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Facile synthesis of urea-and thiocarbamate-tethered glycosyl beta-amino acids†

Hanbing Teng,*[ab] Zengwei Zhang,[a] Yifan Zhou,[a] Zhiyong Chen,[a] Qi Chen,[a] Yang Liu[a] and Wenjin Xu[a]

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We describe here an efficient way to synthesize series of new urea- and thiocarbamate-tethered glycosyl β-amino acids under mild conditions. These glycosyl β-amino acids are elaborately designed on the basis of natural N-linked glycosides. They have the same side chain length as natural *N*-glycosyl amino acid while the main chain is replaced with β-amino acid chain. The linkage is an isostere of natural N-linked bond but exhibits competitive stability to chemical and enzymatic hydrolysis. This facile route is benefit from the choice of the commercially available L-aspartic acid as starting material, which not only provides a β-amino acid moiety, but also the α-carboxy group could be transformed to active isocyanate conveniently and economically. The prospective glycosyl β-amino acids are obtained readily by the reaction of isocyanate with appropriately protected glycosylamines and glycosylthiols.

Introduction

Glycopeptides have gained considerable synthetic attention due to their applications in diverse biochemical processes, such as cellular recognition, adhesion and signaling.[1] To develop homogeneous, stable and readily accessible glycopeptides analogues for biological studies and therapeutic applications, particular attention have been paid to glycopeptide mimics,[2–6] in which natural *O*- and *N*-glycosidic linkages were replaced by non-natural linkages, like carbon–carbon,[7] carbon–sulfur,[2,8] urea,[9] thiourea,[10] carbamate[9a,9d,11] and N-heterocycle.[12]

In the past decade, β-amino acids have become an interesting synthetic target because the presence of a methylene could provide higher conformational flexibility compared to α-amino analogues, which strongly affects the structural and biological properties of β-peptides, such as secondary structure and the rate of enzymatic degradation.[13] Furthermore, β-amino acid-containing peptides exhibit greater stability and higher biological activity than their parent α-peptides.[14]

Currently, considerable research efforts have been devoted to the design and synthesis of glycosyl β-amino acids, which could be utilized into neoglycopeptide syntheses for the formation of hybrid peptides or oligomers in a defined sequence.[15] Different from the prevalent synthesis of glycosyl α-amino acids, in which α-amino acid moiety could be directly originated from the library of natural α-amino acid conveniently,[7–12] the synthesis of glycosyl β-amino acids always involves the construction of a β-amino acid moiety,[15] which makes the synthetic route more complicated.

L-aspartic acid is commercially available natural α-amino acid containing β-amino acid moiety. To the best of our knowledge, it has not been used as starting materials to synthesize glycosyl β-amino acid until recently. Herein, we show a facile route to the design and synthesis of various kinds of glycosyl β-amino acids by the use of L-aspartic acid as starting materials. The prominent advantage of the route is that it significantly avoids the additional construction of a β-amino acid moiety at later steps.

The simplest way to prepare glycosyl β-amino acids, which is highly similar to natural N-linked glycosides in structure, could directly form amide by the condensation reactions of the glycosylamines with α-carboxyl group of L-aspartic acid.[16] The obtained glycosyl β-amino acids have a shorter side chain than natural N-linked glycosides. Moreover, they display the same drawback of the linkage as the natural N-linked glycosides, which is unstable to chemical and enzymatic hydrolysis.[9a,17]

As an interesting candidate for replacing the natural *N*-glycosidic linkage, the urea linkage is capable of increasing resistance to chemical and enzymatic degradation while maintaining the characteristic properties of the natural compounds.[18] Furthermore, the urea motif is well known as its strong hydrogen bonding capacity, which makes the neoglycopeptides more water soluble than natural glycopeptides.[19] We are aiming to synthesize urea-tethered glycosyl β-amino acids based on natural N-linked glycosyl amino acid building blocks. The target compound **II** is shown in Scheme 1. From a

[a]*School of Chemistry, Chemical Engineering and Life Science, Wuhan University of Technology, 122 Luoshi Road, Wuhan 430070, People's Republic of China. E-mail: wdthb@163.com*

[b]*State Key Laboratory of Advanced Technology for Materials Synthesis and Processing, Wuhan University of Technology, 122 Luoshi Road, Wuhan 430070, People's Republic of China*

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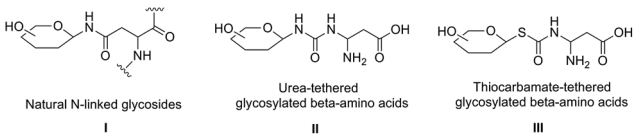
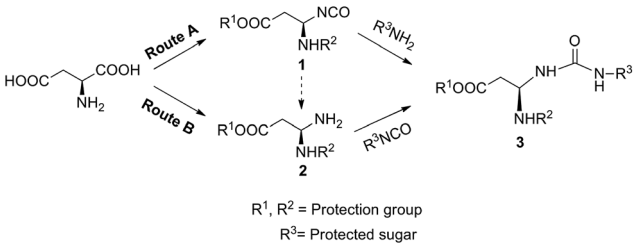


Scheme 1 Natural N-linked glycosides and target urea-tethered and thiocarbamate-tethered glycosyl β-amino acids.



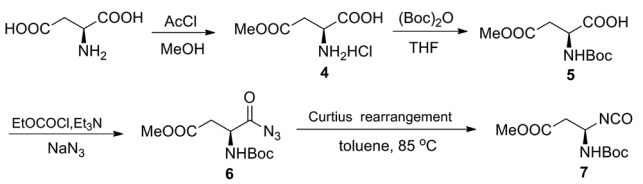
Scheme 2 Two routes to prepared the target urea-tethered glycosyl β-amino acids.

structure aspect, it is very similar to the natural N-linked glycosides **I**, regardless of the factor of the main chain. Only the methylene (–CH_2–) unit is replaced by imino group (–NH–) in the side chain. Namely, besides displacing the α-amino acid chain with β-amino acid chain, we chose a more stable isostere-urea linkage to replace the natural N-linked bond while maintaining the same side chain length. These elaborately modified glycosyl β-amino acids would be attractive building blocks to replace the natural *N*-glycosyl amino acid in the design of neoglycopeptide.

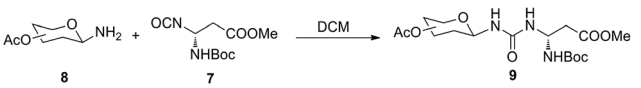
There are two synthetic routes to prepare the target urea-tethered glycosyl β-amino acids (Scheme 2). Route A shows obvious advantageous over Route B, since amine **2** is often synthesized by the active intermediate isocyanate **1**. Furthermore, Route A avoids the preparation of various glycosyl isocyanates R^3NCO, which could be extremely unstable.[20]

Results and discussion

As outlined in Route A, our synthetic route mainly involves converting the α-carboxyl group of L-aspartic acid to isocyanate and binding the glycosylamines with isocyanate by urea. The synthesis of isocyanate 7 is shown in Scheme 3, the α-amino of L-aspartic acid was protected by Boc after the β-carboxy group was esterified selectively.[21,22] The α-carboxy group of compound **5** was then converted to corresponding acyl azide **6** (strong absorption at 2141 cm^{-1} in IR) by the mixed anhydride reacting with NaN_3.[23] Heating acyl azide **6** in toluene at 85 °C *in situ* provided isocyanate 7 (strong absorption at 2249 cm^{-1} in IR) in *ca.* 71% yield from compound **5**. The crude product was used directly without purification for next transformation.



Scheme 3 The synthesis of β-amino acid bearing active isocyanate in the side chain.



Scheme 4 The synthesis of urea-tethered glycosyl β-amino acids.

Table 1 List of the synthesis of urea-tethered glycosyl β-amino acids[a,b]

Entry	Glycosylamines	Time	Yield[c]	Product
1	**8a**	45 min	91	**9a**
2	**8b**	30 min	87	**9b**
3	**8c**	1 h	90	**9c**
4	**8d**	1.5 h	88	**9d**
5	**8e**	1.5 h	85	**9e**

[a] All the solvent were dichloromethane. [b] All reactions were conducted at room temperature. [c] Isolated yield.

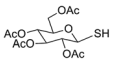
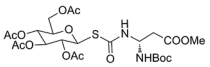
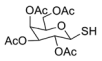
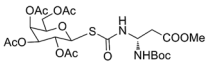
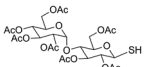
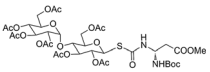
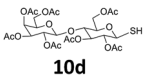
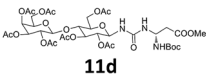
The glycosylamines was prepared according to the literature method.[24,25] All the glycosylamines were reacted with isocyanate 7 to provide the corresponding target urea-tethered glycosyl β-amino acids readily (Scheme 4, Table 1).

We found that the glycosylthiols could also react with isocyanate 7 to provide the corresponding thiocarbamate-tethered glycosyl β-amino acids, a new class in the library of glycosyl β-amino acid (Scheme 5, Table 2). The glycosylthiols was prepared according to the reported method.[26]

The reaction of isocyanate 7 with acetylated 1-hydroxy glucose or galactose afforded too much unexpected by-products. We couldn't obtain carbamate-tethered glycosyl β-amino acids even though adding NEt_3 or DMAP.[9a] The α-carboxy group of

Scheme 5 The synthesis of thiocarbamate-tethered glycosyl β-amino acid.

Table 2 List of the synthesis of thiocarbamate-tethered glycosyl β-amino acids[a,b]

Entry	Glycosylthiols	Time	Yield[c]	Product
1	 **10a**	2 h	92	 **11a**
2	 **10b**	2 h	89	 **11b**
3	 **10c**	2.5 h	86	 **11c**
4	 **10d**	2.5 h	83	 **11d**

[a] All the solvent were dichloromethane. [b] All reactions were conducted at room temperature. [c] Isolated yield.

compound **5** can be easily converted to isocyanate **7** by two steps without used expensive reagent such as DPPA.[27] The infrared (IR) spectra of crude product acyl azide **6** showed that it often contained rearrangement compound **7**. We have attempted to characterize the active intermediate acyl azide **6** and isocyanate **7** with Electrospray ionization mass spectrometry (ESI-MS), only the signal peak of acyl azide **6** was observed at $m/z = 295.1010$ [M + Na], no signal of isocyanate **7** was detected. The reaction of isocyanate **7** with the glycosylamines showed faster reaction rate than that of **7** with glycosylthiols. In these cases, the monosaccharides react faster than the corresponding disaccharides. The representative compound **9a** was choosed to research the epimerization at C-1 position. The crude reaction mixture was detected directly by ^{1}HNMR after removing solvent in vacuum when the reaction was completed. In order to get a clear ^{1}HNMR of crude reaction mixture, the isocyanate was elaborately prepared and it was excessive to avoid the interference from the glucosylamine **8a**. The result showed that no epimerized product was found. The product **9a** was β-anomer ($\delta = 5.19, J_{H1,2} = 9.2$) and its configuration was the same as the raw material glucosylamine **8a**.

Conclusions

We have described a facile method for the preparation of series of new urea- and thiocarbamate-tethered glycosyl β-amino acids based on natural N-linked glycosides under mild conditions. These glycosyl β-amino acids display very distinctive structural features. The natural-N-linkage-based isostere is more stable to chemical and enzymatic hydrolysis while the side chain length is the same as natural N-linked glycoside residues. The advantage of our method is the employment of commercially available L-aspartic acid as starting material, which can provide a β-amino acid moiety, and the α-carboxy group of which can be transformed to the active isocyanate conveniently and economically. The desired urea- and thiocarbamate-tethered glycosyl β-amino acids can be easily obtained in good yield, respectively, by isocyanate reacting with glycosylamines or glycosylthiols. The rout is concise and no costly reagent is used. These new glycosyl β-amino acids can be used as prospective building blocks for the synthesis of neoglycopeptides.

Experimental section

General remarks

All starting materials and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Reagents were used as purchased. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz instrument, using Me_4Si as an internal standard ($\delta = 0$ ppm). ESI-MS spectra were measured by MicrOTOF-Q III UltiMate 3000. Infrared (IR) spectra were measured by Bruker VERTEX80v FTIR vacuum spectrometer. Thin-layer chromatography (TLC) was performed on precoated plates silica gel GF254 with detection by UV light, Iodine or 0.2% ninhydrin in ethanol followed by heating.

General procedure for compound 7

Compound 7. Compound **5** (2.5 g, 10 mmol) was dissolved in dry THF (30 mL) and cooled to −15 °C. After addition of EtOCOCl (1 mL, 11 mmol) and Et_3N (1.7 mL, 12 mmol), the mixture was stirred for 20 min. A solution of NaN_3 (1.6 g, 25 mmol) in H_2O (5 mL) was added and stirred for 1 h at −10 °C. The solution was then diluted with H_2O and extracted with EtOAc (150 mL). The organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give crude acyl azide **6**. The crude acyl azide **6** was dissolved in toluene (35 mL) and heated to 85 °C under stirring for 3 h. The toluene was removed under reduced pressure to afford isocyanate **7** as clear oil 1.73 g (yield *ca.* 71%). This isocyanate **7** was directly used in the next step without further purification.

The synthesis of compound 9a was described as a representative example

To a solution of compound **7** (0.24 g, 1 mmol) in dry CH_2Cl_2 (8 mL), 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (0.35 g, 1 mmol) was added. The mixture was stirred at room temperature for 45 min until the disappearance of the starting material from the TLC plate (CH_2Cl_2–EtOAc, 1 : 1), and the solvents were evaporated. The residue was purified by silica gel column chromatography (CH_2Cl_2–EtOAc, 1 : 1) to get the desired compound.

Spectroscopic data for compound 9a

Column chromatography: 1 : 1 CH_2Cl_2–EtOAc; white solid; yield: 91%. IR: ν (cm^{-1}) 3354 (br), 2968 (br), 1740, 1545, 1508, 1369, 1221, 1032 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ (ppm) 6.43 (br, 1H, N*H*CONH), 6.20 (br, 1H, NHCON*H*), 5.92 (br, 1H, N*H*COO), 5.45 (br, 1H, NHC*H*NH), 5.30 (t, $J = 9.6$ Hz, 1H, H-3), 5.19 (t, $J = 9.2$ Hz, 1H, H-1), 5.05 (t, $J = 9.6$ Hz, 1H, H-4), 4.91 (t, $J = 9.6$ Hz, 1H, H-2), 4.29 (dd, $J = 12.4$, 4.0 Hz, 1H, H-6a), 4.07 (d, $J = 12.4$ Hz, 1H, H-6b), 3.86 (d, $J = 8.4$ Hz, 1H, H-5), 3.67 (s, 3H, COOCH_3), 2.89 (br, 2H, COCH_2), 2.18–1.98 (m, 12H, 4 × COCH_3), 1.40 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$):

δ (ppm) 171.41, 170.70, 170.61, 170.00, 169.64, 155.88, 154.92, 80.14, 79.70, 73.22, 73.09, 70.59, 68.28, 61.88, 55.90, 51.99, 39.18, 28.27, 20.67, 20.63, 20.55 ppm. ESI-Q-TOF MS (*m*/*z*): calcd for $C_{24}H_{37}N_3O_{14}Na$: 614.2168 ([M + Na]$^+$), found: 614.2536.

Spectroscopic data for compound 9b

An equivalent mole triethylamine was used in the reaction. Column chromatography: 1 : 1 CH_2Cl_2–EtOAc; white solid; yield: 87%. IR: *ν* (cm^{-1}) 3358 (br), 2922 (br), 1734, 1551, 1369, 1229, 1036 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.10 (d, J = 3.6 Hz, 1H, N*H*COO), 5.68–5.63 (m, 3H, N*H*CON*H*, H-1), 5.28–5.11 (m, 3H, NHC*H*NH, H-3, H-4), 4.20 (td, J = 7.2, J = 4 Hz, 1H, H-2), 4.18 (dd, J = 12.4, J = 4 Hz, 1H, H-6a), 4.01–3.93 (m, 2H, H-5, H-6b), 3.64 (s, 3H, COOCH_3), 2.76 (t, J = 4.8 Hz, 2H, COCH_2), 2.14–1.97 (m, 12H, 4 × COCH_3), 1.34 (s, 9H C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.35, 171.12, 170.77, 169.21, 168.86, 156.21, 155.35, 91.15, 80.41, 71.56, 69.65, 67.78, 61.70, 55.99, 52.08, 51.57, 39.29, 28.24, 21.04, 20.73, 20.70, 20.59. ESI-Q-TOF MS (*m*/*z*): calcd for $C_{24}H_{37}N_3O_{14}Na$: 614.2168 ([M + Na]$^+$), found: 614.2464.

Spectroscopic data for compound 9c

Column chromatography: 1 : 1 CH_2Cl_2–EtOAc; white solid; yield: 90%. IR: *ν* (cm^{-1}) 3356 (br), 2976 (br), 1740, 1542, 1367, 1223, 1043 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.13 (d, J = 8.0 Hz, 1H, N*H*CONH), 5.80–5.74 (m, 2H, NHCON*H*, N*H*COO), 5.36–5.37 (m, 2H, NHC*H*NH, H-3), 5.02–5.09 (m, 3H, H-1, H-2, H-4), 4.08–4.03 (m, 2H, H-6a,b), 4.01–3.97 (m, 1H, H-5), 3.63 (s, 3H, COOCH_3), 2.85 (br, 2H, COCH_2), 2.08–1.92 (m, 12H, 4 × COCH_3), 1.37 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.37, 170.99, 170.44, 170.13, 169.89, 155.61, 154.95, 80.26, 71.90, 71.17, 68.28, 67.26, 61.11, 60.42, 56.02, 51.98, 39.09, 28.30, 20.75, 20.67, 20.59, 20.55. ESI-Q-TOF MS (*m*/*z*): calcd for $C_{24}H_{37}N_3O_{14}Na$: 614.2168 ([M + Na]$^+$), found: 614.2527.

Spectroscopic data for compound 9d

Column chromatography: 1 : 1 CH_2Cl_2–EtOAc; white solid; yield: 88%. IR: *ν* (cm^{-1}) 3362 (br), 2966 (br), 1738, 1510, 1367, 1225, 1034 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.30 (br, 1H, N*H*CONH), 6.04–5.88 (m, 2H, NHCON*H*, N*H*COO), 5.39 (br, 1H, NHC*H*NH), 5.38–5.33 (m, 3H, H-1, H-1′, H-3′), 5.19 (t, J = 9.2 Hz, H-3), 5.06 (td, J = 2.0, 10.0 Hz, 1H, H-2), 4.87 (ddd, J = 2.0, 5.6, 14.4 Hz, 1H, H-2′), 4.77 (t, J = 9.2 Hz, 1H, H-4′), 4.44 (d, J = 12.4 Hz, 1H, H-4), 4.23 (m, 2H, H-6a, H-6′a), 4.06–3.93 (m, 3H, H-6b, H-5), 3.84–3.81 (m, 1H, H-5′), 3.69 (d, J = 2.8 Hz, 3H, COOCH_3), 2.89 (br, 2H, CH_2CO), 2.13–2.00 (m, 21H, 7 × COCH_3), 1.42 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.36, 170.77, 170.65, 170.58, 170.55, 169.86, 169.84, 169.49, 155.77, 154.97, 95.58, 80.21, 79.40, 75.59, 73.50, 72.80, 71.34, 69.98, 69.32, 68.45, 67.97, 62.98, 61.43, 55.94, 51.98, 39.17, 28.33, 28.28, 20.87, 20.82, 20.66, 20.60, 20.57. ESI-Q-TOF MS (*m*/*z*): calcd for $C_{36}H_{53}N_3O_{22}Na$: 902.3013 ([M + Na]$^+$), found: 902.3429.

Spectroscopic data for compound 9e

Column chromatography: 1 : 1 CH_2Cl_2–EtOAc; white solid; yield: 85%. IR: *ν* (cm^{-1}) 3333 (br), 2972 (br), 1738, 1691, 1504, 1366, 1229, 1040 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.27 (br, 1H, N*H*CONH), 6.05–5.87 (m, 2H, NHCON*H*, N*H*COO), 5.47 (br, 1H, NHC*H*NH), 5.36 (br, 1H, H-1′), 5.28 (t, J = 9.2 Hz, 1H, H-1), 5.14–5.08 (m, 2H, H-2′, H-3), 4.95 (dd, J = 10.4, 2.8 Hz, 1H, H-4′), 4.84 (t, J = 9.2 Hz, 1H, H-2), 4.49 (d, J = 7.6, 1H, H-3′), 4.45 (d, J = 12 Hz, 1H, H-4), 4.16–4.05 (m, 3H, H-6a,b, H-6′a), 3.90 (t, J = 6.8 Hz, 1H, H-6′b), 3.81–3.73 (m, 2H, H-5, H-5′), 3.69–3.70 (m, 3H, OCH_3), 2.89–2.89 (br, 2H, CH_2CO), 2.16–1.96 (m, 21H, 7 × COCH_3), 1.43 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.35, 170.91, 170.48, 170.37, 170.21, 170.13, 169.51, 169.05, 155.69, 154.95, 100.93, 80.15, 79.72, 76.06, 74.13, 72.96, 71.03, 70.91, 70.60, 69.01, 66.62, 62.15, 60.76, 55.92, 51.96, 39.22, 28.30, 20.87, 20.78, 20.67, 20.64, 20.59, 20.5. ESI-Q-TOF MS (*m*/*z*): calcd for $C_{36}H_{53}N_3O_{22}Na$: 902.3013 ([M + Na]$^+$), found: 902.3423.

Spectroscopic data for compound 11a

Column chromatography: 1 : 2 petroleum ether–EtOAc; white solid; yield: 92%. IR: *ν* (cm^{-1}) 3333 (br), 2966 (br), 1740, 1695, 1495, 1369, 1042 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.77 (br, 1H, SCO*NH*), 5.68 (br, 2H, OCON*H*, C*H*(NH)$_2$), 5.29–5.25 (m, 2H, H-1, H-3), 5.16–5.11 (m, 2H, H-2, H-4), 4.31 (d, J = 12.4 Hz, 1H, H-6a), 4.11 (d, J = 12.8 Hz, 1H, H-6b), 3.83 (d, J = 9.6 Hz, 1H, H-5), 3.73 (s, 3H, COOCH_3), 2.90 (br, 2H, COCH_2), 2.09, 2.03, 2.01 (3s, 12H, 4 × COCH_3), 1.44 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.18, 170.69, 170.02, 169.44, 169.40, 162.89, 82.04, 80.68, 76.21, 73.92, 69.02, 67.84, 61.66, 56.26, 52.18, 38.65, 28.26, 20.72, 20.62, 20.57. ESI-Q-TOF MS (*m*/*z*): calcd for $C_{24}H_{36}N_2O_{14}SNa$: 631.1779 ([M + Na]$^+$), found: 631.1746.

Spectroscopic data for compound 11b

Column chromatography: 1 : 2 petroleum ether–EtOAc; white solid; yield: 89%. IR: *ν* (cm^{-1}) 3333 (br), 2957 (br), 1736, 1695, 1499, 1367, 1221, 1045 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.19 (br, 1H, SCON*H*), 5.95–5.93 (m, 1H, N*H*COO), 5.66 (br, 1H, C*H*(NH)$_2$), 5.47 (br, 1H, H-1), 5.30 (br, 2H, H-3, H-2), 5.16 (br, 1H, H-4), 4.15–4.13 (m, 3H, H-5, H-6), 3.72 (s, 3H, COOCH_3), 2.92 (br, 2H, CH_2CO), 2.16, 2.05, 1.99 (3s, 12H, 4 × COCH_3), 1.44 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.14, 170.36, 170.18, 169.86, 169.64, 163.16, 154.42, 82.26, 80.42, 74.73, 71.83, 67.26, 66.53, 61.18, 56.47, 52.03, 38.69, 28.20, 20.64, 20.57, 20.55, 20.48. ESI-Q-TOF MS (*m*/*z*): calcd for $C_{24}H_{36}N_2O_{14}SNa$: 631.1779 ([M + Na]$^+$), found: 631.1756.

Spectroscopic data for compound 11c

Column chromatography: 1 : 1 CH_2Cl_2–EtOAc; white solid; yield: 86%. IR: *ν* (cm^{-1}) 3339 (br), 2968 (br), 1740, 1501, 1369, 1219, 1034 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.95 (br, 1H, SCON*H*), 5.78 (br, 1H, N*H*COO), 5.65 (br, 1H, *CH*(NH)$_2$), 5.40 (br, 1H, H-1′), 5.34 (d, J = 9.6 Hz, 1H, H-1), 5.29 (d, J = 12.0 Hz, 1H, H-3′), 5.06 (t, J = 9.6 Hz, 1H, H-3), 4.98 (t, J = 9.6 Hz, 1H, H-2), 4.86 (d, J = 10.8 Hz, 1H, H-2′), 4.46 (d, J = 12.4 Hz, 1H, H-4′), 4.26–4.23 (m, 2H, H-6a, H-6′a), 4.12 (dd, J = 6.4, 13.6 Hz, 1H, H-4), 4.05–4.02 (m, 2H, H-6b, H-6′b), 3.94 (d, J = 9.6 Hz, 1H, H-5′), 3.82 (d, J = 8.4 Hz, 1H, H-5), 3.72 (s, 3H, COOCH_3), 2.91 (br, 2H, CH_2CO), 2.16–2.00 (m, 21H, 7 × COCH_3), 1.44 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.14, 171.02,

170.57, 170.51, 169.92, 169.84, 169.65, 169.45, 162.84, 154.37, 95.64, 81.56, 80.57, 76.39, 76.18, 72.57, 70.01, 69.30, 68.50, 67.97, 62.76, 61.46, 60.36, 56.39, 52.10, 38.63, 28.22, 20.99, 20.82, 20.78, 20.63, 20.54. ESI-Q-TOF MS (m/z): calcd for $C_{36}H_{52}N_2O_{22}SNa$: 919.2624 ($[M + Na]^+$), found: 919.2585.

Spectroscopic data for compound 11d

Column chromatography: 1 : 1 CH_2Cl_2–EtOAc; white solid; yield: 83%. IR: ν (cm^{-1}) 3337 (br), 2978 (br), 1740, 1501, 1369, 1219, 1043. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.64 (br, 1H, SCON*H*), 5.58 (br, 2H, N*H*COO, C*H*$(NH)_2$), 5.28 (d, J = 2.7 Hz, 1H, H-3′), 5.20–5.12 (m, 2H, H1, H-1′), 5.06–4.95 (m, 2H, H-3, H-2′), 4.87 (dd, J = 10.4, 3.2 Hz, 1H, H-4′), 4.41–4.38 (m, 2H, H-2, H-4′), 4.09–3.99 (m, 4H, H-6′a,b, H-6a,b), 3.82–3.75 (m, 2H, H-5, H-5′), 3.66 (s, 3H, COOCH_3), 2.83 (br, 2H, CH_2CO), 2.08–1.90 (m, 21H, 7 × COCH_3), 1.36 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.17, 170.39, 170.38, 170.17, 170.08, 169.68, 169.57, 169.01, 162.88, 154.33, 100.94, 81.85, 80.64, 75.69, 73.65, 71.01, 70.72, 69.36, 69.00, 66.64, 61.96, 60.88, 60.40, 56.27, 52.15, 38.61, 28.25, 21.05, 20.99, 20.87, 20.76, 20.64, 20.61, 20.51. ESI-Q-TOF MS (m/z): calcd for $C_{36}H_{52}N_2O_{22}SNa$: 919.2624 ($[M + Na]^+$), found: 919.2681.

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