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Note

Synthesis and anticancer activity of novel chiral D-glucose derived bis-imidazoles and their analogs

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Abstract

A series of novel D-glucose derived bis-imidazoles and their analogs, which possess potential in bioorganic and supramolecular chemistry, were designed and synthesized from methyl α-D-glucoside through protection, bis-bromination, N-alkylation and deprotection. All new compounds were characterized by HRMS, ^{1}H, ^{13}C and DEPT NMR spectroscopy as well as elemental analysis. The $^{1}H-^{1}H$ and $^{1}H-^{13}C$ 2D NMR spectra for some compounds were also recorded. Some regular features of ^{13}C and ^{1}H NMR spectra were summarized. The anticancer activity of some compounds was evaluated. © 2001 Published by Elsevier Science Ltd.

Keywords: Carbohydrates; Glucosides; Imidazoles; Organic synthesis; Biological activity; ^{1}H and ^{13}C NMR

1. Introduction

Bis-imidazole compounds not only possess potential as desensitizing agents,[1] as protein analogs[2] and artificial multi-dentate ligands to bind metal ions[3] and as good precursors for the synthesis of imidazolium cyclophanes[4,5] which play wide roles as artificial receptors in molecular recognition, catalysis and self-organization,[6] but also many of them exhibit biological activities as anti-cancer, anti-viral, anti-fungal and anti-bacterial agents.[7,8] Most of these compounds possess antibacterial activity and some possess a stronger ability to kill bacteria than some drugs being used in hospitals.[8] Various types of non-chiral bis-imidazoles such as alkyl,[5h] aralkyl,[2,5g,7a,9] heterocyclic aralkyl,[10] aliphatic multi-ether,[11] bisphenol A diether,[12] aromatic ether and alkanoyl piperazine derivatives have been reported.[1,4,8,13]

It is well known that sugars play important roles in biological systems and this has attracted a great deal of recent attention. Interest in development of sugar derivatives as drugs and artificial receptors[14,15] has been growing in recent years.

This led us to develop chiral sugar derived bis-imidazole compounds as target molecules. These novel molecules possess potential as precursors for the synthesis of sugar imidazolium macrocyclic receptors. In this report we employed D-glucose as a starting material, designed and synthesized a series of novel chiral D-glucose derived bis-imidazole compounds and their analogs (Scheme 1) and investigated their anticancer activity.

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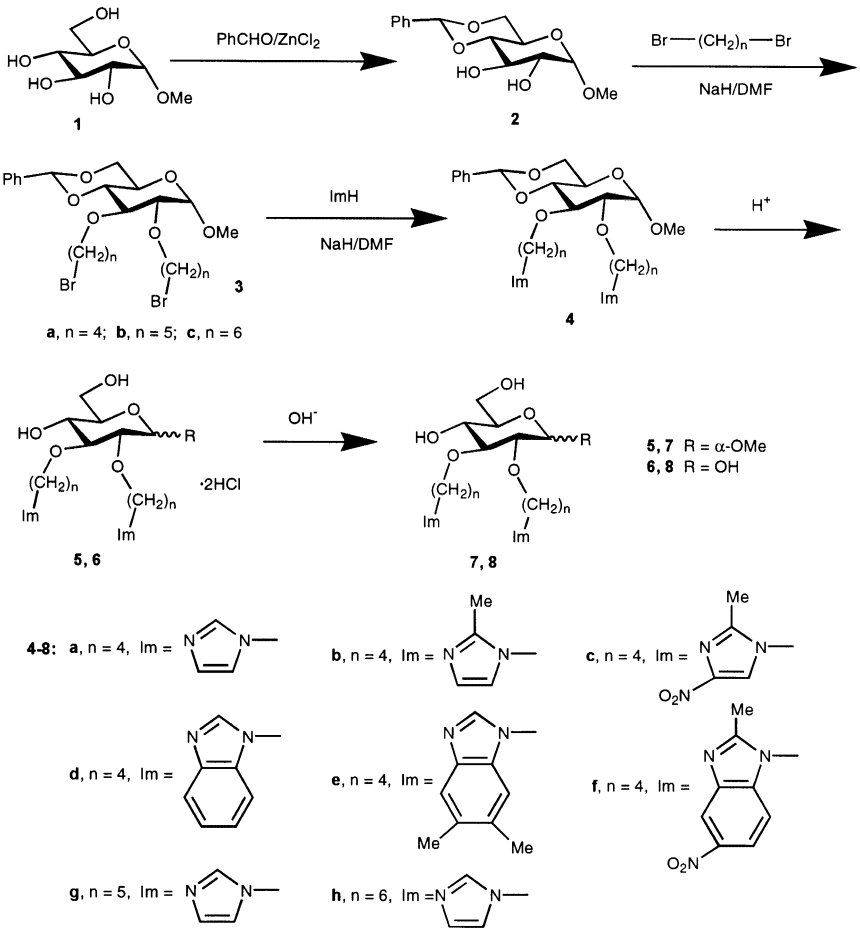

Scheme 1. Synthesis of glucose bis-imidazole compounds and their analogs.

2. Results and discussion

D-*Glucoside bis-alkyl bromides* (**3a**–**c**).—The synthesis of D-glucoside bis-alkyl bromides (**3a**–**c**) was carried out by the reaction of the sodium salt of the bis-hydroxy sugar **2** with an excess of ω-dibromides. The reaction of bis-hydroxy sugar **2** with alkyl dibromides at 0–25 °C readily gave the corresponding bis-bromoalkyl sugars **3a**–**c** as main products, only a small amount of mono-bromoalkyl D-glucoside and cyclization products were obtained. At temperatures higher than 60 °C, this reaction mainly resulted in cyclization products. For example, reaction of compound **2** with 1,4-dibromobutane at 60 °C produced the cyclic compound **9** (Fig. 1) in 58% yield. Under the same reaction conditions, 1,4-dibromohexane gave complex products, while 1,2-dibromoethane or 1,3-dibromopropane surprisingly yielded less of the desired products and most of the sugar was recovered. Reaction of aralkyl dibromide, for example xylylene bromide, with the bis-hydroxy sugar **2** under similar reaction conditions gave mainly cyclic compounds, for instance, compound **10** (Fig. 1) was obtained in 75% yield. Using dibenzo-18-crown-6 and tetrabutylammonium bromide as phase transfer catalysts and sodium hydroxide as the base, the reaction of either alkyl or aralkyl dibromides with bis-hydroxy sugar **2** in *N*,*N*-dimethylformamide only gave one 1 + 1 cyclization products **9** or **10** and no other products were observed. The above facts stress the importance of choosing the proper reac-

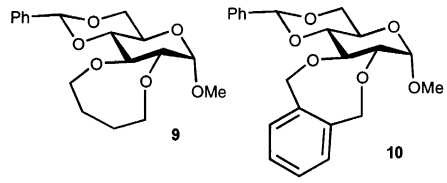

Fig. 1.

tion conditions in order to be able to determine whether open chain or cyclization products are obtained.

D-*Glucoside bis-alkyl imidazoles and their analogs* (**4a**–**h**).—The synthesis of D-glucoside bis-alkyl imidazole **4a** was performed by the dropwise addition of the bis-bromoalkyl D-glucoside (**3a**) to the sodium salt of imidazole. The strong base particularly favors the synthesis of sugar bis-imidazoles. This indicates that the alkylation of the imidazole anions occurs rapidly at the nitrogen atom, while quaternarization byproducts are effectively suppressed. Addition of the sugar dibromide all at once, instead of dropwise, decreased the yield of **4**. Under the same conditions, the reaction of several imidazole derivatives including 2-methylimidazole, and benzimidazole with a series of D-glucoside bis-alkyl bromides (**3a**–**c**) also produced target bis-imidazole and bis-benzimidazole derivatives **4b**, **4d**–**e** and **4g**–**h** in good yields. By contrast, the reaction gave low yields of **4** in the absence of base or when a weak base such as potassium carbonate was used.

Though the bis-imidazoles **4a**–**b**, **4d**–**e** and **4g**–**h** were prepared efficiently by the above method, it was not easy to obtain nitroimidazole derivatives **4c** and **4f** by N-alkylation. Under the above conditions, the reaction of 2-methyl-5-nitroimidazole and its benzo analog gave complicated products. Their anions are insoluble in non-hydroxylic solvents while in hydroxylic solvents the alkyl halides **3** are hydrolyzed or may lead to alkenes. We developed an alternative approach by separating the alkylating agent from the basic medium using a phase transfer catalytic procedure to prepare bis-nitroimidazole and bis-nitrobenzimidazole compounds **4c** and **4f**. This method involves suspension of potassium carbonate in acetonitrile with the nitroimidazole or nitrobenzimidazole, the sugar dibromide **3** and tetrabutylammonium iodide. These reaction conditions gave relatively good yields of the D-glucoside bis-nitroimidazole (**4c**) and bis-nitrobenzimidazole (**4f**). Tetrabutylammonium iodide is effective because the counter cation is only loosely bound to the azole anion.

Deprotection of D-*glucoside bis-imidazoles and their analogs*.—The 4,6-*O*-benzylidene group of the protected sugar bis-imidazoles **4a**–**h** was very easily cleaved with dilute hydrochloric acid, acetic acid or trifluoroacetic acid to afford the partially deprotected methyl α-D-glucoside bis-imidazoles (**5a**–**h**) in almost quantitative yields. The deprotection of the methoxy group required stronger acid concentration, higher reaction temperature and longer hydrolysis time. Concentrated hydrochloric acid–water (2/1, v/v) at 60 °C could deprotect the methoxy group and afford the totally deprotected sugar bis-imidazoles, but different sugar bis-imidazole compounds displayed very different results. For example, the totally deprotected compound **6a** was obtained from **4a** in excellent yield, while under the same reaction conditions **4c** produced a low yield of **6c**, which is difficult to purify. Moreover, as expected, the ^{1}H, ^{13}C and DEPT NMR spectra clearly suggest that the fully deprotected sugar bis-imidazole is a mixture containing α and β anomers. The ^{1}H NMR signals indicated that the amount of these two configurations in the mixture is about equal.[16]

For the deprotection of the sugar bis-imidazole derivatives **4a**–**h**, if hydrochloric acid is used as the deprotecting reagent, the workup is very simple. After the reaction is complete, the solvents were evaporated and the residue was washed with petroleum ether (30–60 °C) to remove benzaldehyde and this afforded the pure hydrochlorides **5** or **6** of deprotected sugar bis-imidazole compounds. These hydrochloric acid salts increase the stability of the deprotected sugar bis-imidazole, and also result in good solubility of the products in water. This high solubility in water is useful in biological activity tests. However, if trifluoroacetic acid is employed as the hydrolytic reagent, due to the formation of trifluoroacetic acid salt, it was very difficult to remove completely trifluoroacetic acid in order to obtain the pure sugar bis-imidazoles.

The salts **5** and **6** were neutralized with ammonium hydroxide to produce the corresponding free D-glucose bis-imidazoles (**7** and **8**). The imidazoles **7** and **8** were soluble in water, but their solubility in water is much lower than that of their salts **5** and **6**. Chloro-

form is not very effective to extract them from water. Instead, after neutralization the mixture was evaporated to dryness, and the solid residue was washed with chloroform. The combined chloroform washings were concentrated to afford pure compounds **7** and **8**. It is advisable to keep compounds **5** and **6** rather than compounds **7** and **8** for long-time storage.

^{13}C NMR spectra.—^{13}C NMR spectra of **3**–**8** were consistent with the assigned structures. When the ^{13}C chemical shifts of **3** are compared with those of the unsubstituted methyl α-D-glucoside (**2**), the bromoalkyl substituted D-glucosides **3a**–**c** display a downfield shift for the C-2, C-3, C-4 and C-6 signals, and upfield shifts for all other sugar carbons. The magnitude of these shifts is dependent on their positions in the D-glucosides. When the Br atoms of the bis-bromoalkyl D-glucosides (**3a**–**c**) were replaced by an imidazolyl group, the resulting bis-imidazole D-glucosides and their analogs **4a**–**h** enhance a small upfield shift for almost all the methoxy carbons, C-6, C-5 and C-4, as well as most of C-2 and C-1 signals. The chemical shift pattern (ppm) was observed as C-1 > C-4 > C-2 > C-3 > C-6 > C-5 > OMe–C.[17]

The deprotected D-glucose derivatives **5a**–**h** and **6**–**8a** display a slightly different ^{13}C chemical shift pattern with their chemical shifts (ppm) in the order C-1 > C-4 > C-2 > C-3 > C-5 > C-6 > OMe–C.[17] Compounds **5a**–**h** showed large upfield shifts for C-3 (6.47–6.78ppm) and C-6 (8.42 ~ 8.60ppm), while C-5 showed a large downfield shift (6.85–7.01ppm) compared to **4**. For the totally deprotected bis-imidazole D-glucoside hydrochloride (**6a**), ^{13}C and DEPT NMR spectra gave two sets of ^{13}C data for the D-glucose moiety, indicating the presence of both α and β configurations. Compared with the β configuration of **6a**, almost all these corresponding D-glucose carbons of α configuration of **6a** exhibit upfield chemical shifts.[18] D-Glucose bis-imidazole dihydrochlorides (**5a** and **6a**) show a higher field chemical shifts as compared to corresponding free compounds **7a** and **8a**.

All imidazolyl groups in the bis-imidazole D-glucosides showed a ^{13}C chemical shift sequence: C-2 > C-4 > C-5. The presence of a 2-methyl group in **4b**–**c** and **5b**–**c** resulted in large downfield chemical shifts of the imidazolyl 2-carbons, while the nitro group cause a large downfield shift (> 15 ppm) for the C-4 signal in **4c** and **5c**. Though the substitutents affect the ^{13}C chemical shifts of the imidazolyl ring in D-glucose bis-imidazole compounds, all imidazolyl ^{13}C signals appear in a similar chemical shift sequence. However, for ^{13}C NMR spectra of benzimidazolyl compounds a different situation was observed. For the benzimidazolyl compounds **4d**–**e** and **5d**–**e** the chemical shifts (ppm) are C-2 > C-9 > C-8 > C-5 > C-6 > C-4 > C-7, while the 2-methyl-5-nitrobenzimidazolyl ^{13}C signals in **4f** and **5f** are in the order C-8 > C-5 > C-2 > C-9 > C-6 > C-7 > C-4. No large differences are found in ^{13}C chemical shifts for all the corresponding OCH_2, $BrCH_2$ and NCH_2 groups in various D-glucoside derivatives.

^{1}H NMR spectra.—In comparison with the bis-hydroxy D-glucoside (**2**), the 2,3-substituted bis-bromoalkyl D-glucosides (**3a**–**c**) show small downfield shifts for H-1 (0.13–0.17 ppm), H-4 (0.06–0.08 ppm), H-5 (0.04–0.07 ppm), equatorial H-6_{eq} (0.02–0.05 ppm), axial H-6_{ax} (0.05–0.11 ppm), and OMe–H (0.04–0.08 ppm) and show only significant upfield shifts for H-2 (0.19–0.20 ppm) and H-3 (0.20–0.22 ppm). All the anomeric H-1 signals in **4a**–**h** give small coupling constants *J* values (3.0–3.6 Hz), this demonstrating that these D-glucose derivatives possess the α configuration. Thus, substitution does not result in a change of the α-D-glucoside configuration.

In D-glucosides **5a**–**h**, all H-1 protons display significant downfield signals (0.07–0.29 ppm) and all equatorial H-6_{eq} give large upfield shifts (between 0.27 and 0.46 ppm). The totally deprotected D-glucose bis-imidazole (**6a**) showed two types of anomeric H-1 signals in a 1:1 ratio at 5.36 and 4.65 ppm, *J* 2.6 and 8.1 Hz, respectively. This clearly indicates two configurations for **6a**, the small *J* value belonging to the α configuration, and the large *J* value to the β configuration. Compared with the protected compound **4a**, the H-1 signal for the α configuration of **6a** displays a large downfield shift (0.69 ppm), while the 1-proton

for the β configuration gave no significant upfield shift. Compounds **7a** and **8a** showed higher field chemical shifts of the 1-proton than their corresponding hydrochlorides **5a** and **6a**.

The proton chemical shifts (ppm) of imidazolyl groups are in the order H-2 > H-4 > H-5. The deprotected hydrochloride compounds **5a**–**c**, **5g**–**h** and **6a** give large downfield shifts compared to **4a**–**c** and **4g**–**h** or to **7a** and **8a**. For benzimidazolyl protons, the chemical shifts (ppm) order is H-2 > H-4 > H-7 > H-5 > H-6 > Me–H. The protons of all the 2-position OCH_2 groups show a smaller chemical shift than those of 3-position OCH_2 groups, whereas, the ^1H spectra of 2-position $BrCH_2$ and NCH_2 groups (linked via a carbon bridge to the D-glucoside) display a larger chemical shift than those of 3-position $BrCH_2$ and NCH_2 groups.

Biological activity.—Anticancer activity of D-glucose derived bis-imidazoles **5a**–**f** and **6a** was evaluated at the National Institute of Health (NIH) Bethesda, MD, USA. The compounds were tested over a range of concentrations (10^{-4}–10^{-8} M). Of these seven compounds, only D-glucose bis(5,6-dimethyl)-benzimidazole hydrochloride derivative **5e** showed significant activity in three cell lines, at one dose essay: NCI-H460 (lung cancer) 13% cell growth (reduced from 100), in MCF7 (breast) 2%, in SF-268 (CNS) essay −70%. Other biological activities are being tested.

Conclusions.—In summary, we have successfully developed a practical method for the synthesis of a series of novel chiral D-glucose derived bis-imidazoles (**4**–**8**), have summarized their regular features of ^1H and ^{13}C NMR spectra and have evaluated their anticancer activities. Carefully controlled conditions are necessary to obtain the bis-bromoalkyl derivative **3** in order to avoid formation of cyclization products. As expected, deprotection of the α-D-glucoside **4a** leads to a mixture of α and β anomers **6a** in a 1:1 ratio. Further applications, for instance, as multidentates to bind metal ions and as precursors for synthesis of gluco-imidazolium macrocycles, are currently under investigation.

3. Experimental

General methods.—All air- and moisture-sensitive reactions were carried out in flame-dried, Ar-flushed, two necked flasks sealed with rubber septa, and the reagents were introduced with a syringe. Tetrahydrofuran (THF) was freshly distilled from sodium–benzophenone. *N*,*N*-Dimethylformamide was distilled from barium oxide after it was dried by solid potassium hydroxide. Chromatography was done on E. Merck silica gel 60 (230–400 mesh), and pre-coated E. Merck Silica Gel plates (60 F_{254}) were used for thin-layer chromatography (TLC). Analytical TLC was visualized with I_2 and UV light, or by spraying the plates with (5:100, g/g) phospho-molybdic acid–EtOH or (5:100, g/g) $KMnO_4$–EtOH and briefly heating. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300, 600 or Varian-500 instrument with Me_4Si as the internal standard; Ph = phenyl ring, Im = imidazolyl ring, Bim = benzimidazolyl ring. Coupling constants were determined directly from ^1H NMR spectra. Mass spectra (CI or FAB) were measured on a Finnigan MAT 4510 or Autospec spectrometer. Melting points were determined on a Electrothermal Digital melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 141 or Dip-1000 digital polarimeter with a path length of 0.1 or 0.5 dm. The concentration for optical rotation is given in g/100 mL. Methyl 4,6-*O*-benzylidene α-D-glucopyranoside (**2**) was prepared from methyl α-D-glucopyranoside (**1**).[19] All other chemicals and reagents were obtained from commercial suppliers and used without further purification.

Methyl 2,3-O-*bis(4-bromobutyl)-4,6*-O-*benzylidene-α*-D-*glucopyranoside* (**3a**).—To a well-stirred suspension of NaH (200 mg 60%, 5 mmol) in dry DMF (5 mL), solid methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**2**) (400 mg, 1.4 mmol) was added slowly as a powder. The resulting mixture was stirred for 60 min, and then cooled to 0 °C with ice. 1,4-Dibromobutane (5 mL) was added. After 4 h, the reaction was allowed to reach 60 °C until the reaction was complete (TLC, 100:1 $CHCl_3$–acetone). Ice-water (50 g) was added

and the mixture was extracted with $CHCl_3$ (2×40 mL). The combined $CHCl_3$ solutions were washed with water, dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using (100:1–5) $CHCl_3$–acetone as eluent to give methyl 2,3-*O*-bis(4-bromobutyl)-α-D-glucoside (**3a**) as an oil (490 mg, 63.6%); $[\alpha]_D^{24}$ +36.57° (*c* 7.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.46 (m, 2 H, Ph H-2,6), 7.38–7.35 (m, 3 H, Ph H-3,4,5), 5.53 (s, 1 H, Ph–C*H*), 4.82 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.27 (dd, 1 H, $J_{6eq,6ax}$ 9, $J_{5,6a}$ 3.7 Hz, H-6_{eq}), 3.85–3.65 (m, 7 H, 2 OCH_2, H-3, H-5 and H-6_{ax}), 3.58–3.43 (m, 6 H, H-4, BrCH_2, OCH_3), 3.37–3.33 (m, 3 H, H-2 and BrCH_2), 2.01–1.87 (m, 4 H, CH_2), 1.79–1.65 (m, 4 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.36 (Ph C-1), 128.98 (Ph C-4), 128.26 (Ph C-3,5), 126.03 (Ph C-2,6), 101.38 (Ph–*C*H), 98.78 (C-1), 82.03 (C-4), 80.33 (C-2), 78.23 (C-3), 72.11 (O*C*H_2), 70.95 (O*C*H_2), 69.07 (C-6), 62.37 (C-5), 55.33 (O*C*H_3), 33.76, 33.58 (*BrC*H_2), 29.61, 29.48, 28.84, 28.62 (CH_2); CIHRMS, *m*/*z* 550.0532 $[M]^+$ ($C_{22}H_{32}Br_2O_6$ requires 550.0566). Anal. Calcd for $C_{22}H_{32}Br_2O_6$: C, 47.84; H, 5.84. Found: C, 47.79; H, 5.84.

*Methyl 2,3-*O*-bis(5-bromopentyl)-4,6-*O*-benzylidene-α-*D*-glucopyranoside* (**3b**).—Compound **3b** was prepared according to the procedure for **3a** from 1,5-dibromo pentane (5 mL), the bis-hydroxy sugar **2** (800 mg, 2.83 mmol), NaH (500 mg 60%, 12.5 mmol) and DMF (5 mL). The pure 2,3-*O*-bis(5-bromopentyl) sugar (**3b**) (1.25 g, 76.4%,) was obtained as an oil; $[\alpha]_D^{25}$ +39.74° (*c* 7.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.46 (m, 2 H, Ph H-2,6), 7.38–7.35 (m, 3 H, Ph H-3,4,5), 5.52 (s, 1 H, Ph–C*H*), 4.80 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.26 (dd, 1 H, $J_{6eq,6ax}$ 9, $J_{5,6eq}$ 3.8 Hz, H-6_{eq}), 3.83–3.63 (m, 7 H, 2OCH_2, H-3, H-5 and H-6_{ax}), 3.48 (t, $J_{4,5}$ 9 Hz 1 H, H-4), 3.42 (s, 3 H, OCH_3), 3.40 (t, 6.6 Hz, 2 H, BrCH_2), 3.32 (dd, 1 H, H-2), 3.28 (t, 6.9 Hz, 2 H, BrCH_2), 1.92–1.41 (m, 12 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.45 (Ph C-1), 128.95 (Ph C-4), 128.22 (Ph C-3,5), 126.05 (Ph C-2,6), 101.35 (Ph–*C*H), 98.92 (C-1), 81.95 (C-4), 80.44 (C-2), 78.23 (C-3), 72.84 (O*C*H_2), 71.68 (O*C*H_2), 69.09 (C-6), 62.40 (C-5), 55.32 (O*C*H_3), 33.85, 33.77 (Br*C*H_2), 32.55, 29.38, 29.20, 24.82, 24.73 (*C*H_2); CIHRMS, *m*/*z* 579.0913 $[M+H]^+$ ($[C_{24}H_{36}Br_2O_6+H]$ requires 579.0957). Anal. Calcd for $C_{24}H_{36}Br_2O_6$: C, 49.67; H, 6.25. Found: C, 49.77; H, 6.21.

*Methyl 2,3-*O*-bis(6-bromohexyl)-4,6-*O*-benzylidene-α-*D*-glucopyranoside* (**3c**).—Compound **3c** was prepared according to the procedure reported for the preparation of **3a**. Starting from 1,6-dibromohexane (15 mL), the bis-hydroxy sugar **2** (1.2 g, 4.25 mmol), NaH (1.0 g 60%, 25 mmol) and DMF (10 mL), the pure 2,3-*O*-bis(6-bromohexyl) sugar (**3c**) (1.82 g, 70.6%) was obtained as an oil; $[\alpha]_D^{22}$ +37.57° (*c* 7.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.44 (m, 2 H, Ph H-2,6), 7.36–7.31 (m, 3 H, Ph H-3,4,5), 5.50 (s, 1 H, Ph–C*H*), 4.78 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.24 (dd, 1 H, $J_{6eq,6ax}$ 9.45, $J_{5,6eq}$ 3.9 Hz, H-6_{eq}), 3.80–3.59 (m, 7 H, 2OCH_2, H-3, H-5 and H-6_{ax}), 3.46 (t, 9 Hz, 1 H, H-4), 3.40 (s, 3 H, OCH_3), 3.37 (t, 6.9 Hz, 2 H, BrCH_2), 3.32 (dd, 1 H, H-2), 3.28 (t, 6.9 Hz, 2 H, BrCH_2), 1.92–1.41 (m, 16 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.52 (Ph C-1), 128.89 (Ph C-4), 128.17 (Ph C-3,5), 126.05 (Ph C-2,6), 101.29 (Ph–*C*H), 98.95 (C-1), 81.95 (C-4), 80.46 (C-2), 78.23 (C-3), 73.03 (O*C*H_2), 71.80 (O*C*H_2), 69.08 (C-6), 62.40 (C-5), 55.29 (O*C*H_3), 33.86, 33.83 (Br*C*H_2), 32.79, 32.73, 30.07, 29.86, 28.00, 27.99, 27.94, 25.82, 25.18 (*C*H_2); CIHRMS *m*/*z* 607.1280 $[M+H]^+$ ($[C_{26}H_{40}Br_2O_6+H]$ requires 607.1270). Anal. Calcd for $C_{26}H_{40}Br_2O_6$: C, 51.33; H, 6.63. Found: C, 51.19; H, 6.59.

*Methyl 2,3-*O*-bis[4-(*N*-imidazolyl)butyl]-4,6-*O*-benzylidene-α-*D*-glucopyranoside* (**4a**).—To a well-stirred suspension of NaH (670 mg 60%, 16.7 mmol) in dry DMF (5 mL), imidazole (680 mg, 10 mmol) was added slowly. The resulting mixture was stirred for 20 min, and then allowed to rise to 50–60 °C. A solution of D-glucoside dibromide (**3a**, 1.1 g, 2 mmol) in THF (20 mL) was added dropwise for 3–5 h. After the reaction was complete, ice-water (30 mL) was added. The mixture was extracted with $CHCl_3$ (2×30 mL). The organic layer was combined, dried with Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column

chromatography on silica gel using CH_2Cl_2–MeOH as eluent affording the pure D-glucoside bis-imidazole (**4a**) as a syrup (605 mg, 57.5%); $[\alpha]_D^{25}$ +20.11° (*c* 9.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 (s, 1 H, Im H-2), 7.33–7.32 (m, 2 H, Ph H-2,6), 7.23–7.20 (m, 4 H, Ph H-3,4,5 and Im H-2), 6.90 (bs, 1 H, Im H-4), 6.85 (bs, 1 H, Im H-4), 6.78 (bs, 1 H, Im H-5), 6.64 (bs, 1 H, Im H-5), 5.38 (s, 1 H, Ph–C*H*), 4.67 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.13 (dd, 1 H, $J_{6eq,6ax}$ 10, $J_{5,6eq}$ 4.5 Hz, H-6_{eq}), 3.81 (t, 7 Hz, 2 H, NCH_2), 3.67–3.63 (m, 4 H, H-5, NCH_2, and one proton of OCH_2), 3.60–3.56 (m, 3 H, H-3, H-6_{ax} and one proton of OCH_2), 3.49–3.46 (m, 2 H, OCH_2), 3.36 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9 Hz, H-4), 3.29 (s, 3 H, OCH_3), 3.20 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 1.72–1.61 (m, 4 H, CH_2), 1.43–1.40 (m, 2 H, CH_2), 1.37–1.33 (m, 2 H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 137.33 (Ph C-1), 136.99 (Im C-2), 136.87 (Im C-2), 129.11 (Im C-4), 129.02 (Ph C-4), 128.93 (Im C-4), 128.20 (Ph C-3,5), 126.02 (Ph C-2,6), 118.79 (Im C-5), 118.72 (Im C-5), 101.44 (Ph–*C*H), 98.49 (C-1), 81.80 (C-4), 80.22 (C-2), 78.11 (C-3), 72.12 (O*C*H_2), 70.78 (O*C*H_2), 68.94 (C-6), 62.29 (C-5), 55.21 (O*C*H_3), 46.61, 46.49 (N*C*H_2), 27.92, 27.78, 26.92, 26.84 (*C*H_2); CIHRMS *m*/*z* 527.2870 $[M+H]^+$ ($[C_{28}H_{38}N_4O_6 + H]$ requires 527.2860). Anal. Calcd for $C_{28}H_{38}N_4O_6$: C, 63.86; H, 7.27; N, 10.64. Found: C, 63.88; H, 7.26; N, 10.69.

*Methyl 2,3-*O*-bis[4-(*N*-(2-methyl)imidazolyl)-butyl]-4,6-*O*-benzylidene-α-*D*-glucopyranoside* (**4b**).—Prepared according to the procedure reported for **4a**. Starting from NaH (800 mg 60%, 20 mmol), the sugar dibromide **3a** (555 mg, 1.01 mmol) and 2-methylimidazole (500 mg, 6.0 mmol), the pure D-glucoside bis-methylimidazole (**4b**, 296 mg, 52.9%) was obtained as a syrup; $[\alpha]_D^{24}$ +37.63° (*c* 16.0, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.30 (m, 2 H, Ph H-2,6), 7.22–7.20 (m, 3 H, Ph H-3,4,5), 6.75 (bs, 1 H, Im H-4), 6.70 (d, *J* 6.00 Hz, 2 H, Im H-4,5), 6.55 (bs, 1 H, Im H-5), 5.38 (s, 1 H, Ph–C*H*), 4.68 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.13 (dd, 1 H, $J_{6eq,6ax}$ 10, $J_{5,6eq}$ 3.9 Hz, H-6_{eq}), 3.71 (t, 7 Hz, 2 H, NCH_2), 3.68–3.53 (m, 7 H, H-3, H-5, H-6_{ax}, OCH_2, NCH_2), 3.49 (t, 6 Hz, 2 H, OCH_2), 3.36 (t, 1 H, $J_{3,4} = J_{4,5}$ 9 Hz, H-4), 3.29 (s, 3 H, OCH_3), 3.21 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 2.23 (s, 3 H, Im 2–CH_3), 2.13 (s, 3 H, Im 2–CH_3), 1.67–1.62 (m, 4 H, CH_2), 1.48–1.37 (m, 4 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.16, 144.10 (Im C-2), 137.27 (Ph C-1), 128.99 (Ph C-4), 128.17 (Ph C-3,5), 126.82, 126.62 (Im C-4), 125.98 (Ph C-2,6), 118.99, 118.88 (Im C-5), 101.42 (Ph–*C*H), 98.48 (C-1), 81.76 (C-4), 80.26 (C-2), 78.14 (C-3), 72.24 (O*C*H_2), 70.85 (O*C*H_2), 68.93 (C-6), 62.27 (C-5), 55.20 (O*C*H_3), 45.67, 45.54 (N*C*H_2), 27.49, 27.40, 27.01, 26.94 (*C*H_2), 12.91, 12.81 (Im 2–*C*H_3); CIHRMS *m*/*z* 555.3170 $[M+H]^+$ ($[C_{30}H_{42}N_4O_6 + H]$ requires 555.3183). Anal. Calcd for $C_{30}H_{42}N_4O_6$: C, 64.96; H, 7.63; N, 10.10. Found: C, 64.85; H, 7.67; N, 10.18.

*Methyl 2,3-*O*-bis[4-(*N*-(2-methyl-4-nitro)-imidazolyl)butyl]-4,6-*O*-benzylidene-α-*D*-gluco-pyranoside* (**4c**).—A mixture of 2-methyl-5-nitroimidazole (162 mg, 1.2 mmol), dry potassium carbonate (677 mg, 4.8 mmol), the D-glucoside dibromide **3a** (316 mg, 0.57 mmol), tetrabutylammonium iodide (50 mg) and MeCN (5 mL) was stirred at 80 °C. After the reaction was complete (TLC, EtOAc), the mixture was cooled and water (30 mL) was added. The resulting solution was extracted with $CHCl_3$ (3 × 30 mL). All the combined $CHCl_3$ solutions were washed with water, dried with anhyd $MgSO_4$ and then concentrated under reduced pressure. The remaining crude product was subjected to column chromatography on silica gel using CH_2Cl_2–MeOH as eluent affording the corresponding pure desired bis-nitroimidazole **4c** as a syrup (248 mg, 67.4%); $[\alpha]_D^{26}$ +26.58° (*c* 15.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (s, 1 H, Im H-5), 7.54 (s, 1 H, Im H-5), 7.43–7.41 (m, 2 H, Ph H-2,6), 7.34–7.31 (m, 3 H, Ph H-3,4,5), 5.51 (s, 1 H, Ph–C*H*), 4.85 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.26 (dd, 1 H, $J_{6eq,6ax}$ 9, $J_{5,6eq}$ 3.9 Hz, H-6_{eq}), 4.01 (t, *J* 7 Hz, 2 H, NCH_2), 3.81–3.73 (m, 7 H, NCH_2, OCH_2, H-3, H-5 and H-6_{ax}), 3.68 (t, *J* 6 Hz, 2 H, OCH_2), 3.51 (t, 1 H, $J_{3,4} = J_{4,5}$ 9 Hz, H-4), 3.44 (s, 3 H, OCH_3), 3.38 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 2.42 (s, 3 H, Im 2–CH_3), 2.27 (s, 3 H, Im 2–CH_3), 1.92–1.77 (m, 4 H, CH_2), 1.65–1.47 (m, 4 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.20, 146.07 (Im C-2), 144.73, 144.62 (Im C-4), 137.23 (Ph C-1), 129.22 (Ph C-4), 128.26 (Ph C-3,5), 126.04 (Ph C-2,6), 120.13, 119.79

(Im C-5), 101.70 (Ph–*C*H), 98.35 (C-1), 81.55 (C-4), 80.36 (C-2), 78.31 (C-3), 72.08 (O*C*H_2), 70.10 (O*C*H_2), 68.97 (C-6), 62.33 (C-5), 55.22 (O*C*H_3), 46.79, 46.64 (N*C*H_2), 27.35, 27.03, 26.67, 26.49 (*C*H_2), 13.02, 12.89 (Im 2–*C*H_3); CIHRMS *m/z* 645.2864 $[M+H]^+$ ($[C_{30}H_{40}N_6O_{10}+H]$ requires 645.2884). Anal. Calcd for $C_{30}H_{40}N_6O_{10}$: C, 55.89; H, 6.25; N, 13.04. Found: C, 55.98; H, 6.23; N, 12.99.

Methyl 2,3-O-*bis[4-(*N-*benzimidazolyl)-butyl]-4,6*-O-*benzylidene*-α-D-*glucopyranoside* (**4d**).—Prepared according to the procedure reported for the synthesis of **4a**. Starting from NaH (100 mg 60%, 2.5 mmol), the 2,3-*O*-bis(4-bromobutyl) sugar (**3a**, 351 mg, 0.63 mmol) and benzimidazole (200 mg, 1.6 mmol), the pure D-glucoside bis-benzimidazole (**4d**, 269 mg, 67.7%) was obtained as a syrup; $[\alpha]_D^{23}$ +30.79° (*c* 15.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (s, 1 H, Bim H-2), 7.76–7.73 (m, 2 H, Bim H-2,4), 7.65 (bs, 1 H, Bim H-4), 7.39–7.37 (m, 2 H, Bim H-7), 7.27–7.24 (m, 4 H, 2Bim H-5, Ph H-2,6), 7.21–7.18 (m, 5 H, 2Bim H-6, Ph H-3,4,5), 5.43 (s, 1 H, Ph–C*H*), 4.71 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 4.20 (dd, 1 H, $J_{6eq,6ax}$ 10, $J_{5,6eq}$ 3.9 Hz, H-6_{eq}), 4.02 (t, *J* 7 Hz, 2 H, NCH_2), 3.88 (t, *J* 7 Hz, 2 H, NCH_2), 3.74–3.58 (m, 5 H, OCH_2, H-3, H-5 and H-6_{ax}), 3.51 (t, *J* 6 Hz, 2 H, OCH_2), 3.42 (t, 1 H, $J_{3,4}=J_{4,5}$ 9 Hz, H-4), 3.34 (s, 3 H, OCH_3), 3.26 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 1.83–1.79 (m, 4 H, CH_2), 1.48–1.37 (m, 4 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.69, 143.64 (Bim C-2), 143.09, 143.06 (Bim C-9), 142.93, 142.90 (Bim C-8), 137.33 (Ph C-1), 129.08 (Ph C-4), 128.25 (Ph C-3,5), 126.05 (Ph C-2,6), 122.82, 122.73 (Bim C-5), 122.06, 121.98 (Bim C-6), 120.20, 120.12 (Bim C-4), 109.78 (Bim C-7), 101.47 (Ph–*C*H), 98.49 (C-1), 81.85 (C-4), 80.23 (C-2), 78.22 (C-3), 72.24 (O*C*H_2), 70.89 (O*C*H_2), 68.98 (C-6), 62.32 (C-5), 55.24 (O*C*H_3), 44.63, 44.57 (N*C*H_2), 27.16, 27.02, 26.75, 26.60 (*C*H_2); CIHRMS *m/z* 627.3177 $[M+H]^+$ ($[C_{36}H_{42}N_4O_6+H]$ requires: 627.3182). Anal. Calcd for $C_{36}H_{42}N_4O_6$: C, 68.99; H, 6.75; N, 8.94. Found: C, 68.91; H, 6.69; N, 8.99.

Methyl 2,3-O-*bis[4-(*N-*(5,6-dimethyl)benzimidazolyl)butyl]-4,6*-O-*benzylidene*-α-D-*glucopyranoside* (**4e**).—Prepared according to the procedure reported for the preparation of **4a**. Starting from NaH (100 mg 60%, 2.5 mmol), 2,3-*O*-bis(4-brombutyl) D-glucoside (**3a**, 100 mg, 0.18 mmol) and 5,6-dimethyl benzimidazole (200 mg, 1.3 mmol), the pure D-glucoside bis-(5,6-dimethyl)benzimidazole (**4e**, 82 mg, 66.7%) was obtained as a syrup; $[\alpha]_D^{30}$ +34.76° (*c* 4.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 1 H, Bim H-2), 7.70 (s, 1 H, Bim H-2), 7.54 (s, 1 H, Bim H-4), 7.53 (s, 1 H, Bim H-4), 7.43–7.40 (m, 2 H, Ph H-2,6), 7.31–7.29 (m, 3 H, Ph H-3,4,5), 7.14 (s, 1 H, Bim H-7), 7.06 (s, 1 H, Bim H-7), 5.48 (s, 1 H, Ph–C*H*), 4.76 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.25 (dd, 1 H, $J_{6eq,6ax}$ 9, $J_{5,6eq}$ 3.8 Hz, H-6_{eq}), 4.09 (t, *J* 7 Hz, 2 H, NCH_2), 3.98–3.87 (m, 2 H, NCH_2), 3.82–3.63 (m, 5 H, OCH_2, H-3, H-5 and H-6_{ax}), 3.58 (m, t, 6 Hz, 2 H, OCH_2), 3.45 (t, 1 H, $J_{3,4}=J_{4,5}$ 9 Hz, H-4), 3.39 (s, 3 H, OCH_3), 3.29 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 2.36 (s, 3 H, Bim 5-CH_3), 2.34 (s, 3 H, Bim 5-CH_3), 2.33 (s, 6 H, Bim 6-CH_3), 1.93–1.79 (m, 4 H, CH_2), 1.57–1.40 (m, 4 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.10, 141.93 (Bim C-2), 141.70 (Bim C-9), 141.58 (Bim C-8), 137.30 (Ph C-1), 132.21, 132.11 (Bim C-5), 131.28, 131.22 (Bim C-6), 129.11 (Ph C-4), 128.28 (Ph C-3,5), 126.03 (Ph C-2,6), 120.04, 119.94 (Bim C-4), 109.96 (Bim C-7), 101.53 (Ph–*C*H), 98.58 (C-1), 81.92 (C-4), 80.29 (C-2), 78.28 (C-3), 72.32 (O*C*H_2), 71.03 (O*C*H_2), 69.05 (C-6), 62.35 (C-5), 55.26 (O*C*H_3), 44.77, 44.69 (N*C*H_2), 27.19, 27.08, 26.76, 26.60 (*C*H_2), 20.61, 20.23 (Bim 5,6-*C*H_3); CIHRMS *m/z* 682.3730 $[M]^+$ ($C_{40}H_{50}N_4O_6$ requires 682.3730). Anal. Calcd for $C_{40}H_{50}N_4O_6$: C, 70.36; H, 7.38; N, 8.20. Found: C, 70.49; H, 7.34; N, 8.16.

Methyl 2,3-O-*bis[4-(*N-*(2-methyl-5-nitro)benzimidazolyl)butyl]-4,6*-O-*benzylidene*-α-D-*glucopyranoside* (**4f**).—Compound **4f** was prepared according to the synthesis of **4c**. Starting from dried potassium carbonate (669 mg, 4.8 mmol), the D-glucoside dibromide (**3a**, 300 mg, 0.54 mmol) and 2-methyl-5-nitrobenzimidazole (201 mg, 1.1 mmol), the pure D-glucoside bis-nitrobenzimidazole (**4f**, 209 mg, 51.8%) was obtained as a syrup; $[\alpha]_D^{24}$ +28.46° (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44–8.42 (m, 1 H, Bim H-4), 8.21–8.14 (m, 1 H, Bim H-4), 8.07 (d, *J* 8.35 Hz, 1 H, Bim H-6), 8.01–7.97 (m, 1 H, Bim H-6), 7.75–7.59

(m, 1 H, Bim H-7), 7.36–7.29 (m, 2 H, Ph H-2,6), 7.26–7.21 (m, 3 H, Ph H-3,4,5), 7.13–7.11 (m, 1 H, Bim H-7), 5.44 (s, 1 H, Ph–C*H*), 4.78 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.23 (dd, 1 H, $J_{6eq,6ax}$ 9, $J_{5,6eq}$ 3.5 Hz, H-6_{eq}), 4.19–4.11 (m, 2 H, NCH_2), 3.97–3.90 (m, 2 H, NCH_2), 3.73–3.58 (m, 7 H, 2OCH_2, H-3, H-5 and H-6_{ax}), 3.48 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9 Hz, H-4), 3.40–3.34 (m, 4 H, H-2, OCH_3), 2.61 (d, *J* 7 Hz, 3 H, Bim 2-CH_3), 2.45 (d, *J* 7 Hz, 3 H, Bim 2-CH_3),1.90–1.73 (m, 4 H, CH_2), 1.61–1.46 (m, 4 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.79, 155.44 (Bim C-8), 147.08, 143.28 (Bim C-5), 143.18, 139.28 (Bim C-2), 137.20 (Ph C-1), 129.16 (Ph C-4), 129.08, 128.14 (Bim C-9), 128.21 (Ph C-3,5), 125.99 (Ph C-2,6), 118.86, 117.90 (Bim C-6), 115.44, 115.32 (Bim C-7), 109.09, 106.11 (Bim C-4), 101.62 (Ph–*C*H), 98.41 (C-1), 81.57 (C-4), 80.46 (C-2), 78.37 (C-3), 72.21 (O*C*H_2), 70.61 (O*C*H_2), 68.97 (C-6), 62.33 (C-5), 55.23 (O*C*H_3), 44.06, 43.91 (N*C*H_2), 27.18, 27.04, 26.66, 26.61 (*C*H_2), 14.18, 13.99 (Bim 2-*C*H_3); ClHRMS *m*/*z* 745.3188 $[M + H]^+$ ($[C_{38}H_{44}N_6O_{10} + H]$ requires 745.3197). Anal. Calcd for $C_{38}H_{44}N_6O_{10}$: C, 61.28; H, 5.95; N, 11.28. Found: C, 61.19; H, 5.93; N, 11.32.

Methyl 2,3-O-*bis[5-(*N-*imidazolyl)pentyl]-4,6*-O-*benzylidene*-α-D-*glucopyranoside* (**4g**). —Compound **4g** was prepared according to the procedure for **4a**. Starting from NaH (1.2 g 60%, 30 mmol), the 2,3-*O*-bis(bromopentyl) sugar (**3b**, 450 mg, 0.77 mmol) and imidazole (544 mg, 8.0 mmol), the pure D-glucoside bis-imidazole (**4g**, 290 mg, 68.6%) was obtained as a syrup; $[\alpha]_D^{25}$ +26.69° (*c* 16.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.41 (m, 3 H, Ph H-2,6, Im H-2), 7.33–7.27 (m, 4 H, Ph H-3,4,5 and Im H-2), 7.00 (d, *J* 10 Hz, 2 H, Im H-4), 6.86 (d, *J* 32 Hz, 2 H, Im H-5), 5.47 (s, 1 H, Ph–C*H*), 4.73 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.21 (dd, 1 H, $J_{6eq,6ax}$ 9, $J_{5,6eq}$ 3.5 Hz, H-6_{eq}), 3.88 (t, *J* 7 Hz, 2 H, NCH_2), 3.75–3.63 (m, 7 H, NCH_2, OCH_2, H-3, H-5 and H-6_{ax}), 3.56 (t, *J* 6 Hz, 2 H, OCH_2), 3.42 (t, 1 H, $J_{3,4} = J_{4,5}$ 9 Hz, H-4), 3.37 (s, 3 H, OCH_3), 3.27 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 1.77–1.72 (m, 2 H, CH_2), 1.66–1.47 (m, 6 H, CH_2), 1.36–1.19 (m, 4 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.43 (Ph C-1), 136.92 (Im C-2), 129.17 (Ph C-4), 129.02 (Im C-4), 128.16 (Ph C-3,5), 126.07 (Ph C-2,6), 118.76 (Im C-5), 101.43 (Ph–*C*H), 98.77 (C-1), 81.73 (C-4), 80.44 (C-2), 78.18 (C-3), 72.57 (O*C*H_2), 71.42 (O*C*H_2), 69.03 (C-6), 62.36 (C-5), 55.27 (O*C*H_3), 46.90, 46.83 (N*C*H_2), 30.79, 30.65, 29.51, 29.45, 23.07, 23.03 (*C*H_2); ClHRMS *m*/*z* 555.3186 $[M + H]^+$ ($[C_{30}H_{42}N_4O_6 + H]$ requires 555.3183). Anal. Calcd for $C_{30}H_{42}N_4O_6$: C, 64.96; H, 7.63; N, 10.10. Found: C, 65.13; H, 7.64; N, 10.06.

Methyl 2,3-O-*bis[4-(*N-*imidazolyl)hexyl]-4,6*-O-*benzylidene*-α-D-*glucopyranoside* (**4h**). —Prepared according to the procedure for the synthesis of **4a**. Starting from NaH (880 mg 60%, 22 mmol), the 2,3-*O*-bis(bromohexyl) D-glycoside (**3c**, 100 mg, 0.16 mmol) and imidazole (584 mg, 8.5 mmol), the pure D-glucoside bis-imidazole (**4h**, 80 mg, 83.6%) was obtained as a syrup; $[\alpha]_D^{27}$ +21.36° (*c* 6.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.39 (m, 4 H, Ph H-2,6 and 2 Im H-2), 7.31–7.29 (m, 3 H, Ph H-3,4,5), 7.01 (d, *J* 6 Hz, 2 H, Im H-4), 6.86 (d, *J* 19 Hz, 2 H, Im H-5), 5.48 (s, 1 H, Ph–C*H*), 4.75 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.23 (dd, 1 H, $J_{6eq,6ax}$ 9, $J_{5,6eq}$ 3.9 Hz, H-6_{eq}), 3.88 (t, *J* 7 Hz, 2 H, NCH_2), 3.77–3.62 (m, 7 H, NCH_2, OCH_2, H-3, H-5 and H-6_{ax}), 3.57 (t, *J* 6 Hz, 2 H, OCH_2), 3.44 (t, 1 H, $J_{3,4} = J_{4,5}$ 9 Hz, H-4), 3.39 (s, 3 H, OCH_3), 3.29 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 1.75–1.68 (m, 2 H, CH_2), 1.63–1.44 (m, 6 H, CH_2), 1.34–1.25 (m, 6 H, CH_2), 1.24–1.17 (m, 2 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.48 (Ph C-1), 136.95 (Im C-2), 129.16 (Ph C-4), 129.03, 128.94 (Im C-4), 128.17 (Ph C-3,5), 126.06 (Ph C-2,6), 118.78 (Im C-5), 101.35 (Ph–*C*H), 98.87 (C-1), 81.85 (C-4), 80.45 (C-2), 78.15 (C-3), 72.87 (O*C*H_2), 71.66 (O*C*H_2), 69.06 (C-6), 62.38 (C-5), 55.27 (O*C*H_3), 46.96, 46.90 (N*C*H_2), 30.99, 30.94, 29.95, 29.81, 26.32, 26.25, 25.47, 25.47 (*C*H_2); ClHRMS *m*/*z* 583.3491 $[M + H]^+$ ($[C_{32}H_{46}N_4O_6 + H]$ requires 583.3496). Anal. Calcd for $C_{32}H_{46}N_4O_6$: C, 65.96; H, 7.96; N, 9.61. Found: C, 65.79; H, 7.91; N, 9.70.

Methyl 2,3-O-*bis[4-(*N-*imidazolyl)butyl]*-α-D-*glucopyranoside dihydrochloride* (**5a**).—A mixture of analytic grade concentrated hydrochloric acid (1 mL), distilled water (3 mL) and methyl 4,6-*O*-benzylidene α-D-glucopyranoside bis-imidazole (**4a**, 40 mg, 0.076 mmol) was stirred at 50 °C for 2 h. The solvents were

evaporated under reduced pressure. The residue was washed with petroleum ether (30–60 °C) to remove benzaldehyde and dried to afford corresponding α-D-glucopyranoside bis-imidazole hydrochloric acid salt (**5a**) as a syrup (38 mg, 98.2%); $[\alpha]_D^{27}$ +42.78° (*c* 1.8, water); ^{1}H NMR (300 MHz, D_2O): δ 8.76–8.75 (m, 2 H, Im H-2), 7.54–7.52 (m, 2 H, Im H-4), 7.49–7.47 (m, 2 H, Im H-5), 4.96 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.28 (t, 7 Hz, 4 H, NCH_2), 3.88–3.60 (m, 8 H, H-3, H-5, H-6$_{eq}$, H-6$_{ax}$, 2 OCH_2), 3.47 (dd, 1 H, $J_{3,4} = J_{4,5}$ 10 Hz, H-4), 3.41 (s, 3 H, OCH_3), 3.38 (dd, 1 H, $J_{2,3}$ 10 Hz, H-2), 2.00–1.94 (m, 4 H, CH_2), 1.64–1.59 (m, 4 H, CH_2); ^{13}C NMR (75 MHz, D_2O): δ 134.43 (Im C-2), 121.79 (Im C-4), 119.81 (Im C-5), 97.28 (C-1), 81.14 (C-4), 79.32 (C-2), 72.51 (OCH$_2$), 71.64(C-3), 70.25 (OCH$_2$), 69.14 (C-5), 60.46 (C-6), 54.88 (OCH$_3$), 49.10, 49.06 (NCH$_2$), 26.36, 26.30, 26.11, 26.03 (CH$_2$); CIHRMS *m*/*z* 439.2565 [M − 2 HCl + H]$^+$ ([$C_{21}H_{36}Cl_2N_4O_6$ − 2 HCl + H] requires 439.2557). Anal. Calcd for $C_{21}H_{36}Cl_2N_4O_6$: C, 49.32; H, 7.09; N, 10.95. Found: C, 49.59; H, 7.20; N, 10.64.

*Methyl 2,3-*O*-bis[4-(*N*-(2-methyl)imidazolyl)butyl]-α-*D*-glucopyranoside dihydrochloride* (**5b**).—Compound **5b** was prepared according to the procedure for **5a**. Starting from the sugar bis-methylimidazole (**4b**, 150 mg, 0.27 mmol), the pure D-glucoside bis-imidazole hydrochloric acid salt (**5b**, 145 mg, ~100%) was obtained as a syrup; $[\alpha]_D^{31}$ + 38.75° (*c* 4.0, water); ^{1}H NMR (300 MHz, D_2O): δ 7.37 (bs, 2 H, Im H-4), 7.31 (bs, 2 H, Im H-5), 4.95 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.13 (bs, 7 Hz, 4 H, NCH_2), 3.82–3.62 (m, 8 H, H-3, H-5, H-6$_{eq}$, H-6$_{ax}$, 2OCH_2), 3.50–3.39 (m, 5 H, H-2, H-4, OCH_3), 2.61 (bs, 6 H, Im 2–CH_3), 1.90 (bs, 4 H, CH_2), 1.61 (bs, 4 H, CH_2); ^{13}C NMR (75 MHz, D_2O): δ 144.05 (Im C-2), 121.52 (Im C-4), 117.78 (Im C-5), 97.28 (C-1), 81.10 (C-4), 79.32 (C-2), 72.57 (OCH$_2$), 71.64 (C-3), 70.32 (OCH$_2$), 69.16 (C-5), 60.51 (C-6), 54.90 (OCH$_3$), 47.17 (NCH$_2$), 26.25, 26.17, 25.91 (CH$_2$), 10.02 (Im–CH$_3$); CIHRMS *m*/*z* 467.2807 [M − 2 HCl + H]$^+$ ([$C_{23}H_{40}Cl_2N_4O_6$ − 2 HCl + H] requires 467.2870). Anal. Calcd for $C_{23}H_{40}Cl_2N_4O_6$: C, 51.20; H, 7.47; N, 10.39. Found: C, 51.38; H, 7.54; N, 10.14.

*Methyl 2,3-*O*-bis[4-(*N*-(2-methyl-4-nitro)imidazolyl)butyl]-α-*D*-glucopyranoside dihydrochloride* (**5c**).—Prepared according to the procedure reported for **5a**. Starting from the D-glucoside bis(2-methyl-4-nitro) imidazole (**4c**, 140 mg, 0.217 mmol), the pure D-glucoside bis-nitroimidazole hydrochloric acid salt (**5c**, 136 mg, ~100%) was obtained as a syrup; $[\alpha]_D^{31}$ +22.12° (*c* 3.3, water); ^{1}H NMR (300 MHz, D_2O): δ 8.14 (s, 1 H, Im H-5), 8.12 (s, 1 H, Im H-5), 4.93 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 4.05–4.00 (m, 4 H, NCH_2), 3.83 (dd, 1 H, $J_{6eq,6ax}$ 12, $J_{5,6eq}$ 2.3 Hz, H-6$_{eq}$), 3.80–3.68 (m, 4 H, H-5, H-6$_{ax}$, OCH_2), 3.60–3.56 (m, 2 H, OCH_2), 3.54–3.40 (m, 2 H, H-3, H-4), 3.39 (s, 3 H, OCH_3), 3.32 (m, 1 H, H-2), 2.42 (s, 6 H, Im 2–CH_3), 1.84–1.80 (m, 4 H, CH_2), 1.58–1.56 (m, 4 H, CH_2); ^{13}C NMR (75 MHz, D_2O): δ 146.77 (Im C-2), 143.33, 143.31 (Im C-4), 122.06 (Im C-5), 97.15 (C-1), 81.07 (C-4), 79.17 (C-2), 72.64 (OCH$_2$), 71.60 (C-3), 70.06 (OCH$_2$), 69.31 (C-5), 60.49 (C-6), 54.85 (OCH$_3$), 47.16, 47.10 (NCH$_2$), 26.22, 26.10, 26.06 (CH$_2$), 11.72 (Im–CH$_3$); CIHRMS *m*/*z* 557.2550 [M − 2 HCl + H]$^+$ ([$C_{23}H_{38}Cl_2N_6O_{10}$ − 2 HCl + H] requires 557.2571). Anal. Calcd for $C_{23}H_{38}Cl_2N_6O_{10}$: C, 43.88; H, 6.08; N, 13.35. Found: C, 43.58; H, 6.21; N, 13.47.

*Methyl 2,3-*O*-bis[4-(*N*-benzimidazolyl)butyl]-α-*D*-glucopyranoside dihydrochloride* (**5d**).—Prepared according to the procedure for **5a**. Starting from the bis-benzimidazole D-glucoside (**4d**, 80 mg, 0.127 mmol), the pure deprotected D-glucoside bis-benzimidazole hydrochloric acid salt (**5d**, 77 mg, 99.2%) was obtained. mp 74–76 °C; $[\alpha]_D^{29}$ +34.50° (*c* 2.0, water); ^{1}H NMR (300 MHz, D_2O): δ 9.18 (s, 1 H, Bim H-2), 9.16 (s, 1 H, Bim H-2), 7.81–7.74 (m, 4 H, Bim H-4,7), 7.59–7.55 (m, 4 H, Bim H-5,6), 4.92 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.43 (t, *J* 7 Hz, 2 H, NCH_2), 4.39 (t, *J* 7 Hz, 2 H, NCH_2), 3.84 (dd, 1 H, $J_{6eq,6ax}$ 12, $J_{5,6eq}$ 2.4 Hz, H-6$_{eq}$), 3.75–3.67 (m, 4 H, OCH_2, H-5 and H-6$_{ax}$), 3.62–3.57 (m, 2 H, OCH_2), 3.54–3.40 (m, 2 H, H-3, H-4), 3.37 (s, 3 H, OCH_3), 3.32 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 1.97–1.89 (m, 4 H, CH_2), 1.59–1.53 (m, 4 H, CH_2); ^{13}C NMR (75 MHz, D_2O): δ 139.80, 139.73 (Bim C-2), 130.82, 130.48 (Bim C-9), 127.03, 126.61 (Bim C-8), 114.67 (Bim C-5,6), 112.84 (Bim C-4,7), 97.12 (C-1), 81.03 (C-4),

79.16 (C-2), 72.46 (O*C*H$_2$), 71.59 (C-3), 69.93 (O*C*H$_2$), 69.23 (C-5), 60.44 (C-6), 54.84 (O*C*H$_3$), 46.77 (N*C*H$_2$), 26.27, 26.18, 25.62, 25.48 (*C*H$_2$); CIHRMS *m*/*z* 539.2856 [M − 2 HCl + H]$^+$ ([$C_{29}H_{40}Cl_2N_4O_6$ − 2 HCl + H] requires 539.2870). Anal. Calcd for $C_{29}H_{40}Cl_2N_4O_6$: C, 56.95; H, 6.59; N, 9.16. Found: C, 57.13; H, 6.69; N, 9.01.

Methyl 2,3-O-*bis[4-(*N-*(5,6-dimethyl)benzimidazolyl)butyl]-α*-D-*glucopyranoside dihydrochloride* (**5e**).—Compound **5e** was prepared according to the procedure reported for the preparation of **5a**. Starting from the protected D-glucoside bis-(5,6-dimethyl)benzimidazole (**4e**, 90 mg, 0.132 mmol), the pure free D-glucoside bis-benzimidazole hydrochloric acid salt (**5e**, 86 mg, 98.0%) was obtained. mp 102–104 °C; $[\alpha]_D^{29}$ + 27.25° (*c* 4.0, water); ^{1}H NMR (300 MHz, D$_2$O): δ 8.99 (s, 1 H, Bim H-2), 8.96 (s, 1 H, Bim H-2), 7.32 (t, 20 Hz, 4 H, Bim H-4,7), 4.93 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.24 (t, *J* 7 Hz, 2 H, NC*H*$_2$), 4.18 (t, *J* 7 Hz, 2 H, NC*H*$_2$), 3.83 (dd, 1 H, $J_{6eq,6ax}$ 12, $J_{5,6eq}$ 2.1 Hz, H-6$_{eq}$), 3.79–3.65 (m, 4 H, OC*H*$_2$, H-5 and H-6$_{ax}$), 3.60–3.55 (m, 2 H, OC*H*$_2$), 3.53–3.40 (m, 2 H, H-3, H-4), 3.37 (s, 3 H, OC*H*$_3$), 3.31 (dd, 1 H, $J_{2,3}$ 10 Hz, H-2), 2.24 (s, 3 H, Bim 5-C*H*$_3$), 2.22 (s, 3 H, Bim 5-C*H*$_3$), 2.21 (s, 3 H, Bim 6-C*H*$_3$), 2.16 (s, 3 H, Bim 6-C*H*$_3$), 1.91–1.80 (m, 4 H, C*H*$_2$), 1.58–1.50 (m, 4 H, C*H*$_2$); ^{13}C NMR (75 MHz, D$_2$O): δ 138.27, 138.17 (Bim C-2), 137.34, 137.29 (Bim C-9), 136.91 (Bim C-8), 129.01 (Bim C-5), 128.69 (Bim C-6), 113.82, 113.76 (Bim C-4), 111.95, 111.89 (Bim C-7), 97.02 (C-1), 80.95 (C-4), 79.02 (C-2), 72.32 (O*C*H$_2$), 71.58 (C-3), 69.61 (O*C*H$_2$), 69.36 (C-5), 60.45 (C-6), 54.83 (O*C*H$_3$), 46.60 (N*C*H$_2$), 26.29, 26.18, 25.69, 25.53 (*C*H$_2$), 19.64, 19.61 (Bim 5-*C*H$_3$), 19.44, 19.41 (Bim 6-*C*H$_3$); CIHRMS *m*/*z* 594.3401 [M − 2 HCl]$^+$ ([$C_{33}H_{48}Cl_2N_4O_6$ − 2 HCl] requires 594.3417). Anal. Calcd for $C_{33}H_{48}Cl_2N_4O_6$: C, 59.36; H, 7.25; N, 8.39. Found: C, 59.61; H, 7.31; N, 8.23.

Methyl 2,3-O-*bis[4-(*N-*(2-methyl-5-nitro)benzimidazolyl)butyl]-α*-D-*glucopyranoside dihydrochloride* (**5f**).—Prepared according to the procedure reported for **5a**. Starting from the protected sugar bis(2-methyl-5-nitro) imidazole (**4f**, 100 mg, 0.134 mmol), the pure D-glucoside bis-benzimidazole hydrochloric acid salt (**5f**, 95 mg, 97.2%) was obtained. mp 146–148 °C; $[\alpha]_D^{29}$ + 20.85° (*c* 10.6, water); ^{1}H NMR (300 MHz, D$_2$O): δ 8.65 (d, *J* 10 Hz, 1 H, Bim H-4), 8.49 (d, *J* 2 Hz, 1 H, Bim H-4), 8.24–8.21 (m, 2 H, Bim H-6), 7.95–7.79 (m, 2 H, Bim H-7), 4.87 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.45 (bs, 4 H, NC*H*$_2$), 3.74–3.44 (m, 8 H, 2 OC*H*$_2$, H-3, H-5, H-6$_{eq}$ and H-6$_{ax}$), 3.40 (t, 1 H, $J_{3,4} = J_{4,5}$ 9 Hz, H-4), 3.30 (s, 3 H, OC*H*$_3$), 3.26 (dd, 1 H, $J_{2,3}$ 10 Hz, H-2), 2.91 (m, 12 H, Bim 2-C*H*$_3$), 1.91 (bs, 4 H, C*H*$_2$), 1.63 (bs, 4 H, C*H*$_2$); ^{13}C NMR (75 MHz, D$_2$O): δ 155.62, 155.55 (Bim C-8), 145.34, 145.16 (Bim C-5), 135.65, 133.89 (Bim C-2), 131.50, 129.40 (Bim C-9), 121.64, 121.14 (Bim C-6), 114.92, 114.49 (Bim C-4), 110.83, 109.49 (Bim C-7), 97.21 (C-1), 81.01 (C-4), 79.30 (C-2), 72.38 (O*C*H$_2$), 71.59 (C-3), 70.14 (O*C*H$_2$), 69.10 (C-5), 60.49 (C-6), 54.84 (O*C*H$_3$), 45.47, 45.40 (N*C*H$_2$), 26.50, 26.41, 25.34, 25.25 (*C*H$_2$), 11.68 (Bim 2-*C*H$_3$); CIHRMS *m*/*z* 657.2830 [M − 2 HCl + H]$^+$ ([$C_{31}H_{42}Cl_2N_6O_{10}$ − 2 HCl + H] requires 657.2884). Anal. Calcd for $C_{31}H_{42}Cl_2N_6O_{10}$: C, 51.03; H, 5.80; N, 11.52. Found: C, 51.39; H, 5.88; N, 11.30.

Methyl 2,3-O-*bis[5-(*N-*imidazolyl)pentyl]-α*-D-*glucopyranoside dihydrochloride* (**5g**).—Prepared as described for **5a**. Starting from the D-glucoside bis-imidazole (**4g**, 80 mg, 0.144 mmol), the pure D-glucoside bis-imidazole hydrochloric acid salt (**5g**, 75 mg, 96.7%) was obtained as a syrup; $[\alpha]_D^{29}$ + 51.11° (*c* 5.4, water); ^{1}H NMR (300 MHz, D$_2$O): δ 8.76–8.75 (m, 2 H, Im H-2), 7.55–7.52 (m, 2 H, Im H-4), 7.49–7.47 (m, 2 H, Im H-5), 4.92 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.28–4.23 (m, 4 H, NC*H*$_2$), 3.85 (dd, 1 H, $J_{6eq,6ax}$ 12, $J_{5,6eq}$ 2.1 Hz, H-6$_{eq}$), 3.76–3.57 (m, 7 H, H-3, H-5, H-6$_{ax}$, 2OC*H*$_2$), 3.42 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9 Hz, H-4), 3.39 (s, 3 H, OC*H*$_3$), 3.34 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 1.97–1.87 (m, 4 H, C*H*$_2$), 1.65–1.58 (m, 4 H, C*H*$_2$), 1.41–1.33 (m, 4 H, C*H*$_2$); ^{13}C NMR (75 MHz, D$_2$O): δ 134.38 (Im C-2), 121.87 (Im C-4), 119.75 (Im C-5), 97.44 (C-1), 81.05 (C-4), 79.30 (C-2), 73.07 (O*C*H$_2$), 71.64 (C-3), 70.89 (O*C*H$_2$), 69.22 (C-5), 60.56 (C-6), 54.96 (O*C*H$_3$), 49.33 (N*C*H$_2$), 29.14, 29.11, 28.74, 28.61 22.18, 22.16 (*C*H$_2$); CIHRMS *m*/*z* 467.2870 [M − 2 HCl + H]$^+$ ([$C_{23}H_{40}Cl_2N_4O_6$ − 2 HCl + H] requires 467.2870). Anal. Calcd for $C_{23}H_{40}Cl_2N_4O_6$: C, 51.20; H, 7.47; N, 10.39. Found: C, 51.37; H, 7.53; N, 10.11.

*Methyl 2,3-*O*-bis[4-(*N*-imidazolyl)hexyl]-α-*D*-glucopyranoside dihydrochloride* (**5h**).—Prepared according to the procedure described for **5a**. Starting from the D-glucoside bis-imidazole (**4h**, 55 mg, 0.094 mmol), the pure D-glucoside bis-imidazole hydrochloric acid salt (**5h**, 51 mg, 95.5%) was obtained as a syrup; $[\alpha]_D^{29}$ +44.75° (*c* 4.0, water); ^{1}H NMR (300 MHz, D_2O): δ 8.75 (bs, 2 H, Im H-2), 7.53–7.48 (m, 4 H, Im H-4,5), 4.94 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.27–4.23 (m, 4 H, NCH_2), 3.86 (dd, 1 H, $J_{6eq,6ax}$ 12, $J_{5,6eq}$ 2.1 Hz, H-6_{eq}), 3.76–3.60 (m, 7 H, H-3, H-5, H-6_{ax}, 2OCH_2), 3.49 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9 Hz, H-4), 3.41 (s, 3 H, OCH_3), 3.36 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 1.90 (bs, 4 H, CH_2), 1.57 (bs, 4 H, CH_2), 1.36 (bs, 8 H, CH_2); ^{13}C NMR (75 MHz, D_2O): δ 134.32 (Im C-2), 121.84 (Im C-4), 119.71 (Im C-5), 97.47 (C-1), 81.03 (C-4), 79.29 (C-2), 73.40 (O*C*H_2), 71.63 (C-3), 71.10 (O*C*H_2), 69.27 (C-5), 60.55 (C-6), 54.98 (O*C*H_3), 49.38 (N*C*H_2), 29.32, 29.28, 29.11, 28.92, 25.25, 25.20, 24.72 (*C*H_2); CIHRMS *m*/*z* 495.3196 $[M-2\ HCl+H]^+$ ($[C_{25}H_{42}N_4O_6-2\ HCl+H]$ requires 495.3183). Anal. Calcd for $C_{25}H_{44}Cl_2N_4O_6$: C, 52.91; H, 7.81; N, 9.87. Found: C, 53.09; H, 7.89; N, 9.66.

*2,3-*O*-bis[4-(*N*-imidazolyl)butyl]-*D*-glucose dihydrochloride* (**6a**).—A mixture of analytic grade conc HCl (4 mL), distilled water (2 mL) and the methyl 4,6-*O*-benzylidene α-D-glucopyranoside bis-imidazole (**4a**, 60 mg, 0.114 mmol) was stirred at 60 °C for 24 h. The solvents were evaporated to dryness under reduced pressure. The resulting solid residue was washed with petroleum ether (30–60 °C) and dried to afford the corresponding totally deprotected D-glucopyranoside bis-imidazole hydrochloric acid salt (**6a**) as a syrup (53 mg, 93.9%); $[\alpha]_D^{25}$ +37.14° (*c* 7.3, watre); ^{1}H NMR (300 MHz, D_2O): δ 8.77 (s, 2 H, Im H-2), 7.54 (bs, 2 H, Im H-4), 7.48 (bs, 1 H, Im H-5), 5.36 (d, $J_{1,2}$ 2.6 Hz, 0.5 H, H-1(α)), 4.65 (d, $J_{1,2}$ 8.1 Hz, 0.5 H, H-1(β)), 4.28 (t, 7 Hz, 4 H, NCH_2), 3.84–3.42 (m, 9 H, H-3, H-4, H-5, H-6_{eq}, 6_{ax} and 2 OCH_2), 3.35 (m, 0.5 H, H-2(α)), 3.08 (t, 0.5 H, H-2(β)), 1.97 (bs, 4 H, CH_2), 1.61 (bs, 4 H, CH_2); ^{13}C NMR (75 MHz, D_2O): δ 134.46 (Im C-2), 121.85 (Im C-4), 119.82 (Im C-5), 95.88 (C-1(β)), 90.08 (C-1(α)), 84.00 (C-4(α)), 82.37 (C-4(β)), 80.83 (C-2(β)), 79.49 (C-4(α)), 75.84 (C-3(β)), 72.59 (O*C*H_2), 71.48 (C-3(α)),70.03 (O*C*H_2), 69.36 (C-5(β)), 69.24 (C-5(α)), 60.69 (C-6(β)), 60.57 (C-6(α)), 49.14 (N*C*H_2), 26.37, 26.25, 26.17, 26.02 (*C*H_2); CIHRMS *m*/*z* 425.2314 $[M-2\ HCl+H]^+$ ($[C_{20}H_{34}Cl_2N_4O_6-2\ HCl+H]$ requires 425.2400). Anal. Calcd for $C_{20}H_{34}Cl_2N_4O_6\cdot H_2O$: C, 48.29; H, 6.89; N, 11.26. Found: C, 48.41; H, 6.99; N, 10.95.

*Methyl 2,3-*O*-bis[4-(*N*-imidazolyl)butyl]-α-*D*-glucopyranoside* (**7a**).—The deprotected D-glucoside bis-imidazole hydrochloride (**5a**, 50 mg, 0.098 mmol) was dissolved in water (5 mL). The resulting solution was neutralized with 28% analytic grade ammonium hydroxide under stirring, and then the mixture was evaporated to dryness. The solid residue was washed with $CHCl_3$ (3 × 20 mL). The combined $CHCl_3$ solution was evaporated to afford the pure compound **7a** as a syrup (41 mg, 96.3%); $[\alpha]_D^{25}$ +50.06° (*c* 8.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J* 8 Hz, 2 H, Im H-2), 6.93 (d, *J* 12 Hz, 2 H, Im H-4), 6.83 (d, *J* 8 Hz, 2 H, Im H-5), 4.71 (d, $J_{1,2}$ 3.3 Hz, 1 H, H-1), 4.29 (bs, 2 H, OH), 3.90–3.82 (m, 4 H, NCH_2, H-6_{eq}, H-5), 3.75 (bs, 2 H, H-4, H-6_{ax}), 3.69 (t, *J* 6 Hz, NCH_2), 3.53–3.44 (m, 5 H, 2 OCH_2, H-2), 3.32 (s, 3 H, OCH_3), 3.18 (m, $J_{2,3}$ 9 Hz, 1 H, H-3), 1.79–1.68 (m, 4 H, CH_2), 1.50–1.40 (m, 4 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.99 (Im C-2), 128.91, 128.54 (Im C-4), 118.98, 118.86 (Im C-5), 97.66 (C-1), 81.31 (C-4), 80.31 (C-2), 72.39 (O*C*H_2), 71.56 (C-3), 70.46 (C-5), 70.14 (O*C*H_2), 61.81 (C-6), 55.01 (O*C*H_3), 46.78, 46.73 (N*C*H_2), 27.92, 27.88, 27.06, 26.87 (*C*H_2); CIHRMS *m*/*z* 439.2553 ($[C_{21}H_{34}N_4O_6+H]$ requires 439.2557). Anal. Calcd for $C_{21}H_{34}N_4O_6$: C, 57.52; H, 7.81; N, 12.78. Found: C, 57.46; H, 7.78; N, 12.96.

*2,3-*O*-bis[4-(*N*-imidazolyl)butyl]-*D*-glucose* (**8a**).—Compound **8a** was prepared according to the procedure reported for the preparation of **7a**. Starting from the totally deprotected D-glucoside bis-imidazole hydrochloride (**6a**, 40 mg, 0.08 mmol), the pure free D-glucoside bis-imidazole (**8a**, 32 mg, 94.1%) was obtained as a syrup; $[\alpha]_D^{25}$ +33.68° (*c* 4.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 2 H, Im H-2), 6.95 (bs, 2 H, Im H-4), 6.86 (bs, 1 H, Im H-5), 5.19 (d, $J_{1,2}$ 2.7 Hz, 0.5 H, H-1(α)), 4.62

(d, $J_{1,2}$ 7.9 Hz, 0.5 H, H-1(β)), 3.91–3.83 (m, 4 H, NCH_2, H-5, H-6$_{eq}$), 3.76–3.39 (m, 9 H, H-3, H-4, H-6$_{ax}$ and 2 OCH_2), 3.16 (m, 0.5 H, H-2(α)), 3.02 (t, 0.5 H, H-1(β), 1.80–1.69 (bs, 4 H, CH_2), 1.58–1.47 (bs, 4 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.95, 136.89 (Im C-2), 128.99,128.60 (Im C-4), 118.86, 118.76 (Im C-5), 96.11 (C-1(β)), 91.01 (C-1(α)), 84.14 (C-4 (α)), 82.58 (C-4(β)), 81.34 (C-2 (β)), 80.18 (C-2(α)), 74.69 (C-3(β)), 72.40 (OCH$_2$), 70.99 (C-3(α)), 70.74 (C-5(β)), 70.57 (C-5(α)), 70.01 (OCH$_2$), 61.86 (C-6(β)), 61.69 (C-6(α)), 46.59, 46.54 (NCH$_2$), 27.91, 27.80, 26.99, 26.85 (CH$_2$); CIHRMS m/z 425.2399 $[M+H]^+$ ($[C_{20}H_{32}N_4O_6+H]$ requires 425.2400). Anal. Calcd for $C_{20}H_{32}N_4O_6$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.48; H, 7.55; N, 13.31.

*Methyl 2,3-*O*-butylene-4,6-*O*-benzylidene-α-*D*-glucopyranoside* (**9**).—Method A: Compound **9** (456 mg, 58.1%) was obtained as a syrup according to the procedure for **3a** from 1,4-dibromo butane (3 mL), the bis-hydroxy sugar (**2**, 660 mg, 2.34 mmol), NaH (400 mg 60%, 10 mmol) and DMF (10 mL). 1,4-Dibromo butane was added at 60 °C. Method B: A mixture of the bis-hydroxy sugar (**2**, 400 mg, 1.4 mmol), dibenzo-18-crown-6 (40 mg, 0.11 mmol), tetrabutylammonium bromide (40 mg, 0.12 mmol), NaOH (500 mg, 12.5 mmol) and 1,4-dibromo butane (10 mL) in DMF (5 mL) was stirred at 100 °C for 2 days. Water (50 ml) was added. The workup was the same as method A. The cyclic D-glucoside (**9**, 67 mg, 97.6%, based on the reacted D-glucoside **2**) was obtained as a syrup; $[\alpha]_D^{25}$ +42.67° (*c* 3.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48–7.45 (m, 2 H, Ph H-2,6), 7.34–7.27 (m, 3 H, Ph H-3,4,5), 5.48 (s, 1 H, Ph–C*H*), 4.74 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.29 (dd, 1 H, $J_{6eq,6ax}$ 9, $J_{5,6eq}$ 3.9 Hz, H-6$_{eq}$), 4.14–4.00 (m, 2 H, OCH_2), 3.85–3.65 (m, 5 H, OCH_2, H-3, H-5 and H-6$_{ax}$), 3.58–3.36 (m, 5 H, H-2, H-4 and OCH_3), 1.87–1.64 (m, 4 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.37 (Ph C-1), 128.92 (Ph C-4), 128.11 (Ph C-3,5), 126.32 (Ph C-2,6), 101.63 (Ph–*C*H), 99.79 (C-1), 81.75 (C-4), 80.05 (C-2), 78.97 (C-3), 73.18 (OCH$_2$), 72.20 (OCH$_2$), 68.99 (C-6), 62.78 (C-5), 55.16 (OCH$_3$), 27.20 (CH$_2$); CIHRMS m/z 337.1639 $[M+H]^+$ ($[C_{18}H_{24}O_6+H]$ requires 337.1651).

*Methyl 2,3-*O*-(1,2-phenylenedimethylene)-4,6-*O*-benzylidene-α-*D*-glucopyranoside* (**10**).—Method A: Compound **10** (576 mg, 75%) was obtained as a syrup according to the procedure for **9** (method A) from 1,2-bis(bromomethyl) benzene (1.32 g, 5 mmol), the bis-hydroxy sugar (**2**, 565 mg, 2 mmol), NaH (400 mg 60%, 10 mmol) and DMF (10 mL). Method B: the D-Glucoside (**10**, 115 mg, 98.5%, based on the reacted D-glucoside **2**) was obtained as a syrup according to the procedure for **9** (method B) from 1,2-bis(bromomethyl) benzene (1.056 g, 4 mmol), the bis-hydroxy sugar (**2**, 508 mg, 1.8 mmol), dibenzo-18-crown-6 (50 mg, 0.138 mmol), tetrabutylammonium bromide (50 mg, 0.155 mmol), NaOH (400 mg, 10 mmol) and DMF (20 mL); $[\alpha]_D^{25}$ +138.75° (*c* 2.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, *J* 6 Hz, 2 H, Ph–H), 7.43–7.39 (m, 3 H, Ph–H), 7.29–7.26 (m, 2 H, Ph–H), 7.18–7.15 (m, 2 H, Ph–H), 5.55 (s, 1 H, Ph–C*H*), 5.24–4.99 (m, 4 H, Ph–CH_2O), 4.90 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.31 (dd, 1 H, $J_{6eq,6ax}$ 9, $J_{5,6eq}$ 5 Hz, H-6eq), 4.06 (t, *J* 9 Hz, 1 H, H-3), 3.89 (ddd, 1 H, H-5), 3.73 (t, $J_{5,6ax}$ 10 Hz, H-6$_{ax}$), 3.67 (dd, 1 H, H-2), 3.56 (t, $J_{3,4}=J_{4,5}$ 9 Hz, 1 H, H-4), 3.46 (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.42, 137.04, 136.26, 130.05, 129.69, 129.14, 128.31, 128.03, 127.89, 126.47 (Ph–C), 101.90 (Ph–*C*H), 99.14 (C-1), 80.51 (C-4), 80.31 (C-2), 78.18 (C-3), 73.64 (OCH$_2$), 73.11 (OCH$_2$), 69.09 (C-6), 62.21 (C-5), 55.28 (OCH$_3$); CIHRMS m/z 384.1561 $[M]^+$ ($C_{22}H_{24}O_6$ requires 384.1573).

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