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Sugar Amino Acids

Approaches to Pyranuronic β-Sugar Amino Acid Building Blocks of Peptidosaccharide Foldamers

Viktória Goldschmidt Gőz,[a] István Pintér,[b] Veronika Harmat,[a] and András Perczel*[a,b]

Abstract: Pyranuronic β-sugar amino acids (β-SAAs) are biocompatible and tuneable building blocks of foldamers and chimera-peptides. The scalable and economical total synthesis of two building blocks is described here. These C-4 epimers, Fmoc-GlcAPU(Me)-OH (**7**) and Fmoc-GalAPU(Me)-OH (**8**), which are suitable for solid phase peptide synthesis, were prepared via a common oxime intermediate **16**. The new synthesis uses nine consecutive steps, starting from methyl α-D-glucopyranoside (**6**). The synthesis is fine-tuned, optimized, and ready for large-scale and cost-efficient production.

Introduction

The excellent compendiums of Risseeuw et al.[1] emphasize the significance of natural and functionalized sugar amino acids (SAAs), which play an important role in inter- and intracellular events in living organisms during the formation of glycomimetics, peptidomimetics, etc. Nowadays, SAAs are widely used in the design and synthesis of foldamers[2] as they have i) a versatile nature; ii) tunable properties in terms of ring size, stereochemistry, substituents, and conformation; iii) adjustable hydrophilic/hydrophobic character as a function of the free/protected nature of their OH groups. Oligomers of these building blocks are biocompatible and biodegradable, though they can resist the action of proteolytic enzymes. Homo- and heterooligomers built up from such building blocks using solid-phase peptide synthesis (SPPS) could form different secondary structural elements and designed backbone scaffolds, similar to those occurring in polypeptides and proteins, but with different dynamic properties.[3–7]

A large number of cyclic SAAs based on α- to ε-amino acid motifs have been described; these mainly have either furanoid or pyranoid rings. The number of furanoid SAAs reported to date is way over 200, and most of these represent different types of structure.[1] The number based on a pyranoid ring is significantly fewer, perhaps <100. This difference is even more significant when comparing β-SAAs: more than 70 furanoid β-SAAs are known,[1] whereas the number of the related pyranoid derivatives is about 10. These are similar to either 2-amino-2-deoxyglucopyranosyl carboxylic acids or 4-amino-4-deoxy-D-glucopyranuronic acids.[1] Thus, it is mostly uronic acid derivatives of furanoid-ring-containing α-, β-, or δ-SAAs that have been synthesized. The corresponding pyranoid SAAs have seldom been used to make foldamers, as the building blocks are unavailable. In the rare instances where pyranoid SAAs have been used for foldamer construction, the easily available D-glucosamine carboxylic acids have been used.[4,8]

As regards the synthesis of peptidomimetics and glycomimetics derived from α-AAs, acyclic or cyclic β-AAs [e.g., ACPC (2-aminocyclopentane-1-carboxylic acid)[9,10] and ACHC (2-aminocyclohexane-1-carboxylic acid)[11,12]], and β-SAAs, we have completed the synthesis of selected 3-amino-3-deoxy-pentofuranuronic acids,[13] and studied their coupling potential to form peptidosaccharides.[14] In a comparative context, our interest turned towards hydrophilic versions of well-known foldamer building blocks (ACHC), as shown in Figure 1, namely methyl 4-amino-4-deoxy-α-D-glucopyranuronic acid [H-GlcAPU(Me)-OH; **1**] and methyl 4-amino-4-deoxy-α-D-galacto-pyranuronic acid [H-GalAPU(Me)-OH; **2**]. Although derivatives (**3** and **4**) of these compounds have already been partially described,[15–17] they have never been considered as building blocks for foldamers.

The synthesis of these two β-SAAs with opposite C-4-configurations was described using two very different synthetic pathways: the D-*gluco* epimer[15] **3** was obtained from methyl α-D-galactopyranoside (**5**), while the D-*galacto* epimer[16] **4** was obtained from methyl α-D-glucopyranoside (**6**). The reason for these two completely separate pathways is that in both cases, the amino group was introduced by the usual sulfonate → azide nucleophilic substitution method. The carboxylic groups of both products were formed by oxidation of the terminal -CH_2OH groups. The first route involves nine consecutive steps, the second as many as thirteen, and overall yields of 39 and 5 %, respectively, were obtained. Both protocols are rather costly, as they use expensive reagents and materials (e.g., methyl α-D-galactopyranoside, Tf_2O, $NaCNBH_3$). Additionally, column chromatography was needed to purify the intermediates for several of the synthetic steps; this makes the overall syntheses environmentally unfriendly and hard to scale up. All

[a] *MTA-ELTE Protein Modeling Research Group, 1117 Budapest, Pázmány Péter sétány 1/A, Hungary*
E-mail: perczel@chem.elte.hu
http://prot.chem.elte.hu/en/
[b] *Laboratory of Structural Chemistry and Biology, Institute of Chemistry, Eötvös University, 1117 Budapest, Pázmány Péter sétány 1/A, Hungary*

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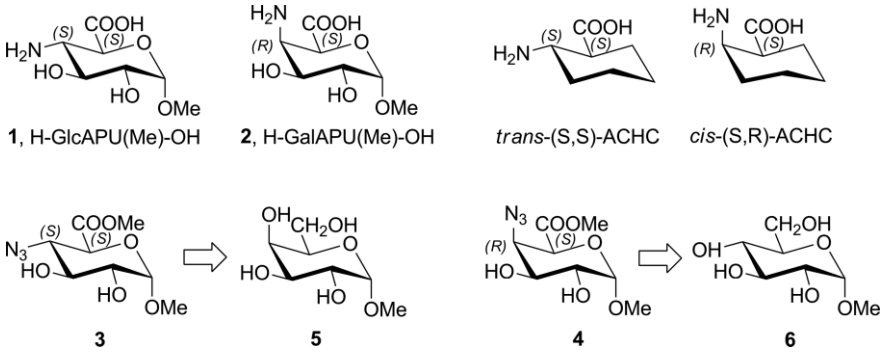


Figure 1. Molecular structures of our target SAAs (**1** and **2**, with unprotected OH groups) with their precursors (**3** and **4**)[15,16] and their carbocyclic analogues (ACHC).

these considerations indicate that there could be serious problems for multigram production. Moreover, with a free amino group and a protected carboxylic group, both molecules (**3** and **4**) are unsuitable for SPPS. Two additional steps have to be implemented to transform them into appropriately N-protected SAAs suitable for SPPS: Fmoc-GlcAPU(Me)-OH (**7**) and Fmoc-GalAPU(Me)-OH (**8**) (Fmoc = fluorenylmethoxycarbonyl).

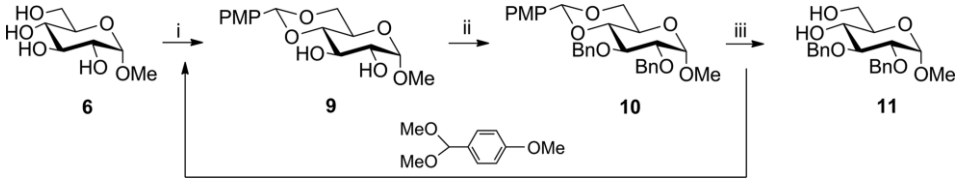
Thus, we have developed a conceptually new and economical approach to make both SAAs **7** and **8** from a common precursor. First, methyl α-D-glucopyranoside (**6**) was converted into methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**11**), the key intermediate. This was then transformed into amino derivatives **14** and **17** in two parallel pathways. In an alternative approach, **11** was transformed into the oxime key intermediate **16**, from which a single reaction protocol led to both amine epimers. The two epimers were separated after transformation into Fmoc N-protected derivatives.

Results and Discussion

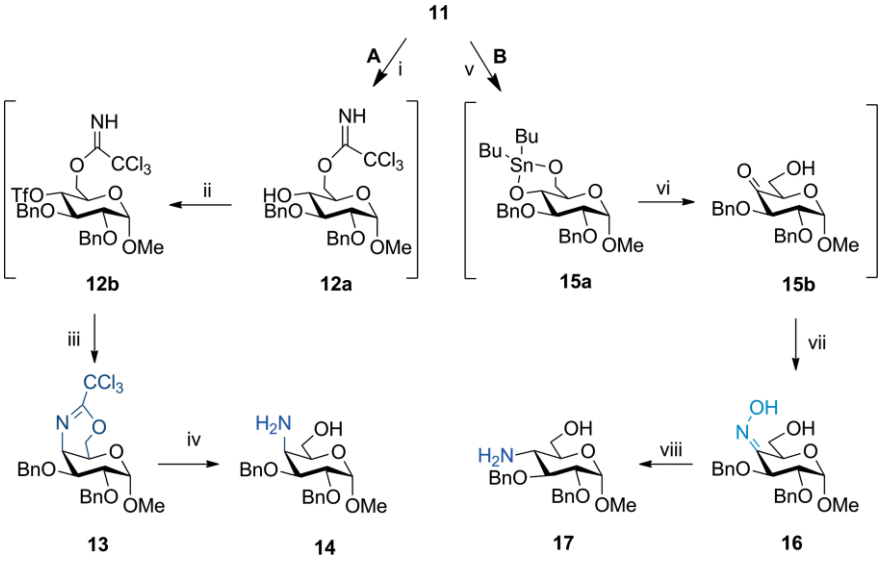
In the first step, methyl α-D-glucopyranoside (**6**) was transformed into its 4,6-anisylidene derivative (**9**). The C-2 and C-3 hydroxy groups were both protected by benzylation[18] (to give **10**), and then 4,6-deprotection[19] was carried out to give the suitably protected diol **11** as white crystals in an overall yield of 85 % (Scheme 1). We considerably improved the efficiency of the process by recovering 98 % of the anisaldehyde dimethyl acetal. This modification resulted in a gainful recycling of the valuable reagent. Also, column chromatography[19] was not used, which resulted in savings in both time and organic solvent.

To form the amino group, we selected two possible precursors, as shown in Scheme 2. For route A, to get D-*galacto* epimer **14**, an oxazine ring was introduced (as in **13**).[20] In a one-pot reaction, diol **11** was converted into 4,6-(trichlorooxazine) derivative **13**. After chromatography, the ring was opened with AcOH (80 % aq.) to give **14** in good yield. On the other hand, to produce D-*gluco* epimer **17** (route B), a new oxime intermediate **16** was synthesized. To achieve this, the required keto compound **15b** was formed via a stannylene derivative[21] **15a**, and this was then converted into the oxime. Compound **16** was purified by crystallization of the crude product from ether/hexane. This key intermediate was then reduced with $LiAlH_4$ under a nitrogen atmosphere to give **17** in 57 % yield.

Generally, selective reduction methods are used in modern chemistry as they tend to give better yields and simpler purifications.[22,23] However, in some cases nonselective approaches are more economical, especially if both epimers of the product are needed. Route B (via oxime intermediate **16**) represents a new alternative synthetic route, namely to carry out a nonselective oxime reduction to give both **14** and **17**, potentially in different ratios. Several reduction protocols were attempted (Table S1 in Supporting Information). However, the reaction was only successful under acidic conditions. The reduction failed when $NaBH(OAc)_3$ was used in *i*PrOH. However, when $NaBH_4$ was used in glacial acetic acid to form $NaBH(OAc)_3$ in situ, the oxime was reduced to give the 4-deoxy-4-hydroxylamine epimers **18** and **19**. The mixture of **18** and **19** was then reduced

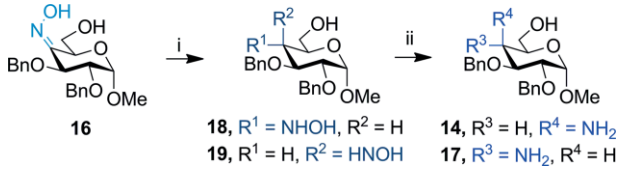


Scheme 1. Preparation of benzylated common intermediate **11**. Reagents and conditions: i) anisaldehyde dimethyl acetal, CSA (camphorsulfonic acid), DMF, 60 °C, 1 h, 98 %; ii) BnBr, NaH, DMF, room temp., 1 h, 89 %; iii) $KHSO_4 \cdot H_2O$, MeOH, room temp., 1 h, 98 %. PMP = *p*-methoxyphenyl.



Scheme 2. Introduction of new amino groups at C-4: A) selective oxazine ring opening to give D-*galacto* epimer **14**; B) selective oxime reduction to give D-*gluco* epimer **17**. Reagents and conditions: i) Cl_3CCN, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), CH_2Cl_2, 0 °C, 5 min; ii) Tf_2O, pyridine, 0 °C, 5 min; iii) DIPEA (diisopropylethylamine), room temp., 3.5 h, overall yield 69 %; iv) 80 % AcOH, room temp., 30 min, 80 %; v) Bu_2SnO, toluene, reflux, 12 h; vi) 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), $CHCl_3$, room temp., 15 min; vii) $NH_2OH{\cdot}HCl$, $NaOAc{\cdot}3H_2O$, AcOH, 60 °C, 5 h, overall yield 62 %; viii) $LiAlH_4$, Et_2O, room temp., 24 h, 57 %.

in an H-Cube reactor with RaNi catalyst in methanol (Scheme 3). This new method gave both 4-amino-4-deoxy epimers **14** and **17** in a 1:1 ratio, as confirmed by ^1H NMR spectroscopy. The products were isolated in an excellent overall yield of 93 %.



Scheme 3. The new nonselective reduction of key oxime intermediate **16** in two steps. Reagents and conditions: i) AcOH, $NaBH_4$, room temp., 1 h, 98 %; ii) H-cube: 80 °C, 50 bar, RaNi catalyst, 97 %.

To explain the different stereoselectivities of the oxime reductions with $LiAlH_4$ in Et_2O and with $NaBH_4$ in AcOH, we propose two mechanisms (Figure 2). In the case of $LiAlH_4$ (a), oxime **16** can form a four-centred C=N$^+$···Al···H complex in which the bulky $[AlH_4]^-$ ion can be attached only to the upper side to the pyranoid ring. The result is the stereoselective formation of the D-*gluco* epimer **17**. The crystal structure of the *Z*-oxime, determined by X-ray diffraction, shows the pyranoid ring conformation, and shows that the bulky substituents cause steric crowding only on the upper face of the oxime group; this supports the proposed mechanistic explanation for the stereoselectivity (Figure 2a and Supporting Information).

On the other hand, under acidic conditions, nonselective reduction takes place: fast protonation of the oxime (HN$^+$–OH) results in a "carbocation", which can be attacked by the H$^-$ anion from either side of the molecule to give the hydroxylamine epimers **18** and **19** in a 1:1 ratio (Figure 2b). This "carbocation" might be stabilized by a -C=N–OH···O- interaction between the oxime OH and the primary 6-OH. The presence of this interaction in solution was unambiguously corroborated for both isomers by the ^1H,^1H NOESY spectrum of oxime **16**. This shows a strong cross-peak between the N–OH proton (δ = 9.13 ppm) and 6-OH (δ = 2.72 ppm) of the *E*-oxime (Figure 3). The ^1H NMR spectrum also shows that the *E*- and *Z*-oximes are present in solution in a 93:7 ratio.

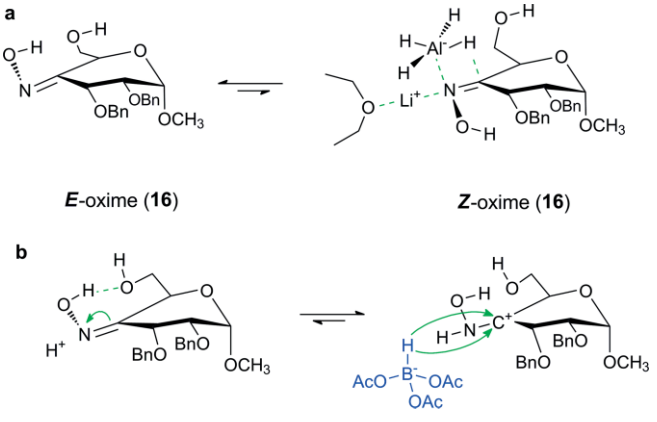


Figure 2. Proposed mechanism for reduction of oxime **16**: (a) with $LiAlH_4$ in Et_2O; and (b) with $NaBH_4$ in AcOH.

We note here that the crystal structure of **16** shows a definite intermolecular O–H···O–H hydrogen bond between the oxime OH and the primary 6-OH of another neighbouring oxime molecule, as indicated in Figure 3b by cyan coloured lines. The occurrence of this arrangement in solution might facilitate the external protonation of the -N=O moiety in **16** to form the "carbocation" also in the case of the *Z*-oxime.

Finally, the amino group of both D-*gluco* **14** and D-*galacto* **17** epimers was N-protected with an Fmoc group, the primary choice for SPPS. At this stage, the two C-4 epimers were separated due to their very different solubilities in Et_2O. Trituration of the mixture gave the D-*gluco* epimer **20** as white crystals;

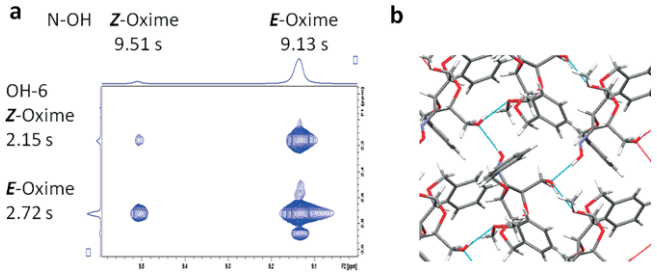
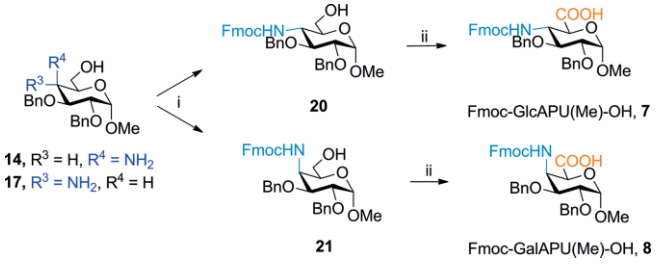


Figure 3. a) $^1H,^1H$ NOESY spectrum of oxime **16**, showing NOESY cross-peaks between the oxime OH group and the primary 6-OH group; b) 3D crystal structure of the *Z*-oxime, showing the intermolecular hydrogen-bond network.

treatment of the mother liquor with hexane gave the D-*galacto* epimer **21** as a white viscous liquid. The carboxylic group was introduced by oxidation[24] of the CH_2OH group with TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] and NaOCl. Both carboxylic products were obtained in excellent yields: 97 % for the D-*gluco* compound **7**, and 85 % for the D-*galacto* epimer **8** (Scheme 4).



Scheme 4. Separation of the two epimers, and final oxidation to give both target β-SAAs **7** and **8**. i) FmocOSu (9-fluorenylmethyl *N*-succinimidyl carbonate), THF, MeOH/water (2:1), $NaHCO_3$, room temp., 24 h, 96 % of **20**, 75 % of **21**; ii) TEMPO/NaOCl, KBr, CH_2Cl_2, 0 °C, 2 h, 96 % of **7**, 85 % of **8**.

These β-SAAs **7** and **8** are now suitable for coupling using SPPS, as i) they are available on a multigram scale; ii) they are soluble and stable in aprotic solvents; iii) their amino groups are Fmoc-protected, while the OH groups are still benzylated; iv) they have a C-terminal COOH group that is easy to activate. The formation of active esters using different coupling reagents was tested for both diastereoisomers, and they were found to be stable enough, even for longer coupling times (e.g., 24 h).

Conclusions

Economical and practical pathways have been developed for the synthesis of two new β-sugar amino acids, namely Fmoc-GlcAPU(Me)-OH (**7**) and Fmoc-GalAPU(Me)-OH (**8**). The new protocol uses a single starting material **6**, and gives both the target β-SAAs in good yields. By introducing **16** as a common key intermediate, we opened up a new synthetic route to protected forms of both C-4 epimers: 4-amino-4-deoxy-D-glucopyranoside (**14**) and 4-amino-4-deoxy-D-galactopyranoside (**17**). The non-selective reduction of oxime **16** gave a mixture of the two C-4 epimers in two steps. They were easily separated afterwards. Additional benefits of this new protocol are as follows: i) column chromatography was omitted for all steps; ii) the valuable anisaldehyde dimethyl acetal reagent was almost completely recycled (98 %). The scalable synthetic process resulted in Fmoc-GlcAPU(Me)-OH (**7**) and Fmoc-GalAPU(Me)-OH (**8**) in overall yields of 46 and 32 %, respectively. These β-SAAs are ready to be used as building blocks for SPPS, to make both homo- and heterofoldamers.

Experimental Section

Methyl 4,6-*O*-(4′-Methoxybenzylidine)-α-D-glucopyranoside (9): Methyl α-D-glucopyranoside (**6**; 40 g, 0.2 mol), camphorsulfonic acid (0.46 g, 2 mmol), and anisaldehyde dimethyl acetal (41.3 mL, 0.22 mol) were mixed with dry DMF (160 mL) in a round-bottomed flask. The mixture was heated under vacuum at 60 °C to remove the methanol. After 1 h, the temperature was raised to 65 °C, and the solvent was evaporated. The residual yellowish oil was poured into a mixture of ice (100 g), saturated aqueous $NaHCO_3$ (200 mL), and ether (200 mL). The product was collected by filtration, then washed with petroleum ether and water to give **9** (61.3 g, 95 %) as a white solid. R_f = 0.67 (EtOAc/methanol, 9:1). M.p. 194 °C; lit.[25] m.p. 194 °C.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-(4′-methoxybenzylidine)-α-D-glucopyranoside (10): Compound **9** (15 g, 0.048 mol) was dissolved in dry DMF (200 mL) under argon at 0 °C in a three-necked flask equipped with a mechanical stirrer. Then NaH (60 % in mineral oil; 4.8 g, 0.12 mol) was added, and the mixture was stirred at room temperature for 15 min. Then, BnBr (14 mL, 0.12 mol) was added dropwise, and the mixture was stirred for 1 h. Then, methanol (40 mL) was added to quench the reaction, and the mixture was stirred for 30 min. The mixture was poured into ice (500 g), and the resulting solid was collected by filtration. The white solid was crystallized from hot ethanol (400 mL) to give **10** (21.1 g, 89 %) as white crystals. R_f = 0.65 (EtOAc/toluene, 1:3). M.p. 142 °C; lit.[25] m.p. 143–144 °C.

Methyl 2,3-Di-*O*-benzyl-α-D-glucopyranoside (11): The synthesis of **11** was carried out from **10** (26.3 g, 0.053 mol) as described,[19] with differences in the purification. Instead of being purified by column chromatography, the crude product was triturated with petroleum ether to give **11** (21.2 g, 98 %) as a white powder. R_f = 0.18 (EtOAc/petroleum ether, 1:1). M.p. 73–75 °C; lit.[26] m.p. 73–75 °C. For recycling the reagent, the petroleum ether phase was concentrated to give the anisaldehyde dimethyl acetal in excellent yield (9.7 mL, 98 %).

Methyl 2,3-Di-*O*-benzyl-α-D-xylopyranoside-4-ulose (15b): Compound **11** (10 g, 0.026 mol) was dissolved in toluene (220 mL) in a flask equipped with a Dean–Stark apparatus. Bu_2SnO (7.9 g, 0.032 mol) was added, and the mixture was heated at reflux for 11 h. Then the mixture was concentrated, and the residue was dried in vacuo for 30 min. The residue was then dissolved in chloroform (220 mL), and DBDMH (4.2 g, 0.014 mol) was added in one portion. The mixture was stirred until it became discoloured. The mixture was then filtered into $Na_2S_2O_3$ solution (10 % aq.; 150 mL). The aqueous phase was separated, and extracted with chloroform (100 mL). The combined organic phase was washed with water (2 × 100 mL) and dried ($MgSO_4$). The mixture was filtered and concentrated to give crude **15b** (9.5 g) as a yellow oil. R_f = 0.41 (EtOAc/petroleum ether, 1:1). IR: $\tilde{\nu}$ = 3462 (OH), 2956–2869 (CH), 1731 (C=O) cm^{-1}. The crude product was converted directly into oxime (**16**) without any purification.

Methyl 2,3-Di-*O*-benzyl-α-D-xylopyranoside-4-ulose Oxime (16): NaOAc (10.9 g, 0.08 mol) and hydroxylamine hydrochloride (5.5 g,

0.08 mol) were dissolved in acetic acid (100 mL). The mixture was heated to 55 °C, and then a solution of compound **15b** (9.9 g, 0.026 mol) in acetic acid (50 mL) was added. The resulting solution was stirred under N_2 for 6 h at 55 °C. The mixture was then poured into ice (300 g) and neutralized with saturated aqueous Na_2CO_3 solution. The mixture was extracted with hexane (2 × 50 mL), then with EtOAc (3 × 100 mL). The hexane extract was discarded, and the combined EtOAc phases were washed with saturated aqueous Na_2CO_3 and water (100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in diethyl ether (50 mL) and crystallized from hexane to give **16** (6.4 g, 62 %) as white crystals. R_f = 0.52 (EtOAc/petroleum ether, 1:1). M.p. 91 °C. $[\alpha]_D^{22}$ = +101.3 (*c* = 1, chloroform). ^{1}H NMR ($CDCl_3$): δ = 9.13 (s, 1 H, OH-oxime), 7.24–7.15 (m, BnO Ar-H), 4.96 (dd, $^3J_{H,H}$ = 5.3, 1.8 Hz, 1 H, 5-H), 4.76 (d, $^3J_{H,H}$ = 3.7 Hz, 1 H, 1-H), 4.53 (d, $^3J_{H,H}$ = 11.6 Hz, 1 H, BnO-3: CH_{2A}), 4.51 (d, $^3J_{H,H}$ = 12.1 Hz, 1 H, BnO-2: CH_{2A}), 4.45 (d, $^3J_{H,H}$ = 12.1 Hz, 1 H, BnO-2: CH_{2B}), 4.28 (d, $^3J_{H,H}$ = 11.6 Hz, 1 H, BnO-3: CH_{2B}), 4.06 (d, $^3J_{H,H}$ = 3.4 Hz, 1 H, 3-H), 3.86 (dt, $^3J_{H,H}$ = 11.5, 5.0 Hz, 1 H, 6-H_A), 3.78–3.74 (overlapped m, 1 H, 6-H_B), 3.77 (overlapped t, $^3J_{H,H}$ = 3.6 Hz, 1 H, 2-H), 3.36 (s, 3 H, CH_3), 2.72 (very br. t, 1 H, 6-OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 153.0 (C-4), 137.6 (BnO-3: C-1′), 137.1 (BnO-2: C-1′), 128.6, 128.5, 128.4 (BnO-3: C-2′, C-3′, C-4′, C-5′, C-6′), 128.2, 128.1, 128.0 (BnO-2: C-2′, C-3′, C-4′, C-5′, C-6′), 97.2 (C-1), 79.0 (C-2), 76.6 (C-3), 72.1 (BnO-2: CH_2′), 70.6 (BnO-3: CH_2′), 68.5 (C-5), 62.1 (C-6), 56.6 (CH_3) ppm. HRMS: calcd. for $C_{21}H_{26}NO_6$ $[M + H]^+$ 388.1760; found 388.1761.

Methyl 2,3-Di-*O*-benzyl-4-deoxy-4-hydroxylamino-α-D-glucopyranoside (18) and Methyl 2,3-Di-*O*-benzyl-4-deoxy-4-hydroxylamino-α-D-galactopyranoside (19): $NaBH_4$ (2.93 g, 0.077 mol) was added in small portions to glacial acetic acid (50 mL) at 15–20 °C. The mixture was stirred for 30 min, then **16** (5 g, 0.013 mol) was added in one portion. The mixture was stirred at room temperature for 2 h. Water (10 mL) was then added, and the mixture was neutralized with saturated aqueous Na_2CO_3. The mixture was extracted with dichloromethane (2 × 100 mL), and the combined organic phases were washed with saturated aqueous Na_2CO_3 (100 mL), dried ($MgSO_4$), and filtered. The mixture was concentrated in vacuo to give a mixture of **18** and **19** (4.9 g, 98 %) as a colourless oil. R_f = 0.41 and 0.46 (EtOAc/petroleum ether, 1:1). The mixture of **18** and **19** was subsequently converted into the corresponding amine derivatives without prior separation.

Methyl 2,3-Di-*O*-benzyl-4-amino-4-deoxy-α-D-glucopyranoside (17) and Methyl 2,3-Di-*O*-benzyl-4-amino-4-deoxy-α-D-galactopyranoside (14) by Nonselective Oxime Reduction: The mixture of **18** and **19** (4.8 g, 0.012 mol) was dissolved in methanol (620 mL), and was reduced in an H-cube reactor. The flow velocity was set with an HPLC pump to 0.3 mL/min; the hydrogen pressure was set to 50 bar; the temperature to 80 °C; a cartridge containing RaNi was used. The resulting solution was concentrated in vacuo to give a mixture of **14** and **17** (4.35 g, 97 %) as a colourless oil. The mixture of **14** and **17** was subsequently converted into the corresponding Fmoc derivatives without prior separation.

Data for compound **17**: R_f = 0.31 (EtOAc/methanol, 9:1). ^{1}H NMR ($CDCl_3$): δ = 7.28–7.16 (m, BnO Ar-H), 4.65 (overlapped d, $^3J_{H,H}$ = 11.5 Hz, 1 H, BnO-3: CH_{2A}), 4.57 (overlapped d, $^3J_{H,H}$ = 11.5 Hz, 1 H, BnO-3: CH_{2B}), 4.57 (overlapped m, 1 H, BnO-2: CH_{2A}), 4.55 (overlapped m, 1 H, BnO-2: CH_{2B}), 4.52 (d, $^3J_{H,H}$ = 3.6 Hz, 1 H, 1-H), 3.63 (overlapped dd, $^3J_{H,H}$ = 6.3 Hz, 2 H, 6-H_A and 6-H_B), 3.47 (t, $^3J_{H,H}$ = 9.5 Hz, 1 H, 3-H), 3.41 (dd, $^3J_{H,H}$ = 9.7, 3.3 Hz, 1 H, 2-H), 3.36 (overlapped dd, $^3J_{H,H}$ = 5.1 Hz, 1 H, 5-H), 3.27 (s, 3 H, CH_3), 2.60 (t, $^3J_{H,H}$ = 9.5 Hz, 1 H, 4-H), 2.29 (very br., 1 H, 6-OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 138.1, 137.8 (BnO-2: C-1′ and BnO-3: C-1′), 128.03, 127.9, 127.3 (BnO-3: C-2′, C-3′, C-4′, C-5′, C-6′), 127.45, 127.41, 126.4 (BnO-2: C-2′, C-3′, C-4′, C-5′, C-6′), 97.7 (C-1), 81.4 (C-3), 80.0 (C-2), 72.5 (BnO-2: CH_2′), 72.0 (BnO-3: CH_2′), 70.4 (C-5), 62.9 (C-6), 54.8 (CH_3), 54.6 (C-4) ppm.

Data for compound **14**: R_f = 0.22 (EtOAc/methanol, 9:1). ^{1}H NMR ($CDCl_3$): δ = 7.28–7.16 (m, BnO-2 Ar-H, BnO-3 Ar-H), 4.95 (d, $^3J_{H,H}$ = 11.4 Hz, 1 H, BnO-3: CH_{2A}), 4.71 (overlapped d, $^3J_{H,H}$ = 12.1 Hz, 1 H, BnO-2: CH_{2A}), 4.64 (overlapped m, 1 H, BnO-2: CH_{2B}), 4.57 (overlapped d, $^3J_{H,H}$ = 11.4 Hz, 1 H, BnO-3: CH_{2B}), 4.57 (overlapped, 1 H, 1-H), 3.73 (overlapped t, $^3J_{H,H}$ = 5.6 Hz, 1 H, 5-H), 3.72 (overlapped t, $^3J_{H,H}$ = 5.2 Hz, 1 H, 6-H_A), 3.72 (overlapped t, $^3J_{H,H}$ = 9.8 Hz, 1 H, 3-H), 3.69 (overlapped t, $^3J_{H,H}$ = 5.2 Hz, 1 H, 6-H_B), 3.6 (dd, $^3J_{H,H}$ = 6.4, 3.7 Hz, 1 H, 2-H), 3.27 (s, 3 H, CH_3), 3.21 (dd, $^3J_{H,H}$ = 3.8 Hz, 1 H, 4-H), 2.29 (br., 1 H, 6-OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 137.9, 137.5 (BnO-2: C-1′ and BnO-3: C-1′), 128.1, 128.06, 127.2 (BnO-3: C-2′, C-3′, C-4′, C-5′, C-6′), 127.6, 127.5, 126.9 (BnO-2: C-2′, C-3′, C-4′, C-5′, C-6′), 98.11 (C-1), 77.4 (C-5), 75.1 (BnO-3: CH_2′), 75.0 (C-2), 72.8 (BnO-2: CH_2′), 68.1 (C-3), 62.4 (C-6), 54.7 (CH_3), 51.1 (C-4) ppm.

Methyl *N*-9-Fluorenylmethoxycarbonyl-2,3-di-*O*-benzyl-4-amino-4-deoxy-α-D-glucopyranoside (20) and Methyl *N*-9-Fluorenylmethoxycarbonyl-2,3-di-*O*-benzyl-4-amino-4-deoxy-α-D-galactopyranoside (21): The mixture of compounds **14** and **17** (2.23 g, 6 mmol) was dissolved in a mixture of methanol and water (2:1; 48 mL), and the pH was adjusted to 9 with saturated aqueous $NaHCO_3$. Then, a solution of Fmoc-OSu (2.21 g, 6.53 mmol) in THF (15 mL) was added, and the mixture was stirred for 24 h. After this time, the THF was evaporated, and the residue was extracted with hexane (2 × 50 mL), then with EtOAc (3 × 50 mL). The hexane extract was discarded. The combined EtOAc phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was treated with ether to give compound **20** (1.7 g, 96 %) as a white solid. R_f = 0.15 (ether/petroleum ether, 4:1). $[\alpha]_D^{22}$ = +28.3 (*c* = 1, chloroform). ^{1}H NMR ($CDCl_3$): δ = 7.68 (dd, $^3J_{H,H}$ = 2.4, 7.2 Hz, 2 H, Fmoc-6-H, Fmoc-6′-H), 7.46 (dd, $^3J_{H,H}$ = 7.0, 3.0 Hz, 2 H, Fmoc-3-H, Fmoc-3′-H), 7.34–7.15 (m, BnO Ar-H, Fmoc-4-H, Fmoc-5-H, Fmoc-4′-H, Fmoc-5′-H), 4.81 (d, $^3J_{H,H}$ = 11.7 Hz, 1 H, BnO-3: CH_{2A}), 4.70 (d, $^3J_{H,H}$ = 11.2 Hz, 1 H, BnO-2: CH_{2A}), 4.58 (overlapped, 2 H, BnO-2: CH_{2B}, BnO-3: CH_{2B}), 4.53 (d, $^3J_{H,H}$ = 3.3 Hz, 1 H, 1-H), 4.48 (dd, $^3J_{H,H}$ = 10.7, 4.2 Hz, 1 H, Fmoc-CH_{2A}), 4.36 (dd, $^3J_{H,H}$ = 10.7, 4.2 Hz, 1 H, Fmoc-CH_{2B}), 4.25 (d, $^3J_{H,H}$ = 6.9 Hz, 1 H, NH), 4.08 (t, $^3J_{H,H}$ = 6.1 Hz, 1 H, Fmoc-1-H), 3.58 (overlapped dd, $^3J_{H,H}$ = 9.8, 3.5 Hz, 1 H, 4-H), 3.57 (overlapped t, $^3J_{H,H}$ = 9.5 Hz, 1 H, 3-H), 3.52 (overlapped dd, $^3J_{H,H}$ = 8.8, 3.2 Hz, 1 H, 2-H), 3.46 (dd, $^3J_{H,H}$ = 12.7, 7.2 Hz, 1 H, 6-H_A), 3.40 (dd, $^3J_{H,H}$ = 12.7, 7.2 Hz, 1 H, 6-H_B), 3.25 (overlapped s, 3 H, CH_3), 3.25 (overlapped m, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 157.1 (Fmoc-C=O), 143.9, 143.3 (Fmoc-C-2 and Fmoc-C-2′), 140.9 (Fmoc-C-7 and Fmoc-C-7′), 137.6 (BnO-3: C-1″), 137.3 (BnO-2: C-1′), 128.1, 128.0 (Fmoc-C-4 and Fmoc-C-4′ and Fmoc-C-5 and Fmoc-C-5′), 127.9, 127.8, 127.6, 127.3 (BnO-3: C-2″, C-3″, C-4″, C-5″, and BnO-2: C-2′, C-3′, C-4′, C-5′), 127.6 (BnO-3: C-6″), 127.5 (BnO-2: C-6′), 124.4 (Fmoc-C-3 and Fmoc-C-3′), 119.6 (Fmoc-C-6 and Fmoc-C-6′), 97.8 (C-1), 79.6 (C-2), 75.9 (C-3), 74.0 (BnO-3: CH_2″), 72.8 (BnO-2: CH_2′), 70.9 (C-5), 66.2 (Fmoc-CH_2), 54.8 (CH_3), 51.4 (C-4), 46.8 (Fmoc-C-1) ppm. HRMS: calcd. for $C_{36}H_{38}NO_7$ $[M + H]^+$ 596.2648; found 596.2631.

The mother liquor was concentrated and treated with hexane to give compound **21** (1.3 g, 75 %) as a white viscous liquid. R_f = 0.23 (ether/petroleum ether, 4:1). $[\alpha]_D^{22}$ = +44 (*c* = 0.5, chloroform). ^{1}H NMR ($CDCl_3$): δ = 7.69 (d, $^3J_{H,H}$ = 7.6 Hz, 2 H, Fmoc-6-H, Fmoc-6′-H), 7.50 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, Fmoc-4-H, Fmoc-4′-H), 7.33–7.17 (m, 14 H, BnO-2 Ar-H, BnO-3 Ar-H, Fmoc-3-H, Fmoc-5-H, Fmoc-3′-H, Fmoc-5′-H), 4.92 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, NH), 4.77 (d, $^3J_{H,H}$ = 12.8 Hz, 1 H,

BnO-3: CH_{2A}), 4.63 (overlapped d, $^3J_{H,H}$ = 12.8 Hz, 1 H, BnO-3: CH_{2B}), 4.62 (overlapped d, $^3J_{H,H}$ = 11.6 Hz, 2 H, BnO-2: CH_{2A}), 4.53 (d, $^3J_{H,H}$ = 3.5 Hz, 1 H, 1-H), 4.50 (d, $^3J_{H,H}$ = 11.6 Hz, 1 H, BnO-2: CH_{2B}), 4.44 (dd, $^3J_{H,H}$ = 10.7, 6.5 Hz, 1 H, Fmoc-CH_{2A}), 4.38 (dd, $^3J_{H,H}$ = 10.7, 6.5 Hz, 1 H, Fmoc-CH_{2B}), 4.27 (dd, $^3J_{H,H}$ = 8.2, 4.9 Hz, 1 H, 4-H), 4.13 (t, $^3J_{H,H}$ = 6.7 Hz, 1 H, Fmoc-1-H), 3.94 (dd, $^3J_{H,H}$ = 9.9, 4.4 Hz, 1 H, 5-H), 3.82 (t, $^3J_{H,H}$ = 6.9 Hz, 1 H, 3-H), 3.45 (m, 1 H, 6-H_A), 3.40 (dd, $^3J_{H,H}$ = 9.8, 3.3 Hz, 1 H, 2-H), 3.35 (m, 1 H, 6-H_B), 3.28 (s, 3 H, CH_3), 3.03 (br. t, $^3J_{OH,H}$ = 5.4 Hz, 1 H, 6-OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 158.0 (Fmoc-C=O), 143.7, 143.4 (Fmoc-C-2 and Fmoc-C-2′), 141.3, 141.2 (Fmoc-C-7 and Fmoc-C-7′), 138.1 (BnO-3: C-1″), 137.8 (BnO-2: C-1′), 128.4, 128.3 (BnO-3: C-2″, C-6″, BnO-2: C-2′, C-6′), 127.9, 127.8 (BnO-3: C-3″, C-5″, BnO-2: C-3′, C-5′), 127.71, 127.70 (BnO-3: C-4″, BnO-2: C-4′), 127.69, 127.94, 127.04, 127.02 (Fmoc-C-4 and Fmoc-C-4′ and Fmoc-C-5 and Fmoc-C-5′), 124.9, 124.8 (Fmoc-C-3 and Fmoc-C-3′), 119.97, 119.95 (Fmoc-C-6 and Fmoc-C-6′), 98.3 (C-1), 75.5 (C-3), 75.3 (C-2), 73.5 (BnO-3: CH_2″), 71.4 (BnO-2: CH_2′), 68.5 (C-5), 66.9 (Fmoc-CH_2), 60.8 (C-6), 55.4 (CH_3), 49.7 (C-4), 47.2 (Fmoc-C-1) ppm. HRMS: calcd. for $C_{36}H_{38}NO_7$ $[M + H]^+$ 596.2648; found 596.2645.

Methyl *N*-9-Fluorenylmethoxycarbonyl-2,3-di-*O*-benzyl-4-amino-4-deoxy-α-D-glucopyranosiduronic Acid (7): Compound **20** (2.36 g, 4 mmol) was dissolved in a mixture of THF and saturated aqueous $NaHCO_3$ (1:1; 96 mL) at 0 °C, and TEMPO (125 mg, 0.8 mmol) and KBr (141 mg, 1.2 mmol) were added. NaOCl (0.47 M aq.; 17.6 mL) was then added dropwise at 0 °C. After 1 h, further NaOCl (0.47 M aq.; 8 mL) and TEMPO (60 mg) were added, and the mixture was stirred for a further 1 h at 0 °C. The solution was extracted with hexane (2 × 20 mL). The aqueous layer was acidified with saturated aqueous $NaHSO_4$ to pH 3, and then it was extracted with EtOAc (4 × 50 mL). The hexane extracts were discarded. The combined EtOAc layers were dried ($MgSO_4$), filtered, and concentrated. The residue was treated with hexane (30 mL) to give compound **7** (2.35 g, 97 %) as a white solid. R_f = 0.18 (methanol/EtOAc/AcOH, 9:1:0.01). M.p. 158–160 °C. $[\alpha]_D^{22}$ = 35.9 (*c* = 0.48, chloroform). ^{1}H NMR ([D_6]DMSO): δ = 7.88 (d, $^3J_{H,H}$ = 7.5 Hz, 2 H, Fmoc-6-H, Fmoc-6′-H), 7.70 (dd, $^3J_{H,H}$ = 7.4 Hz, 2 H, Fmoc-3-H, Fmoc-3′-H), 7.65 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, NH), 7.40–7.18 (m, 14 H, BnO Ar-H, Fmoc-4-H, Fmoc-5-H, Fmoc-4′-H, Fmoc-5′-H), 4.91 (d, $^3J_{H,H}$ = 3.31 Hz, 1 H, 1-H), 4.70 (d, $^3J_{H,H}$ = 11.2 Hz, 1 H, BnO-3: CH_{2A}), 4.65 (overlapped d, $^3J_{H,H}$ = 12.04 Hz, 1 H, BnO-2: CH_{2A}), 4.64 (d, $^3J_{H,H}$ = 11.8 Hz, 1 H, BnO-2: CH_{2B}), 4.55 (d, $^3J_{H,H}$ = 11.2 Hz, 1 H, BnO-3: CH_{2B}), 4.26 (overlapped d, $^3J_{H,H}$ = 9.02 Hz, 1 H), 4.16 (overlapped d, $^3J_{H,H}$ = 9.02 Hz, 1 H, Fmoc-CH_{2A}), 4.14 (overlapped t, 1 H, Fmoc-1-H), 4.03 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, 5-H), 3.83 (t, $^3J_{H,H}$ = 9.7 Hz, 1 H, 3-H), 3.69 (dd, $^3J_{H,H}$ = 10.1 Hz, 1 H, 4-H), 3.51 (dd, $^3J_{H,H}$ = 9.5, 3.4 Hz, 1 H, 2-H), 3.33 (s, 3 H, CH_3) ppm. ^{13}C NMR ([D_6]DMSO): δ = 169.9 (COOH-6), 155.7 (Fmoc-C=O), 143.8, 143.7 (Fmoc-C-2 and Fmoc-C-2′), 140.6 (Fmoc-C-7 and Fmoc-C-7′), 138.6 (BnO-3: C-1″), 138.4 (BnO-2: C-1′), 128.2, 127.9, 127.6, 127.5 (BnO-3: C-2″, C-3″, C-4″, C-5″, C-6″, and BnO-2: C-2′, C-3′, C-4′, C-5′, C-6′), 127.2 (Fmoc-C-5 and Fmoc-C-5′), 127.0 (Fmoc-C-4 and Fmoc-C-4′), 125.3, 125.1 (Fmoc-C-3 and Fmoc-C-3′), 120.1 (Fmoc-C-6 and Fmoc-C-6′), 97.6 (C-1), 79.2 (C-3), 77.9 (C-2), 74.3 (BnO-3: CH_2′), 71.4 (BnO-2: CH_2″), 69.9 (C-5), 65.7 (Fmoc-CH_2), 55.0 (CH_3), 54.0 (C-4), 46.5 (Fmoc-C-1) ppm. HRMS: calcd. for $C_{36}H_{36}NO_8$ $[M + H]^+$ 610.2441; found 610.2450.

Methyl *N*-9-Fluorenylmethoxycarbonyl-2,3-di-*O*-benzyl-4-amino-4-deoxy-α-D-galactopyranosiduronic Acid (8): Compound **8** was synthesized as described for **7**, starting from **21** (1.20 g, 2 mmol). Compound **8** (1.04 g, 85 %) was obtained as a white powder. R_f = 0.38 (methanol/EtOAc/AcOH, 9:1:0.01). M.p. 75–78 °C. $[\alpha]_D^{22}$ = +58.4 (*c* = 0.49, chloroform). ^{1}H NMR ([D_6]DMSO): δ = 7.89 (d, $^3J_{H,H}$ = 7.5 Hz, 2 H, Fmoc-6-H,Fmoc-6′-H), 7.77 (dd, $^3J_{H,H}$ = 7.4 Hz, 2 H, Fmoc-3-H, Fmoc-3′-H), 7.64 (d, $^3J_{H,H}$ = 10.6 Hz, 1 H, NH), 7.44–7.18 (m, 14 H, BnO Ar-H, Fmoc-4-H, Fmoc-5-H, Fmoc-4′-H, Fmoc-5′-H), 4.86 (d, $^3J_{H,H}$ = 5.31 Hz, 1 H, 1-H), 4.72 (overlapped d, $^3J_{H,H}$ = 11.7 Hz, 1 H, BnO-3: CH_{2A}), 4.71 (overlapped t, 1 H, 4-H), 4.69 (overlapped d, $^3J_{H,H}$ = 11.8 Hz, 1 H, BnO-2: CH_{2A}), 4.59 (d, $^3J_{H,H}$ = 11.8 Hz, 1 H, BnO-2: CH_{2B}), 4.49 (d, $^3J_{H,H}$ = 11.7 Hz, 1 H, BnO-3: CH_{2B}), 4.38 (d, $^3J_{H,H}$ = 1.7 Hz, 1 H, 5-H), 4.18 (overlapped t, 1 H, Fmoc-1-H), 4.17 (overlapped m, 2 H, Fmoc-CH_2), 4.0 (dd, $^3J_{H,H}$ = 10.4, 6.7 Hz, 1 H, 3-H), 3.92 (dd, $^3J_{H,H}$ = 10.2, 5.9 Hz, 1 H, 2-H), 3.30 (s, 3 H, CH_3) ppm. ^{13}C NMR ([D_6]DMSO): δ = 169.1 (COOH-6), 156.2 (Fmoc-C=O), 143.8, 143.7 (Fmoc-C-2 and Fmoc-C-2′), 140.6 (Fmoc-C-7 and Fmoc-C-7′), 138.9 (BnO-3: C-1″), 138.6 (BnO-2: C-1′), 128.0, 127.9, 127.6, 127.3 (BnO-3: C-2″, C-3″, C-4″, C-5″, C-6″, and BnO-2: C-2′, C-3′, C-4′, C-5′, C-6′), 127.3 (Fmoc-C-5 and Fmoc-C-5′), 127.2 (Fmoc-C-4 and Fmoc-C-4′), 125.5 (Fmoc-C-3 and Fmoc-C-3′), 120.0 (Fmoc-C-6 and Fmoc-C-6′), 98.2 (C-1), 75.4 (C-2), 74.8 (C-3), 71.8 (BnO-2: CH_2′), 70.2 (BnO-3: CH_2″), 68.3 (C-5), 65.8 (Fmoc-CH_2), 50.5 (C-4), 46.5 (Fmoc-C-1) ppm. HRMS: calcd. for $C_{36}H_{36}NO_8$ $[M + H]^+$ 610.2441; found 610.2440.

CCDC 1575872 (for **16**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Supporting Information (see footnote on the first page of this article): General experimental information, ^{1}H and ^{13}C NMR spectra, tables, and X-ray data for **16**.

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