Synthesis of Glycoaminoxy Acids as Novel Sugar Building Blocks

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Abstract: Glycoaminoxy acids, a new class of sugar building blocks bearing both aminoxy and carboxylic acid functional groups on the sugar ring, have been efficiently synthesized from α-*C*-allyl glycosides. These compounds can be easily used for the synthesis of an *N*-oxy-amide-linked disaccharide and glycosyl amino acid mimetics.

Key words: glycoaminoxy acids, glycopeptides, glycomimetics, glycosides, oligosaccharides

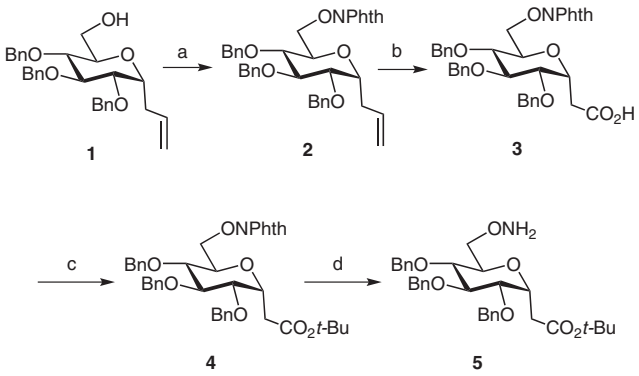
The design and synthesis of new molecules with various functions has attracted much attention from organic, bioorganic, peptide, medicinal, as well as material chemistry. The creation of such cleverly functionalized molecules has a large impact in designing bioactive molecules and for drug discovery. Amino acids and carbohydrates are two fundamental chiral building blocks in Nature, generating diversity in biological systems. Recently, glycoamino acids or sugar amino acids, where amine and carboxylic acid functional groups were incorporated into the sugar ring, have been widely employed as carbohydrate scaffolds for preparing carbohydrate-based molecules with various applications.[1] In the meanwhile, aminoxy acids, a class of unnatural amino acids where an aminoxy function has been introduced in place of the amine group, have emerged as very attractive scaffolds since the discovery of turns and helices structures in peptides containing aminoxy acids.[2] A new family of foldamers has been developed from α-, β-, and γ-aminoxy acids.[3] Oligomeric aminoxypeptides can also be prepared using solid phase techniques.[4] Thanks to the easy formation and stability of the oxime bond, aminoxy-functionalized peptides and proteins have been used as a tool in chemoselective ligation to prepare glycosylated pseudopeptides,[5] an anticancer vaccine,[6] or for high-throughput protein glycomics.[7] Through oxime ligation, peptide dendrimers,[8] protein–polymer conjugates,[9] bifunctional chelating agents,[10] and an oxime-peptide library[11] have also been synthesized.

Aminoxy-functionalized saccharides have been reported for glycoconjugate synthesis[12] or as monosaccharide templates for the synthesis of 'carboproteins'.[13] However, to the best of our knowledge, glycoaminoxy acids or sugar aminoxy acids having both aminoxy and carboxy functional groups incorporated into the sugar frameworks have not previously been reported (Figure 1). As a 'sister' of glycoamino acid, glycoaminoxy acid should represent a new class of multifunctional synthetic building blocks because both aminoxy and carboxylic acid functional groups can be readily used for further derivatization. In this paper, we report the synthesis of a glycoaminoxy acid and its derivatization.

Figure 1 Structure of glycoamino acids and glycoaminoxy acids

Aminoxy and carboxylic acid functions might be introduced into the different positions of furanosyl or pyranosyl sugar rings. Continuing our efforts in the synthesis and application of *C*-glycosyl building blocks,[14] we decided to prepare the first glucopyranosyl aminoxy acid from the known *C*-allyl glucoside **1**[14a] (Scheme 1). The Mitsunobu reaction of **1** with *N*-hydroxyphthalimide led to the protected aminoxy *C*-allyl glucoside **2** in 73% yield. The allyl group was then oxidized to a carboxylic acid by the combination of osmium tetroxide and Jones reagent;[14a] the protected glycoaminoxy acid **3** was obtained in 60% yield. The carboxylic acid function was then protected as the *tert*-butyl ester to give **4** (*t*-BuOH, DCC, DMAP). Cleavage of the phthalimido group was realized with hydrazine hydrate; the desired aminoxy ester **5** was obtained in 77% yield.

The synthesized glycoaminoxy acid derivatives were then tested as building blocks to generate oligosaccharide and glycopeptide mimetics. Coupling of the *N*-phthalimi-



Scheme 1 Reag*ents and conditions*: (a) PhthNOH, Ph_3P, DIAD, toluene, 73%; (b) OsO_4, Jones reagent, 60%; (c) *t*-BuOH, DCC, DMAP, CH_2Cl_2, 64%; (d) $H_2NNH_2{\cdot}H_2O$, MeOH, 77%.

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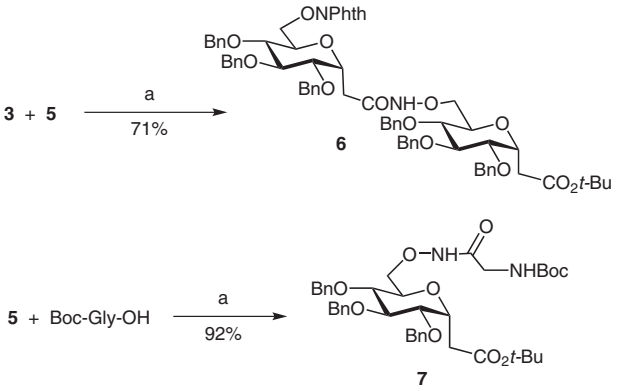
doglycoaminoxy acid **3** with the glycoaminoxy ester **5** furnished the first *N*-oxy-amide-linked disaccharide **6** in 71% yield (Scheme 2). The coupling reagent diethyl cyanophosphonate (DEPC), which we have previously used to prepare oligomers of glycoamino acids,[14c,d] proven to be efficient in this coupling. Reaction of the glycoaminoxy ester **5** with Boc-Gly-OH in the presence of diethyl cyanophosphonate/triethylamine led to the glycosylated amino acid **7** in 92% yield.



Scheme 2 *Reagents and conditions*: (a) DEPC, Et_3N, THF.

In summary, from readily available *C*-allyl glycoside **1**, we have succeeded in the synthesis of first *C*-glycoaminoxy acids, which can be readily converted into oligosaccharide or glycopeptide mimetics. These novel multifunctional sugar derivatives should find wide applications for chemoselective ligation of carbohydrate and peptides/proteins or as building blocks for the synthesis of various glycoconjugates.

All air-sensitive reactions were carried out under N_2. Column chromatography was performed on E. Merck Silica Gel 60 (230–400 mesh). Petroleum ether = PE. Analytical TLC was performed on E. Merck aluminum pre-coated plates of Silica Gel 60F-254 with detection by UV and by spraying with 3 M H_2SO_4 and heating at 300 °C for ~2 min. NMR spectra were recorded at r.t. with Jeol DX 400 spectrometers in $CDCl_3$. HRMS spectra were measured by the Service de Spectrométrie de Masse de l'Université Pierre et Marie Curie-Paris 6.

3-(2,3,4-Tri-*O*-benzyl-6-*O*-phthalimido-α-D-glucopyranosyl)propene (2)

To a soln of 3-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)propene (**1**, 2 g, 4.2 mmol) in toluene (6 mL) was added successively at r.t. under N_2, Ph_3P (1.7 g, 6.72 mmol), PhthNOH (822 mg, 5.04 mmol). After cooling to 0 °C, DIAD (1.24 mL, 6.30 mmol) was then added. The mixture was stirred for 24 h, H_2O–CH_2Cl_2 (2:3) was added, and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (EtOAc–PE, 1:9) gave **2** as a colorless oil; yield: 1.9 g (73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45–2.47 (m, 2 H, H3), 3.72–3.74 (m, 2 H), 3.81 (t, *J* = 7.8 Hz, 1 H), 3.90 (dd, *J* = 8.2, 9.6 Hz, 1 H), 4.05–4.07 (m, 1 H, H1′), 4.35 (dd, *J* = 1.8, 10.6 Hz, 1 H, H6′), 4.41 (dd, *J* = 3.2, 10.6 Hz, 1 H, H6″), 4.59 (d, *J* = 11.5 Hz, 1 H, OCH_2Ph), 4.68 (d, *J* = 11.5 Hz, 1 H, OCH_2Ph), 4.82 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.91 (d, *J* = 11.5 Hz, 1 H, OCH_2Ph), 4.93 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.99 (d, *J* = 11.5 Hz, 1 H, OCH_2Ph), 5.00–5.09 (m, 2 H, H2), 5.72–5.80 (m, 1 H, H1), 7.27–7.30 (m, 15 H, Ph), 7.72–7.80 (m, 4 H, Phth).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.0 (C3), 70.1, 70.8 (CH), 73.1 (CH_2), 73.8 (CH), 75.0, 75.2, 76.5 (CH_2), 77.2, 79.5, 82.1 (CH), 116.8 (C1), 123.5 (Phth), 127.6, 127.8, 127.9, 128.1, 128.4, 128.5, 128.6, 128.9, 129.0, 129.3, 129.9 (Ph), 134.4 (Phth), 135.8 (C2), 138.2, 138.3, 138.7 (C_{ipso}), 163.2 (C=O).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{38}H_{38}NO_7$: 620.2648; found: 620.2641.

2-(2,3,4-Tri-*O*-benzyl-6-*O*-phthalimido-α-D-glucopyranosyl)ethanoic Acid (3)

OsO_4 (4%) in *t*-BuOH(1.08 mL) and Jones reagent (4.8 mL) were added to a magnetically stirred soln of **2** (2.55 g, 4.1 mmol) in anhyd acetone (22 mL). The soln was stirred for 24 h and then a mixture of H_2O–EtOAc (1:1) was added. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated. Purification by flash chromatography (EtOAc–PE, 2:8 to 1:1) afforded **3** as a colorless oil; yield: 1.6 g (60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.75–2.78 (m, 2 H, H2), 3.75–3.89 (m, 4 H), 4.37 (m, 2 H, H6′), 4.59–4.65 (m, 3 H, H1′, OCH_2Ph), 4.79 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.81 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.90 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.91 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 7.27–7.30 (m, 15 H, Ph), 7.72–7.80 (m, 4 H, Phth).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.2 (C1), 71.1 (C1′), 72.1 (CH), 73.4, 75.1, 75.3, 76.6 (CH_2), 76.8, 78.6, 81.6 (CH), 123.6 (Phth), 127.8, 127.9, 128.2, 128.5, 128.6, 129.0 (Ph), 134.5 (Phth), 137.8, 138.1, 138.5 (C_{ipso}), 164.4, 175.6 (C=O).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{37}H_{36}NO_9$: 638.2390; found: 638.2415.

***tert*-Butyl 2-(2,3,4-Tri-*O*-benzyl-6-*O*-phthalimido-α-D-glucopyranosyl)ethanoate (4)**

t-BuOH (260 μL, 2.719 mmol) and DMAP (66 mg, 0.54 mmol) were successively added to a magnetically stirred soln of **3** (856 mg, 1.34 mmol) in anhyd CH_2Cl_2 (8 mL). The mixture was stirred and cooled to 0 °C and DCC (361 mg, 1.750 mmol) was added. After 6 h, a mixture of H_2O–CH_2Cl_2 (2:3) was added and the organic phase was washed with brine, dried with (Na_2SO_4), and evaporated to dryness. Flash chromatography (EtOAc–PE, 2:8 to 3:7) gave **4** as a colorless oil; yield: 594 mg (64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, *t*-Bu), 2.62–2.64 (m, 2 H, H2), 3.71–3.82 (m, 3 H), 3.92 (dd, *J* = 8.7, 10.1 Hz, 1 H), 4.37 (dd, *J* = 2.3, 11.0 Hz, 1 H, H6′), 4.42 (dd, *J* = 3.7, 11.0 Hz, 1 H, H6″), 4.55 (td, *J* = 5.5, 8.7 Hz, 1 H, H1′), 4.65 (s, 2 H, OCH_2Ph), 4.82 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.90 (d, *J* = 11.0 Hz, 2 H, OCH_2Ph), 4.95 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 7.30–7.32 (m, 15 H, Ph), 7.72–7.81 (m, 4 H, Phth).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 (*t*-Bu), 33.7 (C1), 71.6 (CH), 71.8 (C1′), 73.3, 75.2, 75.4 (CH_2), 76.1 (C6′), 77.3 (C_q), 78.9, 80.9, 81.2 (CH), 123.6 (Phth), 127.7, 127.9, 128.2, 128.5, 128.6, 129.0 (Ph), 134.5 (Phth), 137.8, 138.1, 138.5 (C_{ipso}), 163.2, 170.5 (C=O).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{41}H_{43}NNaO_9$: 716.2938; found: 716.2830.

***tert*-Butyl 2-(6-*O*-Amino-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)ethanoate (5)**

A suspension of **4** (300 mg, 0.43 mmol) in MeOH (1.5 mL) was treated with $H_2NNH_2{\cdot}H_2O$ (64%, 65 μL). The resulting mixture was stirred at r.t. for 2 h. The progress of the reaction was monitored by TLC (EtOAc–PE, 3:7). The mixture was diluted with Et_2O and was washed with sat. aq Na_2CO_3 soln. The aqueous layer was extracted with Et_2O (3 ×). The combined organic layers were dried (Na_2SO_4),

filtered, and evaporated. The residue was purified by flash chromatography (EtOAc–PE, 3:7) to afford **5** as a colorless oil; yield: 190 mg (77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, *t*-Bu), 2.62–2.64 (m, 2 H, H2), 3.46–3.49 (m, 1 H), 3.69–3.72 (m, 3 H), 3.82–3.83 (m, 2 H, H6′, H6″), 4.53–4.56 (m, 1 H, H1′), 4.61 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.66 (s, 2 H, OCH_2Ph), 4.80 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.84 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.90 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 7.28–7.30 (m, 15 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2 (*t*-Bu), 33.6 (C1), 71.4 (CH), 71.8 (C1′), 73.2 (CH_2), 74.7 (C6′), 75.2, 75.6 (CH_2), 78.1, 79.3 (CH), 80.9 (C_q), 82.3 (CH), 127.9, 128.5, 128.6 (Ph), 138.0, 138.2, 138.6 (C_{ipso}), 170.6 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{42}NO_7$: 564.2883; found: 564.2950.

***tert*-Butyl 2-(2,3,4-Tri-*O*-benzyl-6-*O*-{[(2,3,4-tri-*O*-benzyl-6-*O*-phthalimido-α-D-glucopyranosyl)carbonyl]amino}-α-D-glucopyranyl)ethanoate (6)**

To a soln of **5** (190 mg, 0.35 mmol) in THF (4 mL), were added **3** (217 mg, 0.35 mmol), DEPC (79 μL, 0.35 mmol), and Et_3N (145 μL, 1.05 mmol). The mixture was stirred overnight under N_2 and then diluted with EtOAc–H_2O (1:1) and separated. The aqueous layer was extracted with EtOAc. The combined organic layers were then washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by chromatography (EtOAc–PE, 3:7) to afford **6** as a colorless oil; yield: 291 mg (71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, *t*-Bu), 2.55 (m, 2 H, CH_2), 2.63 (m, 2 H, CH_2), 3.47 (t, *J* = 8.2 Hz, 1 H, H1), 3.67–3.77 (m, 4 H), 3.84–3.86 (m, 2 H, CH_2), 3.99 (dd, *J* = 6.4, 11.9 Hz, 1 H), 4.09–4.19 (m, 2 H), 4.30 (dd, *J* = 4.6, 14.2 Hz, 1 H), 4.34–4.37 (m, 1 H), 4.46–4.53 (m, 1 H), 4.56–4.91 (m, 13 H), 7.26–7.28 (m, 30 H, Ph), 7.68–7.78 (m, 4 H, Phth), 9.61 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2 (*t*-Bu), 30.8, 33.5 (C1), 71.2, 71.4, 71.5, 72.1 (CH), 72.9, 73.2, 74.8, 75.10, 75.14, 75.4 (CH_2), 76.8 (CH), 77.2 (CH_2), 78.0, 78.3, 79.2, 81.2 (CH), 81.4 (C_q), 81.9 (CH), 123.7 (Phth), 127.7, 127.9, 128.1, 128.2, 128.5, 128.9 (Ph), 134.5 (Phth), 138.0, 138.1, 138.5 (C_{ipso}), 163.5, 167.8, 171.4 (C=O).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{70}H_{74}N_2NaO_{15}$: 1205.5089; found: 1205.4981.

***tert*-Butyl 2-(2,3,4-Tri-*O*-benzyl-6-*O*-{[2-(*tert*-butoxycarbonylamino)acetyl]amino}-α-D-glucopyranosyl)ethanoate (7)**

To a soln of **5** (203 mg, 0.36 mmol) in THF (5 mL) were added Boc-Gly-OH (63 mg, 0.35 mmol), DEPC (82 μL, 0.54 mmol), and Et_3N (152 μL, 1.08 mmol). The mixture was stirred overnight under N_2 and then diluted with EtOAc–H_2O (1:1) and separated. The aqueous layer was extracted with EtOAc. The combined organic layers were then washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by chromatography (EtOAc–PE, 3:7) to afford **7** as a colorless oil; yield: 240 mg (92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, *t*-Bu), 1.44 (s, 9 H, *t*-Bu), 2.64–2.67 (m, 2 H, CH_2), 3.33 (m, 1 H), 3.67–3.88 (m, 6 H), 4.10 (m, 1 H), 4.44 (m, 1 H), 4.62–4.90 (m, 6 H), 5.18 (s, 1 H, NH), 7.24–7.30 (m, 15 H, Ph), 9.66 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2, 28.4 (*t*-Bu), 33.5, 42.1 (CH_2), 70.9, 71.6 (CH), 73.4, 75.2, 75.5, 75.8 (CH_2), 78.0, 79.1 (CH), 81.8 (C_q), 81.9 (CH), 128.0, 128.7 (Ph), 137.6, 137.8, 138.3 (C_{ipso}), 155.9, 166.4, 171.7 (C=O).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{40}H_{52}N_2NaO_{10}$: 743.3622; found: 743.3514.

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