Efficient Synthesis of Unsymmetrical Ureido-Linked Disaccharides

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Keywords: Ureas / Intersaccharidic linkages / Carbohydrates / Glycosides / Oligosaccharides

Five nonsymmetrical urea-linked disaccharides, in which two glycopyranoside units are bound at the 1→2, 1→4, and 1→6 positions, were efficiently synthesized. A mild and safe procedure, in which glycosyl isocyanates were coupled with a glycosylamine, was employed.

Introduction

Naturally occurring oligosaccharides, both as free endogenous molecules and as components of glycoconjugates, have crucial functions in numerous biological processes.[1−3] They mediate cell adhesion and communication and are the characteristic determinants of the human blood groups,[4,5] of tumour-associated antigens[6] and of capsular polysaccharides (CPS) of highly infective bacteria.[7] In the light of these important roles, the development of sugar-based drugs could be of great pharmaceutical interest. However, saccharide chains can be highly sensitive to chemical or enzymatic hydrolysis,[8] thereby causing the cleavage of the *O*-glycosidic linkages and the degradation of the glycoconjugates. Therefore, it is highly desirable to have access to modified structures endowed with an increased stability, while maintaining the biological properties of the natural compounds. Here, we report the synthesis of a series of disaccharides (compounds **1**−**5**, see Figure 1) bound through an ureido group, a stable and yet polar group, with which the stability of the anomeric linkage is ensured. In the last few years, an increasing interest in glycosylureido sugars has emerged, with applications in the field of aminoglycoside antibiotics.[9,10] The glycosyl−urea bond is naturally widespread in glycocinnamoylspermidine antibiotics.[11,12] However, only a few methodologies for the formation of glycosylureas are described in the literature. The first methods employed the acid-catalyzed condensation of D-glucopyranose with urea in water,[13] which was also used in the synthesis of symmetrical disaccharidic ureas,[14] the reaction of silver cyanate with glycosyl halides,[15] and the carbodiimide approach.[16−18] More recently, Ichikawa et al. used highly toxic phosgene or phosgene derivatives to generate the isocyanate intermediate from the glycosylamine precursor.[19] Obviously, the latter, hazardous techniques are not suitable for large-scale preparations. For this reason, we reconsidered the procedure proposed by Ichikawa,[19,20] in which the glycosyl isocyanate is obtained by a mild oxidation of the corresponding isocyanide with pyridine *N*-oxide. In the present work, we extend this approach to a general procedure for the synthesis of intersaccharidic ureido linkages. We focussed on the disaccharidic ureas **1**−**5** (Figure 1), in which ureido linkages between the 1→2, 1→4, and 1→6 positions of two saccharide units are present. In particular, **3** is involved in a β-mannosidic linkage with an axial amino group in position 2 of the mannosamine acceptor. Examples of symmetrical ureas linking two anomeric positions of α- and β-glucopyranosidic subunits are

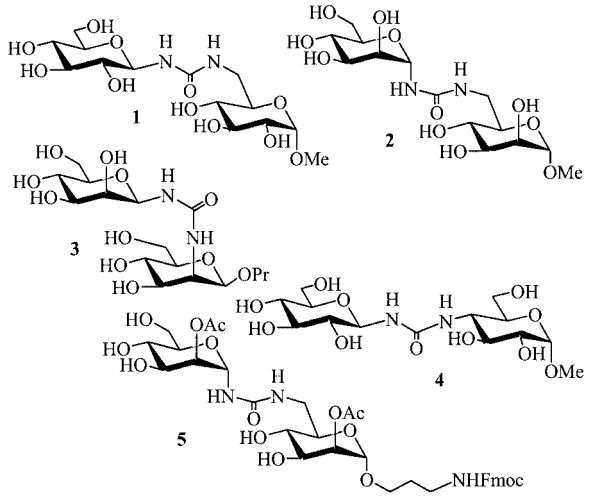

Figure 1. Intersaccharidic ureas **1**−**5**

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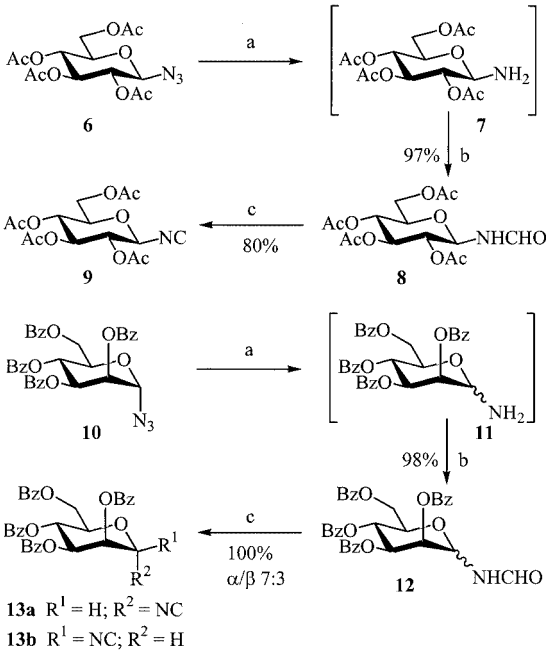
known,[14,19] as well as pseudodisaccharides involving position 5 of a hexofuranosidic acceptor.[21] However, compounds **3** and **4** are the first glycosylureas in which the anomeric position of a hexopyranose is connected to the non-anomeric secondary position of a glycopyranosidic acceptor.

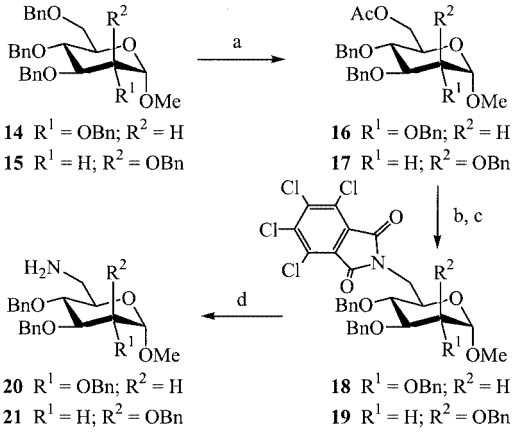
Results and Discussion

The retrosynthetic scheme relies on the coupling of two key synthons for the formation of the glycosylureas: a glycosyl isocyanate, obtained in situ by mild oxidation of the corresponding glycosyl isocyanide and a properly protected monosaccharide partner, containing a free amino group. Glycosyl isocyanides **9**,[22] **13a**, and **13b** were prepared according to Scheme 1. Tetraacetyl-β-glucosyl azide **6**,[23] was converted into the corresponding formamidic derivative **8** after hydrogenation and an in situ reaction with freshly prepared acetoformic anhydride.[24] The ^{1}H NMR spectrum shows that **8** was obtained as a pure β anomer but as a mixture of (*E*) and (*Z*) diastereoisomers, due to the iminic form of the formamido group. The ^{1}H NMR analysis is consistent with the literature data,[25] revealing a considerable prevalence of the (*Z*) isomer, which is evidenced by the presence of a singlet at δ = 8.25 ppm [in the (*E*) isomer, the CHO signal at δ = 8.21 ppm shows a doublet with $J_{CHO,NH}$ = 10.5 Hz]. Dehydration of **8** furnished the desired isocyanide **9** in 80% yield. An analogous procedure was employed to convert the tetrabenzoyl-α-mannosyl azide **10**[26] into the corresponding isocyanide **13a** and **13b** in excellent overall yields (98% for **13a** + **13b**). The ^{1}H NMR spectrum shows that **12** is an inseparable mixture of α and β anomers.[27] The mannosyl formamide **12** was dehydrated and afforded a mixture of α and β anomers (**13a** + **13b**), which was easily separated by silica-gel chromatography (α/β = 7:3). The α-anomeric configuration was attributed to the major product (**13a**) by the aid of an NOE difference experiment performed on both compounds. Compound **13b** showed an NOE contact between 1-H (δ = 5.35 ppm) and 3-H (δ = 5.60 ppm) that clearly demonstrated the β configuration of compound **13b**. This contact is absent in the case of the α anomer **13a**.

The synthesis of the 6-amino derivatives **20**[30] and **21** is illustrated in Scheme 2. Compounds **14**[28] and **15**,[29] obtained from the corresponding commercially available α-methyl glycosides, were submitted to acetolysis and provided the 6-*O*-acetyl derivatives **16** and **17** in almost quantitative yields. Deacetylation, followed by Mitsunobu reaction with tetrachlorophthalimide, provided the *N*-protected derivatives **18** and **19** in excellent yields. The free amines **20** and **21** were generated by deprotection of the corresponding TCP derivatives, **18** and **19**, with ethanolic hydrazine and were immediately used in the following coupling with the appropriate isocyanates. To synthesize the ureas, the isocyanides **9** or **13a** were dissolved in anhydrous acetonitrile and treated with pyridine *N*-oxide in the presence of a catalytic amount of iodine.[31] The resulting isocyanates **22** and **23** were not isolated but they directly afforded protected ureas **24** and **25**, respectively, in high yields upon addition of the amine acceptors (Scheme 3). In the ^{13}C NMR spectra, the ureido carbonyl groups of **24** and **25** exhibit signals at δ = 156.6 and 157.7 ppm, respectively, while the ureido anomeric carbon atoms resonate at δ = 78.5 and 77.5 ppm. Hydrogenolysis, followed by Zémplen deacetylation, afforded ureas **1**[17]and **2** quantitatively.

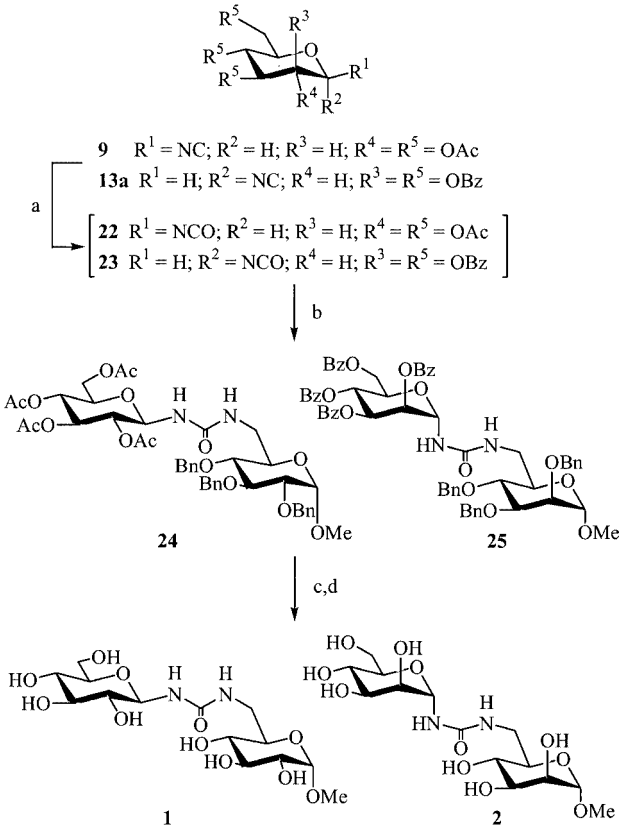


Scheme 1. Reagents and conditions: a) H_2, Pd/C, TEA, diethyl ether/hexane (2:1), 3 h; b) AcOCHO, 10 h; c) PPh_3, CBr_4, TEA, dry DCM, −20 °C, 30 min

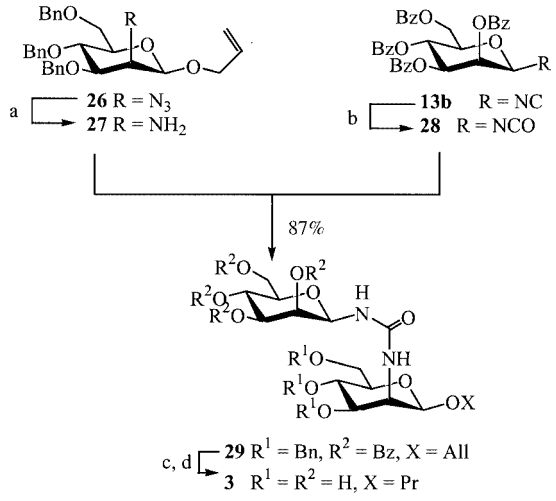


Scheme 2. Reagents and conditions: a) $ZnCl_2$ in acetic anhydride/acetic acid (20:1) for **16**, 1 h, 97%; Ac_2O/TFA (4:1) for **17**, 45 min, 99%; b) 1 M NaOMe, dry MeOH; c) TCPNH, DIAD, PPh_3, dry THF, 30 min, 99%; d) NH_2NH_2, EtOH, 30 min, reflux

Compound **13b** was employed in the synthesis of **29**, a β-mannosylurea, in which bridging occurs at the 2-axial position of the mannosamine derivative **27** (see Scheme 4). This synthesis was achieved from the corresponding allyl 2-azidomannoside **26**[32] by a Staudinger reaction in 90% yield.



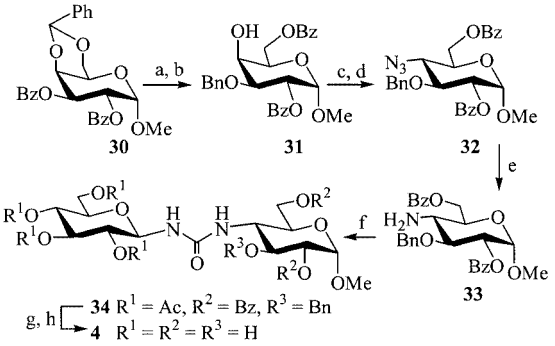
Scheme 3. Reagents and conditions: a) PNO, I_2 cat., MS (3 Å), dry CH_3CN, 10 min; b) **20**/**21**, 30 min, 89% (**24**), 82% (**25**); c) H_2, Pd/C, dry MeOH, 10 h; d) 1 M NaOMe, dry MeOH, 2 h, 100%



Scheme 4. a) PPh_3, H_2O, THF, reflux, 4 h 90%; b) PNO, I_2 cat., MS (3 Å), dry CH_3CN, 10 min; c) H_2, Pd/C, MeOH, 18 h; d) 1 M NaOMe, dry MeOH, 1 h, 100%

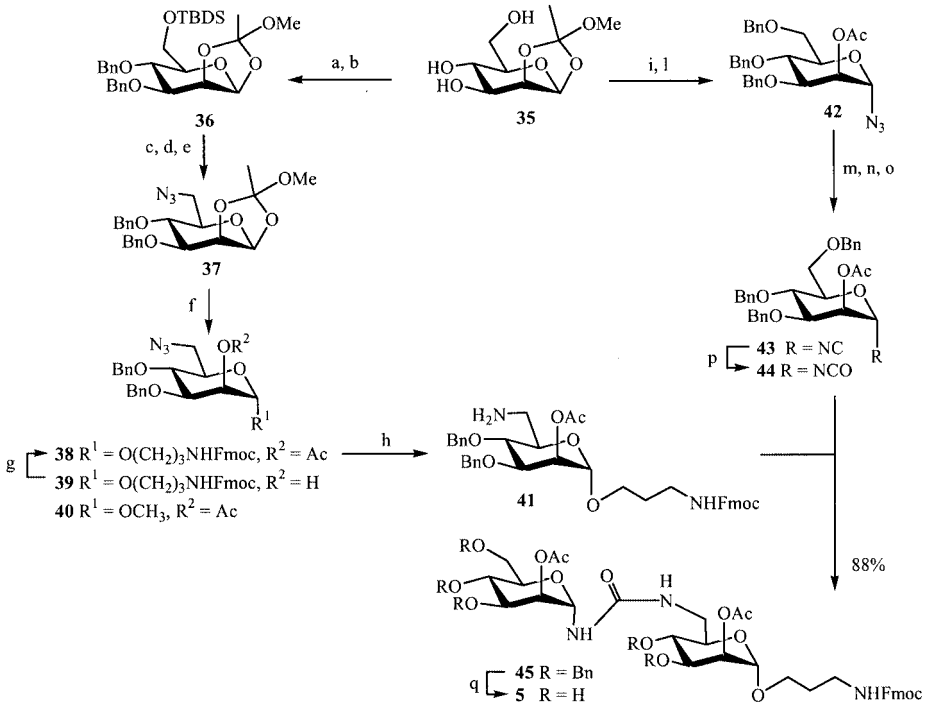
Interestingly, urea **29** was obtained in 87% yield in the β-anomeric configuration at C-1′ only, thus showing that no anomeric equilibration occurred during the formation of the isocyanate (see Scheme 4). A NOESY experiment performed on compound **29** shows a weak contact between 1′-H (δ = 5.87 ppm) and 3′-H (δ = 5.73 ppm), consistent with a β-ureido bond; moreover, in the ^{13}C NMR spectrum, the signals of C-2 (δ = 50.9 ppm), C-1′ (δ = 79.0 ppm) and CONH (δ = 157.3 ppm) confirm the presence of a (1→2)-ureido bond between the saccharide units. Compound **29** was first debenzylated and after Zémplen deacylation it afforded **3** in quantitative yields.

The (1→4)-ureido connection was also explored using **9** as a donor and the 4-aminoglucoside **33** as an acceptor (see Scheme 5).



Scheme 5. Reagents and conditions: a) 90% TFA, DCM, 0 °C; b) Bu_2SnO, TBAI, BnBr, toluene, 60 °C, 77%; c) McCl, dry Py, 0 °C, 2 h; d) NaN_3, dry DMF, 90 °C, 1 h, 91%; e) Pd/C, dry MeOH, H_2, 3 h, 100%; f) **22**, 30 min, 94%, g) H_2, Pd/C, MeOH, 8 h; h) 1 M NaOMe, dry MeOH, 1 h, 100%

Removal of the benzylidene protecting group from compound **30**[33] under acidic conditions (90% TFA in dichloromethane) and subsequent selective monobenzylation gave compound **31**. It is worthy of note that the expected 3-*O*-benzoyl-6-*O*-benzyl derivative was not observed. This can be due to a double migration of the benzoyl group from the 3- to the 6-position, which is favoured by a *syn* arrangement of the 3,4,6-hydroxy groups. In the ^1H NMR spectrum, 3-H and 4-H resonate in the range δ = 3.85−4.15 ppm, while the signals of 6a-H and 6b-H are present as two doublets of doublets at δ = 4.47 and 4.63 ppm, respectively, typical of a CH_2OBz group. The 4-azido epimerization was achieved by an S_N2 reaction on the monochloromesyl[34] (Mc) derivative of **31** and it afforded **32** in excellent yields. The new saccharidic configuration was confirmed by ^1H NMR spectrum, in which the 5-H signal is shifted upfield, while those of 3-H and 4-H are split at δ = 4.16 and 3.72 ppm, respectively, into two triplets, as expected for a glucosidic ring. Subsequent hydrogenolysis in methanol gave the corresponding highly stable amine **33**, which was completely characterized. In the ^1H NMR spectrum, the 4-H signal is shifted upfield (δ = 3.01 ppm), while in the ^{13}C NMR spectrum C-4 resonates at δ = 53.4 ppm. Urea **34** was obtained by reaction of amine **33** with isocyanide **9** under the usual conditions. The presence of both saccharide portions was confirmed by the acetyl (δ = 2.01−2.04 ppm) and methoxy (δ = 3.33 ppm) signals in the ^1H NMR spectrum; the ureido carbonyl signal appears in the ^{13}C NMR spectrum at δ = 155.9 ppm and that of C-1 at δ = 97.2 ppm, while the C-1′ signal is shifted to δ = 80.1 ppm. This compound was deprotected under the same conditions used for **1**−**3** and afforded compound **4**.



Scheme 6. Reagents and conditions: a) imidazole, TBDMSCl, dry THF, 3 h; b) BnBr, NaH, dry DMF, TBAI, 0 °C, 10 h, 73% overall yield (o.y.); c) TBAF, THF, −78 °C, 1 h, then r.t., 2 h; d) McCl, Py, 45 min; e) NaN_3, dry DMF, 1.5 h, 66% o.y.; f) $HO(CH_2)_3NHFmoc$, TMSOTf, dry DCM, 1 h; g) Ac_2O, Py, 1 h; h) H_2, Pd/C, TEA, dry EtOAc, 10 h; i) BnBr, NaH, dry DMF, 15 h; l) $TMSN_3$, $SnCl_4$, dry DCM, 3 h, 81% o.y.; m) H_2, Pd/C, TEA, diethyl ether/hexane (2:1), 3 h; n) AcOCHO, 12 h; o) PPh_3, CBr_4, TEA, dry DCM, 20 min, 68% o.y. for α anomer; p) PNO, I_2 cat., MS (3 Å), dry CH_3CN, 10 min; q) H_2, Pd/C, dry MeOH, 10 min, 100%

The synthesis of compound **5** required a more complex protecting-group pattern than that of the mannosidic urea **2**, both for the donor and the acceptor (see Scheme 6). Moreover, the introduction of a properly *N*-protected propylamino spacer at the anomeric position of the pseudodisaccharide makes the molecule apt to conjugation for biological testing. A common building block was identified in the orthoester **35**. Selective silylation at the primary position and subsequent benzylation provided compound **36**, which was readily converted into the corresponding 6-azido derivative **37** after desilylation and nucleophilic displacement of the corresponding monochloromesylate. The ring opening of the orthoester with Fmoc-aminopropanol[35] in the presence of trimethylsilyl triflate yielded **38** along with two by-products. The ^1H NMR spectrum shows that the major by-product, **39**, was derived from the 2-*O*-deacetylation of **38**. Compound **39** was easily recycled by conversion into **38** (acetic anhydride, pyridine). The minor component, identified as compound **40** (CH_3O signal at δ = 3.37 ppm), was produced by intramolecular rearrangement of the orthoester moiety under Lewis acid catalysis. The synthesis of the donor involved benzylation of **35**, followed by opening of the orthoester ring with trimethylsilylazide in the presence of a catalytic amount of $SnCl_4$. Conversion of the azido group into the isocyanide **43** (α/β mixture in 85:15 ratio) was achieved as described previously. The azido group in **38** was selectively hydrogenated in dry ethyl acetate in the absence of concomitant benzyl removal and acetyl transfer. The resulting amine **41** was coupled in the final step with isocyanate **44** under the same conditions as for compounds **24**, **25**, **29**, and **34**. Hydrogenolysis of compound **45** gave the 2,2′-di-*O*-acetylureidomannosidic disaccharide **5** in quantitative yields. Finally, compounds **1**−**5** were all carefully purified by Sephadex chromatography with a G10-120 column.

Conclusion

In this paper we reported the synthesis of a series of intersaccharidic urea derivatives, in which different monosaccharidic units are used as donors and acceptors. The anomeric position was easily connected to primary and secondary positions, even in the case of axial amino groups. These compounds are suitable to be employed as building blocks for more complex elongations and in the synthesis of stabilized oligosaccharide analogues. Work in this direction is under way in our laboratory.

Experimental Section

List of Abbreviations: APT: attached proton test; DCM: dichloromethane; DIAD: diisopropyl azadicarboxylate; McCl: monochloromethanesulfonyl chloride; PNO: pyridine *N*-oxide; TBDMSCl: *tert*-butyldimethylsilyl chloride; TBAB: tetrabutylammonium bromide; TBAF: tetrabutylammonium fluoride; TBAI: tetrabutylammonium iodide; TCPNH: tetrachlorophthalimide; TEA: triethylamine; TFA: trifluoroacetic acid; THF: tetrahydrofuran; TLC: thin layer chromatography; $TMSN_3$: trimethylsilyl azide; TMSOTf: trimethylsilyl trifluoromethansulfonate.

General Remarks: Reagents and dry solvents were added with oven-dried syringes through septa. Acetonitrile was dried with activated molecular sieves (4 Å) and distilled from calcium hydride. THF and DCM were freshly distilled from sodium/benzophenone and calcium hydride, respectively. Flash chromatography was performed on BDH silica gel (40−63 μm particle size). TLC was performed on Merck silica gel 60 F_{254} plates, and visualized by charring either with a mixture of 96% sulfuric acid (50 mL), methanol (450 mL) and H_2O (450 mL) or with a solution of $(NH_4)_6Mo_7O_{24}$ (21 g), of $CeSO_4$ (1 g) and of 96% H_2SO_4 (31 mL) in 500 mL of H_2O, followed by heating. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC 200, AC 300 or AVANCE 400 instrument. The aromatic signals are omitted. Specific optical rotations ($[\alpha]_D$) were determined with a Perkin−Elmer 241 polarimeter at 20 °C. IR spectra were recorded with a Perkin−Elmer 681 Infrared Spectrophotometer. Melting points were determined with a Büchi apparatus and are uncorrected. Elemental analyses were performed using the Carlo Erba elemental analyzer 1108. Mass spectral analyses were performed with a Bruker OmniFLEX™ Bench-top MALDI-TOF instrument.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl Isocyanide (9):[22] A solution of compound **6**[23] (1.87 g, 5.01 mmol), a catalytic amount of palladium on activated charcoal and TEA (2.1 mL, 15.0 mmol) and a mixture of diethyl ether/hexane (2:1; 100 mL) was stirred under hydrogen for 3 h. The reaction was monitored by TLC (pure EtOAc) and the spot corresponding to the azido compound disappeared. Meanwhile, a solution of acetoformic anhydride was prepared by heating a solution of acetic anhydride (10 mL, 100 mmol) and formic acid (6 mL, 150 mmol) at 60 °C for 3 h. The resulting solution was cooled to room temperature, then added to the amine solution and left under vigorous stirring overnight. The mixture was filtered through Celite and the crude solid obtained after concentration was purified by silica-gel filtration (AcOET) affording formamide **8** (1.82 g, 97%). The formamide was dissolved in dry DCM (60 mL) under nitrogen, together with carbon tetrabromide (4.97 g, 14.99 mmol) and TEA (2.8 mL, 20.0 mmol); the resulting solution was cooled to −20 °C. Triphenylphosphane (3.93 g, 14.95 mmol) in dry DCM (5 mL) was added. After stirring at −20 °C for 30 min, the mixture was diluted with DCM, washed with a saturated solution of ammonium chloride and water, dried with anhydrous sodium sulfate and concentrated. Purification by flash chromatography (EtOAc/hexane, 8:2) afforded isocyanide **9**[22] (1.39 g, 80%).

2,3,4,6-Tetra-*O*-acetyl-*N*-formyl-β-D-glucopyranosylamine (8) [(*Z*) Isomer]:[25] White solid. M.p. 146−148 °C. $[\alpha]_D^{20} = +20.7$ (c = 0.5, $CHCl_3$). IR (KBr, cm^{-1}): $\tilde{\nu}_{max}$ = 3400 (NH), 1750 (CO acetyl), 1700 (CO formyl). ^1H NMR (200 MHz, $CDCl_3$, ppm): δ = 2.03, 2.04, 2.07, 2.09 (s, 3 H, 4 $COCH_3$), 3.83 (ddd, $J_{5,6a}$ = 2.2, $J_{5,6b}$ = 4.5, $J_{5,4}$ = 9.5 Hz, 1 H, 5-H), 4.09 (dd, $J_{6a,5}$ = 2.2, $J_{6a,6b}$ = 12.5 Hz, 1 H, 6a-H), 4.30 (dd, $J_{6b,5}$ = 4.5, $J_{6b,6a}$ = 12.5 Hz, 1 H, 6b-H), 4.94 (t, $J_{2,1} = J_{2,3}$ = 9.5 Hz, 1 H, 2-H), 5.07 (t, $J_{4,5} = J_{4,3}$ = 9.5 Hz, 1 H, 4-H), 5.31 (t, $J_{1,2} = J_{1,NH}$ = 9.5 Hz, 1 H, 1-H), 5.32 (t, $J_{3,2} = J_{3,4}$ = 9.5 Hz, 1 H, 3-H), 6.32 (d, $J_{NH,1}$ = 9.5 Hz, 1 H, NH), 8.25 (s, 1 H, CHO). ^{13}C NMR (50 MHz, $CDCl_3$, APT, ppm): δ = 20.4, 20.5, 20.6, 20.7 ($COCH_3$), 61.3 (C-6), 67.9 (C-4), 70.3 (C-2), 72.7 (C-3), 73.7 (C-5), 76.6 (C-1), 161.0 (NH*C*O), 169.4, 169.5, 170.1, 170.7 (*C*OCH_3). $C_{15}H_{21}NO_{10}$ (375.3): calcd. C 48.00, H 5.64, N 3.73; found C 48.16, H 5.58, N 3.76. MALDI-TOF MS: m/z = 397.6 $[M + Na]^+$.

Compound 9: White solid. M.p. 104−105 °C. $[\alpha]_D^{20} = +6.6$ (c = 1.0, $CHCl_3$). IR (KBr, cm^{-1}): $\tilde{\nu}_{max}$ = 2160 (NC), 1751 (CO). ^1H NMR (200 MHz, $CDCl_3$, ppm): δ = 2.12, 2.12, 2.03, 2.02 (each s, each 3 H, 4 $COCH_3$), 3.74 (ddd, $J_{5,6a}$ = 2.2, $J_{5,6b}$ = 4.6, $J_{5,4}$ = 9.5 Hz, 1 H, 5-H), 4.15 (dd, $J_{6a,5}$ = 2.2, $J_{6a,6b}$ = 12.5 Hz, 1 H, 6a-H), 4.26 (dd, $J_{6b,5}$ = 4.6, $J_{6b,6a}$ = 12.5 Hz, 1 H, 6b-H), 4.82 (br. d, 1 H, 1-H), 5.09−5.20 (m, 3 H, 2-H, 3-H, 4-H). ^{13}C NMR (50 MHz, $CDCl_3$, APT, ppm): δ = 20.4, 20.7 ($COCH_3$), 61.3 (C-6), 67.4 (C-4), 70.8 (C-2), 72.2 (C-3), 74.7 (C-5), 79.6 (C-1), 164.7 (CN), 169.5, 170.2, 170.8 (CO). $C_{15}H_{19}NO_9$ (357.3): calcd. C 50.42, H 5.36, N 3.92; found C 50.25, H 5.47, N 3.84. MALDI-TOF MS: m/z = 379.4 $[M + Na]^+$.

2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl Isocyanide (13a) and 2,3,4,6-Tetra-*O*-benzoyl-β-D-mannopyranosyl Isocyanide (13b): Compound **10**[26] (3.11 g, 5.00 mmol) was submitted to the same procedure as for compound **9**, affording formamide **12** (3.06 g, 98%). Compound **12** was converted into a mixture of **13a** (α anomer) and **13b** (β anomer) (2.96 g, 100%) as for **8**. This mixture was separated by flash chromatography (EtOAc/hexane, 6:4) and a 7:3 ratio was determined. Compound **13a** resulted to be the major product according to an NOE difference experiment (see discussion in the text).

Compound 13a: White solid. M.p. 65−68 °C. $[\alpha]_D^{20} = -37.6$ (c = 1.0, $CHCl_3$). IR (KBr, cm^{-1}): $\tilde{\nu}_{max}$ = 2131 (NC), 1738 (CO). ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 4.51 (dd, $J_{6a,5}$ = 3.8, $J_{6a,6b}$ = 12.5 Hz, 1 H, 6a-H), 4.58 (ddd, $J_{5,6b}$ = 1.9, $J_{5,6a}$ = 3.8, $J_{5,4}$ = 9.9 Hz, 1 H, 5-H), 4.77 (dd, $J_{6b,5}$ = 1.9, $J_{6b,6a}$ = 12.5 Hz, 1 H, 6b-H), 5.58 (d, $J_{1,2}$ = 1.7 Hz, 1 H, 1-H), 5.85 (dd, $J_{2,1}$ = 1.6, $J_{2,3}$ = 3.1 Hz, 1 H, 2-H), 5.96 (dd, $J_{3,2}$ = 3.1, $J_{3,4}$ = 9.9 Hz, 1 H, 3-H), 6.18 (t, $J_{4,3} = J_{4,5}$ = 9.9 Hz, 1 H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$, APT, ppm): δ = 61.8 (C-6), 65.5, 68.9, 69.9 (C-2, C-3, C-4), 72.1 (C-5), 79.1 (C-1), 164.9 (CN), 165.2, 165.9, 166.8, (CO). $C_{35}H_{27}NO_9$ (605.6): calcd. C 69.42, H 4.49, N 2.31; found C 69.38, H 4.51, N 2.32. MALDI-TOF MS: m/z = 628.1 $[M + Na]^+$.

Compound 13b: White solid. M.p. 74−75 °C. $[\alpha]_D^{20} = -101.8$ (c = 1.0, $CHCl_3$). IR (KBr, cm^{-1}): $\tilde{\nu}_{max}$ = 2149 (NC), 1734 (CO). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 4.19 (ddd, $J_{5,6b}$ = 2.5, $J_{5,6a}$ = 4.8, $J_{5,4}$ = 9.8 Hz, 1 H, 5-H), 4.53 (dd, $J_{6a,5}$ = 4.8, $J_{6a,6b}$ = 12.6 Hz, 1 H, 6a-H), 4.76 (dd, $J_{6b,5}$ = 2.5, $J_{6b,6a}$ = 12.6 Hz, 1 H, 6b-H), 5.35 (d, $J_{1,2}$ = 1.2 Hz, 1 H, 1-H), 5.60 (dd, $J_{3,2}$ = 2.6, $J_{3,4}$ = 9.8 Hz, 1 H, 3-H), 6.02 (t, $J_{4,3} = J_{4,5}$ = 9.8 Hz, 1 H, 4-H), 6.08 (d, $J_{2,3}$ = 2.6 Hz, 1 H, 2-H). ^{13}C NMR (100 MHz, $CDCl_3$, APT, ppm): δ = 62.7 (C-6), 66.0, 69.4, 71.5, 75.5 (C-2, C-3, C-4, C-5), 79.2 (C-1), 165.0 (*C*N), 165.1, 165.5, 165.9, 166.4 (*C*O). $C_{35}H_{27}NO_9$ (605.6): calcd. C 69.42, H 4.49, N 2.31; found C 69.46, H 4.48, N 2.31. MALDI-TOF MS: m/z = 628.3 $[M + Na]^+$.

Methyl 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (16): Compound **14**[28] (6.00 g, 10.8 mmol) was dissolved in a mixture of acetic anhydride (20 mL) and acetic acid (10 mL). Melted $ZnCl_2$ (12.0 g, 86.4 mmol), dissolved in the same mixture (10 mL), was added rapidly to the first solution and left at room temperature for 1 h. Saturated $NaHCO_3$ (40 mL) was added dropwise while cooling with an ice bath, then the mixture was extracted with DCM (2 × 50 mL) and the combined organic layers were washed with water, dried with anhydrous sodium sulfate and concentrated. The resulting brown oil was purified by flash chromatography (toluene/diethyl ether, 9:1) to afford 5.32 g (97%) of a yellow oil. $[\alpha]_D^{20} = +28.6$ (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.02 (s, 3 H, $COCH_3$), 3.38 (s, 3 H, OCH_3), 3.47 (dd, $J_{4,5}$ = 10.0, $J_{4,3}$ = 9.0 Hz, 1 H, 4-H), 3.53 (dd, $J_{2,1}$ = 3.6, $J_{2,3}$ = 9.6 Hz, 1 H, 2-H), 3.81 (ddd, $J_{5,6a}$ = 3.8, $J_{5,4}$ = 10.1 Hz, 1 H, 5-H), 4.01 (dd, $J_{3,2}$ = 9.6, $J_{3,4}$ = 9.0 Hz, 1 H, 3-H), 4.25−4.35 (m, 2 H, 6a-H, 6b-H), 4.50−5.00 (m, 7 H, 1-H, 3 CH_2Ph). The ^1H NMR spectroscopic data correspond to those reported in ref.[36] ^{13}C NMR

(50 MHz, $CDCl_3$, APT, ppm): δ = 20.8 ($CO\mathit{C}H_3$), 55.2 ($O\mathit{C}H_3$), 63.0 (C-6), 68.5, 77.3, 79.8, 82.0 (C-2, C-3, C-4, C-5), 73.4, 75.0, 77.7 (3 C, $\mathit{C}H_2Ph$), 99.0 (C-1), 170.7 ($\mathit{C}O$).

Methyl 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (17): Compound **15**[29] (6.00 g, 10.82 mmol) was dissolved in a mixture of acetic anhydride (20 mL) and TFA (5 mL). After 45 min at room temperature, the mixture was cooled to 0 °C and saturated $NaHCO_3$ (20 mL) was added. The resulting mixture was extracted with DCM (2 × 50 mL) and the combined organic layers were washed with water, dried with anhydrous sodium sulfate, and concentrated. Purification by flash chromatography (hexane/EtOAc, 8:2) gave a colourless oil (5.37 g, 98%). $[\alpha]_D^{20}$ = +26.9 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.01 (s, 3 H, $COCH_3$), 3.37 (s, 3 H, OCH_3), 3.48 (t, $J_{4,3} = J_{4,5}$ = 9.6 Hz, 1 H, 4-H), 3.52 (dd, $J_{2,1}$ = 3.7, $J_{2,3}$ = 9.6 Hz, 1 H, 2-H), 3.81 (ddd, $J_{5,6a}$ = 3.4, $J_{5,4}$ = 10.1 Hz, 1 H, 5-H), 4.00 (t, $J_{3,2} = J_{3,4}$ = 9.6 Hz, 1 H, 3-H), 4.25−4.35 (m, 2 H, 6a-H, 6b-H), 4.52−5.03 (m, 7 H, 1-H, 3 CH_2Ph). ^{13}C NMR (50 MHz, $CDCl_3$, APT, ppm): δ = 20.8 ($CO\mathit{C}H_3$), 55.2 ($O\mathit{C}H_3$), 63.0 (C-6), 68.5, 78.8, 79.8, 81.6 (C-2, C-3, C-4, C-5), 73.4, 75.0, 75.7 (3 C, $\mathit{C}H_2$Ph), 98.0 (C-1), 170.8 ($\mathit{C}O$). $C_{30}H_{34}O_7$ (506.6): calcd. C 71.13, H 6.76; found C 71.01, H 6.82. MALDI-TOF MS: *m*/*z* = 528.9 $[M + Na]^+$.

Methyl 2,3,4-Tri-*O*-benzyl-6-deoxy-6-(4,5,6,7-tetrachlorophthalimid-2-yl)-α-D-glucopyranoside (18): Compound **16** (1.09 g, 2.15 mmol) was deacetylated according to Zemplén. A mixture of the resulting 6-OH derivative, TCPNH (0.62 g, 2.15 mmol) and PPh_3 (0.68 g, 2.48 mmol) was dissolved in dry THF (30 mL) under nitrogen. A solution of DIAD (500 μL, 2.48 mmol) in dry THF (5 mL) was added dropwise. The reaction was complete in 30 min (TLC EtOAc/hexane, 3:7). The solvent was removed under reduced pressure and the residue dissolved in DCM (30 mL) and washed twice with water. The organic layers were dried, concentrated, and purified by flash chromatography (EtOAc/hexane, 1:9) to furnish **18** (1.56 g, 99%) as an amorphous white solid. $[\alpha]_D^{20}$ = +28.1 (*c* = 1.2, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, ppm): δ = 3.34 (s, 3 H, OCH_3), 3.45−3.57 (m, 1 H, 5-H), 3.69−4.01 (m, 5 H, 2-H, 3-H, 4-H, 6a-H, 6b-H), 4.55−4.90 (m, 7 H, 1-H, 3 CH_2Ph). ^{13}C NMR (50 MHz, $CDCl_3$, APT, ppm): δ = 39.2 (C-6), 55.4 (OCH_3), 65.5 (C-5), 70.6, 75.3, 75.9 ($\mathit{C}H_2$Ph), 74.0, 79.6, 80.7 (C-2, C-3, C-4), 97.7 (C-1), 163.3 (CO phthal). $C_{35}H_{27}NO_9$ (731.4): calcd. C 59.11, H 4.27, N 1.91; found C 59.18, H 4.23, N 1.85. MALDI-TOF MS: *m*/*z* = 754.0 $[M + Na]^+$.

Methyl 2,3,4-Tri-*O*-benzyl-6-deoxy-6-(4,5,6,7-tetrachlorophtalimid-2-yl)-α-D-mannopyranoside (19): Compound **17** (0.90 g, 1.78 mmol) was submitted to the same procedure as for compound **16** to afford **19** (1.28 g, 99%) as a colourless foam. $[\alpha]_D^{20}$ = +43.0 (*c* = 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 3.26 (s, 3 H, OCH_3), 3.39 (t, $J_{4,3} = J_{4,5}$ = 9.6 Hz, 1 H, 4-H), 3.50 (dd, $J_{2,1}$ = 3.4, $J_{2,3}$ = 9.6 Hz, 1 H, 2-H), 3.72 (dd, $J_{6a,5}$ = 7.1, $J_{6a,6b}$ = 13.7 Hz, 1 H, 6a-H), 3.92−4.10 (m, 1 H, 3-H, 5-H, 6b-H), 4.52 (d, $J_{1,2}$ = 3.4 Hz, 1 H, 1-H), 4.57 (d, *J* = 12.0 Hz, 1 H, CHHPh), 4.61 (d, *J* = 12.0 Hz, 1 H, CHHPh), 4.73 (d, *J* = 11.0 Hz, 1 H, CHHPh), 4.75 (d, *J* = 12.0 Hz, 1 H, CHHPh), 4.97 (d, *J* = 12.0 Hz, 1 H, CHHPh), 4.99 (d, *J* = 11.0 Hz, 1 H, CHHPh). ^{13}C NMR (50 MHz, $CDCl_3$, APT, ppm): δ = 38.9 (C-6), 55.2 (OCH_3), 65.1 (C-5), 71.6, 72.2, 75.3, ($\mathit{C}H_2$Ph), 74.7, 78.6, 80.4 (C-2, C-3, C-4), 97.3 (C-1), 163.2 (CO phthal). $C_{35}H_{27}NO_9$ (731.4): calcd. C 59.11, H 4.27, N 1.91; found C 59.00, H 4.35, N 1.94. MALDI-TOF MS: *m*/*z* = 754.1 $[M + Na]^+$.

Methyl 6-Amino-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside (20)[30] and Methyl 6-Amino-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-mannopyranoside (21): Compound **18** or **19** (1.49 g, 2.03 mmol) and 85% hydrazine (385 μL, 6.52 mmol) were dissolved in absolute ethanol (30 mL) and refluxed for 30 min, until a white precipitate was formed and the starting material had disappeared (TLC: EtOAc/hexane, 1:1). After cooling, the residue was dissolved in a mixture of DCM (50 mL) and 5% NaOH (80 mL). The aqueous phase was extracted twice with DCM and the combined organic layers were washed with water, dried with anhydrous sodium sulfate and concentrated. The crude products **20** and **21** were employed in the next reaction without further purification.

Allyl 2-Amino-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-mannopyranoside (27): Compound **26**[32] (300 mg, 0.58 mmol) and triphenylphosphane (305 mg, 1.16 mmol) were dissolved in THF (5 mL). Water (21 μL, 1.16 mmol) was added and the solution was refluxed for 4 h (TLC: EtOAc/hexane, 9:1). The mixture was concentrated in vacuo and purified by flash chromatography (EtOAc/hexane, 8:2) to yield **27** (257 mg, 90%) as a pale yellow syrup. $[\alpha]_D^{20}$ = −45.7 (*c* = 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, ppm): δ = 3.42 (ddd, $J_{5,6a}$ = 3.9, $J_{5,6a}$ = 4.4, $J_{5,4}$ = 9.3 Hz, 1 H, 5-H), 3.46 (br. d, $J_{2,3}$ = 4.0 Hz, 1 H, 2-H), 3.58 (dd, $J_{6a,6b}$ = 9.0, $J_{6a,5}$ = 3.9 Hz, 1 H, 6a-H), 3.65−3.87 (m, 2 H, 3-H, 6b-H), 3.84 (t, $J_{4,5} = J_{4,3}$ = 9.3 Hz, 1 H, 4-H), 4.09 (br. dd, $J_{A,B}$ = 12.8, $J_{A,X}$ = 6.3 Hz, 1 H, C$\mathit{H}_A$$H_B$CH=$CH_2$), 4.41 (br. dd, $J_{B,A}$ = 12.8, $J_{B,X}$ = 4.8 Hz, 1 H, $CH_A\mathit{H}_B$CH=CH_2), 4.40−4.66 (m, 7 H, CH_2Ph, 2 CHHPh, 1-H, NH_2), 4.74 (d, *J* = 11.8 Hz, 1 H, CHHPh), 4.89 (d, *J* = 11.0 Hz, 1 H, CHHPh), 5.13−5.24 (m, 1 H, CH=CHH), 5.21−5.35 (m, 1 H, CH=CHH), 5.82−6.06 (m, 1 H, CH=CH_2). ^{13}C NMR (50 MHz, $CDCl_3$, APT, ppm): δ = 52.0 (C-2), 69.3, 69.8 (C-6, O$\mathit{C}H_2$CH=CH_2), 71.1, 73.4, 75.0 (3 C, $\mathit{C}H_2$Ph), 74.1, 75.4, 82.2 (C-3, C-4, C-5), 99.7 (C-1), 117.4 (OCH$_2$CH=CH_2), 134.1 (OCH$_2\mathit{C}$H=CH_2). $C_{30}H_{35}NO_5$ (489.6): calcd. C 73.59, H 7.21, N 2.86; found C 73.72, H 7.10, N 2.80. MALDI-TOF MS: *m*/*z* = 490.8 $[M + H]^+$.

Methyl 2,6-Di-*O*-benzoyl-3-*O*-benzyl-α-D-galactopyranoside (31): A solution of **30**[33] (3.50 g, 7.13 mmol) in DCM (100 mL) was cooled to 0 °C. 90% TFA (20 mL) was added and the mixture was left for 30 min. The reaction was quenched with saturated $NaHCO_3$ (40 mL) in an ice bath. The mixture was diluted with DCM (100 mL) and $NaHCO_3$ (100 mL) and extracted twice; the combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and concentrated. The resulting diol was dissolved in dry toluene (300 mL) and dibutyltin oxide (2.60 g, 10.65 mmol) was added in one portion. The mixture was refluxed for 3 h, then concentrated to 1/3 of its volume and cooled to 50−60 °C. TBAI (3.95 g, 10.65 mmol) and BnBr (2.5 mL, 21.3 mmol) were added; the temperature was raised to 95 °C and vigorous stirring was maintained overnight. The reaction was quenched with methanol (20 mL) and the solvent evaporated in vacuo. Flash chromatography afforded **31** (2.69 g, 77%) as a syrup. $[\alpha]_D^{20}$ = +96.3 (*c* = 1.0, $CHCl_3$). IR (KBr, cm^{-1}): $\tilde{\nu}_{max}$ = 3440 (OH), 1720 (CO). ^1H NMR (200 MHz, $CDCl_3$, ppm): δ = 3.38 (s, 3 H, OCH_3), 3.85−4.20 (m, 3 H, 3-H, 4-H, 5-H), 4.47 (dd, $J_{6a,6b}$ = 11.2, $J_{6a,5}$ = 6.5 Hz, 1 H, 6a-H), 4.63 (dd, $J_{6b,6a}$ = 11.2, $J_{6b,5}$ = 5.2 Hz, 1 H, 6b-H), 4.52 (d, *J* = 12.0 Hz, 1 H, CHHPh), 4.64 (d, *J* = 12.0 Hz, 1 H, CHHPh), 5.19 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 5.35 (dd, $J_{2,1}$ = 3.6, $J_{2,3}$ = 9.6 Hz, 1 H, 2-H). ^{13}C NMR (50 MHz, $CDCl_3$, APT, ppm): δ = 55.4 (CH_3O), 63.7 (C-6), 68.3 (C-2), 68.9 (C-4), 69.8 (C-3), 70.8 (C-5), 74.2 ($\mathit{C}H_2$Ph), 97.7 (C-1), 165.2, 166.1, 166.5 (CO). $C_{28}H_{28}O_8$ (492.5): calcd. C 68.28, H 5.73; found C 68.15, H 5.79. MALDI-TOF MS: *m*/*z* = 514.8 $[M + Na]^+$.

Methyl 4-Azido-2,6-di-*O*-benzoyl-3-*O*-benzyl-4-deoxy-α-D-glucopyranoside (32): McCl (155 μL, 1.74 mmol) was added to a stirred solution of **31** (570 mg, 1.16 mmol) in pyridine (8 mL) at 0 °C un-

der nitrogen (TLC: diethyl ether/toluene, 3:7). After 2 h, the solution was diluted with cold water (30 mL) and diethyl ether (50 mL). The extracted organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and brine. After concentration, the crude monochloromesyl derivative was dissolved directly in dry DMF (3 mL). Sodium azide (225 mg, 3.45 mmol) was added under nitrogen and the resulting mixture heated to 90 °C. The reaction proceeded in 1 h. After cooling, the mixture was diluted with water (20 mL) and diethyl ether (30 mL) and extracted. The organic layer was dried with anhydrous sodium sulfate and concentrated in vacuo, affording a dark syrup which was purified by flash chromatography (toluene/diethyl ether, 8:2). Compound **32** (546 mg, 91%, two steps) was obtained as a colourless oil. $[\alpha]_D^{20} = -35.5$ (c = 1.0, $CHCl_3$). IR (CH_2Cl_2 solution, cm^{-1}): $\tilde{\nu}_{max}$ = 2112 (N_3), 1718 (CO). ^1H NMR (200 MHz, $CDCl_3$, ppm): δ = 3.40 (s, 3 H, OCH_3), 3.67 (t, $J_{4,5} = J_{4,3}$ = 9.0 Hz, 1 H, 4-H), 3.88 (ddd, $J_{5,6b}$ = 2.0, $J_{5,6a}$ = 4.3, $J_{5,4}$ = 9.0 Hz, 1 H, 5-H), 4.16 (t, $J_{3,4} = J_{3,2}$ = 9.0 Hz, 1 H, 3-H), 4.54 (dd, $J_{6a,5}$ = 4.3, $J_{6a,6b}$ = 12.1 Hz, 1 H, 6a-H), 4.66 (dd, $J_{6b,5}$ = 2.0, $J_{6b,6a}$ = 12.1 Hz, 1 H, 6b-H), 4.83 (s, 2 H, CH_2Ph), 5.06 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 5.15 (dd, $J_{2,1}$ = 3.6, $J_{2,3}$ = 9.0 Hz, 1 H, 2-H). ^{13}C NMR (50 MHz, $CDCl_3$, APT, ppm): δ = 55.5 (CH_3O), 62.2 (C-4), 63.4 (C-6), 68.0 (C-2), 73.8, 78.4 (C-3, C-5), 75.7 (CH_2Ph), 97.3 (C-1), 165.9, 166.2 (CO). $C_{28}H_{27}N_3O_7$ (517.5): calcd. C 64.98, H 5.26, N 8.12; found C 64.87, H 5.38, N 8.16. MALDI-TOF MS: m/z = 539.9 $[M + Na]^+$.

Methyl 4-Amino-2,6-di-*O*-benzoyl-3-*O*-benzyl-4-deoxy-α-D-glucopyranoside (33): Palladium on activated charcoal (2 mg) was added to a solution of **32** (235 mg, 0.45 mmol) in dry methanol (5 mL). Selective hydrogenolysis of the azido group was achieved quantitatively in 3 h whilst stirring under hydrogen. $[\alpha]_D^{20} = +18.9$ (c = 0.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 3.01 (t, $J_{4,5} = J_{4,3}$ = 9.7 Hz, 1 H, 4-H), 3.40 (s, 3 H, OCH_3), 3.87 (ddd, $J_{5,6b}$ = 4.9, $J_{5,6a}$ = 1.8, $J_{5,4}$ = 9.7 Hz, 1 H, 5-H), 3.93 (t, $J_{3,4} = J_{3,2}$ = 9.7 Hz, 1 H, 3-H), 4.56 (dd, $J_{6a,5}$ = 1.8, $J_{6a,6b}$ = 12.0 Hz, 1 H, 6a-H), 4.69 (dd, $J_{6b,5}$ = 4.9, $J_{6b,6a}$ = 12.0 Hz, 1 H, 6b-H), 4.68 (d, J = 11.1 Hz, 1 H, CHHPh), 4.89 (d, J = 11.1 Hz, 1 H, CHHPh), 5.10 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 5.16 (dd, $J_{2,1}$ = 3.6, $J_{2,3}$ = 9.7 Hz, 1 H, 2-H). ^{13}C NMR (75 MHz, $CDCl_3$, APT, ppm): δ = 53.4 (C-4), 55.2 (CH_3O), 63.9 (C-6), 75.5 (CH_2Ph), 71.0, 74.8, 74.8, (C-3, C-4, C-5), 80.1 (C-2), 97.5 (C-1), 165.9, 166.5 (CO). $C_{28}H_{29}NO_7$ (491.7): calcd. C 68.42, H 5.95, N 2.85; found C 68.38, H 5.97, N 2.86. MALDI-TOF MS: m/z = 492.6 $[M + H]^+$.

3,4-Di-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-1,2-*O*-(1-methoxyethylidene)-β-D-mannopyranose (36):[37] TBDMSCl (1.40 g, 9.33 mmol) was added to a stirred solution of the known orthoester **35**[38] (2.00 g, 8.49 mmol) and imidazole (1.30 g, 18.67 mmol) in THF (40 mL). After 3 h, the mixture was filtered through Celite and the filter cake washed copiously with diethyl ether. The combined filtrates were concentrated. The crude silyl derivative and TBAI (0.12 g, 0.32 mmol) were dissolved in DMF (40 mL), then benzyl bromide (3.30 mL, 27.79 mmol) and NaH (1.10 g, 27.79 mmol) were added portionwise during 30 min at 0 °C. The solution was warmed to room temperature and stirring continued overnight (TLC: EtOAc/hexane, 1:1). The solution was treated with iced water (50 mL) and the mixture extracted with DCM (2 × 50 mL). The combined organic layers were washed with water and brine, dried with anhydrous sodium sulfate, and concentrated to give a brown syrup, which was purified by flash chromatography (EtOAc/hexane, 3:7). The pure benzylated silyl orthoester **36** (3.29 g, 73%) was obtained as a clear yellow oil. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 0.06 [s, 6 H, $(CH_3)_2Si$], 0.89 [s, 9 H, $(CH_3)_3CSi$], 1.73 (s, 3 H, CH_3 orthoester), 3.18−3.24 (m, 1 H, 5-H), 3.27 (s, 3 H, OCH_3), 3.71 (dd, $J_{3,2}$ = 4.0, $J_{3,4}$ = 9.3 Hz, 1 H, 3-H), 3.80 (dd, $J_{6a,5}$ = 1.0, $J_{6a,6b}$ = 11.0 Hz, 1 H, 6a-H), 3.93 (dd, $J_{6b,5}$ = 3.3, $J_{6b,6a}$ = 11.0 Hz, 1 H, 6b-H), 3.99 (t, $J_{4,3} = J_{4,5}$ = 9.3 Hz, 1 H, 4-H), 4.34 (dd, $J_{2,1}$ = 2.1, $J_{2,3}$ = 4.0 Hz, 1 H, 2-H), 4.74 (d, J = 10.8 Hz, 1 H, CHHPh), 4.78 (d, J = 12.2 Hz, 1 H, CHHPh), 4.81 (d, J = 12.2 Hz, 1 H, CHHPh), 4.93 (d, J = 10.8 Hz, 1 H, CHHPh), 5.30 (d, $J_{1,2}$ = 2.1 Hz, 1 H, 1-H). The NMR spectroscopic data are consistent with those reported in ref.[38] $C_{29}H_{42}O_7$ (530.7): calcd. C 65.63, H 7.98; found C 65.64, H 7.98. MALDI-TOF MS: m/z = 553.2 $[M + Na]^+$.

6-Azido-3,4-di-*O*-benzyl-6-deoxy-1,2-*O*-(1-methoxyethylidene)-β-D-mannopyranose (37): Compound **36** (1.35 g, 2.55 mmol) was dissolved in dry THF (15 mL) under nitrogen and cooled to −78 °C. TBAF (1 M) in THF (900 μL, 3.06 mmol) was added dropwise. After 1 h, the solution was warmed to room temperature, until the reaction was complete (additional 2 h; TLC: EtOAc/hexane, 1:1). The mixture was diluted with ethyl acetate (30 mL), washed with brine, dried, and concentrated. The crude product was dissolved in pyridine (10 mL) and McCl (227 μL, 2.55 mmol) was added at 0 °C. The reaction mixture was stirred for 45 min (TLC: toluene/diethyl ether, 7:3). The mixture was diluted with cold water and extracted with DCM. The organic layers were washed with 1 M HCl, saturated $NaHCO_3$, and water. After drying, the solvent was evaporated and the resulting brown syrup employed as such in the next step. A mixture of the crude product and sodium azide (350 mg, 5.28 mmol) was dissolved in dry DMF (6 mL) under nitrogen and left whilst stirring at 80 °C overnight. After cooling, water (20 mL) and diethyl ether (30 mL) were added. The ethereal phase was washed twice with water, dried with anhydrous sodium sulfate, and concentrated, affording a brown foam which was purified by flash chromatography. Compound **37** (744 mg, 66% over 3 steps) was isolated as a colourless foam. $[\alpha]_D^{20} = +14.5$ (c = 1.0, $CHCl_3$). IR (KBr, cm^{-1}): $\tilde{\nu}_{max}$ = 2119 (N_3). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.75 (s, 3 H, CH_3 orthoester), 3.29 (s, 3 H, OCH_3), 3.36−3.43 (m, 2 H, 5-H, 6a-H), 3.51−3.59 (m, 1 H, 6b-H), 3.73 (dd, $J_{3,2}$ = 3.8, $J_{3,4}$ = 8.8 Hz, 1 H, 3-H), 3.88 (t, $J_{4,3} = J_{4,5}$ = 8.8 Hz, 1 H, 4-H), 4.42 (dd, $J_{2,1}$ = 1.4, $J_{2,3}$ = 3.8 Hz, 1 H, 2-H), 4.65 (d, J = 10.8 Hz, 1 H, CHHPh), 4.78 (s, 2 H, CH_2Ph), 4.97 (d, J = 10.8 Hz, 1 H, CHHPh), 5.34 (d, $J_{1,2}$ = 1.4 Hz, 1 H, 1-H). ^{13}C NMR (50 MHz, $CDCl_3$, APT, ppm): δ = 24.0 (CH_3 orthoester), 39.9 (C-6), 50.0 (OCH_3), 74.0, 74.7, 76.8, 78.7 (C-2, C-3, C-4, C-5), 72.4, 75.2 (CH_2Ph), 97.6 (C-1). $C_{23}H_{27}N_3O_6$ (441.5): calcd. C 62.57, H 6.16, N 9.52; found C 62.69, H 6.04, N 9.58. MALDI-TOF MS: m/z = 463.8 $[M + Na]^+$.

***N*-Fmoc-3′-aminopropyl 2-*O*-Acetyl-6-azido-3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside (38):** A solution of **37** (500 mg, 1.11 mmol) and *N*-Fmoc-3-aminopropanol[35] (660 mg, 2.22 mmol) in dry DCM (12 mL) was cooled to 0 °C. After 15 min, TMSOTf (60 μL, 0.33 mmol) was added dropwise. After 1 h, complete disappearance of the starting material was observed, revealing the formation of three spots in TLC (hexane/EtOAc, 6:4). The solution was diluted with DCM (30 mL) and washed with saturated sodium hydrogen carbonate, then water. The organic layers were dried and concentrated in vacuo affording a brown oil. Flash chromatography (hexane/EtOAc, 8:2) gave three products in a quantitative total yield: compound **38** (460 mg, 60%) corresponds to the intermediate spot, the most polar product was attributed to **39** (166 mg, 23%), while the less polar was identified as **40** (83 mg, 17%). Compound **38** was isolated as a yellow syrup. $[\alpha]_D^{20} = +36.9$ (c = 0.9, $CHCl_3$). IR (KBr, cm^{-1}): $\tilde{\nu}_{max}$ = 2120 (N_3), 1749, 1690 (CO). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.72−1.87 (m, 2 H, $OCH_2CH_2CH_2N$), 2.16 (s, 3 H, $COCH_3$), 3.18−3.31 (m, 2 H,

$OCH_2CH_2CH_2N$), 3.32−3.46 (m, 2 H, 6a,b-H), 3.69−3.81 (m, 3 H, 3-H, 4-H, 5-H), 3.90−3.94 (m, 1 H, $OCHCH_2CH_2N$), 4.17−4.25 (m, 1 H, $OCHCH_2CH_2N$), 3.87−4.01 (m, 1 H, $COOCHCH$), 4.16−4.28 (m, 1 H, $COOCHCH$), 4.34−4.42 (m, 1 H, $COOCH_2CH$), 4.52 (d, J = 11.0 Hz, 1 H, $CHHPh$), 4.56 (d, J = 11.1 Hz, 1 H, $CHHPh$), 4.69 (d, J = 11.0 Hz, 1 H, $CHHPh$), 4.79 (s, 1 H, 1-H), 4.91 (d, J = 11.1 Hz, 1 H, $CHHPh$), 4.87−4.99 (br. t, 1 H, NH), 5.34 (br. s, 1 H, 2-H). ^{13}C NMR (50 MHz, $CDCl_3$, APT, ppm): δ = 21.1 ($COCH_3$), 32.3 ($NCCCO$), 38.0 ($COOCH_2CH$), 38.8 (C-6), 47.2 ($NCCCO$), 62.5 ($NCCCO$), 66.5 ($COOCH_2CH$), 68.9, 71.3, 74.4, 78.2 (4 C, C-2, C-3, C-4, C-5), 72.1, 75.2 (CH_2Ph), 97.7 (C-1), 157.3 (CO Fmoc), 170.5 ($COCH_3$). $C_{40}H_{42}N_4O_7$ (690.8): calcd. C 69.55, H 6.13, N 8.11; found C 69.95, H 6.18, N 7.78. MALDI-TOF MS: m/z = 713.9 $[M + Na]^+$.

***N*-Fmoc-3′-aminopropyl 6-Azido-3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside (39):** ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.72−1.87 (m, 2 H, $OCH_2CH_2CH_2N$), 3.15−3.52 (m, 4 H, $OCH_2CH_2CH_2N$, 6a-H, 6b-H), 3.63−3.89 (m, 4 H, 3-H, 4-H, 5-H, $OCHCH_2CH_2N$), 3.97−4.04 (br. s, 1 H, 2-H), 4.17−4.25 (m, 2 H, $OCHCH_2CH_2N$, $COOCHCH$), 4.36−4.44 (m, 2 H, $COOCH_2CH$, $COOCHCH$), 4.57 (d, J = 11.0 Hz, 1 H, $CHHPh$), 4.67 (s, 2 H, CH_2Ph), 4.86 (s, 1 H, 1-H), 4.88 (d, J = 11.0 Hz, 1 H, $CHHPh$), 4.92−5.01 (br. t, 1 H, NH). $C_{38}H_{40}N_4O_6$ (648.7): calcd. C 70.35, H 6.21, N 8.64; found C 70.59, H 6.09, N 8.46. MALDI-TOF MS: m/z = 671.5 $[M + Na]^+$.

Methyl 2-*O*-Acetyl-6-azido-3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside (40): $[\alpha]_D^{20}$ = +58.1 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.16 (s, 3 H, $COCH_3$), 3.37 (s, 3 H, OCH_3), 3.38 (dd, $J_{6a,5}$ = 5.1, $J_{6a,6b}$ = 13.0 Hz, 1 H, 6a-H), 3.52 (d, $J_{6b,6a}$ = 13.0 Hz, 1 H, 6b-H), 3.73 (t, $J_{4,5}$ = $J_{4,3}$ = 8.6 Hz, 1 H, 4-H), 3.73−3.84 (m, 1 H, 5-H), 3.96 (dd, $J_{3,2}$ = 3.1, $J_{3,4}$ = 8.6 Hz, 1 H, 3-H), 4.51 (d, J = 11.2 Hz, 1 H, $CHHPh$), 4.56 (d, J = 11.2 Hz, 1 H, $CHHPh$), 4.69 (d, J = 11.2 Hz, 1 H, $CHHPh$), 4.70 (s, 1 H, 1-H), 4.93 (d, J = 11.2 Hz, 1 H, $CHHPh$), 5.35 (br. s, 1 H, 2-H). ^{13}C NMR (75 MHz, $CDCl_3$, APT, ppm): δ = 21.0 ($COCH_3$), 51.3 (C-6), 55.1 (OCH_3), 68.5, 71.1, 74.9, 77.9 (C-2, C-3, C-4, C-5), 71.7, 75.3 (CH_2Ph), 98.7 (C-1), 170.4 ($COCH_3$). $C_{23}H_{27}N_3O_6$ (441.5): calcd. C 62.57, H 6.16, N 9.52; found C 62.63, H 6.11, N 9.59. MALDI-TOF MS: m/z = 464.2 $[M + Na]^+$.

***N*-Fmoc-3′-aminopropyl 6-Amino-2-*O*-acetyl-3,4-di-*O*-benzyl-6-deoxy-α-D-mannopyranoside (41):** Compound **38** (100 mg, 0.15 mmol) was dissolved in dry ethyl acetate (5 mL) and palladium on activated charcoal (2 mg) was added. Hydrogenolysis was performed under hydrogen (10 h). The mixture was filtered through Celite and the filtrate concentrated in vacuo. The resulting amine **41** was used for the reaction with **43** without further purification.

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl Azide (42): Compound **35** (500 mg, 2.12 mmol) was dissolved in dry DMF (7 mL) under nitrogen. Benzyl bromide (1 mL, 9.54 mmol) was added dropwise and sodium hydride (60% suspension in silicon oil; 560 mg, 14.32 mmol) was added portionwise under vigorous stirring, carefully keeping self-heating controlled. After NaH addition, the mixture was allowed to react overnight (TLC: hexane/EtOAc, 7:3). The solution was quenched with methanol and concentrated in vacuo. The resulting brown syrup was diluted with DCM (30 mL) and washed with water (2 × 30 mL); the organic layers were dried, concentrated, and filtered through sylica gel. The tribenzyl derivative was dissolved in dry DCM (10 mL) at room temperature. $TMSN_3$ (362 μL, 2.76 mmol), and $SnCl_4$ (100 μL) were added and the resulting solution stirred for 3 h (TLC: hexane/EtOAc, 8:2). When the reaction was terminated, saturated $NaHCO_3$ (2 mL) was added and stirring continued for additional 30 min, until a white suspension was formed. The mixture was diluted with water (20 mL) and DCM (20 mL), extracted twice, dried with anhydrous sodium sulfate and concentrated. Flash chromatography (hexane/EtOAc, 9:1) afforded **42** (889 mg, 81%) as a yellow oil. $[\alpha]_D^{20}$ = +41.3 (c = 1.4, $CHCl_3$). IR (CH_2Cl_2 solution, cm^{-1}): $\tilde{\nu}_{max}$ = 2117 (N_3), 1748 (CO). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.16 (s, 3 H, $COCH_3$), 3.72 (d, $J_{6a,6b}$ = 10.9 Hz, 1 H, 6a-H), 3.83 (d, $J_{6b,6a}$ = 10.9 Hz, 1 H, 6b-H), 3.85−3.95 (m, 3 H, 3-H, 4-H, 5-H), 4.48 (d, J = 11.1 Hz, 1 H, $CHHPh$), 4.51 (d, J = 10.8 Hz, 1 H, $CHHPh$), 4.52 (d, J = 12.1 Hz, 1 H, $CHHPh$), 4.66 (d, J = 11.1 Hz, 1 H, $CHHPh$), 4.69 (d, J = 12.1 Hz, 1 H, $CHHPh$), 4.85 (d, J = 10.8 Hz, 1 H, $CHHPh$), 5.22 (s, 1 H, 1-H), 5.41 (s, 1 H, 2-H). ^{13}C NMR (50 MHz, $CDCl_3$, APT, ppm): δ = 21.0 ($COCH_3$), 68.5 (C-2), 68.6 (C-6), 72.0, 73.5, 75.2 (CH_2Ph), 73.6 (C-5), 73.8 (C-4), 77.2 (C-3), 88.0 (C-1), 170.3 ($COCH_3$). $C_{29}H_{31}N_3O_6$ (517.6): calcd. C 67.30, H 6.04, N 8.12; found C 67.26, H 6.05, N 8.11. MALDI-TOF MS: m/z = 540.1 $[M + Na]^+$.

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl Isocyanide (43): The azido compound **42** (233 mg, 0.45 mmol) was transformed into the corresponding isocyanide according to the procedure used for compounds **9** and **13**. Compound **43** (α anomer) (153 mg, 68%) was obtained as a syrup. $[\alpha]_D^{20}$ = +29.3 (c = 1.1, $CHCl_3$). IR (KBr, cm^{-1}): $\tilde{\nu}_{max}$ = 2135 (NC), 1750 (CO). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.16 (s, 3 H, $COCH_3$), 3.70 (d, $J_{6a,6b}$ = 11.2 Hz, 1 H, 6a-H), 3.83 (d, $J_{6b,6a}$ = 11.2 Hz, 1 H, 6b-H), 3.87−3.98 (m, 2 H, 3-H, 4-H), 4.02−4.09 (m, 1 H, 5-H), 4.49 (2d, J = 11.0 Hz, 2 H, 2 $CHHPh$), 4.59 (d, J = 10.8 Hz, 1 H, $CHHPh$), 4.66 (d, J = 11.0 Hz, 1 H, $CHHPh$), 4.69 (d, J = 10.8 Hz, 1 H, $CHHPh$), 4.84 (d, J = 10.8 Hz, 1 H, $CHHPh$), 5.29 (s, 1 H, 1-H), 5.38 (m, 1 H, 2-H). ^{13}C NMR (50 MHz, $CDCl_3$, APT, ppm): δ = 21.2 ($COCH_3$), 68.7 (C-6), 71.8 (C-2), 71.9, 72.5, 75.2 (CH_2Ph), 73.1 (C-5), 74.3 (C-4), 77.0 (C-3), 79.7 (C-1), 164.8 (CN), 170.3 ($COCH_3$). $C_{30}H_{31}NO_6$ (501.6): calcd. C 71.84, H 6.23, N 2.79; found C 71.67, H 6.35, N 2.70. MALDI-TOF MS: m/z = 524.4 $[M + Na]^+$.

Methyl 2,3,4-Tri-*O*-benzyl-6-deoxy-6-[*N*′-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)ureido]-α-D-glucopyranoside (24): PNO (115 mg, 1.2 mmol), dissolved in acetonitrile (0.5 mL), and iodine (8 mg, 0.03 mmol) were added to a mixture of glycosyl isocyanide **9** (143 mg, 0.40 mmol) and powdered molecular sieves (3 Å, 300 mg) in dry acetonitrile (5 mL) under nitrogen. After 10 min, amine **20** (185 mg, 0.40 mmol) dissolved in dry acetonitrile (1 mL) was added and stirring continued for 30 min. The reaction was monitored by TLC (EtOAc/hexane, 4:6). The oxidizing mixture was then quenched with a saturated solution of sodium hydrogen sulfate (5 mL), extracted with DCM (20 mL), and washed with brine (20 mL). After drying with anhydrous sodium sulfate and evaporation of the solvent, the crude product was purified by flash chromatography (EtOAc/hexane, 3:7), affording glycosylurea **24** (298 mg, 89%) as a white solid. M.p. 81−82 °C. $[\alpha]_D^{20}$ = +12.8 (c = 1.0, $CHCl_3$). IR (CH_2Cl_2 solution, cm^{-1}): $\tilde{\nu}_{max}$ = 1758 (CO acetate), 1659 (CO urea). ^1H NMR (200 MHz, $CDCl_3$, ppm): δ = 2.00 (s, 6 H, $COCH_3$), 2.02 (s, 3 H, $COCH_3$), 2.08 (s, 3 H, $COCH_3$), 3.26 (t, $J_{4,5}$ = $J_{4,3}$ = 9.3 Hz, 1 H, 4-H), 3.35 (s, 3 H, OCH_3), 3.35−3.42 (m, 1 H, 6a-H), 3.46 (dd, $J_{6b,5}$ = 3.4, $J_{6b,6a}$ = 9.6 Hz, 1 H, 6b-H), 3.59−3.70 (m, 1 H, 5-H), 3.77 (ddd, $J_{5',6b'}$ = 4.2, $J_{5',6a'}$ = 2.0, $J_{5',4'}$ = 9.3 Hz, 1 H, 5′-H), 3.98 (t, $J_{3,4}$ = $J_{3,2}$ = 9.3 Hz, 1 H, 3-H), 4.06 (dd, $J_{6a',5'}$ = 2.0, $J_{6a',6b'}$ = 12.5 Hz, 1 H, 6a′-H), 4.30 (dd, $J_{6b',5'}$ = 4.2, $J_{6b',6a'}$ = 12.5 Hz, 1 H, 6b′-H), 4.52 (br. t, 1 H, NH), 4.55−5.35 (m, 12 H, 1-H, 1′-H, 2′-H, 3′-H, 4′, 3-H CH_2Ph,

NH). ^{13}C NMR (75 MHz, $CDCl_3$, APT, ppm): δ = 20.6, 20.7 (4 CO*C*H$_3$), 41.2 (C-6), 55.3 (CH$_3$O), 61.9 (C-6′), 68.3, 69.7, 70.6, 73.1, 73.1, 80.1, 80.1, 81.8 (8 C, sugar ring), 73.3, 75.0, 76.7 (3 C, *C*H$_2$Ph), 78.5 (C-1′), 97.9 (C-1), 156.6 (*C*O urea), 169.7, 169.8, 170.6, 170.8 (*C*OCH$_3$). $C_{43}H_{52}N_2O_{15}$ (836.9): calcd. C 61.71, H 6.26, N 3.35; found C 61.68, H 6.27, N 3.35. MALDI-TOF MS: *m*/*z* = 859.6 [M + Na]$^+$.

Methyl 2,3,4-Tri-*O*-benzyl-6-deoxy-6-[*N*′-(2′,3′,4′,6′-tetra-*O*-benzoyl-α-D-mannopyranosyl)ureido]-α-D-mannopyranoside (25): Isocyanide **13a** (242 mg, 0.40 mmol) was submitted to the same procedure as compound **24**. The coupling with compound **21** (185 mg, 0.40 mmol) afforded glycosylurea **25** as a white solid (356 mg, 82%). M.p. 89−90 °C. $[\alpha]_D^{20}$ = +9.0 (*c* = 1.0, $CHCl_3$). IR (CH_2Cl_2 solution, cm^{-1}): $\tilde{\nu}_{max}$ = 1734 (CO benzoate), 1662 (CO urea). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 3.24 (t, $J_{4,5} = J_{4,3}$ = 9.1 Hz, 1 H, 4-H), 3.36 (s, 3 H, OCH$_3$), 3.35−3.47 (m, 3 H, 2-H, 6a-H), 3.59−3.70 (m, 2 H, 5-H, 6b-H), 3.70−3.79 (m, 1 H, 5′-H), 3.99 (t, $J_{3,4} = J_{3,2}$ = 9.1 Hz, 1 H, 3-H), 4.38−4.55 (m, 2 H, 6a′-H, H6b′), 4.62−5.35 (m, 8 H, 1-H, 1′-H, 3 C*H*$_2$Ph), 5.49 (br. s, 1 H, NH), 5.68−5.87 (m, 2 H, 2′-H, 3′-H), 6.14 (t, $J_{4,3} = J_{4,5}$ = 9.2 Hz, 1 H, 4-H). ^{13}C NMR (75 MHz, $CDCl_3$, APT, ppm): δ = 40.8 (C-6), 55.3 (CH$_3$O), 62.5 (C-6′) 66.8, 69.1, 69.8, 70.1, 80.3, 82.0 (8 C, sugar ring), 73.2, 74.9, 75.8 (3 C, *C*H$_2$Ph), 77.5 (C-1′), 97.9 (C-1), 157.7 (CO urea), 165.3, 165.7, 166.1 (*C*OCH$_3$). $C_{63}H_{60}N_2O_{15}$ (1085.2): calcd. C 69.73, H 5.57, N 2.58; found C 69.63, H 5.55, N 2.57. MALDI-TOF MS: *m*/*z* = 1107.5 [M + Na]$^+$.

Allyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-[*N*′-(2′,3′,4′,6′-tetra-*O*-benzoyl-β-D-mannopyranosyl)ureido]-β-D-mannopyranoside (29): Isocyanide **13b** (242 mg, 0.40 mmol) was submitted to the same procedure as compound **24**. Coupling with compound **27** (196 mg, 0.40 mmol) afforded glycosylurea **29** as a white solid (387 mg, 87%). M.p. 113−114. $[\alpha]_D^{20}$ = −92.3 (*c* = 1.0, $CHCl_3$). IR (CH_2Cl_2 solution, cm^{-1}): $\tilde{\nu}_{max}$ = 1733 (CO benzoate), 1658 (CO urea), 1638 (CH=CH$_2$). ^{1}H NMR (400 MHz, $CDCl_3$, COSY, NOESY, ppm): δ = 3.32−3.46 (m, 1 H, 5-H), 3.46−3.52 (br. s, 1 H, NH), 3.58−3.65 (m, 2 H, 6a-H, H6b), 4.06 (dd, *J* = 6.7 Hz, 13.2 Hz, 2 H, C*H*$_2$CH=CH$_2$), 4.25−4.34 (m, 3 H, 3-H, 4-H, 5′-H), 4.46 (s, 1 H, 1-H), 4.46−4.52 (m, 4 H, 2 C*H*HPh, C*H*$_2$Ph), 4.56 (dd, $J_{6a',5'}$ = 3.8, $J_{6a',6b'}$ = 12.2 Hz, 1 H, 6a′-H), 4.70 (s, 1 H, 2-H), 4.71 (dd, $J_{6b',5'}$ = 2.3, $J_{6b',6a'}$ = 12.2 Hz, 1 H, 6b′-H), 4.78 (d, *J* = 11.0 Hz, 1 H, CH*H*Ph), 4.93 (d, *J* = 11.0 Hz, 1 H, CH*H*Ph), 5.17 (d, $J_{A,X}$ = 10.5, 1 H, CH$_X$=C*H*$_A$H$_B$), 5.25 (br. s, 1 H, NH), 5.27 (d, $J_{B,X}$ = 17.2, 1 H, CH$_X$=CH$_A$*H*$_B$), 5.73 (dd, $J_{3',2'}$ = 3.1, $J_{3',4'}$ = 10.1 Hz, 1 H, 3′-H), 5.85−5.89 (m, 1 H, C*H*$_X$=CH$_A$H$_B$), 5.87 (d, $J_{1',NH}$ = 9.5 Hz, 1 H, 1′-H), 5.95 (d, $J_{2',3'}$ = 3.1 Hz, 1 H, 2′-H), 6.15 (t, $J_{4',5'} = J_{4',3'}$ = 9.8 Hz, 1 H, 4′-H). ^{13}C NMR (100 MHz, $CDCl_3$, APT, ppm): δ = 50.9 (C-2), 63.4 (C-6′) 66.8 (C-2′), 69.2 (C-6), 70.2 (allylic CH$_2$), 71.3, 73.6, 75.1 (3 C, *C*H$_2$Ph), 71.9, 73.4, 74.0, 74.5, 75.4, 80.8 (6 C, sugar ring), 79.0 (C-1′), 99.2 (C-1), 117.9 (CH=*C*H$_2$), 157.3 (CO urea), 165.8, 165.8, 165.9, 166.5 (*C*OCH$_3$). $C_{65}H_{62}N_2O_{15}$ (1111.2): calcd. C 70.26, H 5.62, N 2.52; found C 70.24, H 5.66, N 2.54. MALDI-TOF MS: *m*/*z* = 1133.6 [M + Na]$^+$.

Methyl 2,6-Di-*O*-benzoyl-3-*O*-benzyl-4-deoxy-4-[*N*′-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)ureido]-α-D-glucopyranoside (34): Isocyanide **9** (143 mg, 0.40 mmol) was submitted to the same procedure as compound **24**. Coupling with compound **33** (197 mg, 0.40 mmol) afforded glycosylureas **34** as a white solid (325 mg 94%). M.p. 214−215 °C. $[\alpha]_D^{20}$ = +56.4 (*c* = 1.0, $CHCl_3$). IR (CH_2Cl_2 solution, cm^{-1}): $\tilde{\nu}_{max}$ = 1750 (CO acetate), 1734 (CO benzoate), 1662 (CO urea). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 2.01 (s, 3 H, COCH$_3$), 2.04 (s, 9 H, COCH$_3$), 3.33 (s, 3 H, OCH$_3$), 3.70−3.82 (m, 2 H, 5-H, 5′-H), 4.03−4.13 (m, 2 H, 3-H, 6a′-H), 4.15 (t, $J_{4,5} = J_{4,3}$ = 9.8 Hz, 1 H, 4-H), 4.28 (dd, $J_{6b',5'}$ = 4.2, $J_{6b',6a'}$ = 12.3 Hz, 1 H, 6b′-H), 4.39 (dd, $J_{6a,5}$ = 5.5, $J_{6a,6b}$ = 12.2 Hz, 1 H, 6a-H), 4.51−4.63 (m, 3 H, 1-H, 6b-H, C*H*HPh), 4.71 (d, *J* = 11.3 Hz, 1 H, CH*H*Ph), 4.81 (br. t, 1 H, NH), 4.96−5.15 (m, 4 H, 1′-H, 2-H, 2′-H, 4′-H), 5.18−5.24 (br. s, 1 H, NH), 5.26 (t, $J_{3',4'} = J_{3',2'}$ = 9.1 Hz, 1 H, 3′-H). ^{13}C NMR (75 MHz, $CDCl_3$, APT, ppm): δ = 20.6 (CO*C*H$_3$), 52.9 (C-4), 55.3 (CH$_3$O), 61.9 (C-6′), 63.9 (C-6), 68.4, 69.0, 70.6, 72.9, 73.1, 74.3 (6 C, sugar ring), 74.5 (*C*H$_2$Ph), 75.9 (C-1′), 80.1 (C-2), 97.2 (C-1), 155.9 (CO urea), 165.7, 166.4 (CO Bz), 169.6, 169.8, 170.6, 171.2 (*C*OCH$_3$). $C_{43}H_{48}N_2O_{17}$ (864.8): calcd. C 59.72, H 5.59, N 3.24; found C 59.77, H 5.60, N 3.24. MALDI-TOF MS: *m*/*z* = 887.2 [M + Na]$^+$.

***N*-Fmoc-3′′-aminopropyl 2-*O*-Acetyl-3,4-di-*O*-benzyl-6-deoxy-6-[*N*′-(2′-*O*-acetyl-3′,4′,6′-tri-*O*-benzyl-α-D-mannopyranosyl)ureido]-α-D-mannopyranose (45):** Isocyanide **43** (200 mg, 0.40 mmol) was submitted to the same procedure as compound **24**. Coupling with compound **41** (265 mg, 0.40 mmol) afforded glycosylurea **45** as a white solid (416 mg, 88%). M.p. 61−62. $[\alpha]_D^{20}$ = +93.8 (*c* = 1.0, $CHCl_3$). IR (CH_2Cl_2 solution, cm^{-1}): $\tilde{\nu}_{max}$ = 1750 (CO acetate), 1716 (CO Fmoc), 1653 (CO urea). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.67−1.78 (m, 2 H, OCH$_2$C*H*$_2$CH$_2$N), 2.10 (s, 6 H, 2 COCH$_3$), 2.94−3.25 (m, 2 H, OCH$_2$CH$_2$C*H*$_2$N), 3.28−3.46 (m, 2 H, 6a-H, 6b-H), 3.50−3.86 (m, 6 H, 3-H, 4-H, 5-H, 6a′-H, 6b′-H, NH), 3.87−3.94 (m, 4 H, OC*H*HCH$_2$CH$_2$N, 3′-H, 4′-H, 5′-H), 4.11−4.22 (m, 2 H, OCH*H*CH$_2$CH$_2$N, COOC*H*HCH), 4.31−4.42 (m, 2 H, COOCH*H*CH, COOCH$_2$C*H*), 4.48−4.87 (m, 12 H, 5 C*H*$_2$Ph, 1-H, NH), 5.01 (br. s, 1 H, NH), 5.16 (s, 1 H, 2-H), 5.27 (s, 1 H, 1′-H), 5.48 (s, 1 H, 2′-H). ^{13}C NMR (75 MHz, $CDCl_3$, APT, ppm): δ = 20.9 (CO*C*H$_3$) 33.7 (NC*C*CO), 38.0 (CH), 38.2 (C-6), 47.3 (N*C*CCO), 63.3 (NCC*C*O), 66.6 (CH$_2$O), 68.8 (C-6), 68.4, 68.7, 70.6, 71.6, 72.7, 74.1, 74.2, 78.0 (8 C, sugar ring), 78.0 (C-1′), 71.8, 72.1, 73.4, 74.9, 75.2 (5 C, *C*H$_2$Ph), 97.7 (C-1), 156.5 (CO urea), 158.9 (CO Fmoc), 170.1, 170.4 (*C*OCH$_3$). $C_{70}H_{75}N_3O_{14}$ (1182.4): calcd. C 71.11, H 6.39, N 3.55; found C 71.01, H 6.45, N 3.50. MALDI-TOF MS: *m*/*z* = 1204.5 [M + Na]$^+$.

Methyl 6-Deoxy-6-[*N*′-(β-D-glucopyranosyl)ureido]-α-D-glucopyranoside (1): Compound **24** (210 mg, 0.25 mmol) was dissolved in methanol (2 mL), containing a suspension of palladium on activated charcoal (2 mg). Stirring was continued under hydrogen until the starting material disappeared (TLC: EtOAc/hexane, 2:1). The mixture was filtered through Celite, that was washed abundantly with methanol. Collected methanolic solutions were reduced to 2 mL and freshly prepared 1 M NaOMe was added (25 μL) (TLC: EtOAc/MeOH/H$_2$O, 8:2:1). The basicity was neutralized with Amberlite IR-120 (H$^+$ form). The resin was filtered and the solvent evaporated in vacuo, quantitatively affording **1** (100 mg, 100%) as a white solid, which was purified by Sephadex chromatography with a G10-120 column (eluent water) and lyophilised. $[\alpha]_D^{20}$ = +71.2 (*c* = 1.5, D$_2$O). NMR spectroscopic data are in agreement with those previously reported.[17] $C_{14}H_{26}N_2O_{11}$ (398.4): calcd. C 42.21, H 6.58, N 7.03; found C 42.23, H 6.57, N 7.04. MALDI-TOF MS: *m*/*z* = 420.7 [M + Na]$^+$.

Methyl 6-Deoxy-6-[*N*′-(α-D-mannopyranosyl)ureido]-α-D-mannopyranoside (2): Compound **25** (210 mg, 0.25 mmol) was submitted to the same procedure as for compound **1** affording **2** (100 mg, 100%) as a white solid. M.p. 85−87 °C. $[\alpha]_D^{20}$ = +58.7 (*c* = 1.0, MeOH). ^{1}H NMR (300 MHz, D$_2$O, ppm): δ = 3.27−3.41 (m, 2 H, 6a-H, 6b-H), 3.42 (s, 3 H, OCH$_3$), 3.43−3.44 (m, 1 H, 5′-H), 3.52−3.96 (m, 9 H, 2-H, 2′-H, 3-H, 3′-H, 4-H, 4′-H, 5-H, 6a′-H, 6b′-H), 4.81 (s, 1 H, 1′-H), 5.12 (s, 1 H, 1-H). ^{13}C NMR (75 MHz, D$_2$O, APT, ppm): δ = 41.2 (C-6), 55.8 (CH$_3$O), 61.8 (C-6′) 67.3, 71.1, 71.4,

71.7, 72.0, 73.7, 74.3, 78.0 (8 C, sugar ring), 79.7 (C-1′), 99.9 (C-1), 160.1 (CO urea). $C_{14}H_{26}N_2O_{11}$ (398.4): calcd. C 42.21, H 6.58, N 7.03; found C 42.21, H 6.57, N 7.03. MALDI-TOF MS: m/z = 420.4 $[M + Na]^+$.

Propyl 2-Deoxy-2-[*N*′-(β-D-mannopyranosyl)ureido]-β-D-mannopyranoside (3): Compound **29** (278 mg, 0.25 mmol) was submitted to the same procedure as for compound **1** affording **3** (107 mg, 100%) as a white solid. M.p. 92−93 °C. $[\alpha]_D^{20}$ = −36.3 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, D_2O, ppm): δ = 0.80 (t, J = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 1.50 (q, J = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 3.27−3.41 (m, 3 H, 4′-H, 5-H, 5′-H), 3.46−3.56 (m, 2 H, 3′-H, 4-H), 3.60−3.74 (m, 6 H, 3-H, 6a-H, 6a′-H, $OCH_2CH_2CH_3$), 3.80−3.88 (m, 3 H, 2′-H, 6b-H, 6b′-H), 4.23 (br. d, $J_{2,NH}$ = 3.6 Hz, 2-H), 4.70 (s, 1 H, 1′-H), 5.01 (s, 1 H, 1-H). ^{13}C NMR (100 MHz, D_2O, APT, ppm): δ = 10.0 ($OCH_2CH_2CH_3$), 22.5 ($OCH_2CH_2CH_3$), 54.1 (C-2), 61.1, 61.4 (C-6, C-6′), 67.0, 67.5, 70.9, 72.7, 73.9, 76.9, 77.6 (7 C, sugar ring), 71.9 ($OCH_2CH_2CH_3$), 79.2 (C-1′), 99.7 (C-1), 159.8 (CO urea). $C_{16}H_{30}N_2O_{11}$ (426.4): calcd. C 45.07, H 7.09, N 6.57; found C 45.10, H 7.07, N 6.58. MALDI-TOF MS: m/z = 448.4 $[M + Na]^+$.

Methyl 4-Deoxy-4-[*N*′-(β-D-glucopyranosyl)ureido]-α-D-glucopyranoside (4): Compound **34** (216 mg, 0.25 mmol) was submitted to the same procedure as for compound **1** affording **4** (100 mg, 100%) as a white solid. M.p. 87−88 °C. $[\alpha]_D^{20}$ = +76.1 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, D_2O, ppm): δ = 3.30 (t, $J_{4,5} = J_{4,3}$ = 9.1 Hz, 1 H, 4′-H), 3.32−3.35 (m, 1 H, 2-H), 3.35 (s, 3 H, OCH_3), 3.41−3.47 (m, 1 H, 5′-H), 3.47 (t, $J_{3,4} = J_{3,2}$ = 9.1 Hz, 1 H, 3′-H), 3.51−3.57 (m, 1 H, 5-H), 3.56 (dd, $J_{6b,5}$ = 3.7, $J_{6b,6a}$ = 9.5 Hz, 1 H, 6b-H), 3.59−3.71 (m, 5 H, -H 2′-H, 3-H, 4-H, 6a-H, 6a′-H), 3.81 (dd, $J_{6b',5'}$ = 2.0, $J_{6b',6a'}$ = 12.3 Hz, 1 H, 6b′-H), 4.76 (d, $J_{1,2}$ = 6.5 Hz, 1′-H), 4.78 (br. s, 1 H, 1-H). ^{13}C NMR (100 MHz, D_2O, APT, ppm): δ = 52.6 (C-4), 55.4 (OCH_3), 61.0, 61.3 (C-6, C-6′), 69.8, 71.4, 71.5, 72.0, 72.3, 76.9, 77.5 (7 C, sugar ring), 81.5 (C-1′), 99.6 (C-1), 159.7 (CO urea). $C_{14}H_{26}N_2O_{11}$ (398.4): calcd. C 42.21, H 6.58, N 7.03; found C 42.23, H 6.58, N 7.04. MALDI-TOF MS: m/z = 399.2 $[M + Na]^+$.

***N*-Fmoc-3′′-aminopropyl 2-*O*-Acetyl-6-deoxy-6-[*N*′-(2′-*O*-acetyl-α-D-mannopyranosyl)ureido]-α-D-mannopyranose (5):** Compound **45** (355 mg, 0.30 mmol) was dissolved in methanol (5 mL), containing a suspension of palladium on activated charcoal (5 mg). Stirring was continued under hydrogen until the starting material had disappeared (TLC: EtOAc/hexane, 4:1). The mixture was filtered through Celite, which was washed abundantly with methanol. Evaporation of the solvent afforded **5** (117 mg, 98%) as a white foam which was purified by Sephadex chromatography with a G10-120 column (eluent water) and lyophilised. $[\alpha]_D^{20}$ = +14.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, D_2O, ppm): δ = 1.69−1.75 (m, 2 H, $OCH_2CH_2CH_2N$), 2.10 (s, 6 H, 2 $COCH_3$), 2.95−3.26 (m, 2 H, $OCH_2CH_2CH_2N$), 3.27−3.42 (m, 2 H, 6a-H, 6b-H), 3.45−3.89 (m, 8 H, 3-H, 3′-H, 4-H, 4′-H, 5-H, 5′-H, 6a′-H, 6b′-H), 3.91−3.94 (m, 1 H, $OCHHCH_2CH_2N$,), 4.11−4.22 (m, 2 H, $OCHHCH_2CH_2N$, $COOCHHCH$), 4.30−4.39 (m, 2 H, $COOCHHCH$, $COOCH_2CH$), 4.87 (s, 1 H, 1-H), 5.18 (s, 1 H, 2-H), 5.23 (s, 1 H, 1′-H), 5.39 (s, 1 H, 2′-H). ^{13}C NMR (50 MHz, D_2O, APT, ppm): δ = 20.9 ($COCH_3$), 33.8 ($NCCCO$), 38.2 (CH), 38.3 (C-6), 47.3 ($NCCCO$), 63.2 ($NCCCO$), 66.5 (CH_2O), 68.1 (C-6′), 69.2, 69.4 (2 C, C-2, C-2′), 71.2, 71.3, 72.5, 73.2, 75.3, 77.9 (6 C, sugar ring), 78.8 (C-1′), 99.7 (C-1), 158.9 (CO Fmoc), 160.5 (CO urea). $C_{35}H_{45}N_3O_{14}$ (731.7): calcd. C 57.45, H 6.20, N 5.74; found C 57.49, H 6.18, N 5.73. MALDI-TOF MS: m/z = 753.9 $[M + Na]^+$.

Acknowledgments

This work was supported by Regione Lombardia, Assessorato alla Sanità and CNR Istituto di Scienze e Tecnologie Molecolari.

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Received July 31, 2003

