC₄-NO₂), 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 C₁₅H₁₈N₃O₇⁺ [M + H]⁺: 352.11. Found: 352.33.

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 CHCl₃-MeOH); $[\alpha]_D^{25} = +2$ (c 0.30, MeOH); ¹H NMR (360 MHz, D₂O) 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'); ¹³C NMR (90 MHz, D₂O) δ (ppm): 145.9 (PhC₄-NH₂), 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 C₁₅H₂₀N₃O₅⁺ [M + H]⁺: 322.14. Found: 322.33.

1-O-Acetyl-2,3,4,6-tetra-O-benzyl-β-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 Ac₂O (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 CHCl₃ (3 × 25 mL). The combined organic phase was washed with 10% aq. HCl solution (2 × 20 mL), satd aq. NaHCO₃ 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); ¹H NMR (CDCl₃) 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 (PhCH₂), 3.97–3.55 (sugar protons), 2.12 (s, α-CH₃), 2.03 (s, β-CH₃); ¹³C NMR (CDCl₃) δ (ppm) 169.5 (α-C=O), 169.3 (β-C=O), 138.7, 138.5, 138.2, 138.1 (2), 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-PhCH₂), 75.8, 75.4, 73.6, 73.3 (4 × α-PhCH₂), 21.2 (α-CH₃), 21.1 (β-CH₃).

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 BF₃·OEt₂ (53 μL, 0.43 mmol, 0.05 equiv.) were added to a solution of 1-O-acetyl-2,3,4,6-tetra-O-benzyl-β-D-glucopyranose (**9α,β**, 5 g, 8.58 mmol) in anhydrous CH₃CN (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. NaHCO₃ 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); ¹H NMR (CDCl₃) δ (ppm) 7.35–7.12 (aromatics), 4.96–4.42 (PhCH₂), 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). ¹³C NMR (CDCl₃) 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 × PhCH₂).

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); $[\alpha]_D^{25} = +27$ (c 1.00, CHCl₃) (lit. $[\alpha]_D^{25} = +29$ (c 1, CHCl₃);¹⁶ +16.7 (c 1.3, CHCl₃);¹⁸ +25 (c 1.5, CHCl₃)²⁰); ¹H NMR (CDCl₃) δ (ppm): 7.33–7.12 (20H, m, aromatics), 4.93, 4.84 (2 × 1H, 2d, $J = 10.2$ Hz, PhCH₂), 4.87, 4.84 (2 × 1H, 2d, $J = 10.5$ Hz, PhCH₂), 4.79, 4.54 (2 × 1H, 2d, $J = 10.7$ Hz, PhCH₂), 4.60, 4.53 (2 × 1H, 2d, $J = 12.1$ Hz, PhCH₂), 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); ¹³C NMR (CDCl₃) 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 × PhCH₂), 68.3 (C-6). Anal. calcd for C₃₅H₃₅NO₅ (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) Ac₂O (13.1 mL, 138.71 mmol; 1.5 equiv.) was added at 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 CHCl₃ (3 × 250 mL). The combined organic phase was extracted with 10% aq. HCl solution (2 × 200 mL), satd aq. NaHCO₃ solution (200 mL) and brine (200 mL), respectively. The separated organic layer was dried over MgSO₄, 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 $\text{BF}_3 \cdot \text{OEt}_2$ (571 μL , 4.62 mmol, 0.05 equiv.) were added, and the stirring 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 **10 β** was obtained by crystallisation from EtOH as described above.

C-(2,3,4,6-Tetra-O-benzyl- β -D-glucopyranosyl)formamidinium hydrochloride (**11**)

A. To a solution of cyanide **10 β** (1 g, 1.82 mmol) in a mixture of anhydrous MeOH (5 mL) and CHCl_3 (1.5 mL) was added a 1 M 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; $[\alpha]_D^{25} = +35$ (c 1.00, CHCl_3); ^1H 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 ($2 \times 1\text{H}$, 2d, $J = 10.8$ Hz, PhCH_2), 4.86, 4.54 ($2 \times 1\text{H}$, 2d, $J = 10.5$ Hz, PhCH_2), 4.78, 4.54 ($2 \times 1\text{H}$, 2d, $J = 11.0$ Hz, PhCH_2), 4.52, 4.44 ($2 \times 1\text{H}$, 2d, $J = 11.8$ Hz, PhCH_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 ($4 \times \text{PhCH}_2$), 68.6 (C-6). MS-ESI (m/z , positive mode): calcd for $\text{C}_{35}\text{H}_{39}\text{N}_2\text{O}_5^+ [\text{M} + \text{H}]^+$: 567.29. Found: 567.75. Anal. calcd for $\text{C}_{35}\text{H}_{39}\text{ClN}_2\text{O}_5$ (603.15): C, 69.70; H, 6.52; N, 4.64. Found: C, 69.00; H, 6.68; N, 4.60.

B. 1 M NaOMe in MeOH (4.09 mL, 4.09 mmol, 0.75 equiv.) was added to a solution of cyanides **10 $\alpha\beta$** (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 **10 α** and **12**, respectively, indicating the significantly poorer reactivity of **10 α**). NH_4Cl (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 **10 α** . Yield of

the title compound, identical with the material described above, was 1.35 g (41%).

C. Starting from compound **8** (46.4 g, 85.81 mmol) the crude mixture of **10 α,β** was obtained as described above. It was then dissolved in a mixture of anhydrous MeOH (250 mL) and CHCl_3 (75 mL), a 1 M 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 **10 β** (3 g, 5.46 mmol) in a mixture of anhydrous MeOH (15 mL) and CHCl_3 (5 mL) was added a 1 M 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); $[\alpha]_D^{25} = +12$ (c 0.60, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.72 (1H, broad s, NH), 7.34–7.15 (20H, m, aromatics), 4.90, 4.84 ($2 \times 1\text{H}$, 2d, $J = 11.1$ Hz, PhCH_2), 4.81, 4.56 ($2 \times 1\text{H}$, 2d, $J = 10.8$ Hz, PhCH_2), 4.68, 4.54 ($2 \times 1\text{H}$, 2d, $J = 10.6$ Hz, PhCH_2), 4.59, 4.54 ($2 \times 1\text{H}$, 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 ($4 \times \text{PhCH}_2$), 68.8 (C-6'), 53.3 (OCH_3). MS-ESI (m/z , positive mode): calcd for $\text{C}_{36}\text{H}_{40}\text{NO}_6^+ [\text{M} + \text{H}]^+$: 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); $[\alpha]_D^{25} = +6$ (c 0.55, CHCl_3); ^1H 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 ($2 \times 1\text{H}$, 2d, $J = 11.1$ Hz, PhCH_2), 4.85, 4.50 ($2 \times 1\text{H}$, 2d, $J = 10.9$ Hz, PhCH_2), 4.56 (1H, d, $J = 9.3$ Hz, H-1'), 4.50, 4.29 ($2 \times 1\text{H}$, 2d, $J = 10.5$ Hz, PhCH_2), 4.47, 4.41 ($2 \times 1\text{H}$, 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

\times PhCH₂), 69.0 (C-6'). ESI-MS positive mode (*m/z*): calcd for C₄₃H₄₃N₂O₅⁺ [M + H]⁺: 667.32. Found: 667.44.

Compound 14a. Yield: 19 mg (7%), colourless syrup. *R*_f = 0.55 (3 : 2 hexane–EtOAc); [α]_D = –2 (c 0.50, CHCl₃); ¹H NMR (360 MHz, CDCl₃) 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, COCH₂), 4.96, 4.84 (2 × 1H, 2d, *J* = 10.9 Hz, PhCH₂), 4.81, 4.48 (2 × 1H, 2d, *J* = 10.8 Hz, PhCH₂), 4.71, 4.62 (2 × 1H, 2d, *J* = 10.2 Hz, PhCH₂), 4.57 (1H, d, *J* = 9.8 Hz, H-1'), 4.37, 4.32 (2 × 1H, 2d, *J* = 12.1 Hz, PhCH₂), 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'); ¹³C NMR (90 MHz, CDCl₃) 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 × PhCH₂), 69.1 (C-6'), 52.3 (CH₂CO). ESI-MS positive mode (*m/z*): calcd for C₅₁H₄₉N₂O₆⁺ [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.

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), [α]_D = +23 (c 0.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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, PhCH₂), 4.86, 4.54 (2 × 1H, 2d, *J* = 10.9 Hz, PhCH₂), 4.60 (1H, d, *J* = 9.4 Hz, H-1'), 4.52, 4.30 (2 × 1H, 2d, *J* = 10.3 Hz, PhCH₂), 4.46, 4.40 (2 × 1H, 2d, *J* = 12.1 Hz, PhCH₂), 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'). ¹³C NMR (100 MHz, CDCl₃) 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 × PhCH₂), 69.1 (C-6'). ESI-MS positive mode (*m/z*): calcd for C₄₇H₄₅N₂O₅⁺ [M + H]⁺: 717.33. Found: 717.42.

Compound 14b. Yield: 23 mg (8%), colourless syrup. *R*_f = 0.49 (3 : 2 hexane–EtOAc); [α]_D = +7 (c 0.55, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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, COCH₂), 4.98, 4.86 (2 × 1H, 2d, *J* = 11.0 Hz, PhCH₂), 4.79, 4.47 (2 × 1H, 2d, *J* = 10.8 Hz, PhCH₂), 4.72, 4.66 (2 × 1H, 2d, *J* = 10.3 Hz, PhCH₂), 4.67 (1H, d, *J* = 9.8 Hz, H-1'), 4.33, 4.29

(2 × 1H, d, *J* = 12.3 Hz, PhCH₂), 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'); ¹³C NMR (100 MHz, CDCl₃) 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 × PhCH₂), 69.1 (C-6'), 52.5 (CH₂CO). ESI-MS positive mode (*m/z*): calcd for C₅₉H₅₃N₂O₆⁺ [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); [α]_D = +34 (c 0.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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, imidazole CH), 4.97, 4.89 (2 × 1H, 2d, *J* = 11.0 Hz, PhCH₂), 4.87, 4.56 (2 × 1H, 2d, *J* = 10.9 Hz, PhCH₂), 4.58 (1H, d, *J* = 9.3 Hz, H-1'), 4.53, 4.32 (2 × 1H, 2d, *J* = 10.5 Hz, PhCH₂), 4.45, 4.41 (2 × 1H, 2d, *J* = 12.1 Hz, PhCH₂), 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); ¹³C NMR (101 MHz, CDCl₃) δ (ppm): 146.2 (2), 140.9 (PhC₄-NO₂, 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 × PhCH₂), 69.1 (C-6'). ESI-MS positive mode (*m/z*): calcd for C₄₃H₄₂N₃O₇⁺ [M + H]⁺: 712.30. Found: 712.25.

Acknowledgements

This work was supported by the Hungarian Scientific Research Fund (OTKA PD 105808). E. Sz. thanks the International Visegrád Fund for a scholarship (V4EaP program, contracts 51300722 and 51401335) as well as Collegium Talentum (Edu-tus College, Tatabánya) for a stipend.

References

- 1 L. Zhang, X. M. Peng, G. L. V. Damu, R. X. Geng and C. H. Zhou, *Med. Res. Rev.*, 2014, **34**, 340–437.
- 2 J. Zeidler, D. Baraniak and T. Ostrowski, *Eur. J. Med. Chem.*, 2015, **97**, 409–418.
- 3 E. De Clercq, *J. Med. Chem.*, 2016, **59**, 2301–2311.
- 4 T. Granier and A. Vasella, *Helv. Chim. Acta*, 1995, **78**, 1738–1746.
- 5 É. Bokor, S. Kun, T. Docsa, P. Gergely and L. Somsák, *ACS Med. Chem. Lett.*, 2015, **6**, 1215–1219.
- 6 A. L. Kantsadi, É. Bokor, S. Kun, G. A. Stravodimos, D. S. M. Chatzileontiadou, D. D. Leonidas, É. Juhász-Tóth,

- A. Szakács, G. Batta, T. Docsa, P. Gergely and L. Somsák, *Eur. J. Med. Chem.*, 2016, **123**, 737–745.
- 7 T. Docsa, K. Czifrák, C. Hüse, L. Somsák and P. Gergely, *Mol. Med. Rep.*, 2011, **4**, 477–481.
- 8 T. Guan, Y. Qian, X. Tang, M. Huang, L. Huang, Y. Li and H. Sun, *J. Neurosci. Res.*, 2011, **89**, 1829–1839.
- 9 W. R. Tracey, J. L. Treadway, W. P. Magee, J. C. Sutt, R. K. McPherson, C. B. Levy, D. E. Wilder, L. J. Yu, Y. Chen, R. M. Shanker, A. K. Mutchler, A. H. Smith, D. M. Flynn and D. R. Knight, *Am. J. Physiol.: Heart Circ. Physiol.*, 2004, **286**, H1177–H1184.
- 10 C. E. Zois, E. Favaro and A. L. Harris, *Biochem. Pharmacol.*, 2014, **92**, 3–11.
- 11 L. Somsák and V. Nagy, *Tetrahedron: Asymmetry*, 2000, **11**, 1719–1727, Corrigendum 2247.
- 12 É. Bokor, A. Fekete, G. Varga, B. Szócs, K. Czifrák, I. Komáromi and L. Somsák, *Tetrahedron*, 2013, **69**, 10391–10404.
- 13 M. Benlifa, S. Vidal, B. Fenet, M. Msaddek, P. G. Goekjian, J.-P. Praly, A. Brunyánszki, T. Docsa and P. Gergely, *Eur. J. Org. Chem.*, 2006, 4242–4256.
- 14 S. Cecioni, O.-A. Argintaru, T. Docsa, P. Gergely, J.-P. Praly and S. Vidal, *New J. Chem.*, 2009, **33**, 148–156.
- 15 É. Bokor, E. Szilágyi, T. Docsa, P. Gergely and L. Somsák, *Carbohydr. Res.*, 2013, **381**, 179–186.
- 16 M.-T. Garcia-Lopez, F. G. De Las Heras and A. S. Félix, *J. Carbohydr. Chem.*, 1987, **6**, 273–279.
- 17 M. G. Hoffmann and R. R. Schmidt, *Liebigs Ann.*, 1985, 2403–2419.
- 18 G. Singh and H. Vankayalapati, *Tetrahedron: Asymmetry*, 2001, **12**, 1727–1735.
- 19 W. Kudelska, *Z. Naturforsch., B: J. Chem. Sci.*, 1998, **53**, 1277–1280.
- 20 S. Sipos and I. Jablonkai, *Carbohydr. Res.*, 2011, **346**, 1503–1510.
- 21 P. Franchetti, S. Marchetti, L. Cappellacci, J. A. Yalowitz, H. N. Jayaram, B. M. Goldstein and M. Grifantini, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 67–69.
- 22 L. Somsák, *Carbohydr. Res.*, 1996, **286**, 167–171.
- 23 E. Ósz, L. Somsák, L. Szilágyi, L. Kovács, T. Docsa, B. Tóth and P. Gergely, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1385–1390.
- 24 W. A. Loughlin, L. C. Henderson, K. E. Elson and M. E. Murphy, *Synthesis*, 2006, 1975–1980.
- 25 R. U. Lemieux, K. B. Hendriks, R. V. Stick and K. James, *J. Am. Chem. Soc.*, 1975, **97**, 4056–4062.
- 26 Z. Han, M. C. Achilonu, P. S. Kendrekar, E. Joubert, D. Ferreira, S. L. Bonnett and J. H. van der Westhuizen, *J. Nat. Prod.*, 2014, **77**, 583–588.