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Design and synthesis of novel multivalent mannosides targeting the mannose receptor

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Abstract—According to the characteristics of C-type lectin-like domains in the mannose receptor (MR), a novel design of multivalent mannosides targeting the MR was accomplished. Beginning with a divalent mannoside as the sugar unit, a series of multivalent mannosides with variations in both valence and space were synthesized in a convergent approach. The synthetic multivalent mannosides are to be explored to study MR–sugar binding events.

Keywords: Multivalent; Mannoside; Mannose receptor

1. Introduction

It has been widely accepted that carbohydrate–protein interactions play a crucial role in a large number of biological processes, such as pathogenic infections, receptor-mediated endocytosis, inflammation and metastasis.[1–3] Binding affinities for individual carbohydrate–protein interactions are generally weak, with dissociation constants in the millimolar range. Since most proteins possess multiple carbohydrate-recognition domains and typically exist as oligomeric structures, this limitation is often overcome through multivalency.[4–8]

The mannose receptor (MR) found on peripheral and bone marrow macrophages, dendritic cells and sinusoidal liver cells is a multi-domain membrane-associated protein that recognizes and internalizes a variety of pathogenic microorganisms and potentially harmful glycoproteins with terminal mannose, fucose, 2-acetamido-2-deoxy-D-glucose (*N*-acetylglucosamine), or glucose residues.[9,10] It has been assumed that MR enhances pathogen uptake by phagocytosis, regulates levels of endogenous proteins, and removes pituitary hormones such as lutropin and thyrotropin from the circulation.[11–15] Recent studies indicate that the MR may be involved in HIV-1 infections[16,17] and HIV-1 neuropathogenesis.[18,19]

The extracellular region of the mannose receptor consists of an N-terminal, cysteine-rich domain and a fibronectin type II repeat unit as well as eight C-type lectin-like domains (CTLDs). In contrast to other multi-domain receptors, the eight CTLDs, which are responsible for specificity as well as affinity for oligosaccharide ligands, locate within a single polypeptide chain.[20] Recent structure–function studies propose that CTLDs 1–3 have at most very weak affinity for carbohydrates; therefore, CTLDs 4–8 are required for high affinity binding to mannose-terminated ligands, but CTLD 4 is the only CTLD to display a monosaccharide specificity characteristic when expressed in isolation.[21] In addition, CTLDs 5–8 retain weak affinity, while CTLDs 6–8 do not present binding activity. This suggests a weak activity located in CTLD 5. Sequence examination reveals that only CTLD 4 and CTLD 5 contain the residues required for Ca^{2+}-dependent sugar binding.[22] Proteolysis experiments indicate the presence of close contacts between three pairs of domains (CTLD 1 and 2, CTLD 4 and 5, CTLD 7 and 8) and exposed linker regions separating CTLD 3 and 6 from their neighbouring domains.[23] The mannose receptor is like

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other carbohydrate-binding proteins, in which several CTLDs, each with weak affinity for single sugars, are clustered to achieve high affinity binding to oligosaccharides.[21,22] To further study the multivalent binding properties of the MR, we describe herein the design and synthesis of novel mannose derivatives having well-organized and characterized multivalencies.

2. Results and discussion

As mentioned above, the CTLDs of MR exist as three close contact pairs separated by CTLD 3 and 6, of which CTLD 4 and 5 are two domains most important for binding oligosaccharides. Since each CTLD embeds only one mannose binding site, we first constructed a divalent mannoside by using a flexible linker, and then a series of multivalent mannosides based on the divalent compound were synthesized, which may bridge multiple copies of MR, or/and bind MR in chelating manner.

Scheme 1 summarizes the steps for the synthesis of the divalent mannoside. Treating mannosyl trichloroacetimidate **1**[24] with readily available 2-azido-1,3-propandiol (**2**)[25] in the presence of $BF_3{\cdot}Et_2O$ produces divalent mannoside **3** in excellent yields. This divalent mannoside carries an azide group at the focal point of the scaffold, which can be easily converted into an amino group and further coupled with different poly-carboxylic acids to produce multivalent mannosides. There are diverse approaches to reduce the azide, among which hydrogenation is most easily operated. Hydrogenation of **3** on Pd/C was sluggish and gave the desired amine **4** in low yield. Other reducing agents such as H_2S and Ph_3P also did not give satisfactory results. Finally, using $Pd(OH)_2$ furnished **4** in good yields within 3 h. Although a little amount of starting material remains, prolonging the reaction time only produced undesired products. Without purification, treating **4** with spacer arms such as butanedioic acid, octanedioic acid, *N*-Cbz-glutamic acid and 1,3,5-benzenetricarboxylic acid in dry THF in the presence of HOBt and DCC gives tetra- and hexavalent mannosides (**7**, **8**, **12** and **16**) in yields of 80–90% (Scheme 2).

The free amine product **13** was obtained in nearly quantitative yield after treating **12** with H_2 over Pd/C in CH_3OH. Coupling of **13** with octanedioic acid gave octavalent mannosides **18**.

All the target compounds were obtained after O-deacetylation under classical CH_3ONa–CH_3OH conditions in essentially quantitative yields.

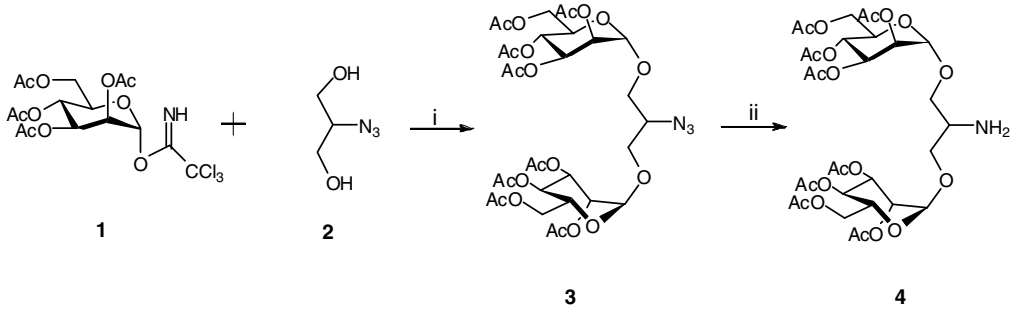
3. Experimental

3.1. General methods

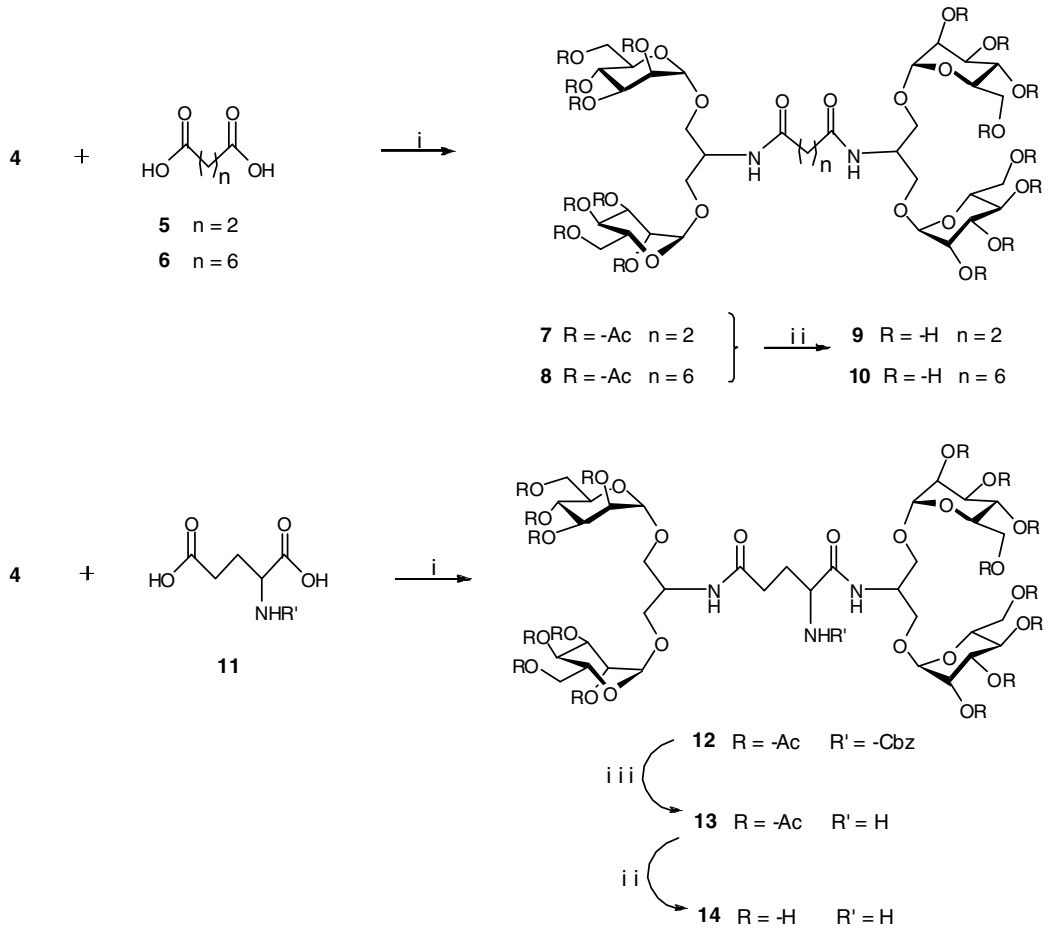
Optical rotations were recorded using an Optical Activity AA-10R type polarimeter. NMR spectra were recorded with Varian JEOL-300 spectrometers, with $CDCl_3$ and D_2O as solvents. Mass spectra were recorded with an IBI-MDS Sciexciex Q-star and Autospec-Ultima ETOF mass spectrometers. Purity of the products was verified by TLC on Silica Gel GF_{254} (Hai Yang Chemical Factory, Qingdao, Shandong, PR China). Column chromatography was performed on Silica Gel H_{60} (Hai Yang Chemical Factory, Qingdao, Shandong, PR China). Solvents were purified by standard procedures.

3.2. Synthesis of multivalent mannosides

3.2.1. 2-Azido-1,3-di-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)propane (3). To a solution of 2-azido-1,3-propandiol (**2**, 317 mg, 2.71 mmol) and mannosyl trichloroacetimidate (**1**, 4.00 g, 8.13 mmol) in dry CH_2Cl_2 (40 mL) were added 4 Å molecular sieves (3.00 g). The suspension was stirred under nitrogen for 30 min, then cooled to 0 °C before the addition of a solution of $BF_3{\cdot}Et_2O$ complex (206.0 μL, 1.63 mmol) in CH_2Cl_2 (1 mL). The temperature was maintained for 2 h at 0 °C, and then the mixture was stirred at room temperature overnight. The mixture was then diluted with CH_2Cl_2 (100 mL) and washed with aq $NaHCO_3$ and water, dried



Scheme 1. Synthesis of divalent mannoside. Reagents and conditions: (i) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 85%; (ii) $Pd(OH)_2$, 1:1 EtOAc–EtOH, H_2 (0.4 MPa), rt.



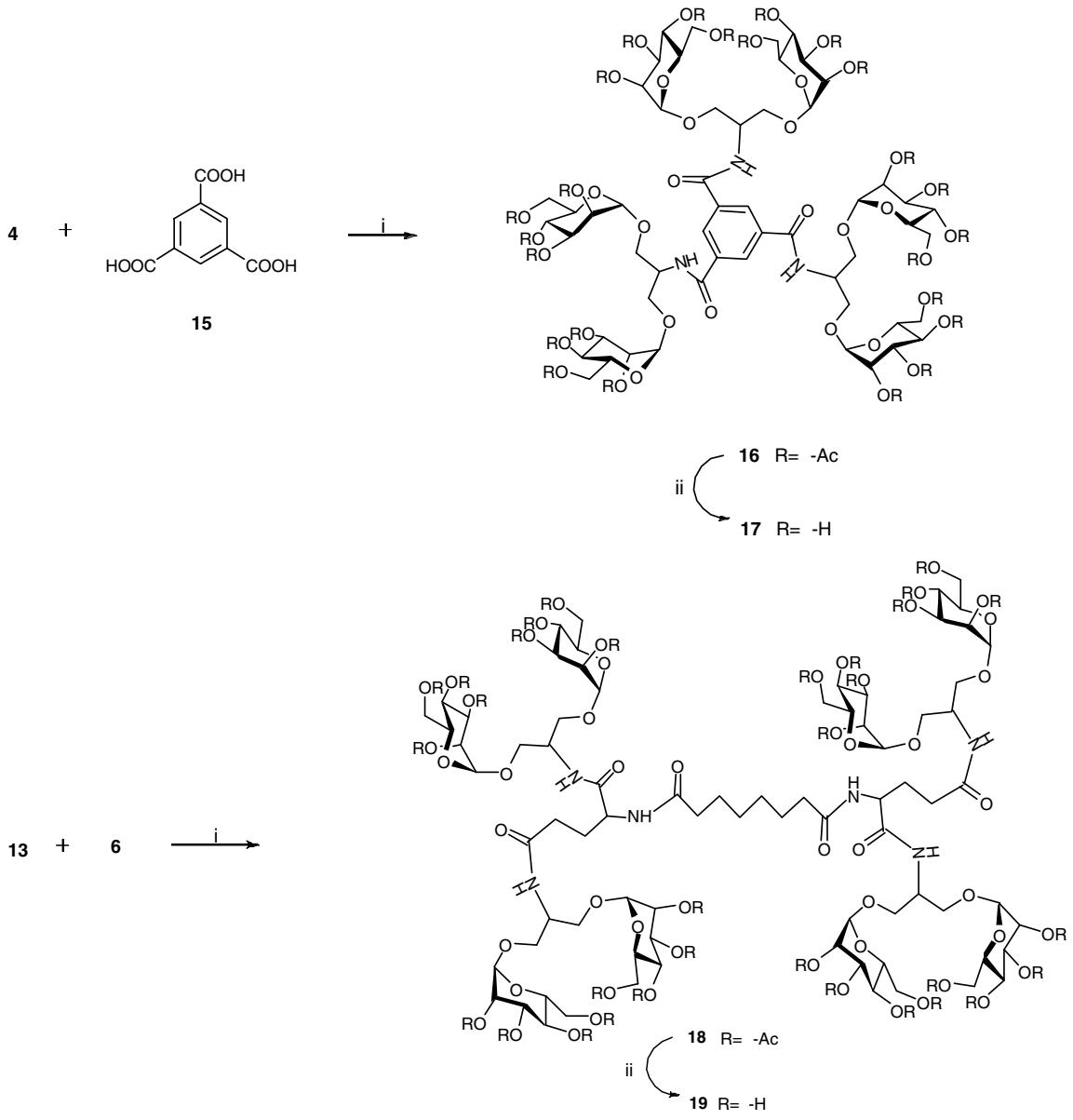
Scheme 2. Synthesis of tetra-, hexa- and octavalent mannosides. Reagents and conditions: (i) HOBt, DCC, THF, rt; (ii) CH_3ONa, CH_3OH, rt; (iii) Pd/C, H_2 (0.4 MPa), CH_3OH, rt.

(Na_2SO_4) and evaporated under diminished pressure. The crude product was purified by flash chromatography with 2:1 petroleum ether (60–90 °C)–ethyl acetate as eluent to afford 1.79 g of **3** as white foam in an 85% yield: $[\alpha]_D$ +47.3 (*c* 0.93, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.26–5.32 (m, 3H, H-2, H-3, H-4), 4.88 (d, $J = 1.2$ Hz, 1H, H-1), 4.32 (dd, $J = 5.1$ Hz, 12 Hz, 1H), 4.11–4.17 (m, 1H), 4.03–4.06 (m, 1H), 3.83–3.89 (m, 2H), 3.60–3.65 (m, 1H), 2.00, 2.05, 2.12, 2.17 (s, 12H, 4 CH_3CO–); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7–170.6 (C=O), 97.9, 97.8, 69.1, 68.9, 68.7, 67.3, 67.1, 65.8, 65.8, 62.3, 59.6, 20.6–20.8. HRESIMS Calcd for $C_{31}H_{43}N_3O_{20}$ $[M+H]^+$, *m*/*z* 778.2513. Found: *m*/*z* 778.2513; $[M+NH_4]^+$, *m*/*z* 795.2778. Found: *m*/*z* 795.2767; $[M+Na]^+$, *m*/*z* 800.2332. Found: *m*/*z* 800.2339.

3.2.2. General procedure for coupling between amines (4 and 13) and acids (5, 6, 11 and 15). *The preparation of* **4**: To a solution of compound **3** (214 mg, 0.28 mmol) in 1:1 EtOAc–EtOH (6 mL) was added $Pd(OH)_2$ (50 mg, 50% moisture), and the mixture was stirred under 0.4 MPa of H_2 for 3 h at room temperature. The mixture was then filtered through Celite, and the filtrate was concentrated under reduced pressure. The white foam **4** was used in the coupling reaction without any purification.

Preparation of **13**: To a solution of compound **12** (200 mg, 0.11 mmol) in MeOH (10 mL) was added Pd/C (50 mg, 50% moisture), and the mixture was stirred under 0.4 MPa of H_2 for 2 h at room temperature. The mixture was then filtered through Celite, and the filtrate was concentrated under reduced pressure. The white foam **13** was used in the coupling reaction without further purification.

Coupling reaction: To a solution of acids (0.10 mmol) in anhyd THF (3.0 mL) at 0 °C was added HOBt ($2 \times N_{COOH}$ mmol) and DCC ($2 \times N_{COOH}$ mmol). To this mixture was added dropwise a solution of amines ($0.11 \times N_{COOH}$ mmol) in dry THF (10 mL) dropwise. The mixture was stirred for 2 h at 0 °C, then allowed to rise to room temperature with stirring for an additional 36 h. The mixture was concentrated, and the residue was then diluted with CH_2Cl_2 (20 mL). The solution was filtered, and the filtrate was washed with aq $NaHCO_3$ and water, dried (Na_2SO_4) and evaporated



Scheme 2 (*continued*)

under diminished pressure. The crude product was purified by flash chromatography.

3.2.2.1. *N*-{2-[1,3-Di-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)]propanyl}butanediamide (7). Yield: 134 mg (85%), as a white foam. $[\alpha]_D$ +48.2 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.79 (d, $J = 8.7$ Hz, 2H, –NHCO–), 5.12–5.33 (m, 12H, 4 × H-2, 4 × H-3, 4 × H-4), 4.84–4.87 (m, 4H, 4 × H-1), 4.28–4.44 (m, 6H), 4.08–4.15 (m, 4H), 4.00–4.04 (m, 4H), 3.78–3.88 (m, 4H), 3.61 (dd, $J = 6.6$ Hz, 9.9 Hz, 2H), 3.52 (dd, $J = 6.0$ Hz, 9.6 Hz, 2H), 2.61 (s, 4H, $-COCH_2-$), 1.99, 1.99, 2.05, 2.07, 2.11, 2.13, 2.15 (s, 48H, CH_3CO-); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7–172.6 (C=O), 97.9, 69.2, 69.0, 68.8, 66.9, 66.6, 65.8, 62.2, 47.8 (–*C*H(NHCO)–), 32.0 ($-CH_2CO$), 20.6–20.8 (CH_3CO-); ESI-TOF MS: Calcd for $C_{66}H_{92}N_2O_{42}$ *m*/*z* 1584.5. Found: *m*/*z* 1585.5 $[M+H]^+$, 1602.5 $[M+NH_4]^+$, 1607.4 $[M+Na]^+$.

3.2.2.2. *N*-{2-[1,3-Di-(2,3,4,6-tetra-*O*-acetyl-α-D- mannopyranosyloxy)]propanyl}octane-1,8-diamide (8). Yield 136 mg (83%), as a white foam. $[\alpha]_D$ +53.1 (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.98 (d, $J = 8.7$ Hz, 1H, –NHCO–), 5.22–5.33 (m, 6H, 2 × H-2, 2 × H-3, 2 × H-4), 4.87 (d, $J = 1.2$ Hz, 1H, H-1), 4.84 (s, 1H, H-1′), 4.27–4.37 (m, 3H), 4.08–4.15 (m, 2H), 3.96–4.00 (m, 2H), 3.87 (dd, $J = 4.2$ Hz, 10.2 Hz, 1H), 3.79 (dd, $J = 5.4$ Hz, 10.5 Hz, 1H), 3.69 (dd, $J = 4.5$ Hz, 10.5 Hz, 1H), 3.48 (dd, $J = 6.3$ Hz, 9.6 Hz, 1H), 2.18–2.25 (m, 2H, $-COCH_2-$), 2.00, 2.06, 2.11, 2.16 (s, 24H, CH_3CO-), 1.65 (br s, 2H, $-CH_2-$), 1.37

(br s, 2H, –CH_2–); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6–172.8 (C=O), 98.0, 97.7, 69.1, 69.0, 68.7, 66.0, 65.7, 62.2, 47.5 (–*C*H(NHCO)–), 36.3 (–*C*H_2CO), 28.7 (–CH_2–), 25.3 (–CH_2–), 20.6–20.8 (*C*H_3CO–); ESI-TOF MS: Calcd for $C_{70}H_{100}N_2O_{42}$ *m*/*z* 1640.6. Found: *m*/*z* 1641.5 $[M+H]^+$, 1658.6 $[M+NH_4]^+$, 1663.5 $[M+Na]^+$.

3.2.2.3. *N*-{2-[1,3-Di-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)]propanyl}-2-carbo benzyloxyamino-pentane-1,5-diamide (12). Yield 148 mg (85%), as a white foam. $[\alpha]_D$ +44.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.35 (m, 5H, Ar), 6.62 (d, *J* = 8.7 Hz, 1H, –NHCO–), 6.47 (d, *J* = 5.7 Hz, 1H, –NHCO–), 5.13–5.33 (m, 4 × H-2, 4 × H-3, 4 × H-4, Ph–CH_2–), 5.00 (d, *J* = 12.9 Hz, Ph–CH_2–), 4.84–4.88 (4H, 4 × H-1), 4.28–4.37 (m, 6H), 4.08–4.22 (m, 5H), 4.00 (br s, 4H), 3.78–3.85 (m, 4H), 3.62–3.65 (m, 2H), 3.45–3.52 (m, 2H), 2.46 (br s, 2H, –$COCH_2$–), 1.95–2.19 (m, 50H, 16 CH_3CO–, –*C*H_2CHNHCbz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7–171.6 (C=O), 136.4, 128.4, 128.0, 127.9, 97.9, 97.7, 70.0, 68.7, 68.6, 66.6, 65.8, 62.2, 54.4, 47.8–48.2 (2C, –*C*H(NHCO)–), 28.1–31.9 (2C, –*C*H_2CO, –*C*H_2CHNH–), 20.6–20.8 (*C*H_3CO–). ESI-TOF MS: Calcd for $C_{75}H_{101}N_3O_{44}$ *m*/*z* 1747.6. Found: *m*/*z* 1748.6 $[M+H]^+$, 1765.6 $[M+NH_4]^+$, 1770.6 $[M+Na]^+$.

3.2.2.4. *N*-{2-[1,3-Di-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)]propanyl}benzene-1,3,5-triamide (16). Yield 181 mg (75%), as a white foam. $[\alpha]_D$ +53.1 (*c* 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (s, 1H, Ar), 7.45 (d, *J* = 8.1 Hz, 1H, –NHCO–), 5.22–5.31 (m, 6H, 2 × H-2, 2 × H-3, 2 × H-4), 4.90–4.93 (2s, 2 × H-1), 4.50–4.65 (m, 1H), 4.25–4.31 (m, 2H), 4.12–4.18 (m, 2H), 3.96–4.03 (m, 4H), 3.83 (dd, *J* = 6.3 Hz, 10.2 Hz, 1H), 3.66 (dd, *J* = 7.2 Hz, 9.6 Hz, 1H), 1.97, 1.99, 2.01, 2.02, 2.08, 2.12, 2.14, 2.15 (s, 24H, CH_3CO–); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2–170.8 (C=O), 135.1, 129.1, 97.8, 97.5, 69.1, 69.0, 68.9, 66.5, 65.8, 65.7, 62.3, 49.2 (–*C*H(NHCO)–), 20.6–20.7 (*C*H_3CO–); MALDI-TOF MS: Calcd for $C_{102}H_{135}N_3O_{63}$ *m*/*z* 2409.7. Found: *m*/*z* 2432.5 $[M+Na]^+$, 2448.5 $[M+K]^+$.

3.2.2.5. *N*-{2-*N*-{2-[1,3-Di-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)]propanyl}pentane-1,5-diamidyl}-octane-1,8-diamide (18). Yield 236 mg (70%), as a white foam. $[\alpha]_D$ +31.5 (*c* 8.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.4 Hz, 1H, –NHCO–), 7.24 (d, *J* = 6.3 Hz, 1H, –NHCO–), 6.87 (d, *J* = 8.7 Hz, 1H, –NHCO–), 5.21–5.34 (m, 12H, 4 × H-2, 4 × H-3, 4 × H-4), 4.85–4.90 (m, 4H, 4 × H-1), 4.31–4.35 (m, 7H), 4.02–4.16 (m, 9H), 3.85 (br s, 3H), 3.47–3.68 (m, 4H), 2.69 (br s, 2H, –CH_2–), 2.42–2.44 (br s, 2H, –CH_2–), 1.98–2.18 (m, 50H, 16 CH_3CO–, –*C*H_2CH(CO)NHCbz), 1.59 (br s, 2H, –CH_2–), 1.31 (br s, 2H, –CH_2–); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6–173.4 (C=O), 97.8, 97.6, 69.2, 69.0, 68.6, 66.5, 65.7, 62.1, 52.6, 48.0, 47.7, 36.1, 32.0, 30.8, 28.9, 28.4, 25.4, 20.6–20.7 (*C*H_3CO–). MALDI-TOF MS: Calcd for $C_{142}H_{200}N_6O_{86}$ *m*/*z* 3365.1. Found: *m*/*z* 3387.8 $[M+Na]^+$, 3404.0 $[M+K]^+$.

3.2.3. General procedure for O-deacetylation (7, 8, 13, 16 and 18). A catalytic amount of sodium was added to a solution of compound (100 mg) in dry MeOH (10 mL). The mixture was stirred at room temperature for 12 h, and then neutralized with H^+ cation-exchange resin. The solution was filtered and concentrated, and the residue was dissolved in 20 mL of water and lyophilized to give a white foam.

3.2.3.1. *N*-{2-[1,3-Di-α-D-mannopyranosyloxy]propanyl}butane-1,4- diamide (9). Yield 57.0 mg (99%), as a white foam. $[\alpha]_D$ +76.5 (*c* 11.5, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 4.65–4.71 (m, 2H, 2 × H-1), 4.09 (br s, 1H), 3.41–3.75 (m, 16H), 2.38 (s, 2H, –$COCH_2$–); ^{13}C NMR (75 MHz, D_2O): δ 175.1 (C=O), 100.7, 100.2, 73.4, 71.0, 70.5, 67.3, 67.0, 66.9, 61.4, 49.4 (–*C*H(NHCO)–), 49.3 (–*C*H(NHCO)–), 31.3 (–CO*C*H_2–); HRESIMS: Calcd for $C_{34}H_{60}N_2O_{26}$ $[M+H]^+$, *m*/*z* 913.3507. Found: *m*/*z* 913.3503; $[M+Na]^+$, *m*/*z* 935.3327. Found: *m*/*z* 935.3338.

3.2.3.2. *N*-[2-(1,3-Di-α-D-mannopyranosyloxy)propanyl]octane-1,8-diamide (10). Yield 45 mg (99%), as a white foam. $[\alpha]_D$ +73.0 (*c* 11.5, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 4.60–4.77 (m, 2H, 2 × H-1), 4.11 (m, 1H), 3.42–3.74 (m, 16H), 2.09 (m, 2H, –$COCH_2$–), 1.41 (br s, 2H, –CH_2–), 1.14 (br s, 2H, –CH_2–); ^{13}C NMR (75 MHz, D_2O): δ 177.7 (C=O), 100.8, 100.2, 73.4, 71.1, 71.0, 70.5, 67.2, 66.9, 61.4, 49.4 (–*C*H-(NHCO)–), 49.2 (–*C*H(NHCO)–), 36.3 (–CO*C*H_2–), 28.4 (–CH_2–), 25.9 (–CH_2–); HRESIMS: Calcd for $C_{38}H_{68}N_2O_{26}$ $[M+H]^+$, *m*/*z* 969.4133. Found: *m*/*z* 969.4122; $[M+Na]^+$, *m*/*z* 991.3953. Found: *m*/*z* 991.3937.

3.2.3.3. *N*-[2-(1,3-Di-α-D-mannopyranosyloxy)propanyl]-2-carbobenzyloxyamino-pentane-1,5-diamide (14). Yield 57 mg (98%), as a white foam. $[\alpha]_D$ +41.9 (*c* 8.6, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 4.60–4.65 (m, 4H, 4 × H-1), 4.12–4.14 (m, 2H), 3.90 (br s, 1H), 3.43–3.76 (m, 32H), 2.28 (br s, 2H), 1.97–2.00 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ 174.4, 169.8, 100.7, 100.3, 73.5, 71.0, 70.4, 69.6, 67.2, 66.7, 61.4, 53.1, 49.6, 49.4, 31.4, 27.7; HRESIMS: Calcd for $C_{35}H_{63}N_5O_{26}$ $[M+H]^+$, *m*/*z* 942.3773. Found: *m*/*z* 942.3734; $[M+Na]^+$, *m*/*z* 964.3592. Found: *m*/*z* 964.3560.

3.2.3.4. *N*-[2-(1,3-Di-α-D-mannopyranosyloxy)propanyl]benzene-1,3,5- triamide (17). Yield 57 mg (98%), as a white foam. $[\alpha]_D$ +48.0 (*c* 5.0, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 8.12 (s, Ar), 4.65–4.72 (m, 2H, 2 × H-1). 4.39 (br s, 1H), 3.42–3.77 (m, 16H); ^{13}C NMR (75 MHz, D_2O): δ 169.6, 135.4, 129.9, 100.9, 100.3, 73.5, 71.0, 70.5, 67.2, 67.0, 61.4, 50.4, 49.4; HR-ESIMS: Calcd for $C_{54}H_{87}N_3O_{39}$ $[M+H]^+$, *m*/*z* 1402.4990. Found: *m*/*z* 1402.4904.

3.2.3.5. *N*-{2-*N*-[2-(1,3-Di-α-D-mannopyranosyloxy)-propanyl]pentane-1,5-diamidyl}octane-1,8-diamide (19). Yield 59 mg (99%), as a white foam. $[\alpha]_D$ +33.0 (*c* 10.9, H_2O); ^1H NMR (300 MHz, D_2O): δ 4.55–4.80 (m, 4H, 4 × H-1), 4.12 (br s, 3H), 3.42–3.75 (m, 32H), 2.10–2.21 (m, 4H), 1.78–1.90 (m, 2H), 1.42 (br s, 2H), 1.15 (br s, 2H); ^{13}C NMR (75 MHz, D_2O): δ 177.7, 175.3, 174.0, 100.8, 100.7, 100.2 (2C), 73.4, 71.1, 71.0, 70.5, 67.2, 67.0, 61.5, 53.9, 49.4, 35.9, 32.5, 28.5, 28.0, 25.7; HRESIMS: Calcd for $C_{78}H_{136}N_6O_{54}$, $[(M+H+K)/2]^+$ *m*/*z* 1030.3898. Found: *m*/*z* 1030.3837.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.08.017.

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