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Synthesis of novel amino acid glycoside conjugates

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Abstract

A new class of non-anomeric amino acid glycoconjugates can be prepared starting from either ω-amino- or ω-halodeoxyglucosides. Treatment of an ether-protected methyl 7-amino-6,7-dideoxy-α-D-glucoheptopyranoside with methyl aspartate isocyanate gave an urea-linked conjugate of methyl glucoheptopyranoside and aspartic acid. Nucleophilic displacement of the ether-protected methyl 6-chloro-6-deoxy-α-D-glucopyranoside with potassium succinimide followed by imide ring opening and amidation of the succinic acid monoamide with dimethyl iminodiacetate led to a conjugate of methyl 6-amino-6-deoxy-α-D-glucopyranoside and iminodiacetate bridged by succinate. © 1997 Elsevier Science Ltd.

Keywords: Amino acid glycoconjugates; Non-anomeric; Succinimide; Amino acid ester isocyanate

1. Introduction

Glycoconjugates of lipids and proteins are recognized to be biologically important. Due to their glycosylation patterns, they are responsible for recognition and adhesion of cells as well as of toxins, viruses etc. Other important aspects incorporate structure- and solubility-determining effects of peptide glycosylation. Many glycoprotein structures with *N*- or *O*-glycosylation have been synthesized and studied intensively [1–5]. Besides these anomerically linked sugar–peptide derivatives, only a few analogs have been prepared, such as a 6-*O*-peptidyl glycopyranose [6]. In this contribution, attempts have been made to synthesize model compounds having *N*-linked amino acid or peptide side-chains attached to a saccharide backbone. The choice of the amino acids, aspartic and iminodiacetic acid, was determined with the idea of obtaining carbohydrate-derived anionic (poly)electrolytes which resemble building units of peptidoglycans. As a model for further studies with starch, the 4-methylated methyl glucoside was chosen.

2. Results and discussion

The 6-deoxy-6-haloderivatives of mono-, oligo-, or poly-saccharide hexosides can be readily prepared [7,8] and are suitable substrates for nucleophilic substitution reactions [9,10]. Therefore, they constitute good starting materials for the desired conjugates. With respect to the time-consuming preparation of 4-substituted methyl glucosides, the halogenation reaction was integrated into the synthesis of the starch model. In addition to the 6-chloro glycoside **5**, the analogous tosylate **3** was also used as a less-sensitive substitute for the more reactive iodo compound.

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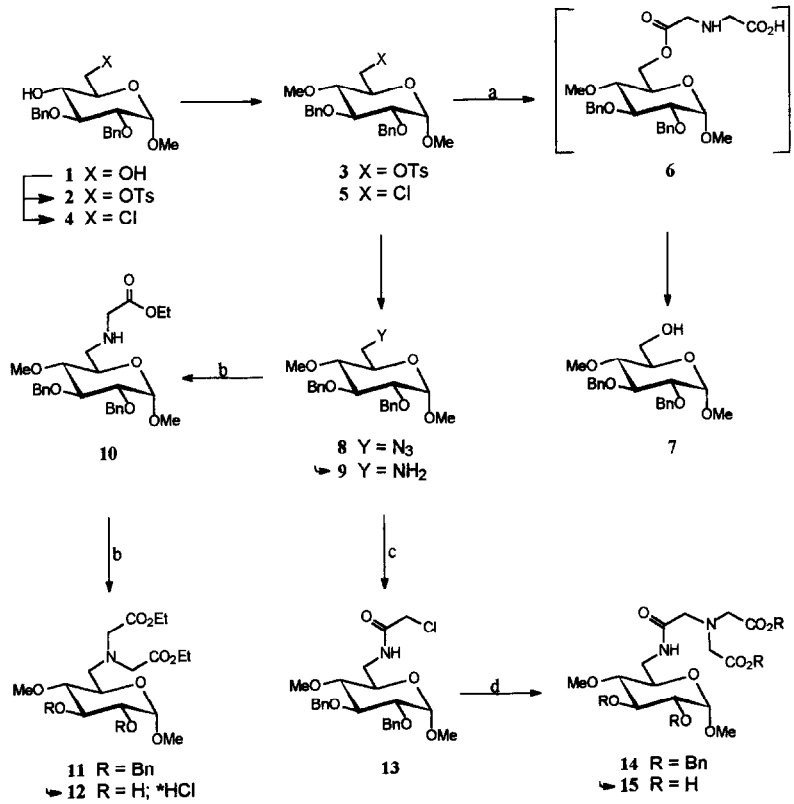
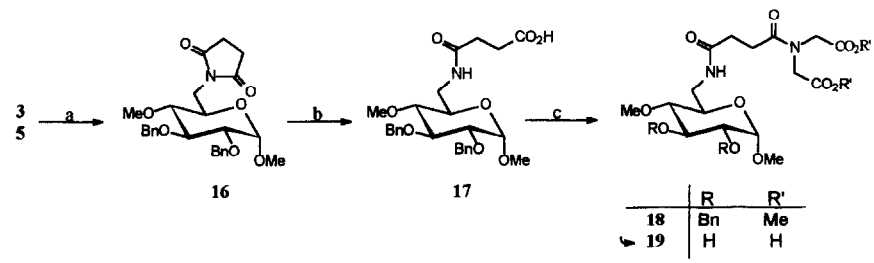


Scheme 1. (a) $HN(CH_2CO_2H)_2$, base; (b) $BrCH_2CO_2Et$, NEt_3; (c) $ClCH_2COCl$; (d) $HN(CH_2CO_2Bn)_2$.

At first, a direct substitution of the halide with various iminodiacetic acid (IDA) derivatives was attempted, however, in no case could the amino sugar derivative of the type of **11** be obtained. Instead, when **3** or **5** were heated with IDA and a tertiary amine in dimethylformamide, the formation of **7** was observed after work up. This implies the intermediate formation of an amino acid ester **6**. To realize structure **11**, compound **5** was transformed into the aminoglycoside **9** following standard conditions [9] and reacted with ethyl bromoacetate. Although the formation of **11** was successful, the yield was not convincing and the reaction time long. Apparently, this reaction is less favorable and it does not allow many variations with respect to the amino acid.

A better result can be achieved by chloroacetylation of the 6-amino-6-deoxyglycoside **9**, followed by nucleophilic displacement of the activated chloride in **13** with an iminodiacetic acid ester to yield compound **14**. Hydrogenolysis led to the unprotected model compound **15**. This synthesis should be applicable for various amino acids. The yields are reasonable and may be further improved, however, the required reaction times for the substitution are quite long (Scheme 1).

The leaving groups in **3** and **5** can be easily substituted in a Gabriel-type of reaction [11] with potassium succinimide [12]. This kind of synthesis is applicable even for unprotected or acylated sugars and does not give rise to side reactions. The cyclic



Scheme 2. (a) Potassium succinimide, DMF; (b) NaOH, glyme; (c) $HN(CH_2CO_2Me)_2$, EEDQ, CH_2Cl_2.

imide in the resulting 6-deoxy-6-imido-glycoside **16** was opened by simple alkaline hydrolysis and led to the acid compound **17**. Treatment with protected amino acids, following standard peptide conditions [13], gave the succinic amide-spacered glycoside conjugates. As an example, the reaction with iminodiacetic acid dimethyl ester was performed, and after stepwise deprotection the unprotected conjugate compound **19** was isolated in about 60% overall yield (Scheme 2).

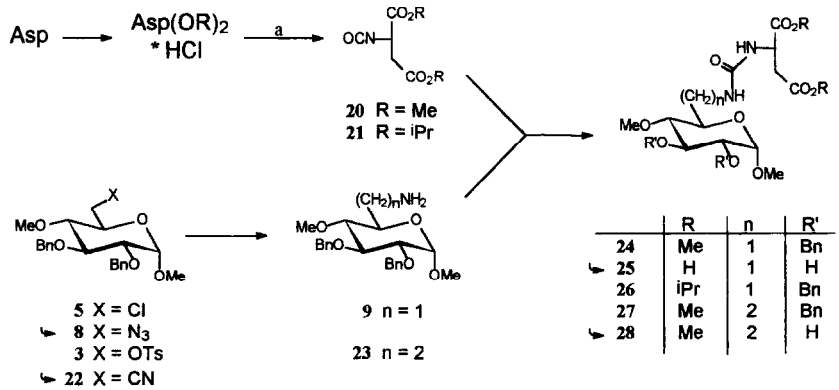
A conceptionally easier way to amino acid–glycoside conjugates could be introduced by treatment of an aminoglycoside with an amino acid ester isocyanate. The isocyanate derivatives were easily prepared by phosgenolysis [14–17] of the corresponding amino acid ester hydrochlorides and purified by distillation. They are quite sensitive towards hydrolysis and must be stored under an inert atmosphere. In addition to the aspartic acid dimethyl ester isocyanate **20**, the corresponding diisopropyl ester **21** was also synthesized. The advantage of this reagent is associated with the preparation procedures of the ester hydrochlorides. Whereas the isopropyl derivative could be isolated by heating aspartic acid in hydrogen chloride containing 2-propanol within a few hours, formation of the methyl derivative required several days at room temperature [18].

As aminodeoxy glycosides, the 6-amino-glucopyranoside derivative **9** and a corresponding heptoside **23** were chosen. The heptoside was obtained by substitution of tosylate **3** with sodium cyanide. Instead of the proposed dimethyl sulfoxide [10], dimethylacetamide was preferred as solvent, and some tetramethylurea was added for better solubility of the salt. For the reduction of the nitrile **22**, catalytic hydrogenolysis [19–21] was selected instead of the borane–dimethyl sulfide complex [10]. These changes are of importance with respect to the final debenzylation step, which is notoriously problematic in case of sulfur containing contaminations.

The urea-linked aspartic acid glucoside conjugates were isolated in good yields and high purity. Stepwise deprotection of **24** yielded the unprotected compound **25**, which showed complex NMR spectra. In the sugar part several signals appeared doubled; however, the amino acid signals, especially Asp H-2 and Asp C-2, were single. Apparently, there is a conformational equilibrium with regard to the urea linkage and this was supported by observation of coalescence when the frequency for the ^1H NMR was increased to 500 MHz (Scheme 3).

3. Experimental

General methods.—Melting points were determined with a Leitz melting point apparatus and were uncorrected. Specific rotations were measured on a Perkin–Elmer model 241 polarimeter. TLC was performed on Silica Gel 60 GF_{254} aluminium sheets (E. Merck, Darmstadt, Germany); detection was effected by observation under UV light (254 nm), then spraying with 20% ethanolic H_2SO_4 and charring with a heat gun. Amines were detected by the ninhydrin color reaction. Column chromatography was conducted with Silica Gel 60 (0.040–0.063 mm, E. Merck) using the flash procedure. NMR spectra were recorded at 300 K in $CDCl_3$ (unless otherwise specified) on Bruker AMX 400 (100.67 MHz for ^{13}C). Chemical shifts are expressed in ppm downfield from Me_4Si. Spectra in D_2O were calibrated on HDO (4.65 ppm) or internal acetonitrile (0.80 ppm for ^1H, 1.98 ppm for ^{13}C).



Scheme 3. (a) Cl_3COCl, dioxane, 60 °C.

Methyl 2,3-di-O-benzyl-4-O-methyl-6-O-p-toluenesulfonyl-α-D-glucopyranoside (**3**).—To an ice-cooled mixture of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside [22] (**1**, 20.0 g, 53 mmol), tetrabutylammonium hydrogensulfate (2.5 g, 7.4 mmol), CH_2Cl_2 (500 mL), and 5% aq NaOH (100 mL) was added *p*-toluenesulfonyl chloride (10.9 g, 57 mmol, 1.1 equiv). The reaction was vigorously stirred for 1.5 h under further cooling. Half of the waterphase was removed and the same amount of 50% aq NaOH added. After treatment with dimethyl sulfate (5 mL, 53 mmol) the mixture was allowed to warm to room temperature and stirred for a another 2 h. To achieve complete methylation, a further amount of dimethyl sulfate (2.5 mL, 26 mmol) was added and stirring continued for 5 h. The organic phase was separated, washed twice with water, dried over $MgSO_4$ and concd to a syrup. The product was purified by column chromatography using toluene and EtOAc (17:1 → 4:1) to give **3** (22.5 g, 79% pure and 3.4 g, 12% slightly contaminated material) as a slowly crystallizing syrup; mp 47 °C; $[\alpha]_D^{21}$ +34° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.81–7.77 (m, 2 H, Ts*H*), 7.35–7.26 (m, 12 H, Ph*H*, Ts*H*), 4.92 (d, ^2J 11.0 Hz, Ph^aCH_2), 4.76 (d, Ph^aCH_2), 4.75 (d, ^2J 12.0 Hz, Ph^bCH_2), 4.60 (d, Ph^bCH_2), 4.49 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.24 (dd, $J_{5,6a}$ 5.0, $^2J_{6a,6b}$ 10.0 Hz, H-6a), 4.19 (dd, $J_{5,6b}$ 2.0 Hz, H-6b), 3.82 (dd, $J_{2,3} = J_{3,4}$ 9.0 Hz, H-3), 3.66 (ddd, $J_{4,5}$ 9.5 Hz, H-5), 3.41, 3.30 (2 s, 2 × 3 H, Me*H*), 3.40 (dd, H-2), 3.14 (dd, H-4), 2.43 (s, 3 H, $TsCH_3$). Anal. Calcd for $C_{29}H_{34}O_8S$ (542.64): C, 64.18; H, 6.31; S, 5.90. Found: C, 64.24; H, 6.36; S, 5.81.

Methyl 2,3-di-O-benzyl-6-chloro-6-deoxy-α-D-glucopyranoside (**4**).—A soln of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**1**, 10.0 g, 27 mmol) in DMF (150 mL) was heated to 80 °C, and methanesulfonyl chloride (6 mL, 35 mmol) was slowly added. After 3 h, the reaction was cooled, treated with 4 M aq NaOH (7 mL) and filtered. The solvent was evaporated and the residue taken up in EtOAc and water. The organic layer was washed with aq $NaHCO_3$ and water, dried over $MgSO_4$, decolorized with carbon, and concd to a syrup. To remove formyl group the crude product was deacylated in dry MeOH (100 mL) with a catalytic amount of NaOMe yielding **4** (10.4 g, 98%) as a yellow syrup; $[\alpha]_D^{22}$ +24° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.40–7.27 (m, 10 H, Ph*H*), 5.05 (d, ^2J 11.0 Hz, Ph^aCH_2), 4.76 (d, ^2J 11.0 Hz, Ph^bCH_2), 4.69–4.62 (m, 3 H, H-1, 2 $PhCH_2$), 3.96–3.89, 3.81–3.74 (m, 3 + 1 H, H-3, H-5, H-6a, H-6b), 3.54 (dd, $J_{1,2}$ 4.0, $J_{2,3}$ 10.0 Hz), 3.48 (ddd, $J_{3,4} = J_{4,5}$ 9.0, $J_{4,OH}$ 2.0 Hz, H-4), 3.41 (s, 3 H, Me*H*), 2.33 (d, 4-O*H*). ^{13}C NMR: δ 138.17, 137.45 (C), 128.25, 128.10, 127.67, 127,62, 127.55 (CH), 97.72 (C-1), 80.69, 79.33 (C-2, C-3), 74.95, 72.25 (CH_2), 70.25, 69.87 (C-4, C-5), 54.91 (CH_3), 44.13 (C-6). Anal. Calcd for $C_{21}H_{25}ClO_5$ (392.88): C, 64.20; H, 6.41; Cl, 9.02. Found: C, 64.45; H, 6.66; Cl, 8.87.

Methyl 2,3-di-O-benzyl-6-chloro-6-deoxy-4-O-methyl-α-D-glucopyranoside (**5**).—A soln of **4** (21.4 g, 54 mmol) in 1,4-dioxane (200 mL) was treated with freshly powdered NaOH (10.0 g, 250 mmol). After stirring for 30 min, dimethyl sulfate (6.0 mL, 64 mmol) was added and stirring was continued overnight. Excess of the methylating agent was destroyed by MeOH (5 mL) and 1 h further stirring. The solvent was removed, the residue taken up in CH_2Cl_2, washed with water, dried over $MgSO_4$, and decolorized with carbon. Concentration of the soln gave **5** (20.7 g, 95%) as a colorless syrup; $[\alpha]_D^{22}$ +50° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.40–7.27 (m, 10 H, Ph*H*), 4.95 (d, ^2J 11.0 Hz, Ph^aCH_2), 4.79 (d, Ph^aCH_2), 4.78 (d, ^2J 11.0 Hz, Ph^bCH_2), 4.64 (d, Ph^bCH_2), 4.61 (d, $J_{1,2}$ 4.0 Hz, H-1), 3.98 (dd, $J_{2,3}$ 10.0, $J_{3,4}$ 9.0 Hz, H-3), 3.91–3.80 (m, 3 H, H-5, H-6a, H-6b), 3.57, 3.39 (2 s, 2 × 3 H, Me*H*), 3.50 (dd, H-2), 3.24 (dd, $J_{4,5}$ 9.0 Hz, H-4). Anal. Calcd for $C_{22}H_{27}ClO_5$ (406.91): C, 64.93; H, 6.68; Cl, 8.71. Found: C, 64.81; H, 6.94; Cl, 8.45.

Methyl 6-azido-2,3-di-O-benzyl-6-deoxy-4-O-methyl-α-D-glucopyranoside (**8**).—A mixture of **5** (15.6 g, 38 mmol), NaN_3 (8.3 g, 128 mmol), tetramethylurea (0.4 mL), and DMF (380 mL) was heated to 150 °C for 2 h. The solvent was evaporated, the residue taken up in EtOAc and washed with water. After drying over $MgSO_4$ and concn, pure **8** (14.7 g, 93%) was isolated without further purification as a pale yellow syrup. Alternatively, **5** (2.5 g, 4.6 mmol) could be transformed analogously but at 120 °C, giving the identical material **8** (1.8 g, 96%); $[\alpha]_D^{22}$ +62° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.39–7.26 (m, 10 H, Ph*H*), 4.94 (d, ^2J 11.0 Hz, Ph^aCH_2), 4.79 (d, Ph^aCH_2), 4.78 (d, ^2J 12.0 Hz, Ph^bCH_2), 4.65 (d, Ph^bCH_2), 4.60 (d, $J_{1,2}$ 3.5 Hz, H-1), 3.86 (dd, $J_{2,3} = J_{3,4}$ 9.0 Hz, H-3), 3.69 (ddd, $J_{4,5}$ 9.5, $J_{5,6a}$ 2.0, $J_{5,6b}$ 5.5 Hz, H-5), 3.48, 3.40 (2 s, 2 × 3 H, Me*H*), 3.49 (dd, H-2), 3.49 (dd, $^2J_{6a,6b}$ 12.0 Hz, H-6a), 3.39 (dd, H-6b), 3.14 (dd, H-4). ^{13}C NMR: δ 138.71, 138.10 (C), 128.49, 128.38, 128.06, 127.97, 127.64, 127.00 (CH), 99.10 (C-1), 81.69, 80.47, 79.81 (C-2, C-3, C-4), 76.71, 73.43 (CH_2), 70.03 (C-5), 60.89,

55.40 (CH_3), 51.48 (C-6). Anal. Calcd for $C_{22}H_{27}N_3O_5$ (413.47): C, 63.90; H, 6.58; N, 10.16. Found: C, 64.10; H, 6.62; N, 9.74.

For reduction, the azide **8** (13.0 g, 3.1 mmol) was dissolved in MeOH (150 mL), treated with Et_3N (2 mL) and 10% palladium on charcoal (200 mg), and stirred under hydrogen atmosphere for about 1 day. After removal of the catalyst, the soln was concd leaving *methyl 6-amino-2,3-di-*O*-benzyl-6-deoxy-4-*O*-methyl-α-*D*-glucopyranoside* (**9**, 1.7 g, 99%) as a clear colorless syrup; $[\alpha]_D^{21}$ +51° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.39–7.27 (m, 10 H, Ph*H*), 4.94 (d, ^2J 11.0 Hz, Ph^aCH_2), 4.80 (d, Ph^aCH_2), 4.78 (d, ^2J 12.0 Hz, Ph^bCH_2), 4.65 (d, Ph^bCH_2), 4.55 (d, $J_{1,2}$ 4.0 Hz, H-1), 3.87 (dd, $J_{2,3} = J_{3,4}$ 9.0 Hz, H-3), 3.53, 3.38 (2 s, 2 × 3 H, Me*H*), 3.45 (dd, H-2), 3.52–3.40 (m, H-5), 3.05 (dd, $J_{4,5}$ 9.0 Hz, H-4), 3.06–2.97 (m, H-6a), 2.81–2.70 (m, H-6b); ^{13}C NMR: δ 139.0, 128.5 (C), 128.45, 128.36, 128.08, 127.99, 127.88, 127.58 (CH), 97.98 (C-1), 81.88, 81.36, 79.98 (C-2, C-3, C-4), 75.62, 73.36 (CH_2), 72.2 (C-5), 60.79, 55.11 (CH_3), 42.9 (C-6). Anal. Calcd for $C_{22}H_{29}NO_5$ (387.48): C, 68.19; H, 7.54; N, 3.61. Found: C, 67.47; H, 7.56; N, 3.35.

For ethoxycarbonylmethylation, a soln of **9** (1.8 g, 4.6 mmol) in 5:4 dry dioxane–EtOH (9 mL) was treated with Et_3N (3 mL, 22 mmol) and ethyl bromoacetate (2 mL, 18 mmol) and refluxed for 10 h. After removal of the solvent, the residue was dissolved in ether, washed with aq $NaHCO_3$, and dried over Na_2SO_4. Chromatographic separation (5:1 toluene–EtOAc) led to *methyl 2,3-di-*O*-benzyl-6-(*N,N*-bis-ethoxycarbonylmethylamino)-6-deoxy-4-*O*-methyl-α-*D*-glucopyranoside* (**11**, 950 mg, 37%) as an orange syrup; $[\alpha]_D^{22}$ +36° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.40–7.24 (m, 10 H, Ph*H*), 4.93 (d, ^2J 10.5 Hz, Ph^aCH_2), 4.78 (d, Ph^aCH_2), 4.76 (d, ^2J 12.0 Hz, Ph^bCH_2), 4.63 (d, Ph^bCH_2), 4.51 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.13 (q, 4 H, ^3J 7.0 Hz, Et-CH_2), 3.86 (dd, $J_{2,3}$ 9.5, $J_{3,4}$ 9.0 Hz, H-3), 3.67 ddd, $J_{4,5}$ 9.0, $J_{5,6a}$ 1.5, $J_{5,6b}$ 7.0 Hz, H-5), 3.63, 3.61 (2 s, 2 × 2 H, CH_2COOEt), 3.52, 3.38 (2 s, 2 × 3 H, Me*H*), 3.42 (dd, H-2), 3.14 (dd, $^2J_{6a,6b}$ 12 Hz, H-6a), 3.13 (dd, H-4), 2.88 (dd, H-6b), 1.24 (t, 6 H, Et-CH_3). Debenzylation of **11** (300 mg, 0.54 mmol) was achieved by hydrogenolysis using 5% palladium on charcoal in MeOH containing more than 1 mol/equiv of HCl. *Methyl 6-(*N,N*-bis-ethoxycarbonylmethylamino)-6-deoxy-4-*O*-methyl-α-*D*-glucopyranoside hydrochloride* (**12**, 210 mg, 94%) was isolated as a red syrup; $[\alpha]_D^{22}$ +70° (*c* 1.0, water); ^{1}H NMR (D_2O): δ 4.73 (d, $J_{1,2}$ 4.0 Hz, H-1), 4.30–4.10 (m, 5 H, Et-CH_2, CH_2COOEt), 4.04–3.92 (m, 1 H, CH_2COOEt), 3.68 (dd, $J_{2,3} = J_{3,4}$ 10.0 Hz, H-3), 3.73–3.60 (m, H-6a), 3.59–3.15 (m, 3 H, H-2, H-5, H-6b), 3.47, 3.39 (2 s, 2 × 3 H, Me*H*), 3.01 (dd, $J_{4,5}$ 10.0 Hz, H-4), 1.38 (t, 6 H, ^3J 7.0 Hz, Et-CH_3); ^{13}C NMR: δ 167.28 (COOEt), 100.31 (C-1), 81.18 (C-4), 72.62, 71.12 (C-2, C-3), 66.60 (C-5), 64.10 (Et-CH_2), 60.53, 75.16 (CH_3), 56.62, 55.48 (C-6, CH_2COOEt), 13.61 (CH_3).

*Methyl 2,3-di-*O*-benzyl-6-chloroacetamido-6-deoxy-4-*O*-methyl-α-*D*-glucopyranoside* (**13**).—To a soln of **9** (4.0 g, 10 mmol) and Et_3N (3.5 mL, 25 mmol) in CH_2Cl_2 (100 mL) was added chloroacetyl chloride (2 mL, 25 mmol). The mixture was stirred for 2 h, diluted with CH_2Cl_2 and washed with water, dil HCl, and aq $NaHCO_3$. After drying with $MgSO_4$ and concn, the crude product was purified by column chromatography (40:1 CH_2Cl_2–acetone) giving **13** (5.2 g, 83%) as a colorless solid; mp 116.3 °C; $[\alpha]_D^{22}$ +28° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.38–7.27 (m, 10 H, Ph*H*), 6.87 (dd, $J_{6a,NH} = J_{6b,NH}$ 4.5 Hz, NH), 4.92 (d, ^2J 11.0 Hz, Ph^aCH_2), 4.79 (d, Ph^aCH_2), 4.77 (d, ^2J 12.0 Hz, Ph^bCH_2), 4.58 (d, Ph^bCH_2), 4.55 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.27 (s, 2 H, $ClCH_2CONH$), 3.87 (dd, $J_{2,3} = J_{3,4}$ 9.0 Hz, H-3), 3.65–3.53 (m, 3 H, H-5, H-6a, H-6b), 3.55, 3.36 (2 s, 2 × 3 H, Me*H*), 3.45 (dd, H-2), 3.21 (dd, $J_{4,5}$ 10.0 Hz, H-4). Anal. Calcd for $C_{24}H_{30}ClNO_6$ (463.96): C, 62.13; H, 6.51; Cl, 7.64; N, 3.01. Found: C, 62.06; H, 6.60; Cl, 7.58; N, 2.98.

Biscarboxymethylamination was done by refluxing a soln of **13** (1.6 g, 3.5 mmol), iminodiacetic acid dibenzylester [$IDA(OBn)_2$, 2.7 g, 8.6 mmol], and 2-propanol (70 mL) for 2 days. The solvent was evaporated, the residue dissolved in CH_2Cl_2 and washed with aq $NaHCO_3$. After drying and concn, the crude product was purified by column chromatography (2:1 toluene–EtOAc, 1% Et_3N) leaving unchanged **13** (800 mg, 50%) and *methyl 2,3-di-*O*-benzyl-6-{[*N,N*-bis-(benzyloxycarbonylmethyl)-amino]-acetamido}-6-deoxy-4-*O*-methyl-α-*D*-glucopyranoside* (**14**, 1.05 g, 46%) as a clear syrup; $[\alpha]_D^{22}$ +19° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.88 (dd, N*H*), 7.39–7.14 (m, 20 H, Ph*H*), 5.11 (s, 4 H, $PhCH_2OCO$), 4.93 (d, ^2J 10.5 Hz, Ph^aCH_2), 4.81 (d, Ph^aCH_2), 4.77 (d, ^2J 12.0 Hz, Ph^bCH_2), 4.65 (d, Ph^bCH_2), 4.59 (d, $J_{1,2}$ 3.5 Hz, H-1), 3.89 (dd, $J_{2,3}$ 9.5, $J_{3,4}$ 9.0 Hz, H-3), 3.67 (m_c, 2 H, $HNCOCH_2N$), 3.64 (ddd, $J_{4,5}$ 9.0, $J_{5,6a}$ 4.0, $J_{5,6b}$ 5.5 Hz, H-5), 3.59–3.52 (m, 2 H, H-6a, H-6b), 3.57, 3.55 (2 s, 2 × 3 H, Me*H*), 3.51 (dd, H-2), 3.43–3.39 (m, 2 H, CH_2COOBn^a), 3.35 (s, 2 H, CH_2COOBn^b), 3.02 (dd, H-4). Debenzylation of **14** (166 mg, 0.22 mmol) was achieved by

hydrogenolysis (100 kPa hydrogen) using palladium on charcoal in MeOH containing AcOH to give *methyl 6-{[*N,N-*bis-(hydroxycarbonylmethyl)-amino]-acetamido}-6-deoxy-4-*O-*methyl-α-*D-*glucopyranoside* (**15**, 80 mg, 94%) as an amorphous solid; $[\alpha]_D^{22}$ +73° (*c* 1.0, water); ^{1}H NMR (D_2O): δ 4.68 (d, $J_{1,2}$ 4.0 Hz, H-1), 4.04 (s, 2 H, NHCOCH_2N), 3.85 (s, 4 H, NCH_2COOH), 3.65 (dd, $J_{2,3}$ 9.0, $J_{3,4}$ 9.5 Hz, H-3), 3.61 (dt, $J_{4,5}$ 9.5, $J_{5,6}$ 4.5 Hz, H-5), 3.51 (d, 2 H, H-6), 3.47 (dd, H-2), 3.46, 3.28 (2 s, 2 × 3 H, Me*H*), 2.81 (dd, H-4); ^{13}C NMR: δ 167 (COOH, CONH, CON), 99.47 (C-1), 80.96 (C-4), 73.08, 71.56 (C-2, C-3), 68.9 (C-5), 60.9, 55.43 (CH_3), 57.0, 56.1 (CH_2), 40.5 (C-6).

*Methyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-methyl-6-succinimido-α-*D*-glucopyranoside* (**16**).—A mixture of **3** (1.0 g, 1.8 mmol), potassium succinimide (500 mg, 3.6 mmol), and tetramethylurea (0.2 mL) was heated in DMF (20 mL) to 80 °C for 1 h. The solvent was evaporated, the residue taken up in EtOAc and washed with water. After drying over $MgSO_4$ and concn, the crude product was purified by column chromatography (20:1 CH_2Cl_2–acetone) leaving **16** as a solid. Alternatively **5** (10.0 g, 25 mmol) was transformed analogously at 150 °C yielding identical **16** (8.0 g, 75%, not optimized); mp 67.5–68 °C; $[\alpha]_D^{21}$ +65° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.38–7.24 (m, 10 H, Ph*H*), 4.93 (d, ^2J 10.5 Hz, Ph^{a}CH_2), 4.78 (d, Ph^{a}CH_2), 4.75 (d, ^2J 12.0 Hz, Ph^{b}CH_2), 4.61 (d, Ph^{b}CH_2), 4.50 (d, $J_{1,2}$ 3.5 Hz, H-1), 3.91–3.82 (m, 2 H, H-5, H-6a), 3.86 (dd, $J_{2,3} = J_{3,4}$ 9.5 Hz, H-3), 3.72 (dd, $J_{5,6a}$ 9.0, $^2J_6$ 13.0 Hz, H-6b), 3.57, 3.24 (2 s, 2 × 3 H, Me*H*), 3.46 (dd, H-2), 3.03 (dd, $J_{4,5}$ 9.5 Hz, H-4), 2.70 (s, 4 H, CH_2). Anal. Calcd for $C_{26}H_{31}NO_7$ (496.53): C, 66.50; H, 6.65; N, 2.98. Found: C, 66.54; H, 6.61; N, 2.97.

*Methyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-methyl-6-succinamido-α-*D*-glucopyranoside* (**17**).—Compound **16** (6.5 g, 14 mmol) was dissolved in 20:1 1,4-dioxane–water (300 mL), treated with powdered NaOH (3.3 g, 81 mmol, 5.9 equiv), and stirred at room temperature for 2 h. The reaction mixture was neutralized with 2 M HCl and concd. The residue was taken up in CH_2Cl_2, washed with dil HCl, dried over $MgSO_4$, and concd to a syrup. Purification was achieved by crystallization in ether–EtOAc to give **17** (6.0 g, 88%); mp 164.8 °C; $[\alpha]_D^{22}$ +3° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.38–7.26 (m, 10 H, Ph*H*), 5.96 (dd, $J_{6a,NH} = J_{6b,NH}$ 5.5 Hz, N*H*), 4.92 (d, ^2J 10.5 Hz, Ph^{a}CH_2), 4.79 (d, Ph^{a}CH_2), 4.78 (d, ^2J 12.0 Hz, Ph^{b}CH_2), 4.64 (d, Ph^{b}CH_2), 4.54 (d, $J_{1,2}$ 3.5 Hz, H-1), 3.87 (dd, $J_{2,3} = J_{3,4}$ 9.0 Hz, H-3), 3.71, 3.52 (2 s, 2 × 3 H, Me*H*), 3.70–3.63 (m, H-6a), 3.62–3.57 (m, H-6b), 3.46–3.39 (m, H-5), 3.44 (dd, H-2), 2.98 (dd, $J_{4,5}$ 9.0 Hz, H-4), 2.72–2.67, 2.51–2.45 (2 m, 2 × 2 H, CH_2). Anal. Calcd for $C_{26}H_{33}NO_8$ (487.55): C, 64.05; H, 6.82; N, 2.87. Found: C, 63.88; H, 6.86; N, 2.85.

*Methyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-methyl-6-[4-[*N,N*-bis-(methoxycarbonylmethyl)-amino]-succinamido]-α-*D*-glucopyranoside* (**18**).—A soln of **17** (2.0 g, 4.1 mmol) in dry CH_2Cl_2 (5 mL) was treated with iminodiacetic acid dimethyl ester (780 mg, 4.9 mmol, 1.2 equiv) and EEDQ (1.25 g, 5 mmol). The mixture was stirred for 4 h at room temperature, diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and concd to a syrup. Chromatography (20:1 CH_2Cl_2–acetone for quinoline derivatives and 50:1 CH_2Cl_2–MeOH for the product) afforded **18** (2.3 g, 89%) as yellow crystals; mp 96.5 °C; $[\alpha]_D^{22}$ +5° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.39–7.26 (m, 10 H, Ph*H*), 6.09–6.03 (m, N*H*), 4.92 (d, ^2J 10.5 Hz, Ph^{a}CH_2), 4.79 (d, Ph^{a}CH_2), 4.78 (d, ^2J 12.0 Hz, Ph^{b}CH_2), 4.64 (d, Ph^{b}CH_2), 4.54 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.20, 4.11 (2 d, 2 × 1 H, IDA-CH_2^a), 4.17 (s, 2 H, IDA-CH_2^b), 3.86 (dd, $J_{2,3} = J_{3,4}$ 9.0 Hz, H-3), 3.75, 3.69 (2 s, 2 × 3 H, COOCH_3), 3.63–3.53 (m, 2 H, H-6a, H-6b), 3.52, 3.35 (2 s, 2 × 3 H, Me*H*), 3.48–3.42 (m, H-5), 3.45 (dd, H-2), 2.98 (dd, $J_{4,5}$ 9.0 Hz, H-4), 2.68, 2.52 (2 t, 2 × 2 H, ^3J 6.5 Hz, Succ-CH_2). Anal. Calcd for $C_{32}H_{42}N_2O_{11}$ (630.12): C, 60.94; H, 6.71; N, 4.44. Found: C, 60.76; H, 6.77; N, 4.48.

Deprotection was done by treatment of **18** (2.3 g, 3.7 mmol) with NaOH (690 mg, 17 mmol) in 1,4-dioxane–water, according to the synthesis of **17**, followed by hydrogenolysis in MeOH using palladium on charcoal to give *methyl 6-deoxy-4-*O*-methyl-6-{[*N,N*-bis-(hydroxycarbonylmethyl)-amino]-succinamido}-α-*D*-glucopyranoside* **19** (1.3 g, 97%) as a slightly brown solid; mp 109.3 °C; $[\alpha]_D^{22}$ +48° (*c* 1.0, water); ^{1}H NMR (D_2O): δ 4.66 (d, $J_{1,2}$ 4.0 Hz, H-1), 4.26, 4.06 (2 s, 2 × 2 H, IDA-CH_2), 3.62 (dd, $J_{2,3} = J_{3,4}$ 9.5 Hz, H-3), 3.56 (dt, $J_{4,5}$ 10.0, $J_{5,6}$ 5.0 Hz, H-5), 3.47 (dd, H-2), 3.41 (d, 2 H, H-6), 3.42, 3.26 (2 s, 2 × 3 H, Me*H*), 2.98 (dd, H-4), 2.63 (dd, ^3J 7.0 Hz, Succ-CH_2), 2.53–2.40 (m, 2 H, Succ-CH_2); ^{13}C NMR: (D_2O): δ 175.69, 175.31, 173.65, 173.56 (COOH, CONH), 99.42 (C-1), 80.96 (C-4), 73.16, 71.60, 69.14 (C-2, C-3, C-5), 60.35, 55.35 (CH_3), 51.30, 49.97 (IDA-CH_2), 40.03 (C-6), 30.72, 28.38 (Succ-CH_2).

Preparation of L*-aspartic acid dimethylester isocyanate* (**20**).—Aspartic acid dimethyl ester (10.0 g,

50 mmol) [18] was treated with diphosgene (4.6 mL, 40 mmol) in dry 1,4-dioxane (50 mL) at 55 °C under a nitrogen atmosphere. After 8 h, the solvent was evaporated and the product distilled in vacuum leaving **20** (7.7 g, 81%) as a hygroscopic liquid; $bp_{2.5\,hPa}$ 87 °C, lit. $bp_{0.5\,hPa}$ 65 °C [23]; d 1.2 g/mL; $[\alpha]_D^{23}$ −27° (*c* 1.0, $CHCl_3$); lit. n_D^{25} 1.4455 [23]; ^{1}H NMR: δ 4.42 (dd, $J_{2,3a}$ 5.0, $J_{2,3b}$ 6.5 Hz, H-2), 3.85, 3.74 (2 s, 2 × 3 H, Me*H*), 2.88 (dd, $^2J_{3a,3b}$ 17.0 Hz, H-3a), 2.82 (dd, H-3b); ^{13}C NMR: δ 170.50, 169.96 (COOMe), 127.55 (NCO), 53.65, 53.62 (CH_3), 52.27 (C-2), 37.91 (C-3). Anal. Calcd for $C_7H_9NO_5$ (187.15): C, 44.92; H, 4.84; N, 7.48. Found: C, 44.68; H, 4.96; N, 7.77.

L-*Aspartic acid diisopropylester isocyanate* (**21**). —Aspartic acid diisopropyl ester (2.5 g, 10 mmol) was treated with diphosgene (1.5 mL, 8 mmol) in dry 1,4-dioxane (10 mL) at 55 °C under a nitrogen atmosphere like **20**. After distillation **21** (1.5 g, 62%, not optimized) was isolated as a hygroscopic liquid; $bp_{2.5\,hPa}$ 120 °C; d 1.2 g/mL; $[\alpha]_D^{23}$ −26° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 5.12, 5.06 (2 tt ≈ 2 p, 2 × 1 H, ^3J 6.0 Hz, ^{i}Pr-C*H*), 4.32 (t, $J_{2,3}$ 5.5 Hz, H-2), 2.79 (d, 2 H, H-3), 1.31, 1.29, 1.26, 1.25 (4 d, 4 × 3 H, ^{i}Pr-CH_3); ^{13}C NMR: δ 169.52, 168.85 (COOR), 127.77 (NCO), 71.02, 69.01 (^{i}Pr-CH), 53.95 (C-2), 38.46 (C-3), 21.75, 21.74, 21.68, 21.63 (^{i}Pr-CH_3). Anal. Calcd for $C_{11}H_{17}NO_5$ (243.26): C, 54.31; H, 7.04; N, 5.75. Found: C, 53.70; H, 7.08; N, 5.76.

*Methyl 2,3-di-*O*-benzyl-6-cyano-6-deoxy-4-*O*-methyl-α-*D*-glucopyranoside* (**22**).—To a soln of **3** (1.58 g, 2.9 mmol) in Me_2SO (5 mL) was added sodium cyanide (200 mg, 4.1 mmol), and the mixture was heated to 80 °C for 2 days. The solvent was evaporated and the residue was dissolved in EtOAc, washed with water, dried over $MgSO_4$, and concd to a syrup. The crude product was purified by chromatography (6:1 light petroleum–acetone) to give **22** (940 mg, 81%) as a colorless syrup. The analogous reaction of **3** (1.3 g, 2.4 mmol) in dimethylacetamide afforded chromatographically pure **22** (960 mg, quant.); $[\alpha]_D^{22}$ +56° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.39–7.26 (m, 10 H, Ph*H*), 4.94 (d, ^2J 11.0 Hz, Ph^aCH_2), 4.76 (d, ^2J 12.0 Hz, Ph^bCH_2), 4.65 (d, Ph^bCH_2), 4.57 (d, $J_{1,2}$ 4.0 Hz, H-1), 3.85 (dd, $J_{2,3}$ 9.5, $J_{3,4}$ 9.0 Hz, H-3), 3.71 (ddd, $J_{4,5}$ 9.5, $J_{5,6a}$ 4.0, $J_{5,6b}$ 6.5 Hz, H-5), 3.55, 3.37 (2 s, 2 × 3 H, Me*H*), 3.50 (dd, H-2), 3.04 (dd, H-4), 2.68 (dd, $^2J_{6a,6b}$ 17.0 Hz, H-6a), 2.57 (dd, H-6b). ^{13}C NMR: δ 138.19, 137.93 (C), 128.45–126.80 (CH), 117.01 (CN), 98.08 (C-1), 82.30, 81.31, 79.60 (C-2, C-3, C-4), 75.46, 73.34 (CH_2), 66.31 (C-5), 61.55, 55.44 (CH_3), 20.70 (C-6). Anal. Calcd for $C_{23}H_{27}NO_5$ (397.47): C, 69.50; H, 6.84; N, 3.52. Found: 68.13; H, 6.75; N, 3.43.

Reduction of **22** (410 mg, 1.0 mmol) was achieved in ammonia satd MeOH (20 mL) using 5 MPa hydrogen atmosphere and 5% rhodium on Al_2O_3 (100 mg) to give *methyl 7-amino-2,3-di-*O*-benzyl-6,7-dideoxy-4-*O*-methyl-α-*D*-glucoheptopyranoside* (**23**, 375 mg, 91%) as a colorless syrup; $[\alpha]_{546}^{21}$ +40° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.39–7.22 (m, 10 H, Ph*H*), 4.93 (d, ^2J 11.0 Hz, Ph^aCH_2), 4.79 (d, Ph^aCH_2), 4.76 (d, ^2J 12.0 Hz, Ph^bCH_2), 4.63 (d, Ph^bCH_2), 4.51 (d, $J_{1,2}$ 4.0 Hz, H-1), 3.83 (dd, $J_{2,3} = J_{3,4}$ 10.0 Hz, H-3), 3.61–3.52 (m, H-5), 3.54, 3.34 (2 s, 2 × 3 H, Me*H*), 3.45 (dd, H-2), 2.93–2.82 (m, H-7a), 2.89 (dd, $J_{4,5}$ 10.0 Hz, H-4), 2.80–2.71 (m, H-7b), 1.97–1.87 (m, H-6a), 1.61–1.48 (m, H-6b); ^{13}C NMR: δ 138.85, 138.24 (C), 128.45, 128.37, 128.09, 128.04, 127.89, 127.60 (CH), 97.90 (C-1), 84.14, 81.89, 79.92 (C-2, C-3, C-4), 75.66, 73.36 (CH_2), 69.03 (C-5), 61.01, 55.10 (CH_3), 39.24 (C-7), 35.53 (C-6).

N-*(Methyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-methyl-α-*D*-glucopyranoside-6-ylaminocarbonyl)-*L*-aspartic acid dimethylester* (**24**).—A soln of **9** (2.0 g, 4.8 mmol) was treated with **20** (950 μL, 6 mmol) and the mixture was stirred at room temperature for 1 h. After concn, the crude product was crystallized from toluene–EtOAc to give **24** (1.96 g, 68%, not optimized); mp 143.4 °C; $[\alpha]_D^{22}$ +45° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.32–7.18 (m, 10 H, Ph*H*), 5.53 (bs, N*H*), 4.86 (d, ^2J 11.5 Hz, Ph^aCH_2), 4.72 (d, Ph^aCH_2), 4.71 (d, ^2J 12.0 Hz, Ph^bCH_2), 4.71–4.63 (m, 2 H, N*H*, Asp-2), 4.57 (d, Ph^bCH_2), 4.49 (d, $J_{1,2}$ 3.5 Hz, H-1), 3.80 (dd, $J_{2,3} = J_{3,4}$ 9.0 Hz, H-3), 3.66, 3.59 (2 s, 2 × 3 H, COOCH_3), 3.52 (ddd, $J_{4,5}$ 9.5, $J_{5,6a}$ 4.0, $J_{5,6b}$ 5.0 Hz, H-5), 3.47, 3.30 (2 s, 2 × 3 H, Me*H*), 3.44–3.32 (m, 2 H, H-6a, H-6b), 3.36 (dd, H-2), 2.95 (dd, H-4), 2.94 (dd, $J_{Asp2,3a}$ 4.5, $^2J_{Asp3a,3b}$ 17.0 Hz, Asp-3a), 2.76 (dd, $J_{Asp2,3b}$ 4.5 Hz, Asp-3b). Anal. Calcd for $C_{29}H_{38}N_2O_{10}$ (574.63): C, 60.61; H, 6.66; N, 4.87. Found: C, 60.62; H, 6.70; N, 4.93.

Deprotection of **24** (208 mg, 0.35 mmol) was achieved by treatment with NaOH (50 mg, 1.25 mmol) in aq dioxane followed by hydrogenolysis in aq MeOH to give N-*(methyl 6-deoxy-4-*O*-methyl-α-*D*-glucopyranoside-6-ylaminocarbonyl)-*L*-aspartic acid* **25** (125 mg, 93%) as a solid; mp 118–119 °C; $[\alpha]_D^{22}$ +70° (*c* 1.0, water); ^{1}H NMR: δ 4.67–4.63 (m, H-1), 4.52 (dd, $J_{Asp2,3a} = J_{Asp2,3b}$ 5.5 Hz, Asp-2), 3.61 (dd, $J_{2,3} = J_{3,4}$ 9.5 Hz, H-3), 3.57–3.49 (m, H-5), 3.48–3.37 (m, 2 H, H-6a, H-6b), 3.42 (s, Me*H*), 3.29–3.20 (m, H-2), 3.25 (2 s, 3 H, Me*H*), 3.02–2.94 (m, H-4), 2.88–2.77 (m, 2 H, Asp-3a,

Asp-3b); ^{13}C NMR: δ 175.80, 175.14 (COOH), 159.98 (NCON), 99.32 (C-1), 81.00/80.94 (2 × C-4), 73.09 (C-3), 71.68 (C-2), 69.74 (C-5), 60.25/60.22, 55.26/55.23 (CH_3), 50.15 (Asp-2), 40.81 (C-6), 36.90 (Asp-3).

N-*(Methyl 2,3-di-O-benzyl-6-deoxy-4-O-methyl-α-D-glucopyranoside-6-ylaminocarbonyl)-L-aspartic acid diisopropyl ester* (**26**).—A soln of **9** (100 mg, 0.26 mmol) in CH_2Cl_2 (2.5 mL) was treated with **21** (80 mg, 0.33 mmol). After 2 h, the solvent was removed and the crude product purified by column chromatography (2:1 toluene–EtOAc) to give **26** (130 mg, 80%) as a pale yellow syrup which crystallized from toluene–EtOAc; mp 95–97 °C; $[\alpha]_D^{21}$ +32° (*c* 2.0, $CHCl_3$); ^1H NMR: δ 7.38–7.26 (m, 10 H, Ph*H*), 6.47 (d, $J_{Asp2,NH}$ 9.0 Hz, Asp-N*H*), 6.30 (dd, $J_{6a,NH} = J_{6b,NH}$ 6.0 Hz, 6-N*H*), 4.94–4.84 (m, 2 H, ^{i}Pr-C*H*), 4.82 (d, ^2J 11.5 Hz, Ph^{a}CH_2), 4.78 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.71 (d, Ph^{a}CH_2), 4.69–4.61 (m, 2 H, Ph^{b}CH_2), 4.48 (ddd, $J_{Asp2,3a} = J_{Asp2,3b}$ 5.5 Hz, Asp-2), 3.67 (dd, $J_{2,3} = J_{3,4}$ 9.0 Hz, H-3), 3.45–3.16 (m, 4 H, H-2, H-5, H-6a, H-6b), 3.43, 3.31 (2 s, 2 × 3 H, Me*H*), 2.96 (dd, $J_{4,5}$ 9.5 Hz, H-4), 2.74–2.61 (m, 2 H, Asp-3a, Asp-3b), 1.21–1.14 (m, 12 H, ^{i}Pr-CH_3); ^{13}C NMR: δ 171.11, 170.84 (COOR), 157.42 (RHNCONHR), 138.69, 138.12 (C), 128.47, 128.38, 138.34, 128.09, 128.04, 127.94, 127.91, 127.63 (CH), 97.92 (C-1), 81.65, 80.69, 79.74 (C-2, C-3, C-4), 75.68, 73.43 (CH_2), 69.93, 69.26, 68.43 (C-5, ^{i}Pr-CH), 60.92, 55.33 (CH_3), 49.73 (Asp-2), 41.17 (C-6), 37.43 (Asp-3), 21.78, 21.74, 21.62 (CH_3). Anal. Calcd for $C_{33}H_{46}N_2O_{10}$ (630.73): C, 62.84; H, 7.35; N, 4.44. Found: C, 62.84; H, 7.51; N, 4.46.

N-*(Methyl 2,3-di-O-benzyl-6,7-dideoxy-4-O-methyl-α-D-glucoheptopyranoside-7-ylaminocarbonyl)-L-aspartic acid dimethylester* (**27**).—A soln of **23** (370 mg, 0.92 mmol) in CH_2Cl_2 (10 mL) was treated with **20** (180 μL, 1.2 mmol). After 2 h, the solvent was removed and the crude product purified by column chromatography (3:2 toluene–EtOAc) to yield **27** (490 mg, 90%) as a colorless syrup which crystallized from toluene–EtOAc; mp 139.5–141 °C; $[\alpha]_D^{24}$ +44° (*c* 1.0, $CHCl_3$); IR (KBr): 1728 (ester-CO), 1632 (urea-CO); ^1H NMR: δ 7.39–7.26 (m, 10 H, Ph*H*), 5.28 (d, $J_{Asp2,HN}$ 7.5 Hz, Asp-N*H*), 4.93 (d, ^2J 11.0 Hz, Ph^{a}CH_2), 4.83–4.73 (m, 2 H, Asp-2, 6-N*H*), 4.78 (d, Ph^{a}CH_2), 4.77 (d, ^2J 12.0 Hz, Ph^{b}CH_2), 4.65 (d, Ph^{b}CH_2), 4.56 (d, $J_{1,2}$ 3.5 Hz, H-1), 3.82 (dd, $J_{2,3}$ 9.5, $J_{3,4}$ 9.0 Hz, H-3), 3.74, 3.68 (2 s, 2 × 3 H, COOCH_3), 3.57 (ddd, $J_{4,5}$ 9.0, $J_{5,6a}$ 2.0, $J_{5,6b}$ 9.5 Hz, H-5), 3.54, 3.36 (2 s, 2 × 3 H, Me*H*), 3.45 (dd, H-2), 3.45–3.37 (m, H-7a), 3.29–3.20 (m, H-7b), 3.01 (dd, $J_{Asp2,3a}$ 4.5, $^2J_{Asp3}$ 17.0 Hz, H-3a), 2.89 (dd, H-4), 2.84 (dd, $J_{Asp2,3b}$ 4.5 Hz, Asp-3b), 2.06–1.97 (m, H-6a), 1.67–1.54 (m, H-6b). Anal. Calcd for $C_{30}H_{40}N_2O_{10}$ (588.65): C, 61.92; H, 6.84; N, 4.75. Found: C, 60.92; H, 6.89; N, 4.73.

N-*(Methyl-6,7-dideoxy-4-O-methyl-α-D-glucoheptopyranoside-7-ylaminocarbonyl)-L-aspartic acid* (**28**).—Compound **27** (260 mg, 440 mmol) was dissolved in MeOH (50 mL) and debenzylated at room temperature and 100 kPa hydrogen pressure using palladium on charcoal as catalyst. The raw product was dissolved in water and freeze-dried to give **28** (185 mg, quant.) as an amorphous solid; mp 93–98 °C; $[\alpha]_D^{23}$ +78° (*c* 1.0, MeOH); ^1H NMR (D_2O): δ 4.66 (d, $J_{1,2}$ 4.0 Hz, H-1), 4.57 (t, $J_{Asp2,3}$ 6.0 Hz, Asp-2), 3.66, 3.62 (2 s, 2 × 3 H, COOCH_3), 3.60 (dd, $J_{2,3}$ 10.0, $J_{3,4}$ 9.0 Hz, H-3), 3.47 (dd, H-2), 3.45, 3.29 (2 s, 2 × 3 H, Me*H*), 3.25–3.10 (m, 2 H, H-7a, H-7b), 2.91 (dd, $J_{4,5}$ 9.5 Hz, H-4), 2.84 (d, 2 H, Asp-3), 1.99–1.89 (m, H-6a), 1.64–1.54 (m, H-6b). Anal. Calcd for $C_{16}H_{28}N_2O_{10}$ (408.41): C, 47.05; H, 6.91; N, 6.85. Found: C, 46.79; H, 6.93; N, 6.62.

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