6-*O*-Amino-2-*O*-carboxymethyl Glucopyranoside as Novel Glycoaminoxy Acid Building Block for the Construction of Oligosaccharide Mimetics

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Received 22 April 2011; revised 13 June 2011

Abstract: The synthesis of diversely functionalized carbohydrate building blocks is of great interest towards the generation of new carbohydrate mimetics. Glycoaminoxy acids are recently developed glycoamino acid analogues with both an aminoxy and a carboxyl group connected to the sugar scaffold. These molecules could be readily used for the synthesis of various glycoconjugates through *N*-oxy amide or oxime bond, thus providing a potent tool for the design of novel functional carbohydrate mimetics. Here, the efficient synthesis of 2,6-functionalized pyranoid glycoaminoxy acid from commercially available methyl glucopyranoside is reported. The subsequent assembly of this glycoaminoxy acid building unit via N-acylation led successfully to the novel 2,6-linked oligosaccharide mimetics.

Key words: aminoxy acids, glycoaminoxy acids, oligosaccharide mimetics, carbohydrates, oligomers

Development of diversely functionalized carbohydrate building blocks represents a useful tactic for the synthesis of novel carbohydrate mimetics. Multifunctionalized carbohydrate derivatives such as sugar amino acids have been successfully utilized as building blocks toward the construction of various glycoconjugates as well as the design of bioactive molecules for drug discovery.[1]

Recently, aminoxy acids, a unique class of unnatural amino acids wherein an aminoxy function was introduced in place of the amine group (Figure 1), have emerged as very attractive chemical scaffolds since specific turns and helix conformations could be discovered in peptidomemitics comprising these moieties.[2] We first synthesized the pyranoid glycoaminoxy acid **C** (Figure 1) with aminoxy and carboxylic functions on the 1,6-position of the sugar ring as a new range of sugar building block from the respective α-*C*-allyl glycoside.[3] This compound has been successfully applied for the synthesis of *N*-oxy amide-linked disaccharide and glycosyl amino acid mimetics. Moreover, the synthesis of the oligomers of furanoid glycoaminoxy acids **A**[4] and **B**[5] have also been reported.

On the other hand, aminoxy-functionalized sugars have been reported for the glycoconjugate synthesis,[6] as monosaccharide templates for the synthesis of 'carboproteins',[7] or as chemoselective reagents for the covalent capture of glycans in microarray.[8] Preparation of various glycoaminoxy acid derivatives would therefore furnish versatile building units for the subsequent chemical ligations with peptides or numerous other biomolecules through either amide, oxime, or oxyamine bonds.[9]

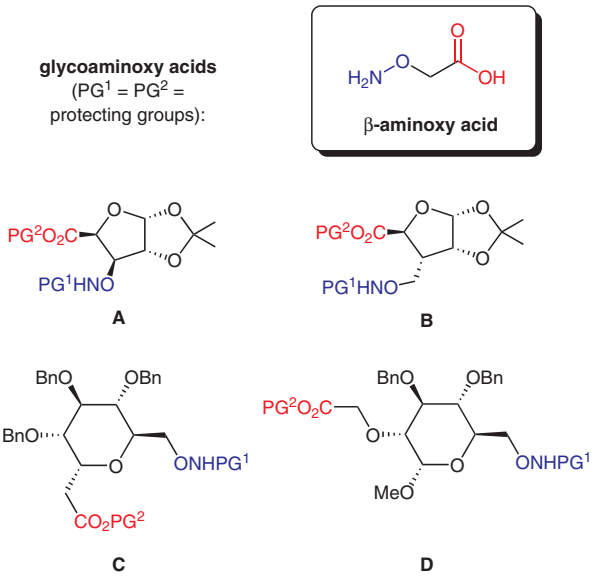


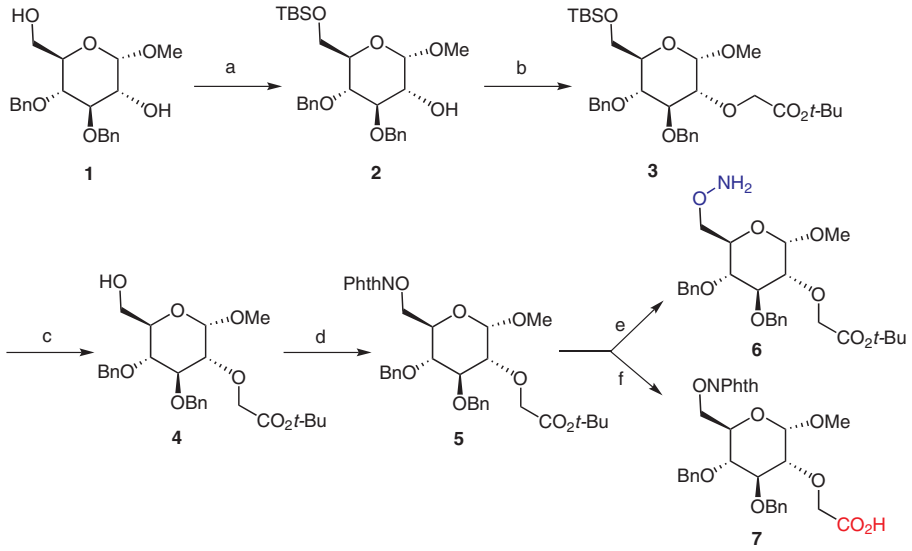
Figure 1 Structures of aminoxy acid and glycoaminoxy acid building blocks

To the best of our knowledge, only three glycoaminoxy acids (compounds **A**, **B**, and **C**, Figure 1) have been developed up to date. As a continuing program on the synthesis of functional carbohydrate mimetics,[10,11] we report herein the synthesis of a novel pyranoid glycoaminoxy acid **D** (Figure 1) with aminoxy and carboxylic function on 2,6-position of the sugar template as well as the construction of their oligomers.

To prepare pyranoid glycoaminoxy acid derivatives **D**, the commercially available methyl 3,4-di-*O*-benzyl-α-D-glucopyranoside (**1**)[12] was chosen as the starting material to introduce aminoxy and carboxylic functions onto its 2,6-positions (Scheme 1).

The 6-hydroxy group was first regioselectively protected via TBSCl to the TBS ether **2**. The carboxyl function was then easily introduced onto the 2-position through O-

SYNTHESIS 2011, No. 17, pp 2761–2766
Advanced online publication: 28.07.2011
DOI: 10.1055/s-0030-1260139; Art ID: H42811SS



Scheme 1 Synthesis of glycoaminoxy acid building blocks **6** and **7**. *Reagents and conditions*: (a) TBSCl, DMAP, pyridine, 92%; (b) $BrCH_2CO_2t$-Bu, NaH, DMF, 75%; (c) AcCl (cat.), MeOH, 94%; (d) Ph_3P, DIAD, PhthNOH, CH_2Cl_2, 83%; (e) H_2NNH_2, MeOH, 75%; (f) TFA, CH_2Cl_2, 85%.

alkylation with $BrCH_2CO_2t$-Bu in 75% yield. Notably, with catalytic amount of AcCl, the TBS group could be selectively eliminated without deprotecting the *tert*-butyl ester on the 2-position of the sugar ring.

Mitsunobu reaction of **4** with *N*-hydroxyphthalimide sequentially led to the glycoaminoxy ester **5** in its fully protected form in 83% yield. Nevertheless, it was noticed that the introduction of the phthalimido group at the 6-position of compound **1** using Mitsunobu reaction followed by 2-O-alkylation reaction failed to give the desired compound **5**, due most likely to the instability of phthalimidoxy group under basic or nucleophilic conditions.[5] A following hydrazinolysis of **5** gave the oxyamine **6**, while treatment of the same compound with TFA offered the carboxylic acid **7** as the sole product.

After obtaining these functionalized glycoaminoxy acid building blocks, the coupling of the oxyamine **6** with the carboxylic acid **7** was sequentially realized. Under the action of EDC/HOBt in a mixture of CH_2Cl_2 and DMF, the corresponding dimer **8** was obtained in 74% yield (Scheme 2). Subsequent treatment of **8** with hydrazine or TFA similarly gave the corresponding oxyamine **9** and the carboxylic acid **10** in modest yields, respectively. Ligation of the dimer **10** with the monomeric oxyamine **6** led to the trimer **11** in 51% yield. Eventually, the tetramer **12** could be obtained by the N-acylation of dimers **9** and **10** in a moderate yield of 48%.

The structures of these oligomers have been confirmed by NMR and HRMS. The protons of all *N*-oxy amide bonds appeared at around 10 ppm in their ^{1}H NMR spectra (compounds **8**–**12**, see Supporting Information) in $CDCl_3$ solution.

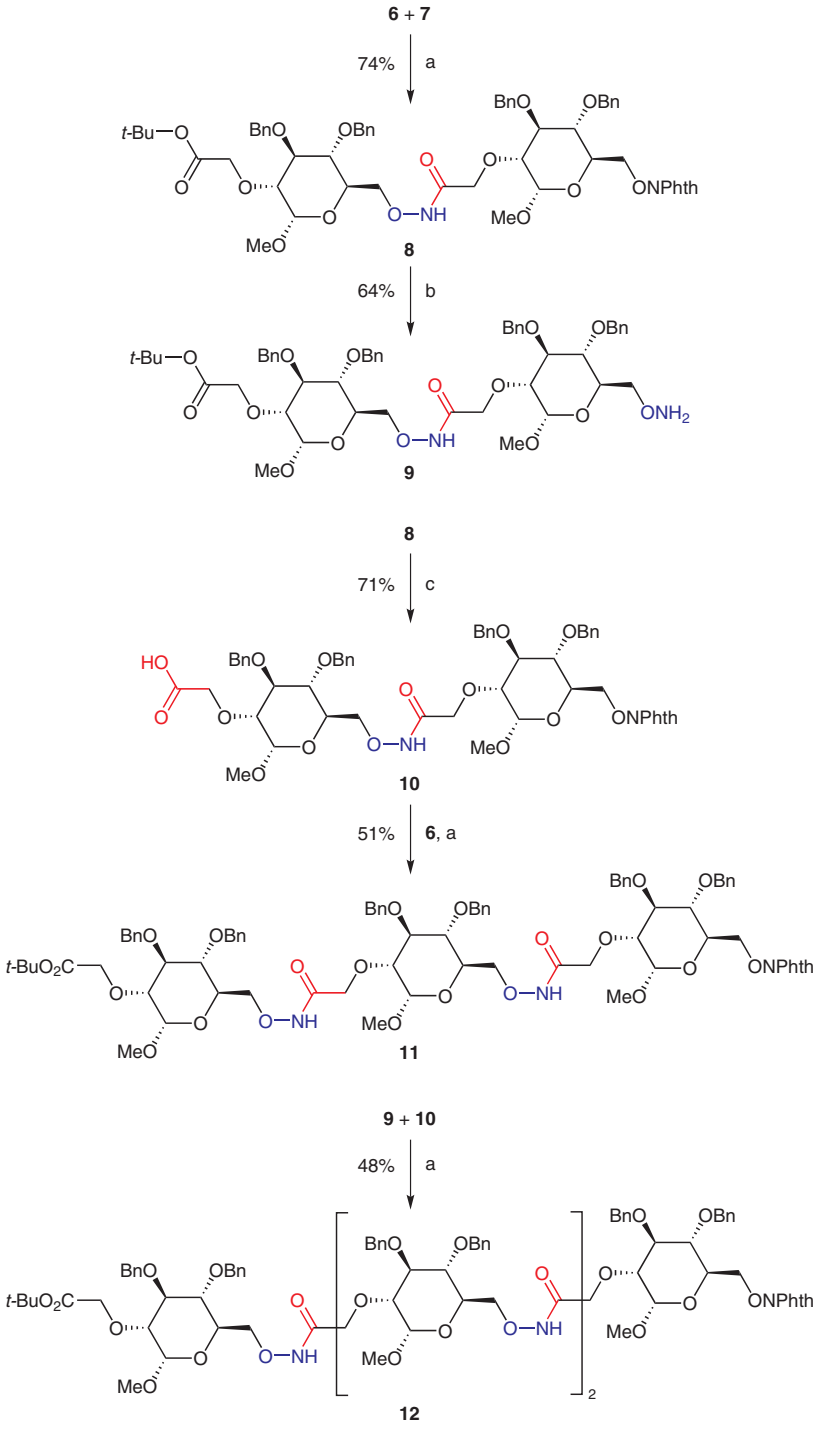
In summary, this paper depicts the efficient synthesis of new glycoaminoxy acid derivatives in which aminoxy and carboxylic acid functions have been easily introduced onto the 2,6-position of a methyl 3,4-di-*O*-benzyl-α-D-glucopyranoside template. Such a method should be applicable to the synthesis of other glycoside-derived glycoaminoxy acids. Furthermore, the obtained glycoaminoxy acid was successfully used as a building block to construct novel 2,6-linked oligosaccharide mimetics via N-acylation.

It is projected that the glycoaminoxy acid building units may serve as useful tools for the subsequent chemical ligations with various amines, carboxylic acids or aldehydes through, respectively, the amide, oxime or oxyamine bond, leading to a novel flourish class of oligosaccharide mimetics with potentially diverse practicalities. Programs related to this subject are currently underway in our laboratories.

Solvents were purified by standard procedures. Petroleum ether (PE) used refers to the fraction boiling in the range 60–90 °C. The organic extracts were dried over $MgSO_4$. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer in $CDCl_3$ solutions using TMS as the internal standard (chemical shifts in parts per million). Standard abbreviations are used to describe the signal multiplicity. All reactions were monitored by TLC (Yantai Marine Chemical Co. Ltd., P. R. of China). Optical rotations were measured using a Perkin-Elmer 241 polarimeter at r.t. in a 10 cm, 1 mL cell. High-resolution mass spectra (HRMS) were recorded on a Waters LCT Premier XE spectrometer using standard conditions (ESI, 70 eV).

Methyl 3,4-Di-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-α-D-glucopyranoside (2)

To a solution of compound **1** (560 mg, 1.50 mmol) in pyridine (10 mL) were added TBSCl (271 mg, 1.80 mmol) and DMAP (36 mg, 0.30 mmol) at 0 °C. The resulting mixture was stirred at r.t. for 5 h under argon and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried, filtered, and evaporated. The residue was purified by column chromatography over silica gel (EtOAc–PE, 1:8) to afford **2** as a white powder (672 mg, 92%); R_f = 0.52 (EtOAc–PE, 1:3); $[\alpha]_D^{25}$ +64.2 (*c* 0.39, CH_2Cl_2).



Scheme 2 Synthesis of oligo glycoaminoxy acids. *Reagents and conditions*: (a) EDC, HOBt, CH_2Cl_2–DMF; (b) H_2NNH_2, MeOH; (c) TFA, CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.23 (m, 10 H), 4.84 (d, *J* = 11.2 Hz, 1 H), 4.63 (m, 3 H), 4.58 (d, *J* = 3.6 Hz, 1 H), 4.03 (t, *J* = 9.2 Hz, 1 H), 3.75–3.74 (m, 2 H), 3.54 (ddd, *J* = 2.4, 4.0, 9.6 Hz, 1 H), 3.40 (t, *J* = 9.2 Hz, 1 H), 3.30 (dd, *J* = 3.6, 9.6 Hz, 1 H), 3.27 (s, 3 H), 0.84 (s, 9 H), –0.001 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 138.2, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 97.3, 79.9, 77.6, 74.5, 73.6, 73.0, 71.2, 62.5, 54.9, 28.1, 28.0, 26.0, 18.4, –5.1, –5.3.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{40}O_6Si$ + Na: 511.2492; found: 511.2497.

Methyl 3,4-Di-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-2-*O*-*tert*-butoxycarbonylmethyl-α-D-glucopyranoside (3)

To a solution of compound **2** (590 mg, 1.21 mmol) in DMF (5 mL) were added NaH (43.7 mg, 1.82 mmol) and *tert*-butyl bromoacetate (292 mL, 1.82 mmol) at 0 °C. After stirring at r.t. for 2 h under argon, the reaction was quenched with H_2O (2–3 mL), and the mixture extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried, filtered, and evaporated. The residue was purified by column chromatography over silica gel (EtOAc–PE, 1:20) to afford **3** as a yellow paste (547 mg, 75%); R_f = 0.59 (EtOAc–PE, 1:5); $[\alpha]_D^{25}$ +35.2 (*c* 0.33, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 10 H), 4.94 (d, *J* = 10.8 Hz, 1 H), 4.75 (d, *J* = 12.4 Hz, 1 H), 4.60 (d, *J* = 10.8 Hz, 1 H), 4.59 (d, *J* = 12.4 Hz, 1 H), 4.48 (d, *J* = 3.6 Hz, 1 H), 4.37 (d, *J* = 15.6 Hz, 1 H), 4.23 (d, *J* = 15.6 Hz, 1 H), 3.79–3.73 (m, 3 H), 3.53–3.51 (m, 2 H), 3.47 (dd, *J* = 3.6, 9.6 Hz, 1 H) 3.27 (s, 3 H), 1.42 (s, 9 H), 0.85 (s, 9 H), –0.003 (d, *J* = 1.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 138.6, 138.3, 128.4, 128.3, 128.0, 127.8, 127.6, 97.7, 83.4, 81.6, 81.1, 77.1, 75.0, 73.3, 71.3, 68.4, 62.2, 54.8, 28.0, 25.9, 18.3, –5.2, –5.4.

HRMS (ESI): *m*/*z* calcd for $C_{33}H_{52}O_8Si$: 603.3353; found: 603.3356.

Methyl 3,4-Di-*O*-benzyl-2-*O*-*tert*-butoxycarbonylmethyl-α-D-glucopyranoside (4)

To a solution of compound **3** (883 mg, 1.47 mmol) in MeOH (10 mL MeOH) was added AcCl (16 mL, 0.22 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min under argon and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried, filtered, and evaporated. The residue was purified by column chromatography over silica gel (EtOAc–PE, 1:4) to afford **4** as a white powder (674 mg, 94%); R_f = 0.32 (EtOAc–PE, 1:2); $[\alpha]_D^{25}$ +72.5 (*c* 0.17, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 10 H), 4.99 (d, *J* = 10.8 Hz, 1 H), 4.79 (d, *J* = 12.0 Hz, 1 H), 4.67 (d, *J* = 10.8 Hz, 1 H), 4.63 (d, *J* = 12.0 Hz, 1 H), 4.47 (d, *J* = 3.6 Hz, 1 H), 4.43 (d, *J* = 15.6 Hz, 1 H), 4.29 (d, *J* = 16.0 Hz, 1 H), 3.83 (t, *J* = 9.2 Hz, 1 H), 3.75 (dd, *J* = 2.4, 11.6 Hz, 1 H), 3.67 (dd, *J* = 4.0, 12.0 Hz, 1 H), 3.61–3.57 (m, 1 H), 3.55–3.54 (m, 1 H), 3.50 (dd, *J* = 4.0, 9.6 Hz, 1 H), 3.30 (s, 3 H), 1.46 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 138.2, 129.8, 129.0, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 123.3, 98.0, 83.1, 81.4, 80.0, 70.5, 61.9, 55.1, 28.1.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{36}O_8$ + Na: 511.2308; found: 511.2309.

Methyl 3,4-Di-*O*-benzyl-2-*O*-*tert*-butoxycarbonylmethyl-6-*O*-phthalimido-α-D-glucopyranoside (5)

To a solution of compound **4** (150 mg, 0.31 mmol) in CH_2Cl_2 (8 mL) were added Ph_3P (113 mg, 0.43 mmol), PhthNOH (60 mg, 0.37 mmol), and DIAD (85 mL, 0.43 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h under argon and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried, filtered, and evaporated. The residue was purified by column chromatography over silica gel (EtOAc–PE, 1:5) to afford **5** as a white powder (163 mg, 83%); R_f = 0.63 (EtOAc–PE, 1:2); $[\alpha]_D^{25}$ +7.1 (*c* 0.16, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 3.2, 5.6 Hz, 2 H), 7.74 (dd, *J* = 2.8, 5.2 Hz, 2 H), 7.40–7.23 (m, 10 H), 5.08 (d, *J* = 10.4 Hz, 1 H), 5.01–4.95 (m, 1 H), 4.87 (d, *J* = 10.8 Hz, 1 H), 4.80 (d, *J* = 12.0 Hz, 1 H), 4.63 (d, *J* = 12.4 Hz, 1 H), 4.51 (d, *J* = 3.2 Hz, 1 H), 4.46–4.39 (m, 3 H), 4.29 (d, *J* = 15.6 Hz, 1 H), 3.88–3.81 (m, 3 H), 3.59 (dd, *J* = 3.6, 9.2 Hz, 1 H), 3.35 (s, 3 H), 1.46 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 163.2, 156.6, 138.3, 138.2, 134.5, 127.7, 123.5, 98.1, 83.1, 81.3, 79.5, 75.1, 73.4, 71.3, 70.0, 69.2, 55.5, 28.1, 21.9.

HRMS (ESI): *m*/*z* calcd for $C_{35}H_{39}NO_{10}$ + Na: 656.2472; found: 656.2474.

Methyl 6-*O*-Amino-3,4-di-*O*-benzyl-2-*O*-*tert*-butoxycarbonylmethyl-α-D-glucopyranoside (6)

To a solution of compound **5** (300 mg, 0.47 mmol) in MeOH (6 mL), was added $N_2H_4{\cdot}H_2O$ (46 mL, 0.94 mmol) at r.t. The resulting mixture was stirred at r.t. for 2 h under argon and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried, filtered, and evaporated. The residue was purified by column chromatography over silica gel (EtOAc–PE, 1:2) to afford **6** as a yellow paste (180 mg, 75%); R_f = 0.29 (EtOAc–PE, 1:1); $[\alpha]_D^{25}$ +28.3 (*c* 0.25, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 10 H), 4.98 (d, *J* = 10.8 Hz, 1 H), 4.78 (d, *J* = 12.4 Hz, 1 H), 4.65 (d, *J* = 10.8 Hz, 1 H), 4.62 (d, *J* = 12.4 Hz, 1 H), 4.49 (d, *J* = 3.2 Hz, 1 H), 4.42 (d, *J* = 15.6 Hz, 1 H), 4.28 (d, *J* = 15.6 Hz, 1 H), 3.86–3.85 (m, 2 H), 3.80 (t, *J* = 8.8 Hz, 1 H), 3.73–3.67 (m, 1 H), 3.54–3.51 (m, 2 H), 3.31 (s, 3 H), 1.46 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 150.6, 138.3, 138.1, 135.5, 127.7, 123.5, 115.5, 114.2, 98.0, 83.2, 81.3, 79.8, 73.4, 71.3, 70.9, 69.4, 55.1, 28.1.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{39}NO_8$: 504.2597; found: 504.2596.

Methyl 3,4-Di-*O*-benzyl-2-*O*-carboxymethyl-6-*O*-phthalimido-α-D-glucopyranoside (7)

To a solution of compound **5** (300 mg, 0.47 mmol) CH_2Cl_2 (10 mL) was added CF_3CO_2H (35 mL, 0.47 mmol) at 0 °C. The resulting mixture was stirred at r.t. for 45 min under argon and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried, filtered, and evaporated. The residue was purified by column chromatography over silica gel (EtOAc–PE, 3:1) to afford **7** as a white powder (233 mg, 85%); R_f = 0.21 (EtOAc–PE, 5:1); $[\alpha]_D^{25}$ +99.2 (*c* 0.18, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 2.8, 5.6 Hz, 2 H), 7.77 (dd, *J* = 3.2, 5.6 Hz, 2 H), 7.41–7.30 (m, 10 H), 5.01 (d, *J* = 10.8 Hz, 1 H), 4.88 (d, *J* = 10.8 Hz, 1 H), 4.76 (d, *J* = 12.0 Hz, 1 H), 4.67 (d, *J* = 12.0 Hz, 1 H), 4.61 (d, *J* = 3.6 Hz, 1 H), 4.47 (dd, *J* = 3.2, 11.6 Hz, 1 H), 4.42–4.35 (m, 3 H), 4.03 (t, *J* = 10.0 Hz, 1 H), 3.81–3.77 (m, 2 H), 3.68–3.60 (m, 1 H), 3.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 163.2, 137.4, 136.6, 134.6, 128.5, 128.2, 123.6, 97.2, 82.2, 78.4, 77.0, 75.6, 75.2, 73.0, 70.4, 69.5, 55.5.

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{31}NO_{10}$ + Na: 600.1846; found: 600.1845.

Methyl 3,4-Di-*O*-benzyl-2-*O*-*tert*-butoxycarbonylmethyl-6-*O*-[(methyl 3,4-di-*O*-benzyl-6-*O*-phthalimido-α-D-glucopyranosid-2-yloxy)methylcarbonylamino]-α-D-glucopyranoside (8)

To a solution of compounds **6** (147 mg, 0.25 mmol) and **7** (125.8 mg, 0.25 mmol) in CH_2Cl_2–DMF (15 mL, 2:1 v/v) were added EDC·HCl (86 mg, 0.45 mmol) and HOBt (61 mg, 0.45 mmol) at r.t. The resulting mixture was stirred at r.t. for 3 h under argon and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried, filtered, and evaporated. The residue was purified by column chromatography over silica gel (EtOAc–PE, 1:2) to afford **8** as a white paste (199 mg, 74%); R_f = 0.57 (EtOAc–PE, 1:1), $[\alpha]_D^{25}$ +39.1 (*c* 0.18, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.04 (s, 1 H), 7.82–7.79 (m, 2 H), 7.76–7.73 (m, 2 H), 7.38–7.25 (m, 20 H), 4.96 (d, *J* = 10.8 Hz, 1 H), 4.91 (d, *J* = 10.4 Hz, 1 H), 4.85 (d, *J* = 10.8 Hz, 1 H), 4.75 (d, *J* = 12.4 Hz, 1 H), 4.66 (d, *J* = 12.0 Hz, 2 H), 4.61 (d, *J* = 12.0 Hz, 2 H), 4.58 (t, *J* = 3.6 Hz, 2 H), 4.42–4.40 (m, 2 H), 4.39 (d, *J* = 15.6 Hz, 2 H), 4.25 (d, *J* = 15.6 Hz, 1 H), 3.99–3.91 (m, 3 H), 3.82 (d, *J* = 9.6 Hz, 1 H), 3.77 (d, *J* = 9.2 Hz, 2 H), 3.74–3.69 (m, 1 H), 3.53 (dd, *J* = 3.2, 9.6 Hz, 1 H), 3.49 (dd, *J* = 3.6, 9.6 Hz, 1 H), 3.44 (t, *J* = 9.2 Hz, 1 H), 3.32 (s, 3 H), 3.30 (s, 3 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 166.9, 163.2, 138.4, 138.2, 137.3, 137.2, 134.6, 128.7, 128.2 (2), 128.0, 127.9, 127.7, 97.9, 97.5, 81.2, 75.0, 74.9, 73.3, 73.0, 71.5, 71.3, 69.5, 69.3, 60.4, 55.5, 55.3, 28.1.

HRMS (ESI): *m*/*z* calcd for $C_{58}H_{66}N_2O_{17}$ + Na: 1085.4259; found: 1085.4261.

Methyl 3,4-Di-*O*-benzyl-2-*O*-*tert*-butoxycarbonylmethyl-6-*O*-[(methyl 6-*O*-amino-3,4-di-*O*-benzyl-α-D-glucopyranosid-2-yloxy)methylcarbonylamino]-α-D-glucopyranoside (9)

Compound **8** (77 mg, 0.07 mmol) in MeOH (5 mL) was hydrazinolyzed with $N_2H_4{\cdot}H_2O$ (7 mL, 0.14 mmol) as for compound **5**. Purification by column chromatography over silica gel (EtOAc–PE, 1:3) afforded **9** as a white paste (43 mg, 64%); R_f = 0.27 (EtOAc–PE, 1:1); $[\alpha]_D^{25}$ +100.4 (*c* 0.11, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.10 (s, 1 H), 7.35–7.24 (m, 20 H), 4.90 (d, *J* = 10.8 Hz, 1 H), 4.77 (d, *J* = 12.0 Hz, 1 H), 4.72 (d, *J* = 11.2 Hz, 1 H), 4.66–4.56 (m, 6 H), 4.48 (d, *J* = 3.2 Hz, 1 H), 4.41–4.37 (m, 3 H), 4.24 (d, *J* = 15.6 Hz, 1 H), 3.96 (dd, *J* = 4.4, 10.4 Hz, 1 H), 3.87–3.82 (m, 3 H), 3.77–3.73 (m, 2 H), 3.67–3.65 (m, 2 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 167.2, 138.4, 138.2, 137.0, 128.7, 128.2 (2 C), 128.1, 127.9, 127.6, 97.9, 97.3, 81.2, 75.3, 74.9 (2 C), 73.3, 72.8, 71.3, 69.5, 69.0, 55.2, 28.1.

HRMS (ESI): *m*/*z* calcd for $C_{50}H_{65}N_2O_{15}$: 933.4385; found: 933.4383.

Methyl 3,4-Di-*O*-benzyl-2-*O*-carboxymethyl-6-*O*-[(methyl 3,4-di-*O*-benzyl-6-*O*-phthalimido-α-D-glucopyranosid-2-yloxy)methylcarbonylamino]-α-D-glucopyranoside (10)

Compound **8** (130 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was treated with CF_3CO_2H (10 mL, 0.13 mmol) as for compound **5**. Purification by column chromatography over silica gel (EtOAc–PE, 3:1) afforded **10** as a white paste (87 mg, 71%); R_f = 0.30 (EtOAc–PE, 4:1); $[\alpha]_D^{25}$ +78.8 (*c* 0.1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.22 (s, 1 H), 7.83–7.81 (m, 2 H), 7.77–7.75 (m, 2 H), 7.40–7.26 (m, 20 H), 4.99 (d, *J* = 10.8 Hz, 1 H), 4.87 (td, *J* = 10.8 Hz, 1 H), 4.74–4.58 (m, 8 H), 4.47 (d, *J* = 3.6 Hz, 2 H), 4.40 (d, *J* = 11.2 Hz, 2 H), 4.35–4.27 (m, 2 H), 4.00–3.97 (m, 2 H), 3.85 (d, *J* = 8.8 Hz, 1 H), 3.80 (d, *J* = 9.6 Hz, 1 H), 3.71–3.66 (m, 2 H), 3.56–3.49 (m, 3 H), 3.47 (dd, *J* = 3.2, 9.6 Hz, 1 H), 3.30 (s, 3 H), 3.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 163.2, 137.2, 136.4, 134.6, 128.6, 128.2, 123.6, 97.5, 96.9, 81.8, 78.2, 77.3, 75.5, 75.1, 73.0, 72.8, 70.3, 69.5, 69.4, 55.6, 55.4.

HRMS (ESI): *m*/*z* calcd for $C_{54}H_{59}N_2O_{17}$: 1007.3814; found: 1007.3832.

Trimer 11

To a solution of compounds **6** (20 mg, 0.04 mmol) and **10** (40 mg, 0.04 mmol) in CH_2Cl_2–DMF (9 mL, 2:1 v/v) were added EDC·HCl (15 mg, 0.08 mmol) and HOBt (11 mg, 0.08 mmol) at r.t. The resulting mixture was stirred at r.t. for 3 h under argon and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried, filtered, and evaporated. The residue was purified by column chromatography over silica gel (EtOAc–PE, 1:2) to afford **11** as a white paste (30 mg, 51%); R_f = 0.52 (EtOAc–PE, 2:1); $[\alpha]_D^{25}$ +52.4 (*c* 0.1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.20 (s, 1 H), 10.06 (s, 1 H), 7.83–7.80 (m, 2 H), 7.76–7.74 (m, 2 H), 7.40–7.24 (m, 30 H), 4.98 (d, *J* = 10.8 Hz, 1 H), 4.88 (d, *J* = 11.2 Hz, 1 H), 4.85 (d, *J* = 11.2 Hz, 1 H), 4.75 (d, *J* = 12.0 Hz, 1 H), 4.68 (d, *J* = 12.0 Hz, 2 H), 4.62–4.59 (m, 8 H), 4.47 (dd, *J* = 3.6, 15.6 Hz, 3 H), 4.40–4.36 (m, 4 H), 4.24 (d, *J* = 15.6 Hz, 1 H), 4.01–3.96 (m, 2 H), 3.92 (dd, *J* = 5.2, 10.8 Hz, 1 H), 3.84–3.81 (m, 3 H), 3.78–3.76 (m, 1 H), 3.73–3.63 (m, 4 H), 3.58–3.54 (m, 2 H), 3.48–3.39 (m, 4 H), 3.30 (s, 3 H), 3.29 (s, 3 H), 3.28 (s, 3 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 167.2, 163.2, 138.4, 138.2, 137.3, 137.2, 137.1, 134.6, 127.6, 123.6, 97.9, 97.5, 97.2, 80.8, 79.3, 77.6, 77.0, 75.1, 73.3, 72.8, 69.5, 69.0, 58.4, 55.5, 55.3 55.2, 28.1.

HRMS (ESI): *m*/*z* calcd for $C_{81}H_{93}N_3O_{24}$ + Na: 1514.6047; found: 1514.6082.

Tetramer 12

To a solution of compounds **9** (35 mg, 0.04 mmol) and **10** (40 mg, 0.04 mmol) in CH_2Cl_2–DMF (9 mL, 2:1 v/v) were added EDC·HCl (15 mg, 0.08 mmol) and HOBt (11 mg, 0.08 mmol) at r.t. The resulting mixture was stirred at r.t. for 3 h under argon and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried, filtered, and evaporated. The residue was purified by column chromatography over silica gel (EtOAc–PE, 1:1) to afford **12** as a white powder (34 mg, 48%); R_f = 0.31 (EtOAc–PE, 2:1); $[\alpha]_D^{25}$ +43.8 (*c* 0.09, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.23 (s, 2 H), 10.09 (s, 1 H), 7.83–7.81 (m, 2 H), 7.77–7.75 (m, 2 H), 7.40–7.26 (m, 40 H), 4.99 (d, *J* = 10.8 Hz, 1 H), 4.87 (d, *J* = 10.4 Hz, 1 H), 4.85 (d, *J* = 10.4 Hz, 1 H), 4.75 (d, *J* = 11.6 Hz, 1 H), 4.70–4.45 (m, 14 H), 4.46 (d, *J* = 3.6 Hz, 2 H), 4.39–4.35 (m, 5 H), 4.23 (d, *J* = 15.6 Hz, 1 H), 3.99–3.90 (m, 4 H), 3.74–3.63 (m, 10 H), 3.56 (dd, *J* = 2.8, 9.6 Hz, 2 H), 3.51–3.38 (m, 10 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 3.27 (s, 3 H), 3.26 (s, 3 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 167.2, 163.2, 138.4, 138.2, 137.2, 134.6, 128.3, 127.6, 123.6, 97.9, 97.5, 97.2, 83.0, 80.7, 80.5, 79.5, 79.3, 75.4, 73.0, 72.8, 71.3, 69.5, 58.5, 55.4, 55.3, 28.1.

HRMS (ESI): *m*/*z* calcd for $C_{104}H_{120}N_4O_{31}$ + Na: 1943.7834; found: 1943.7827.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

X.-P. He gratefully acknowledges the French Embassy in Beijing, China for a co-tutored doctorate fellowship. This project was supported by National Natural Science Foundation of China (Grant No. 20876045), Shanghai Science and Technology Community (No. 10410702700) and the Fundamental Research Funds for the Central Universities (No. WK1013002).

References

(1) For reviews, see: (a) Sears, O.; Wong, C. H. *Angew. Chem. Int. Ed.* **1999**, *38*, 2300. (b) Schweizer, F. *Angew. Chem. Int. Ed.* **2002**, *41*, 230. (c) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491. (d) Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S. *Curr. Med. Chem.* **2002**, *9*, 421. (e) Gervay-Hague, J.; Weathers, T. M. Jr. *J. Carbohydr. Chem.* **2002**, *7-9*, 867. (f) Chakraborty, T. K.; Srinivasu, P.; Tapadar, S.; Mohan, B. K. *J. Chem. Sci.* **2004**, *116*, 187. (g) Chakraborty, T. K.; Srinivasu, P.; Tapadar, S.; Mohan, B. K. *Bioconjugate J.* **2005**, *22*, 83. (h) Risseeuw, M. D. P.; Overhand, M.; Fleet, G. W. J.; Simone, M. I. *Tetrahedron: Asymmetry* **2007**, *18*, 2001. (i) Koester, D. C.; Holkenbrink, A.; Werz, D. B. *Synthesis* **2010**, 3217.

(2) (a) Yang, D.; Ng, F.-F.; Li, Z.-J.; Wu, Y.-D.; Chan, K. W. K.; Wang, D.-P. *J. Am. Chem. Soc.* **1996**, *118*, 9794. (b) Yang, D.; Qu, J.; Li, B.; Ng, F.-F.; Wang, X.-C.; Cheung, K.-K.; Wang, D.-P.; Wu, Y.-D. *J. Am. Chem. Soc.* **1999**, *121*, 589. (c) Shin, I.; Lee, M.; Lee, J.; Jung, M.; Lee, W.;

Yoon, J. *J. Org. Chem.* **2000**, *65*, 7667. (d) Yang, D.; Li, B.; Ng, F.-F.; Yan, Y.-L.; Qu, J.; Wu, Y.-D. *J. Org. Chem.* **2001**, *66*, 7303. (e) Chen, F.; Song, K.-S.; Wu, Y.-D.; Yang, D. *J. Am. Chem. Soc.* **2008**, *130*, 743. (f) Li, X.; Wu, Y.-D.; Yang, D. *Acc. Chem. Res.* **2008**, *41*, 1428. (g) Li, X.; Yang, D. *Chem. Commun.* **2006**, 3367. (h) Yang, D.; Zhang, D.-W.; Hao, Y.; Wu, Y.-D.; Luo, S.-W.; Zhu, N.-Y. *Angew. Chem. Int. Ed.* **2004**, *43*, 6719. (i) Yang, D.; Zhang, X.-W.; Zhang, D.-W.; Jiang, Z.-F.; Song, K.-S.; Zhang, Y.-H.; Zhu, N.-Y.; Weng, L.-H.; Chen, M.-Q. *J. Org. Chem.* **2010**, *75*, 4796. (j) Zhang, Y.-H.; Song, K.; Zhu, N.-Y.; Yang, D. *Chem. Eur. J.* **2010**, *16*, 577.

(3) Malapelle, A.; Ramozzi, R.; Xie, J. *Synthesis* **2009**, 888.

(4) Chandrasekhar, S.; Rao, C. L.; Reddy, M. S.; Sharma, G. D.; Kiran, M. U.; Naresh, P.; Chaitanya, G. K.; Bhanuprakash, K.; Jagadeesh, B. *J. Org. Chem.* **2008**, *73*, 9443.

(5) Gong, Y.; Sun, H.; Xie, J. *Eur. J. Org. Chem.* **2009**, 6027.

(6) (a) Rodriguez, E. C.; Marcaurelle, L. A.; Bertozzi, C. R. *J. Org. Chem.* **1998**, *63*, 7134. (b) Duléry, V.; Renaudet, O.; Philouze, C.; Dumy, P. *Carbohydr. Res.* **2007**, *342*, 894. (c) Chen, W.; Xia, C.; Cai, L.; Wang, P. G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3859.

(7) (a) Brask, J.; Jensen, K. J. *J. Pept. Sci.* **2000**, *6*, 290. (b) Brask, J.; Jensen, K. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 697. (c) Tofteng, A. P.; Hansen, T. H.; Brask, J.; Nielsen, J.; Thulstrup, P. W.; Jensen, K. J. *Org. Biomol. Chem.* **2007**, *5*, 2225. (d) Jiménez-Castells, C.; de la Torre, B. G.; Gutiérrez Gallego, R.; Andreu, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5155.

(8) Clo, E.; Blixt, O.; Jensen, K. J. *Eur. J. Org. Chem.* **2010**, 540.

(9) Tejler, J.; Salameth, B.; Leffler, H.; Nilsson, U. J. *Org. Biomol. Chem.* **2009**, *7*, 3982.

(10) (a) Xie, J. *Eur. J. Org. Chem.* **2002**, 3411. (b) Xie, J. *Carbohydr. Res.* **2003**, *338*, 399. (c) Xie, J.; Durrat, F.; Valéry, J. M. *J. Org. Chem.* **2003**, *68*, 7896. (d) Durrat, F.; Xie, J.; Valéry, J. M. *Tetrahedron Lett.* **2004**, *45*, 1477. (e) Ménand, M.; Blais, J.-C.; Hamon, L.; Valéry, J.-M.; Xie, J. *J. Org. Chem.* **2005**, *70*, 4423. (f) Ménand, M.; Blais, J.-C.; Valéry, J.-M.; Xie, J. *J. Org. Chem.* **2006**, *71*, 3295. (g) Ayadi, E.; Czernecki, S.; Xie, J. *J. Chem. Soc., Chem. Commun.* **1996**, 347.

(11) (a) Song, S.-X.; Zhang, H.-L.; Kim, C.-K.; Sheng, L.; He, X.-P.; Long, Y.-T.; Li, J.; Chen, G.-R. *Tetrahedron* **2010**, *66*, 9974. (b) Yang, J. W.; He, X.-P.; Li, C.; Gao, L.-X.; Sheng, L.; Xie, J.; Shi, X.-X.; Tang, Y.; Li, J.; Chen, G.-R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1092. (c) He, X.-P.; Wang, X.-W.; Jin, X.-P.; Zhou, H.; Shi, X.-X.; Chen, G.-R.; Long, Y.-T. *J. Am. Chem. Soc.* **2011**, *133*, 3649.

(12) (a) Mereyala, H. B.; Gurrala, S. R.; Mohan, S. K. *Tetrahedron* **1999**, *55*, 11331. (b) He, X.-P.; Li, C.; Jin, X.-P.; Song, Z.; Zhang, H.-L.; Zhu, C.-J.; Shen, Q.; Zhang, W.; Shi, X.-X.; Tang, Y.; Li, J.; Chen, G.-R.; Xie, J. *New J. Chem.* **2011**, *35*, 622.