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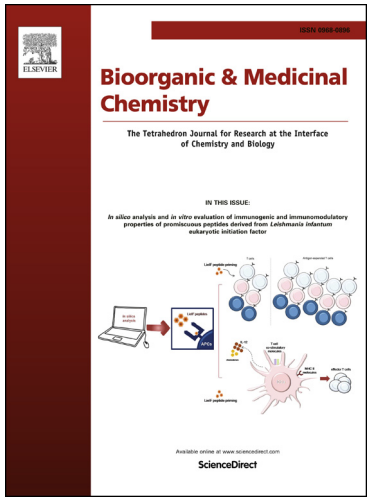

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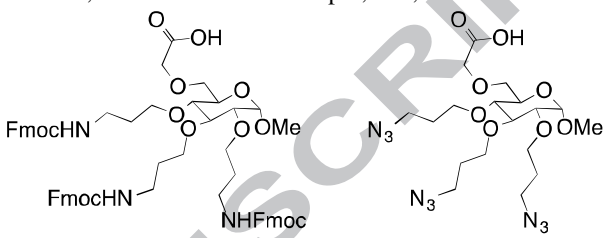

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New branched amino acids for high affinity dendrimeric DC-SIGN ligands

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ABSTRACT

A branched amino acid was synthesized from methyl glucopyranoside; this amino acid presents three amino groups protected by Fmoc and one acid group and can be used in classic peptide synthesis. In parallel, similar azido terminated blocks were synthesized.

Successive coupling reaction and deprotection afforded dendrimers with up to 27 azido functional groups. As an example of application, D-mannose and L-fucose residues were linked through CuAAC coupling and resulting glycodendrimers were evaluated in their interaction with DC-SIGN using SPR competition assay.

Introduction

DC-SIGN (dendritic cell-specific ICAM-3-grabbing non integrin) also called CD209 is a type II transmembrane C-type lectin with a single C-terminal Carbohydrate Recognition Domain (CRD). This receptor binds to "self" glycan ligands found on human cells as well as to "foreign" glycans derived from bacterial or parasitic pathogens [1]. It facilitates intra cellular DC delivery of high-mannose-type structure and related structure and promotes their processing towards antigen presentation. A critically important example of such involvement of DC-SIGN is its strong binding to highly mannosylated HIV gp120 promoting virus transposition from mucosal surface to lymphoid system and thus the transfer of HIV to T-cell [2]. We plan to use this property in a program aiming the preparation of vaccines: a suitable construction equipped with a DC-SIGN ligand as war head will be able to deliver antigenic protein intra DC and thus promoted its presentation by DC to the immuno competent cells [3].

DC-SIGN recognizes both mannosylated and fucosylated ligands. Although protein-carbohydrate interactions are essential to many biological processes, individual interactions usually exhibit weak binding affinities (mM range). Mammen et al. [4] demonstrated that nature uses multivalency to overcome this problem. Thus multiple copies of binding sites on the lectin but also multiple ligands are necessary. In fact, for DC-SIGN, a large bouquet of mannose is required for good affinity (ca 30 D-mannoses) [5]. Our project is the construction of very active yet simple mannosylated/ fucosylated synthetic ligands for DC-SIGN. Different approaches were found in the literature mainly with mannosylated polymers and mannosylated dendrimers whereas fucosylated conjugates (dendrimer and polymers) are less frequently prepared [6]. Dendrimers allow a better control both in geometry and in homogeneity (macroscopic and microscopic) than polymeric carriers. Various studies have shown the usefulness of dendritic manosylated ligands in the design of high affinity DC-SIGN ligands with mannose derivatives or α D-Man 1->2 Man terminated branches [7].

Results

We want here to present new highly branched glycodendrimers as potent DC-SIGN ligands. As many carbohydrates ligands are needed, a less commonly used 3-branched dendrimer is proposed to produce high valency more rapidly. With a tripler unit, a 27-branches dendrimer needs a generation 2 and 14 synthetic blocks (9+3+1), whereas with a doubler unit, a 32-branches dendrimer needs a generation 4 and 31 blocks (16+8+4+2+1) and the double of coupling steps. Amide linkage was selected as the dendrimer building function for its stability, biocompatibility and its potential biodegradability. Dendrimers made from amino acid are not new, as dendrimers of lysine are well established;

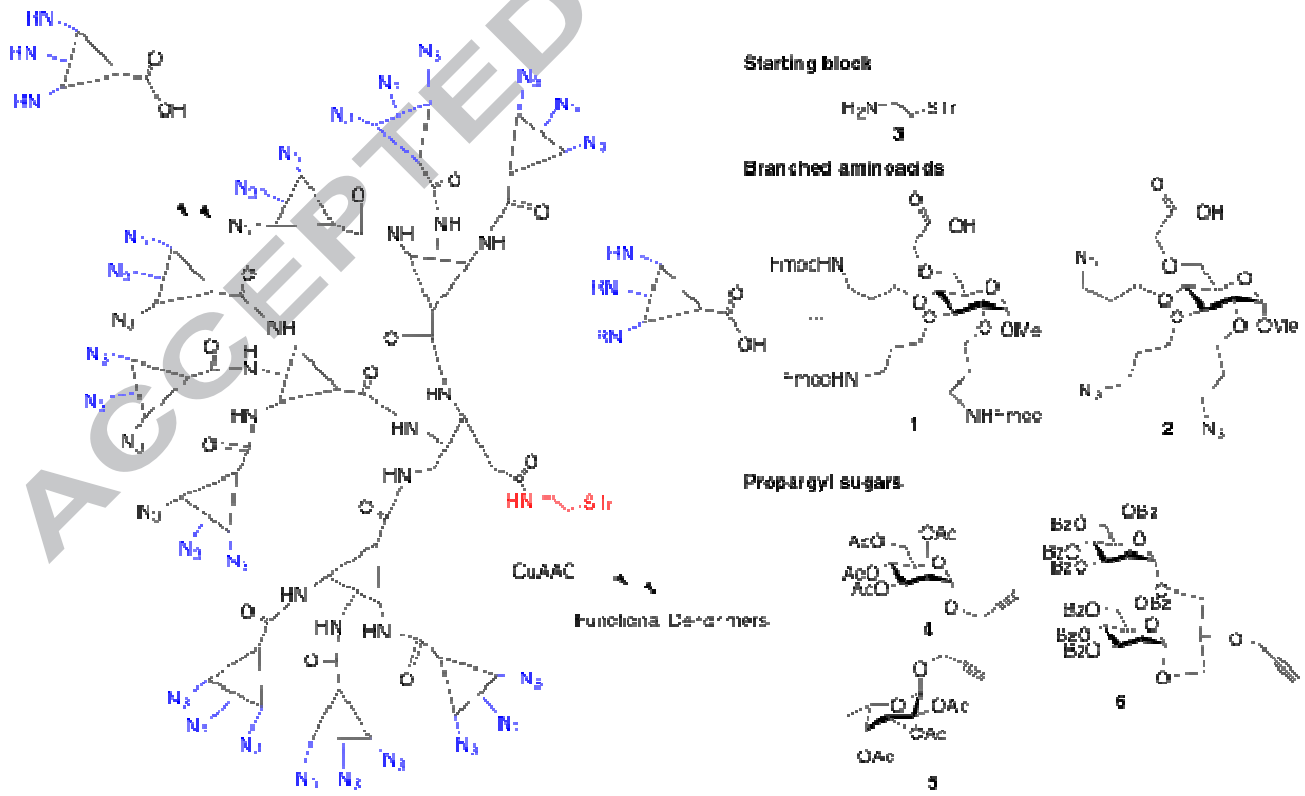
however this core offers only two branches and of very different length.

We propose here the first member of new amino acids family originated from carbohydrates (scheme 1). This glucose amino acid derivative combines a rigid and chiral core with short flexible arms. This approach can be extended to various sugars and gives us the possibility to use solid phase synthesis and an automated synthesis to build dendrimers. In addition, this offers also the possibility to add/insert natural amino acid as spacer (such as glycine) inside the core to expand it or to introduce charges (Glu, Asp, Arg, Lys) to modulate solubility and charges.

The "last layer" of the dendrimer will be terminated by azido groups (for click CuAAC functionalization of protected sugars such as **4, 5** or **6**) using a triazido aminoacid **2** as the terminator group. R. Riguera [8] already showed the versatility of this strategy for the preparation of clikable dendrimers. The other end will be functionalized by a thiol, a cysteamine protected as *S*-trityl ether **3** [9]. This thioester, once deprotected, will allow specific and orthogonal linkage in various uses. Alternatively, the trityl may deserve as an anchor on surface as described. [10]

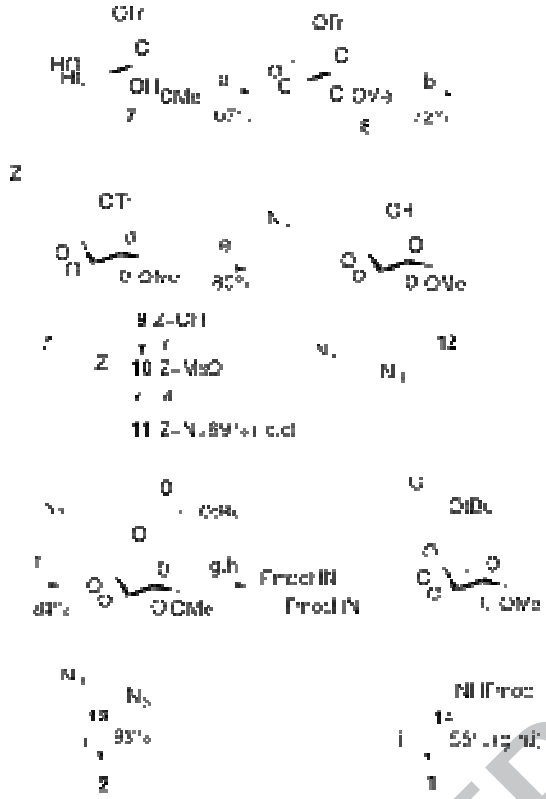
We used first a glucose scaffold starting from methyl α-D-glucoside, an inexpensive derivative, presenting one primary alcohol (to link the acid function) and three secondary hydroxyl groups of similar reactivity for the installation of 3-amino propyl group. The synthesis is depicted on scheme 2. A trityl was selected as primary alcohol protection to give **7** [11]. T. Lindhorst in her preparation of octopus carbohydrate [12] compared various methods for amino alkyl introduction and finally selected hydroboration of allyl groups as her preferred route for multiple carbohydrate alcohols substitution. Thus the three secondary alcohol functions were allylated. The allyl groups were hydroborated (9-BBN) and the generated alcohol function transformed into an azido group. Finally, the trityl group was removed and replaced with a terbutyloxy carbonymethyl group under phase transfert catalysis conditions to give the key block **13** (scheme 2). Further transformations involved: reduction of the azido groups with Ph_3P followed by in situ introduction of Fmoc [13] and tert butyl ester cleavage with TFA.

The dendrimer construction is straightforward as depicted in scheme 3, it involved iterative coupling steps starting from S-trityl cysteamine: amide formation promoted by DCC, removal of Fmoc (DBU/octyl thiol) [14]. This latter method uses a strong base (DBU) in presence of octyl thiol, a powerful nucleophile that traps the dibenzofulvene and avoids side reaction of amine. Thus two versatile key dendrimeric scaffolds were prepared: **IIc** (generation 1 with nine azido terminal groups, from block **1** and three blocks **2**) and **IIIc** (generation 2 with 27 azido terminal groups, from four blocks **1** and nine blocks **2**. (scheme 3)



Scheme 1: Strategy, general structure and synthetic blocks for glycodendrimers

The azido dendrimers were then coupled with acylated propargyl glycosides by CuAAC to give the protected glycodendrimers**.** Compounds **4** [15] and **5** [16] were prepared according to literature procedure. In addition, a block **6** with two mannoses was prepared on a glycerol scaffold (it was prepared from 1,3-benzylidene glycerol via 2-propargyl glycerol [17] and its mannosylation using pentabenzoyl mannose) to increase further the numbers of branches.



Scheme 2: Elongating and terminating blocks: (a) allyl bromide, NaH 60% in oil, DMF, 12h ; (b) 0.5M 9-BBN in THF, 100°C, 2h ; then H_2O 0°C, 3M aq NaOH, 35% H_2O_2, 12h ; (c) MsCl, Et_3N, CH_2Cl_2, 0°C, 15min ; (d) NaN_3, DMF, 65°C, 2h ; (e) PTSA (cat) 1 :1 CH_2Cl_2/ Methanol, 50°C, 12h ; (f) tert-butyl 2-bromoacetate, NBu_4Br (cat), 50% aq NaOH, toluene, 80°C, 2h ; (g) Ph_3P, THF, H_2O, 15h ; (h) FmocOSu, Et_3N, 15min ; (i) TFA/CH_2Cl_2, RT, 5h

After deacylation, the four dendrimers **If, Id, Ih, IId** (Scheme 3) was purified on Sephadex columns and characterized in NMR and mass spectrometry (Fig. 1). Although NMR gave correct spectra integration, like others [7d], we were not able to obtain clean mass spectra for the IIIg (27 Man dendrimer) MW 12226

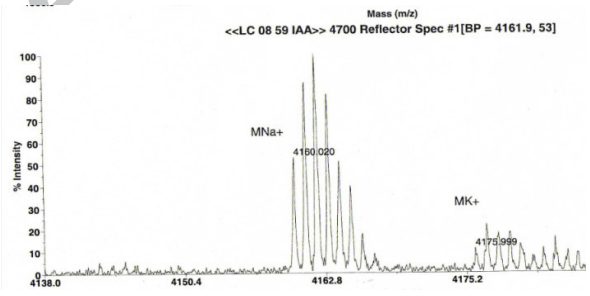


Figure 1: Maldi Mass spectra of IIg

Affinities of all compounds were measured by SPR in the previously established competition assay [18] that measure the ability of compounds to inhibit the binding of extracellular (ECD) DC-SIGN to mannosylated bovine serum albumin (BSA-Man) surface onto the CM4 sensor chip. A fixed amount of DC-SIGN ECD and increasing concentrations of dendrimers were injected over the surface. The natural monosaccharide D-mannose and L-fucose were used both to control the surface stability and to estimate the ß factor value [4]. This value corresponds to the capability of dendrimers displaying several D-mannose or L-fucose copies to improve their inhibitory potency related to the monovalent species. The inhibition curves and IC_{50} values are shown in Fig 2 (the initial sensorgrams can be seen in supplementary Figure S1). The ß factor values are summarized in Table 1.

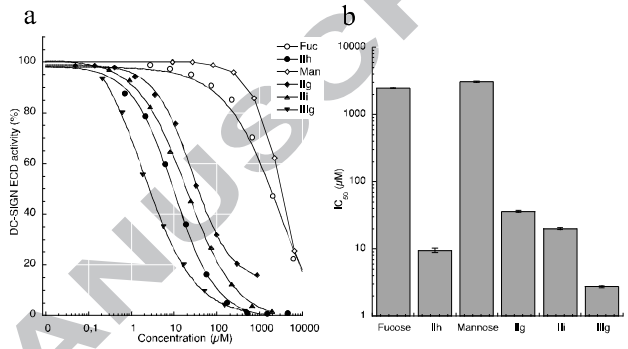


Figure 2: DC-SIGN inhibition activities of dendrimers bearing L-fucose or D-mannose ligands. DC-SIGN ECD (20 µM) and compounds were co-injected over a BSA-Man surface. (a) Comparison of the inhibitory potency of compounds toward DC-SIGN ECD/ BSA-Man interaction. (b) IC_{50} (grey bars) are expressed as dendrimer concentration (µM).

The affinity and the relative potency inhibitory (ß factor) of dendrimers increase with the number of D-mannose or L-fucose displaying by dendrimers. A significant ß factor, superior to 40, was obtained for **IIIg** bearing 27 copies of D-mannose. The potency enhancement for DC-SIGN results from different molecular mechanisms including clustering, statistical rebinding and potentially the chelation effect [6f,19]. Compared to others scaffolds already tested with our DC-SIGN competition assay [7b,20], the multivalent compound **IIIg** is able to generate, up to date, one of the best avidity for DC-SIGN.

Table 1: Valency, IC_{50} and avidity values of dendrimers inhibiting binding of DC-SIGN ECD to immobilized BSA-Man.

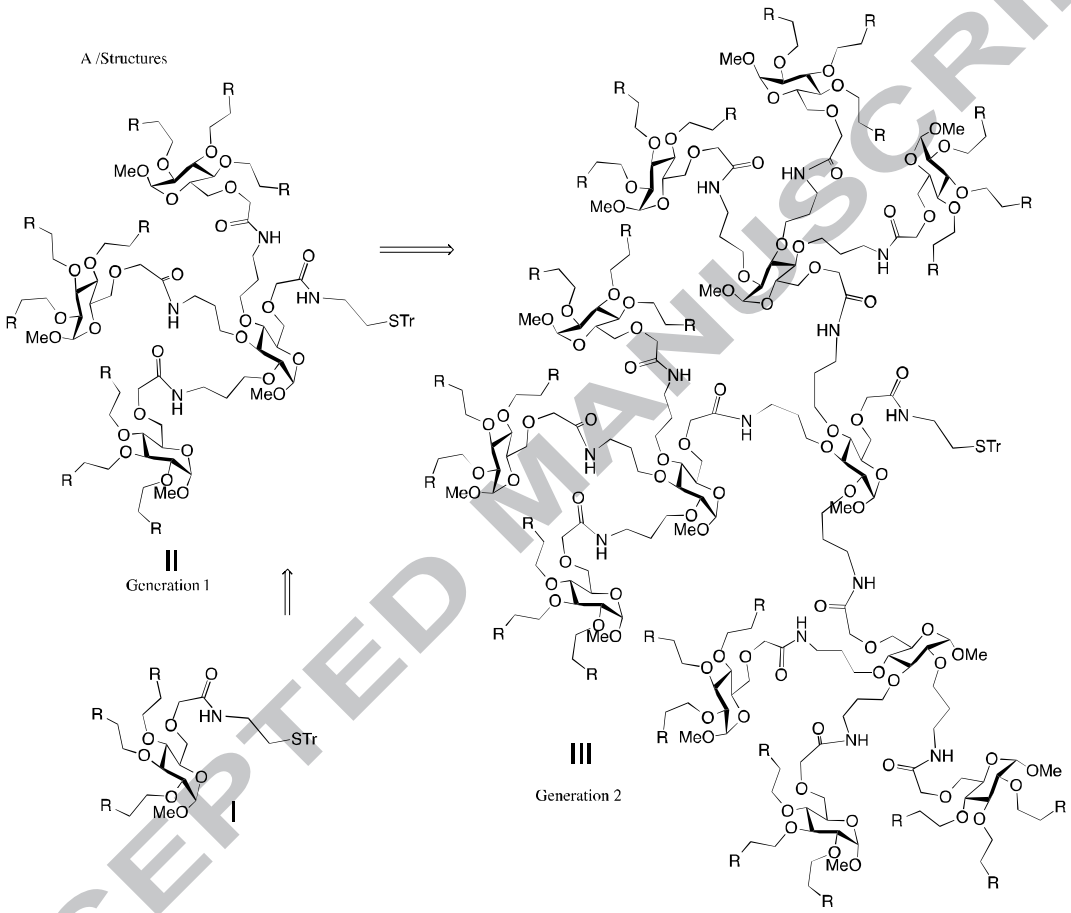
compound	valency	ligand	IC_{50} (µM)	β □□□ □□□
Fucose	1	Fuc	**2480 ± 17**	1
IIh	9	Fuc	**9.5 ± 0.7**	29
Mannose	1	Man	**3057 ± 66**	1
IIg	9	Man	**36.1 ± 1.3**	9
IIi	18	Man	**20 ± 0.7**	8
IIIg	27	Man	**2.75 ± 0.1**	41

This remarkable affinity may relies on the peculiar feature of the dendrimer, the presence of a rigid and chiral core with flexible and short arm that allows large inter group distance with a limited global flexibility and binding entropy.

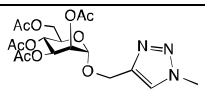
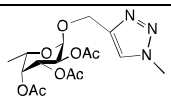
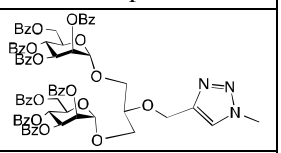
Moreover, comparison of inhibitory potencies of **IIh** and **IIg** reveals that for an identical valency, monovalent ligands play a decisive role in DC-SIGN binding. The 9 L-fucose of **IIh** with an IC_{50} of 9.5 µM inhibits three times more than the corresponding dendrimer with 9 D-mannose **IIg**. On the other hand, the ligand presentation of **IIi** influences negatively the multivalent interactions for his target leading to the same range avidity than **IIg**.

Conclusion

We have described the synthesis of a branched amino acid from methyl glucopyranoside used in the preparation of key polyazido dendrimers, easily functionalized by CuAAC with sugars (mannose or fucose) to give 9 or 27-branch ligands. Preliminary studies on these glycosylated dendrimers have shown nice cooperative effect, in DC-SIGN recognition. This strategy is currently extended to other highly branched amino acids (with various sugars cores), in solid phase synthesis for an easy approach to lectin ligands



B/ substituants

a	b	c
FmocHN	H_2N	N_3
d	e	f
		
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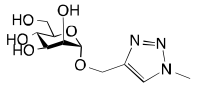
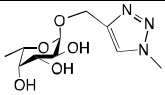
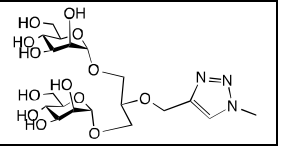
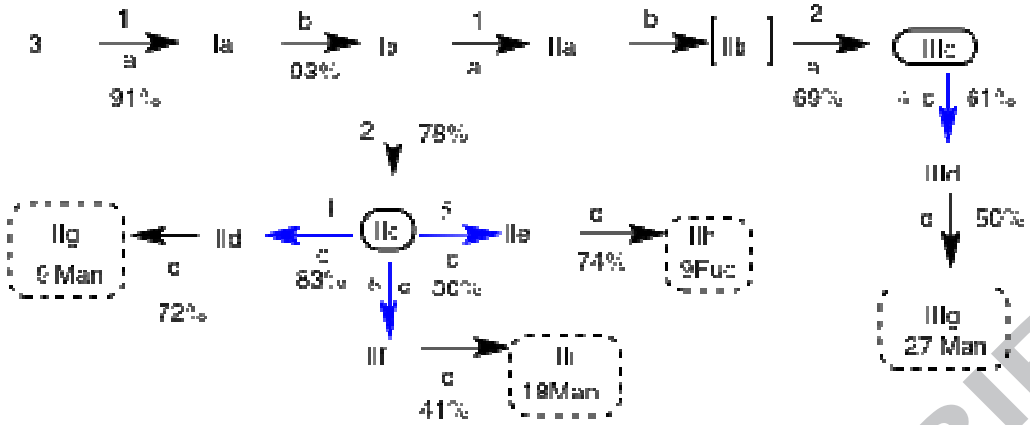
		

Scheme 3: Structure of the dendrimers (I, II and III)



Scheme 3 part C) Synthetic scheme for dendrimers preparation: reagents and conditions : a) DCC, CH_2Cl_2; b) DBU, n-octylthiol, THF; c) click reaction: $CuSO_4$, Na+ ascorbate, dioxane / water; d) NaOH, MeOH

Experimental

Chemical synthesis: All compounds were homogeneous by TLC analysis and had spectral properties consistent with their assigned structures. Compound purity was checked by TLC on Silica gel 60 F254 (E. Merck) with detection by charring with sulfuric acid. Column chromatography was performed on Silica gel 60 (E. Merck). NMR spectra were recorded with Brüker 300, 400 MHz instruments. CyHex stands for cyclohexane.

Methyl-2,3,4-tri-*O*-(3-azidopropyl)-6-*O*-carboxymethyl -α-D-glucopyranoside (2) :To a solution of **13** (500 mg, 0.8967 mmol) in dry CH_2Cl_2 (18 mL) was added TFA (2 mL). The mixture was stirred for 3 hours at room temperature, washed with water (10 mL), the resulting organic layer was dried over $MgSO_4$, and concentrated to give **2** (417mg, 93%) as a yellow syrup. $[\alpha]_D$ +62 (*c* 1, $CHCl_3$). ESI-HRMS m/z $[M-H]^-$ calculated for $C_{18}H_{30}N_9O_8$: 500.2217, found: 500.2206. ^1H NMR (300 MHz, $CDCl_3$) δ 4.75 (d, *J* = 3.5 Hz, 1H, H_1), 4.19 (d, *J* = 17.3 Hz, 1H, H_{7a}), 4.13 (d, *J* = 17.3 Hz, 1H, H_{7b}), 3.87 – 3.73 (m, 4H, 2 × -C<u>H</u>$_2$-O-), 3.73 – 3.55 (m, 5H, -C<u>H</u>$_2$-O-, H_5, H_6), 3.51 (t, *J* = 9.2 Hz, H_3), 3.41 – 3.27 (m, 9H, 3 × N_3-C<u>H</u>$_2$-, O-C<u>H</u>$_3$), 3.26 – 3.19 (m, 2H, H_2, H_4), 1.90 – 1.66 (m, 6H, 3 × -C<u>H</u>$_2$-). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.16 (<u>C</u>OOH), 97.62 (C_1), 81.36 (C_3), 80.48 (C_2), 77.49 (C_4), 70.31 (-<u>C</u>H$_2$-O), 70.02 (-<u>C</u>H$_2$-O), 69.97 (C_5), 69.41 (-<u>C</u>H$_2$-O), 68.47 (C_7), 67.76 (C_6), 55.36 (O<u>C</u>H$_3$), 48.41 (N_3-<u>C</u>H$_2$-), 48.25 (N_3-<u>C</u>H$_2$-), 48.17 (N_3-<u>C</u>H$_2$-), 29.75 (-<u>C</u>H$_2$-), 29.57 (-<u>C</u>H$_2$-), 29.43(-<u>C</u>H$_2$-).

Compound 1 : Compound **14** was dissolved in a mixture of dry CH_2Cl_2 (80 mL) and TFA (20 mL). After 5 hours stirring at room temperature, the solution was concentrated and the residue was dissolved in the minimum of CH_2Cl_2 and cold diethyl ether (300 mL) was added to promote precipitation. The mixture was kept overnight at 4°C and filtered to give **1** (6.09g, 55% over 3 steps). R_f: 0.57 (CH_2Cl_2/MeOH 95:5). $[\alpha]_D$ +27 (*c* 1, $CHCl_3$). ESI-HRMS m/z $[M+H]^+$ calculated for $C_{63}H_{68}N_3O_{14}$: 1090.4701, found: 1090.4746. ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 – 7.05 (m, 24H, H_{ar}), 5.50 – 5.13 (m, 3H, N<u>H</u>Fmoc), 4.80 – 4.61 (br s, 1H, H_1), 4.46 – 3.89 (m, 11H, 3 × C<u>H</u>$_2$Fmoc, 3 × C<u>H</u>Fmoc, H_7), 3.89 – 3.33 (m, 10H, 3 × -C<u>H</u>$_2$-O-, H_6, H_5, H_3), 3.32 – 2.97 (m, 11H, 3 × FmocNH-C<u>H</u>$_2$-, -O-C<u>H</u>$_3$, H_4, H_2), 1.77 – 1.45 (app.s, 6H, 3 × -C<u>H</u>$_2$-). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.44 (-<u>C</u>OOH), 156.76 (NH<u>C</u>OFmoc), 156.60 (NH<u>C</u>OFmoc), 156.55 (NH<u>C</u>OFmoc), 143.98 (6 × Cq $_{ar}$), 141.33 (6 × Cq $_{ar}$), 127.67 (6 × Cq $_{ar}$), 127.04 (6 × Cq $_{ar}$), 124.98 (6 × Cq $_{ar}$), 119.98 (6 × Cq $_{ar}$), 97.31 (C_1), 81.43 (C_3), 80.03 (C_2), 77.65 (C_4), 71.54 (-<u>C</u>H$_2$-O-), 70.73 (-<u>C</u>H$_2$-O-), 70.26 (C_6), 70.11 (C_5), 68.74 (C_7), 68.40 (-<u>C</u>H$_2$-O-), 66.64 (<u>C</u>H$_2$Fmoc), 66.32 (<u>C</u>H$_2$Fmoc), 65.90 (<u>C</u>H$_2$Fmoc), 55.16 (O-<u>C</u>H$_3$), 47.32 – 47.25 (3 × <u>C</u>HFmoc), 39.04 (FmocNH-<u>C</u>H$_2$-), 38.80 (FmocNH-<u>C</u>H$_2$-), 38.62 (FmocNH-<u>C</u>H$_2$-), 30.44 (-<u>C</u>H$_2$-), 30.22 (-<u>C</u>H$_2$-), 29.60 (-<u>C</u>H$_2$-).

Compound 6: step 1: Synthesis of 1,3-Propanediol, 2-(2-propyn-1-yloxy) - To a solution of 2-phenyl-1,3-dioxan-5-ol (500 mg, 2.77 mmol, 1 equiv.) in dry DMF (5mL) were added propargyl bromide 80 wt. % in toluene (618 µL, 5.55 mmol, 2 equiv.) and sodium hydride 60 wt. % (222 mg, 5.55 mmol, 2 equiv.) portionwise. The mixture was stirred overnight and the sodium hydride was quenched by addition of MeOH and the solution was concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (2 × 10 mL). The organic layers were combined, dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (CyHex 100% then CyHex/AcOEt 70:30) to get the propargyl derivative (498 mg, 83%). MS ESI-HRMS m/z [M+Na]+ calcd for $C_{13}H_{14}NaO_3^+$ 241.0835, found 241.0837. ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H, H_{ar}), 7.43 – 7.35 (m, 3H, H_{ar}), 5.59 (s, 1H, H Benzylidene), 4.47 – 4.31 (m, 4H, CH_2, C<u>H</u>$_2$ propargyl), 4.11 (dddd, *J* = 12.8, 1.5 Hz, 2H, C<u>H</u>$_2$), 3.67 (p, *J* = 1.7 Hz, 1H, C<u>H</u>), 2.47 (t, *J* = 2.4 Hz, 1H, H alkyne). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0 (Cq $_{ar}$), 128.93 (C$_{ar}$), 128.2 (2 × Cq $_{ar}$), 126.1 (2 × Cq $_{ar}$), 101.3 (C Benzylidene), 79.4 (-<u>C</u>≡CH), 74.9(-C≡<u>C</u>H), 68.8 (<u>C</u>H), 68.7 (2 × <u>C</u>H$_2$), 55.6 (<u>C</u>H$_2$ propargyl).

Step 2: To a mixture of CH_2Cl_2, TFA and water (10 mL, 8/1/1 *v/v/v*) was added the propargyl derivative (200 mg, 0.917 mmol). The mixture was stirred overnight at room temperature and TFA was carefully neutralized by triethylamine. The solution was concentrated and the residue was purified by column chromatography on silica gel (CyHex 100% then CyHex/AcOEt 50:50) to get the 1,3-propanediol, 2-(2-propyn-1-yloxy) (104 mg, 67%). ^1H NMR (300 MHz, $CDCl_3$) δ 4.25 (d, *J* = 2.3 Hz, 2H, C<u>H</u>$_2$ propargyl), 3.82 – 3.53

(m, 5H, 2 × $C\underline{H}_2$, $C\underline{H}$), 3.04 (s, 2H, OH), 2.46 (t, *J* = 2.3 Hz, 1H, H alkyne). ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.0 (-$\underline{C}$≡CH), 79.3 ($\underline{C}$H), 75.0 (-C≡$\underline{C}$H), 61.9 (2 × $\underline{C}H_2$), 57.3 ($\underline{C}H_2$ propargyl).

Step 3: To a solution of step 2 compound (20 mg, 0.1538 mmol, 1 equiv.) in dry CH_2Cl_2 (3 mL) were added 1,2,3,4,6-penta-O-benzoyl-α,β-D-mannopyranoside (323 mg, 0.4615 mmol, 3 equiv.) and BF_3,Et_2O (0.3 mL, 2.30 mmol, 15 equiv.). The mixture was stirred overnight under argon at room temperature. Then the reaction was diluted with CH_2Cl_2 (5 mL) and BF_3, Et_2O was neutralized with aq sat $NaHCO_3$. The organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (CyHex/AcOEt 8:2) to give **6** (115 mg, 58%). MS ESI-HRMS m/z [M+Na]+ calcd for $C_{74}H_{62}NaO_{21}^+$ 1309.3676, found 1309.3656. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 – 7.17 (m, 40H, H_{ar}), 6.34 – 6.14 (m, 2H, 2 × $H_{4\ Man}$), 6.12 – 5.93 (m, 2H, 2 × $H_{3\ Man}$), 5.88 – 5.80 (m, 2H, 2 × $H_{2\ Man}$), 5.26 (2d, *J* = 1.7 Hz, 2 × $H_{1\ Man}$), 4.89 – 4.77 (m, 4H, 4 × $H_{6\ Man}$), 4.74 – 4.55 (m, 6H, 2 × $H_{6\ Man}$, 2 × $H_{5\ Man}$), 4.50 (app. dd, *J* = 2.3, 0.8 Hz, 2H, $C\underline{H}_2$ propargyl), 4.30 – 4.17 (m, 1H, $C\underline{H}$), 4.16 – 4.01 (m, 2H, $C\underline{H}_2$), 3.92 – 3.77 (m, 2H, $C\underline{H}$), 2.73 (t, *J* = 2.4 Hz, 1H, H alkyne). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 – 165.3 (8 × CO Bz), 133.4 – 128.3 (40 × C_{ar}, 8 × $C_{q\ ar}$), 98.2 ($C_{1\ Man}$), 97.7 ($C_{1\ Man}$), 79.8 (-$\underline{C}$≡CH), 76.3 ($\underline{C}$H), 75.5 (-C≡$\underline{C}$H), 70.4 ($C_{2\ Man}$), 70.4 ($C_{2\ Man}$), 70.13 (2 × $C_{3\ Man}$), 69.2 ($C_{5\ Man}$), 69.1 ($C_{5\ Man}$), 67.8 ($\underline{C}H_2$), 67.3 ($\underline{C}H_2$), 66.8 ($C_{4\ Man}$), 66.76 ($C_{4\ Man}$), 62.8 ($C_{6\ Man}$), 62.8 ($C_{6\ Man}$), 58.4 ($\underline{C}H_2$ propargyl).

Methyl 2,3,4-tri-*O*-allyl-6-*O*-trityl-α-D-glucopyranoside (8): To a solution of methyl 6-O-trityl-α-D-glucopyranoside **7** (9.55 g, 21.88 mmol, 1 equiv.) in dry DMF (200 mL) were added portionwise under argon allyl bromide (8.52 mL, 98.46 mmol, 4.5 equiv.) and sodium hydride (3.28 g, 82.04 mmol, 3.75 equiv.). Then, the mixture was heated at 60°C for 1 hour. The excess of sodium hydride was quenched with methanol (100 mL) and the solution was concentrated. The residue was dissolved in CH_2Cl_2 (300 mL) and washed with water (3 × 100 mL). The aqueous layers were combined and washed with CH_2Cl_2. The organic layers were combined, dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (CyHex/AcOEt 95:5 then 90:10) to give **8** (8.13g, 67%), as a colourless oil. R_f: 0.89 (CyHex/AcOEt 80:20). $[\alpha]_D$ +62 (*c* 1, $CHCl_3$). ESI-HRMS m/z $[M+Na]^+$ calculated for $C_{35}H_{40}NaO_6$: 579.2723, found: 579.2737. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.50 (m, 6H, H_{ortho} Trt), 7.42 – 7.20 (m, 9H, H_{ar} Trt), 6.13 – 5.92 (m, 2H, H All), 5.72 – 5.52 (m, 1H, H All), 5.45 – 5.28 (m, 4H, H All), 5.28 – 5.17 (m, 2H, H All), 5.11 – 4.99 (m, 2H, H All), 4.94 (d, *J* = 3.6 Hz, 1H, H_1), 4.47 – 4.14 (m, 5H, 2 × $C\underline{H}_2$-O-, -$C\underline{H}_a\underline{H}_b$O-), 3.90 – 3.80 (m, 1H, -$CH_a\underline{H}_b$O-), 3.80 – 3.72 (m, 2H, H_3, H_5), 3.62 – 3.43 (m, 6H, OCH_3, H_2, H_4, H_{6a}), 3.19 (dd, *J* = 10.0, 4.4 Hz, 1H, H_{6b}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.05 (3 × $C_{q\ ar}$ Trt), 135.34 (H_2C=$\underline{C}$H), 135.03(H_2C=$\underline{C}$H), 134.77 (H_2C=$\underline{C}$H), 128.83 (6 × C_{ar} Trt), 127.80 (6 × C_{ar} Trt), 126.97 (3 × C_{ar} Trt), 117.52 ($H_2\underline{C}$=CH), 116.90 ($H_2\underline{C}$=CH), 116.88 ($H_2\underline{C}$=CH), 98.08 (C_1), 86.30 (C_q Trt), 81.77 (C_3), 79.77 (C_2), 77.99 (C_4), 74.55(-$\underline{C}H_2$-O-), 73.81 (-$\underline{C}H_2$-O-), 72.63 (-$\underline{C}H_2$-O-), 70.20 (C_5), 62.57 (C_6), 54.88 (O$\underline{C}H_3$).

Methyl 2,3,4-tri-*O*-(3-hydroxypropyl)-6-*O*-trityl-α-D-glucopyranoside (9) : **8** (6.62 g, 11.90 mmol, 1 equiv.) was dissolved in 9-BBN 0.5M in THF (142 mL, 71.37 mmol, 2 equiv. / allyl). The solution was stirred under reflux for 2 hours under argon. Then, the solution was cooled at 0°C and the excess of 9-BBN was quenched with cold water (50 mL). Then, 3M aq sodium hydroxide (150 mL) and hydrogen peroxide (35%) (150mL) were added carefully at 0°C. The mixture was stirred from 0°C to room temperature overnight and CH_2Cl_2 (400 mL) was added. The aqueous layer was discarded and the organic layer was further washed with a saturated solution of $Na_2S_2O_3$ (200 mL) and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (AcOEt/MeOH 95:5) to give **9** (5.23 g, 72%) as a white foam. R_f: 0.28 (AcOEt/MeOH 95:5). $[\alpha]_D$ +67 (*c* 1, $CHCl_3$). ESI-HRMS m/z $[M+Na]^+$ calculated for $C_{35}H_{46}NaO_9$: 633.3040, found: 633.3055. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.1 Hz, 6H, H_{ortho} Trt), 7.30 – 7.09 (m, 9H, H_{ar} Trt), 4.90 (d, *J* = 3.3 Hz, 1H, H_1), 3.86 (t, *J* = 5.7 Hz, 2H, -$C\underline{H}_2$-O-), 3.81 – 3.60 (m, 7H, 2 × HO-$C\underline{H}_2$-, -$C\underline{H}_a\underline{H}_b$-O-, -$C\underline{H}_2$-O-), 3.58 (m, 1H, H_5), 3.47 (m, 1H, H_3), 3.42 – 3.18 (m, 9H, H_2, H_4, H_{6b}, O-CH_3, HO-CH_2-, -$CH_a\underline{H}_b$-O-), 3.02 (dd, *J* = 10.1, 4.1 Hz, 1H, H_{6a}), 2.68 (br s, 3H, OH), 1.87 – 1.68 (m, 4H, 2 × -$C\underline{H}_2$-), 1.37 (m, 2H, -$C\underline{H}_2$-). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.99 (3 × $C_{q\ ar}$ Trt), 128.92 (6 × C_{ar} Trt), 127.98 (6 × C_{ar} Trt), 127.20 (3 × C_{ar} Trt), 97.13 (C_1), 86.48 (C_q Trt), 81.42 (C_3), 80.49 (C_2), 78.73 (C_4), 72.39 (-$\underline{C}H_2$-O-), 71.07 (-$\underline{C}H_2$-O-), 70.40 (C_5), 69.26 (-$\underline{C}H_2$-O-), 62.26 (C_6), 61.30 (HO-$\underline{C}H_2$-), 61.12 (HO-$\underline{C}H_2$-), 60.85 (HO-$\underline{C}H_2$-), 55.12 (O-$\underline{C}H_3$), 32.77(-$\underline{C}H_2$-), 32.61 (-$\underline{C}H_2$-), 32.37(-$\underline{C}H_2$-).

Methyl 2,3,4-tri-*O*-(3-azidopropyl)-6-*O*-trityl-α-D-glucopyranoside (11): To a solution of **9** (8.52 g, 13.95 mmol, 1 equiv.) in dry CH_2Cl_2 (100 mL) at 0°C were added under argon triethylamine (7.9 mL, 55.81 mmol, 4 equiv.) and slowly mesyl chloride (4.1 mL, 50.22 mmol, 3.6 equiv.). The solution was stirred at 0°C for 1 hour, diluted with CH_2Cl_2 (100 mL) and washed with water (50 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue **10** was dissolved in dry DMF (80 mL) in the presence of sodium azide (9.07 g, 139.5 mmol, 10 equiv.) and the solution was heated at 65°C overnight. The mixture was diluted in water (300 mL), then extracted with CH_2Cl_2 (3×100 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (CyHex/AcOEt 90:10 then 80:20) to give **11** (6.65g, 69%) as a white syrup. R_f: 0.16 (CyHex/AcOEt 90:10). $[\alpha]_D$ +51 (*c* 1, $CHCl_3$). ESI-HRMS m/z $[M+Na]^+$ calculated for $C_{35}H_{43}N_9NaO_6$: 708.3234, found: 708.3261. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (dt, *J* = 8.6, 2.0 Hz, 6H, H_{ar}), 7.28 – 7.09 (m, 9H, H_{ar}), 4.83 (d, *J* = 3.5 Hz, 1H, H_1), 3.77 (dt, *J* = 9.7, 6.2 Hz, 1H, -$CH_a\underline{H}_b$-O-), 3.71 – 3.52 (m, 5H, -$C\underline{H}_a\underline{H}_b$-OR, -$CH_a\underline{H}_b$-O-, -$C\underline{H}_a\underline{H}_b$-O-, H_5), 3.45 (t, *J* = 9.2, 1H, H_3), 3.41 – 3.20 (m, 10H, H_2, H_4, H_{6a}, O-$C\underline{H}_3$, 2 × N_3-$C\underline{H}_a\underline{H}_b$-), 3.12 (ddd, *J* = 9.2, 7.1, 5.3 Hz, 1H, -$C\underline{H}_a\underline{H}_b$-OR), 3.05 – 2.91(m, 2H, H_{6b}, N_3-$CH_a\underline{H}_b$-), 2.82 (m, 1H, N_3-$C\underline{H}_a\underline{H}_b$-), 1.87 – 1.71 (m, 4H, 2 × -$C\underline{H}_2$-), 1.43 (m, 2H, -$C\underline{H}_2$-). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.91 (3 × $C_{q\ ar}$ Trt), 128.80 (6 × C_{ar} Trt), 127.81 (6 × C_{ar} Trt), 127.05 (3 × C_{ar} Trt), 97.42 (C_1), 86.34 (C_q Trt), 81.67 (C_3), 80.85 (C_4 or C_2), 78.41 (C_4 or C_2), 70.18 (C_5), 70.11 (-$\underline{C}H_2$-O-), 69.41 (-$\underline{C}H_2$-O-), 67.72(-$\underline{C}H_2$-O-), 62.30 (C_6), 54.94 (O-$\underline{C}H_3$), 48.48 (N_3-$\underline{C}H_2$-), 48.30 (N_3-$\underline{C}H_2$-), 48.27 (N_3-$\underline{C}H_2$-), 29.83 (-$\underline{C}H_2$-), 29.57 (-$\underline{C}H_2$-), 29.50 (-$\underline{C}H_2$-).

Methyl 2,3,4-tri-O-(3-azidopropyl)-α-D-glucopyranoside (12) : To a solution of **11** (18.95 g, 27.64 mmol, 1 equiv.) in a mixture CH_2Cl_2/MeOH 1:1 (200 mL) was added TsOH (1.57 g, 8.292 mmol, 0.3 equiv.). The solution was stirred for 18 hours and neutralized with triethylamine (1.54 mL, 11.06 mmol, 0.4 equiv.). The solution was concentrated and the residue was purified by column chromatography on silica gel (CyHex 100% then CyHex/AcOEt 60:40) to give **12** (9.83g, 80%) as an oil. R_f: 0.08 (CyHex/AcOEt 70: 30). $[\alpha]_D$ +78 (*c* 1, $CHCl_3$). ESI-HRMS m/z $[M+Na]^+$ calculated for $C_{16}H_{29}N_9NaO_6$: 466.2138, found: 466.2144. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 (d, *J* = 3.5 Hz, 1H, H_1), 3.91 – 3.53 (m, 8H, 3 × -C<u>H</u>$_2$-O-, H_6), 3.53 – 3.43 (m, 2H, H_3, H_5), 3.43 – 3.27 (m, 9H, OC<u>H</u>$_3$, 3 × N_3-C<u>H</u>$_2$-), 3.26 – 3.13 (m, 2H, H_2, H_4), 2.04 (br s, 1H, OH), 1.89 – 1.69 (m, 6H, 3 × -C<u>H</u>$_2$-).^{13}C NMR (75 MHz, $CDCl_3$) δ 97.54 (C_1), 81.33 (C_3), 80.75 (C_2), 77.72 (C_4), 70.69 (C_5), 69.95 (-<u>C</u>H_2-O-), 69.45 (-<u>C</u>H_2-O-), 67.70 (-<u>C</u>H_2-O-), 61.59 (C_6), 55.15 (O<u>C</u>H_3), 48.43 (N_3-<u>C</u>H_2-), 48.30 (N_3-<u>C</u>H_2-), 48.18 (N_3-<u>C</u>H_2-), 29.78 (-<u>C</u>H_2-), 29.61 (-<u>C</u>H_2-), 29.46 (-<u>C</u>H_2-).

Methyl-2,3,4-tri-*O*-(3-azidopropyl)-6-*O*-tertbutyloxycarbonylmethyl-α-D-glucopyranoside (13) : To a solution of **12** in toluene (120 mL) were added *tert*-butyl bromoacetate (14.4 mL, 97.92 mmol, 5 equiv.), tetrabutylammonium bromide (631 mg, 1.958 mmol, 0.1 equiv.) and an aqueous 12.5M sodium hydroxide (62 mL, 783 mmol, 40 equiv.). The reaction was stirred vigorously for 2 hours at 80°C, then diluted with AcOEt (200 mL). The organic layer was washed with an aq 1M HCl (50 mL) and sat aq $NaHCO_3$ (100 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified by column chromatography on silica gel (CyHex 100% then CyHex/AcOEt 85:15) to give **13** (9.17g, 84%) as an oil. R_f: 0.47 (CyHex/AcOEt 70:30). $[\alpha]_D$ +59 (*c* 1, $CHCl_3$). ESI-HRMS m/z $[M+Na]^+$ calculated for $C_{22}H_{39}N_9NaO_8$: 580.2819, found: 580.2825. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (d, *J* = 3.5 Hz, 1H, H_1), 4.08 (d, *J* = 16.5 Hz, 1H, H_{7a}), 4.02 (d, *J* = 16.5 Hz, 1H, H_{7b}), 3.91 – 3.57 (m, 9H, H_5,H_6, 3 × -C<u>H</u>$_2$-O-), 3.56 (t, *J* = 9.6 Hz, 1H, H_3), 3.48 – 3.33 (m, 10H, 3 × N_3-C<u>H</u>$_2$-, OC<u>H</u>$_3$, H_4), 3.30 (dd, *J* = 9.6, 3.5 Hz, 1H, H_2), 1.93 – 1.79 (m, 6H, 3 × -C<u>H</u>$_2$-), 1.48 (s, 9H, C<u>H</u>$_3$ *t*Bu).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.31 (<u>C</u>O ester), 97.57 (C_1), 81.54 (C_q *t*Bu), 81.47 (C_3), 80.56 (C_2), 77.53 (C_4), 70.11 (C_5), 69.90 (-<u>C</u>H_2-O-), 69.77 (-<u>C</u>H_2-O-), 69.38 (-<u>C</u>H_2-O-), 69.16 (C_7), 67.69 (C_6), 55.19 (O<u>C</u>H_3), 48.45(N_3-<u>C</u>H_2-), 48.38 (N_3-<u>C</u>H_2-), 48.20 (N_3-<u>C</u>H_2-), 29.80 (-<u>C</u>H_2-), 29.66 (-<u>C</u>H_2-), 29.47 (-<u>C</u>H_2-), 28.11 (3 × <u>C</u>H_3 *t*Bu).

Compound 14 : To a solution of **13** (5.65 g, 10.14 mmol, 1 equiv.) in THF (75 mL) was added triphenylphosphine (26.5 g, 101.4 mmol, 10 equiv.). The reaction was stirred for 5 hours at room temperature and iminophosphorane was hydrolyzed by addition of water (37.5 mL). The mixture was stirred overnight. Then, the reaction mixture was diluted with THF until solubilization and $N(Et)_3$ (5.63 mL, 40.56 mmol, 4 equiv.) and FmocOSu (12.31 g, 36.50 mmol, 4 equiv.) were added. The mixture was stirred for 1 hour at room temperature and concentrated. The residue was purified by column chromatography on silica gel (CyHex/AcOEt 50:50). $[\alpha]_D$ +23 (*c* 1, $CHCl_3$). ESI-HRMS m/z $[M+Na]^+$ calculated for $C_{67}H_{75}N_3O_{14}Na$: 1168.5147, found: 1168.5095. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.08 (m, 39H, Har), 5.74 (br t, *J* = 5.8 Hz, 1H, N<u>H</u>), 5.64 (br t, *J* = 5.7 Hz, 1H, N<u>H</u>), 5.55 (m, 1H, N<u>H</u>), 4.85 (d, *J* = 3.4 Hz, 1H, H_1), 4.53 – 4.32 (m, 6H, 3 × C<u>H</u>$_2$Fmoc), 4.27 – 4.13 (m, 4H, 3 × C<u>H</u>Fmoc, H_{7a}), 4.06 (d, *J* = 16.6 Hz, 1H, H_{7b}), 3.96 (dd, *J* = 10.6, 3.3 Hz, 1H, H_{6a}), 3.91 – 3.79 (m, 4H, 2 × -C<u>H</u>$_2$-O-), 3.75 – 3.51 (m, 5H, -C<u>H</u>$_2$-O-, H_3, H_5, H_{6b}), 3.49 – 3.18 (m, 11H, 3 × FmocNH-C<u>H</u>$_2$-, O-C<u>H</u>$_3$, H_2, H_4), 1.94 – 1.63 (m, 6H, 3 × -C<u>H</u>$_2$-), 1.50 (s, 9H, C<u>H</u>$_3$ *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.61 (<u>C</u>O ester), 156.61 (2 × NH<u>C</u>OFmoc), 156.56 (NH<u>C</u>OFmoc), 144.07 – 119.97 (Car), 97.30 (C_1), 81.79 (Cq *t*Bu), 81.56 (C_3), 80.11 (C_2), 77.61 (C_4), 71.61 (-<u>C</u>H_2-O-), 70.64 (-<u>C</u>H_2-O-), 70.23 (C_5), 69.95 (C_6), 69.24 (C_7), 68.43 (-<u>C</u>H_2-O-), 66.57 (<u>C</u>H_2Fmoc), 66.39 (<u>C</u>H_2Fmoc), 66.30 (<u>C</u>H_2Fmoc), 55.08 (O-<u>C</u>H_3), 47.35 (<u>C</u>HFmoc), 47.30 (2 × <u>C</u>HFmoc), 39.10 (FmocNH-<u>C</u>H_2-), 38.83(FmocNH-<u>C</u>H_2-), 38.61 (FmocNH-<u>C</u>H_2-), 30.44 (-<u>C</u>H_2-), 30.27(-<u>C</u>H_2-), 30.21 (-<u>C</u>H_2-), 28.17 (3 × <u>C</u>H_3 *t*Bu).

Dendrimer assembly

Dendrimer Ia : To a solution of **1** (300mg, 0.2752 mmol, 1 equiv.) and **3** (105mg, 0.3303 mmol, 1.2 equiv.) in dry CH_2Cl_2 (5 mL) was added DMAP (cat.). The solution was cooled at 0°C and DCC (113mg, 0.550 mmol, 2 equiv.) was added. The reaction was stirred for 3 hours from 0°C to room temperature, filtered and concentrated. The residue was purified by column chromatography on silica gel (DCM/EtOH 98 : 2) to give **Ia** (349mg, 91%) as a white foam. R_f: 0.42 (CH_2Cl_2 /EtOH 95 : 5). [α] (c = 1, $CHCl_3$). ESI-HRMS m/z $[M+Na]^+$ calculated for $C_{84}H_{86}N_4NaO_{13}S$: 1413.5810, found : 1413.5817. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.02 (m, 39H, H_{ar}), 6.96 – 6.83 (br s, 1H, N<u>H</u>CO), 5.38 – 5.27 (br s, 1H, N<u>H</u>Fmoc), 5.27 – 5.19 (br s, 1H, N<u>H</u>Fmoc), 5.14 – 5.00 (br s, 1H, N<u>H</u>Fmoc), 4.65 (d, *J* = 3.2 Hz, 1H, H_1), 4.42 – 4.21 (m, 6H, 3 × C<u>H</u>$_2$Fmoc), 4.17 – 4.01 (m, 3H, 3 × C<u>H</u>Fmoc), 3.89 (s, 2H, H_7), 3.79 – 3.30 (m, 10H, 3 × -C<u>H</u>$_2$-O-, H_3, H_5, H_6), 3.30 – 2.98 (m, 13H, 3 × FmocNH-C<u>H</u>$_2$-, -OC<u>H</u>$_3$, H_2, H_4, H_8), 2.33 (t, *J* = 6.3 Hz, 2H, H_9), 1.77 – 1.49 (m, 6H, -C<u>H</u>$_2$-). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.51 (NH<u>C</u>O), 156.54 (2 × NH<u>C</u>O Fmoc), 156.47 (NH<u>C</u>O Fmoc), 144.58 (Cq ar), 144.02 (Cq ar), 143.98 (Cq ar), 141.32 (Cq ar), 129.55 – 119.98 (Car), 97.15 (C_1), 81.33 (C_3), 80.21 (C_2), 77.97 (C_4), 71.51 (-<u>C</u>H_2-O-), 70.99 (-<u>C</u>H_2-O-), 70.57 (C_7), 70.33 (-<u>C</u>H_2-O-), 69.98 (C_5), 68.42 (C_6), 66.87 (Cq Trt), 66.53 (<u>C</u>H_2 Fmoc), 66.42 (<u>C</u>H_2 Fmoc), 66.34 (<u>C</u>H_2 Fmoc), 55.09 (-O<u>C</u>H_3), 47.33 (<u>C</u>H Fmoc), 47.27 (2 × <u>C</u>H Fmoc), 38.92 (FmocNH-<u>C</u>H_2-), 38.81 (FmocNH-<u>C</u>H_2-), 38.72 (FmocNH-<u>C</u>H_2-), 37.67 (C_8), 32.18 (C_9), 30.47 (-<u>C</u>H_2-), 30.35 (-<u>C</u>H_2-), 29.69 (-<u>C</u>H_2-).

Dendrimer Ib : To a solution of **Ia** (349 mg, 0.2509 mmol, 1 equiv.) dissolved in dry THF (20 mL) were added octan-1-thiol (1.311 mL, 7.527 mmol, 10 equiv. / Fmoc) then DBU (4 µl, 0.02509 mmol, 0.1 equiv.). The reaction was stirred overnight at room temperature and concentrated. The residue was diluted in diethyl ether (50 mL) and centrifuged. The supernatant was kept aside and the pellet was washed with diethyl ether and centrifuged once again. The ether layers were combined and washed with water (10 mL). The aqueous layer is combined with the centrifuged residue then lyophilized to get the compound **Ib** (170mg, 93%) as oil. ESI-HRMS m/z $[M+H]^+$ calculated pour $C_{39}H_{57}N_4O_7S$: 725.3948,

found : 725.3955. ^{1}H NMR (300 MHz, CD_3OD) δ 7.49 – 7.37 (m, 6H, H ortho Trt), 7.37 – 7.18 (m, 9H, H_{ar}), 4.84 (d, J = 3.5 Hz, 1H, H_1), 4.01 (s, 2H, H_7), 3.92 – 3.54 (m, 9H, 3 × -CH_2-O-, H_5, H_6), 3.50 (t, J = 9.2 Hz, 1H, H_3), 3.34 (s, 3H, OCH_3) 3.32 – 3.23 (m, 2H, H_2, H_4), 3.20 – 3.12 (m, 2H, H_8), 2.88 – 2.64 (m, 6H, 3 × H_2N-CH_2-), 2.43 (t, J = 6.5 Hz, 2H, H_9), 1.93 – 1.53 (m, 6H, 3 × -CH_2-).^{13}C NMR (75 MHz, MeOD) δ 170.91 (CO amid), 144.73 (3 × Cq ar Trt), 129.38 (6 × C_{ar} Trt), 127.68 (6 × C_{ar} Trt), 126.60 (3 × C_{ar} Trt), 97.38 (C_1), 81.29 (C_3), 80.24 (C_2), 77.83 (C_4), 71.22 (-CH_2-O-), 70.99 (-CH_2-O-), 70.17 (C_5), 69.93 (C_7), 68.63 (C_6), 66.53 (C_q Trt), 54.28 (O-CH_3), 38.84 (2 × H_2N-CH_2-), 38.75 (H_2N-CH_2)-, 37.30 (C_8), 33.08 (-CH_2-), 33.01 (-CH_2-), 32.47 (-CH_2), 31.63 (C_9).

Dendrimer IIa: To a solution of **Ib** (94 mg, 0.1298 mmol, 1 equiv.) and **1** (467 mg, 0.4285 mmol, 3.3 equiv.) in dry CH_2Cl_2 (15 mL) was added DMAP (cat.). The solution was cooled at 0°C and DCC (161 mg, 0.7788 mmol, 6 equiv.). The reaction was stirred for 6 hours under argon from 0°C to room temperature, filtered and concentrated. The residue was purified by column chromatography on silica gel ($CH_2Cl_2$100% then CH_2Cl_2/EtOH 95:5) to get **IIa** (397mg, 78%) as a slightly yellow foam. R_f: 0.39 (DCM/EtOH 95:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.05 (m, 87H, H_{ar}), 7.01 – 6.75 (m, 4H, NHCO), 5.54 – 5.17 (m, 9H, NHFmoc), 4.73 – 4.63 (br s, 3H, 3× H_1), 4.57 (d, J = 2.8 Hz, 1H, H_1), 4.40 – 4.17 (m, 18H, CH_2 Fmoc), 4.17 – 3.97 (m, 9H, CH Fmoc), 3.98 – 3.88 (s, 6H, 3 × H_7), 3.88 – 3.81 (s, 2H, H_7), 3.79 – 3.32 (m, 46H, 3 × -CONHCH_2-, 12 × -CH_2-O-, 4 × H_3, 4 × H_5, 4 × H_6), 3.31 – 2.94 (m, 40H, 4 × OCH_3, 9 × FmocNHCH_2-, 4 × H_2, 4 × H_4, H_8), 2.33 (t, J = 6.3 Hz, 2H, H_9), 1.78 – 1.44 (app.s, 24H,, 12 × -CH_2-).

Dendrimer IIIc: To a solution of **IIa** (154 mg, 39 µmol, 1 equiv.) dissolved in dry THF (15 mL) was added octan-1-thiol (610 µL, 3.517 mmol, 90 equiv.) then DBU (0.6µl, 4 µmol, 0.1 equiv.). The reaction was stirred overnight at room temperature and concentrated. The residue was taken in diethyl ether (50 mL). After centrifugation, the supernatant was removed and the pellet was washed with diethyl ether and centrifuged once again. The final pellet was dried under vacuum to get the **IIb**, which was immediately used in the following step (65 mg, 86%). MALDI m/z $[M+H]^+$ calculated for $C_{93}H_{162}N_{13}O_{28}S^+$: 1941.137, found : 1941.1607). The compound was dissolved in dry CH_2Cl_2 in the presence of **2** (166 mg, 0.3315 mmol, 9.9 equiv.) and DMAP (cat.). The solution was cooled at 0°C and DCC (124 mg, 0.6028 mmol, 18 equiv.) was added. The solution was stirred overnight under argon from 0°C to room temperature, filtered and concentrated. The residue obtained was purified by column chromatography on silica gel (DCM/MeOH/NH_3 aq 95: 5: 0.5) to get the **IIIc** as a yellow oil (144mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (d, J = 7.8 Hz, 6H, H_{ar} Trt), 7.31 – 7.13 (m, 9H, H_{ar} Trt), 7.05 – 6.79 (m, 13H, NHCO), 4.82 – 4.74 (m, 12H, 12 × H_1), 4.71 (d, J = 2.7 Hz, 1H, H_1), 4.06 – 3.94 (s, 26H, 13 × H_7), 3.90 – 3.45 (m, 130H, 39 × -CH_2-O-, 13 × H_3, 13 × H_5, 13 × H_6), 3.45 – 3.30 (m, 117H, 13 × OCH_3, 27 × N_3-CH_2-, 12 × CONHCH_2-), 3.29 – 3.07 (m, 28H, 13 × H_2, 13 × H_4, H_8), 2.38 (t, J = 6.4 Hz, 2H, H_9), 2.10 – 1.60 (m, 78H, 39 × -CH_2-). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.64 (NHCO), 144.62 (Cq ar), 129.54 (C ar Trt), 127.96 (C ar Trt), 126.81 (C ar Trt), 97.55 (13 × C_1), 81.37 (13 × C_3), 80.64 (13 × C_2), 77.77 (13 × C_4), 70.98 – 67.71 (13 × -CH_2-O-, 13 × C_5, 13 × C_6, 13 × C_7), 66.82 (Cq Trt), 55.30 (13 × OCH_3), 48.43 – 48.19 (27 × N_3-CH_2), 37.69 (C_8), 36.59 – 36.26 (12 × CONH-CH_2-), 32.11 (C_9), 29.79 – 29.49 (39 × -CH_2-).

Dendrimer IIc: A solution of **Ib** (177mg, 0.2451 mmol, 1 equiv.), DMAP (cat.) and **2** (442mg, 0.8824 mmol, 3.6 equiv.) dissolved in dry CH_2Cl_2 The solution was cooled at 0°C and DCC (303mg, 1.471 mmol, 6 equiv.) was added. The reaction was stirred 3 hours under argon from 0°C to room temperature, filtered and concentrated. The residue obtained was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 95:5) to get **IIc** (312mg, 59%) as a yellow oil. R_f: 0.57 (DCM/MeOH 95 : 5). [α] + 55 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 6H, H_{ortho} Trt), 7.36 – 7.18 (m, 9H, H ar Trt), 7.12 – 6.82 (m, 4H, NH), 4.84 (d, J = 3.1 Hz, 3H, 3 × H_1), 4.74 (d, J = 3.1 Hz, 1H, H_1), 4.15 – 4.01 (br s, 8H, 4 × H_7), 4.01 – 3.51 (m, 40H, 12 × -CH_2-O-, 4 × H_3, 4 × H_5, 4 × H_6), 3.50 – 3.11 (m, 46H, 4 × OCH_3, 9 × N_3-CH_2-, 3 × -NH-CH_2, 4 × H_2, 4 × H_4, H_8), 2.49 – 2.37 (t, J = 6.3 Hz, 2H, H_9), 1.99 – 1.68 (m, 24H, 12 × -CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.71 – 169.61 (4 × CO amide), 144.59 (3 × Cq), 129.72 – 126.84 (15 × Car), 97.55 (4 × C_1), 81.37 (4 × C_3), 80.61 (4 × C_2), 77.76 (4 × C_4), 71.00 – 67.73 (12 × -CH_2-O, 4 × C_5, 4 × C_6, 4 × C_7), 66.81 (Cq Trt), 55.32 (4 × OCH_3), 48.43 – 48.18 (9 × N_3-CH_2), 37.71 (C_8), 36.67 (CONH-CH_2-), 36.42 (CONH-CH_2-), 36.31 (CONH-CH_2-), 32.09 (C_9), 29.79 – 29.49 (12 × -CH_2-).

Dendrimer IId: To a solution of **IIc** (58 mg, 26.66 µmol, 1 equiv.) and **4** (111 mg, 0.288 mmol, 10.8 equiv.) in dioxane (2.5 mL) was added a solution of $CuSO_4$, 5 H_2O (30 mg, 0.120 mmol, 0.5 equiv. / azide) and sodium ascorbate (31 mg, 0.1680 mmol, 0.7 equiv. / azide) in water (0.5 mL). The mixture was stirred overnight at room temperature and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with a aq solution of Na_2EDTA 0.05M (2 × 5 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified by column chromatography on silica gel (CH_2Cl_2/AcOEt/MeOH 5:4:1) to get **IId** (126 mg, 83%) as a white foam. R_f: 0.16 (DCM/AcOEt/MeOH 5:4:1). $[\alpha]_D$ +71 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.56 (br s, 9H, H Triaz), 7.32 (d, J = 7.4 Hz, 6H, H_{ortho} Trt), 7.18 (m, 9H, H Trt), 7.05 – 6.76 (br s, 4H, NH), 5.35 – 5.10 (m, 27H, 9 × $H_{2\ Man}$, 9 × $H_{3\ Man}$, 9 × $H_{4\ Man}$), 4.92 (s, 9H, 9 × $H_{1\ Man}$), 4.86 – 4.71 (m, 13H, 9 × O-CH_aH_b-Triaz, 4 × $H_{1\ Gluc}$), 4.70 – 4.54 (m, 9H, 9 × O-CH_aH_b-Triaz), 4.53 – 4.34 (br s, 18H, 9 × Triaz-CH_2-C), 4.31 – 4.17 (dd, J = 12.1, 4.0 Hz, 9H, 9 × $H_{6a\ Man}$), 4.15 – 3.86 (m, 26H, 9 × $H_{5\ Man}$, 9 × $H_{6b\ Man}$, 4 × H_7), 3.85 – 3.42 (m, 40H, 12 × -CH_2-O-, 4 × $H_{3\ Gluc}$, 4 × $H_{5\ Gluc}$, 4 × $H_{6\ Gluc}$), 3.41 – 3.00 (m, 28H, 4 × -OCH_3, 3 × CONH-CH_2-, 4 × $H_{2\ Gluc}$, 4 × $H_{4\ Gluc}$, H_8), 2.34 (t, J = 6.3 Hz, 2H, H_9), 2.23 – 2.00 (m, 78H, 12 × -CH_2-, 9 × CH_3 Ac, 9 × CH_3 Ac), 1.96 (s, 27H, 9 × CH_3 Ac), 1.90 (s, 27H, 9 × CH_3 Ac). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.69 – 169.67 (36 × CO Ac, 4 × CO amid), 144.57, 129.63, 129.50, 127.96, 127.92, 127.86, 127.76, 127.69, 127.17, 126.81, 123.91 – 123.15 (9 × CH Triaz), 97.17 (4 × $C_{1\ Gluc}$), 96.90 – 96.86 (9 × $C_{1\ Man}$), 81.41 (4 × $C_{3\ Gluc}$), 80.52 (4 × $C_{2\ Gluc}$), 77.81 ($C_{4\ Gluc}$), 70.69 – 67.06 (4 × C_7, 12 × -CH_2-O-, 4 × $C_{5\ Gluc}$, 4 × $C_{6\ Gluc}$, 9 × $C_{2\ Man}$, 9 × $C_{3\ Man}$, 9 × $C_{5\ Man}$), 66.82 (Cq Trt), 65.91 (9 × $C_{4\ Man}$), 62.31 (9 × $C_{6\ Man}$), 60.68 (9 × O-CH_2-Triaz), 55.26 – 55.14 (4 × OCH_3), 47.69 – 47.35 (9 × Triaz-CH_2-C), 37.65 (C_8), 36.62 – 36.32 (3 × CONH-CH_2-), 32.04 (C_9), 31.07 – 29.67 (12 × -

$\underline{C}H_2$-), 20.89 – 20.69 (27 × $\underline{C}H_3$ Ac).

Dendrimer IIe: To a solution of **IIc** (32 mg, 14.7 µmol, 1 equiv.) and ***5*** (87 mg, 0.265 mmol, 18 equiv.) in dioxane (1.0 mL) was added a solution of $CuSO_4$, 5 H_2O (16.5 mg, 66 µmol, 0.5 equiv. / azide) and sodium ascorbate (18.4 mg, 92 µmol, 0.7 equiv. / azide) in water (0.5 mL). The reaction was stirred overnight at room temperature at 40°C and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL). The solution was washed with an aq solution of Na_2EDTA 0.05M (2 × 5 mL). The organic layer was dried over $MgSO_4$, concentrated. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 95: 5) to obtain **IIe** (41mg, 55%). [α]- 64 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.58 (m, 9H, H Triaz), 7.44 – 7.35 (m, 6H, H ortho Trt), 7.33 – 7.19 (m, 9H, H Trt), 7.09 – 6.88 (m, 4H, NH), 5.41 – 5.24 (m, 18H, 9 × $H_{3\ Fuc}$, 9 × $H_{4\ Fuc}$), 5.22 – 5.18 (m, 9H, 9 × $H_{1\ Fuc}$), 5.17 – 5.09 (m, 9H, 9 × $H_{2\ Fuc}$), 4.90 – 4.79 (m, 12H, 9 × -O-C$\underline{H}_a$$H_b$-Triaz, 3× $H_{1\ Gluc}$), 4.76 (d, *J* = 3.3 Hz, 1H, 1 × $H_{1\ Gluc}$), 4.71 – 4.59 (m, 9H, 9 × -O-C$H_a\underline{H}_b$), 4.57 – 4.40 (m, 18H, 9 × -Triaz-C$\underline{H}_2$-C), 4.30 – 4.15 (m, 9H, 9 × $H_{5\ Fuc}$), 4.07 – 3.99 (app. s, 8H, 4 × H_7), 3.98 – 3.48 (m, 40H, 12 × -C$\underline{H}_2$-O-, 4 × $H_{3\ Gluc}$, 4 × $H_{5\ Gluc}$, 4 × $H_{6\ Gluc}$), 3.43 (app. s, 12H, 4 × OC$\underline{H}_3$), 3.40 – 3.06 (m, 16H, 3 × CONH-C$\underline{H}_2$-, 4 × $H_{2\ Gluc}$, 4 × $H_{4\ Gluc}$, H_8), 2.43 (t, *J* = 6.5 Hz, 2H, H_9), 2.28 – 2.10 (app. s, 51H, 12 × -CH_2-, 9 × C$\underline{H}_3$ Ac), 2.05 (s, *27*H, 9 × C$\underline{H}_3$ Ac), 1.99 (s, 9 × C$\underline{H}_3$ Ac), 1.16 (d, *J* = 6.5 Hz, 27H, 9 × $H_{6\ Fuc}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.62 – 169.70 (27 × $\underline{C}$O Ac, 4 × $\underline{C}$O Amid), 144.60 (3 × Cq ar Trt), 144.08 – 143.93 (9 × Cq Triaz), 129.54 (6 × Car Trt), 127.98 (6 × Car Trt), 126.84 (3 × Car Trt), 123.08 – 122.79 (9 × $\underline{C}$H Triaz), 97.23 (4 × $C_{1\ Gluc}$), 95.64 (9 × $C_{1\ Fuc}$), 81.45 (4 × $C_{3\ Gluc}$), 80.57 (4 × $C_{2\ Gluc}$), 77.27 (4 × $C_{4\ Gluc}$), 71.11 (9 × $C_{4\ Fuc}$), 70.79 – 70.09 (4 × C_7, -$\underline{C}H_2$-O-), 69.98 (4 × $C_{5\ Gluc}$), 69.73 (4 × $C_{6\ Gluc}$), 69.10 (-$\underline{C}H_2$-O-), 68.04 (9 × C Fuc: C_3 or C_2), 67.90 (9 × C Fuc: C_3 or C_2), 66.93 (-$\underline{C}H_2$-O-), 66.80 (Cq Trt), 64.72 (9 × $C_{5\ Fuc}$), 61.21 (9 × O-$\underline{C}H_2$-Triaz), 55.28 (4 × OC$\underline{H}_3$), 47.39 – 47.07 (Triaz-$\underline{C}H_2$-C), 37.57 (C_8), 36.9 – 36.0 (3 × CONH-$\underline{C}H_2$-) 32.07 (C_9), 31.23 – 30.82 (12 × -$\underline{C}H_2$-), 20.86 (9 × $\underline{C}H_3$ Ac), 20.72 (9 × $\underline{C}H_3$ Ac), 20.68 (9 × $\underline{C}H_3$ Ac), 15.89 (9 × $C_{6\ Fuc}$).

Dendrimer IIi: To a solution of **IIf** (60.0 mg, 4.36 µmol, 1 equiv.) in MeOH (3.14 mL) was added aq 1M sodium hydroxide (3.14 mL). The reaction mixture was stirred for 48 hours at room temperature and neutralized with aq HCl 1M (3.14 mL) and concentrated. The residue was purified by column chromatography on Sephadex G25 to obtain after lyophilisation **IIi** as a white foam (11mg, 41%). MS MALDI m/z [M+Na]+ calcd for $C_{255}H_{413}N_{31}NaO_{145}S^+$ 6284.55 found 6284.92.

Dendrimer IIf : To a solution of **IIc** (31 mg, 14.3 µmol, 1 equiv.) and **6** (330 mg, 257 µmol, 18 equiv.) in dioxane (5 mL) were added a solution of $CuSO_4$, 5 H_2O (16 mg, 64µmmol, 0.5 equiv. / azide) and sodium ascorbate (18 mg, 90 µmol, 0.7 equiv. / azide) in water (1 mL). The mixture was stirred overnight at room temperature and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with aq Na_2EDTA (2 × 5 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified by column chromatography on silica gel (CH_2Cl_2/AcOEt/MeOH 5:4:1) to get **IIf** (60 mg, 30%) as a white foam.^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0 – 164.2 (72 × $\underline{C}$O Bz), 143.8 – 143.6 (9 × Cq Triaz), 132.4 – 132.0 (Car), 128.9 – 126.9 (Car), 122.1 – 122.0 (9 × $\underline{C}$H Triaz), 97.2 (9 × $C_{1\ Man}$), 96.9 (9 × $C_{1\ Man}$), 96.2 (4 × $C_{1\ Glc}$), 80.4 (4 × $C_{3\ Glc}$), 79.5 (4 × $C_{2\ Glc}$), 76.5 (4 × $C_{4\ Glc}$), 76.4 ($\underline{C}$H), 69.2 – 66.8 (-$\underline{C}H_2$-O-, 18 × $C_{3\ Man}$, 4 × $C_{5\ Glc}$, 4 × $C_{6\ Glc}$, 4 × C_7), 68.2 (18 × $C_{5\ Man}$), 66.8 (-$\underline{C}H_2$-O-), 66.0 (-$\underline{C}H_2$-O-), 65.5 (18 × $C_{4\ Man}$), 62.9 (18 × $C_{6\ Man}$), 61.6 (9 × O-$\underline{C}H_2$-Triaz), 54.2 (4 × O$\underline{C}H_3$), 46.5 – 46.10 (9 × Triaz-$\underline{C}H_2$-C), 30.2 – 28.7 (12 × -$\underline{C}H_2$-).

Dendrimer IIg: To a solution of **IId** (20.0 mg, 3.54 µmol, 1 equiv.) in MeOH was added 1M aq sodium hydroxide (1.270 mL) The reaction was stirred for 48 hours at room temperature, neutralized with aq 1M HCl (1.270 mL) and concentrated. The residue was purified by column chromatography on Sephadex G25 to give after lyophilisation **IIg** (10.5 mg, 72%). MALDI m/z $[M+Na]^+$ calculated for $C_{174}H_{269}N_{31}NaO_{82}S^+$: 4159.745, found : 4160.020.

Dendrimer IIh: To a solution of **IIe** (21.0 mg, 4.1 µmol, 1 equiv.) in MeOH (1.1 mL) was added an aq 1M sodium hydroxide (1.100 mL). The reaction was stirred for 48 hours at room temperature and neutralized with aq 1M HCl (1.100 mL).The residue was purified by column chromatography on Sephadex G25 to obtain after lyophilisation **IIh** as white foam (12.1 mg, 74%). ^{1}H NMR (300 MHz, D_2O) δ 7.98 – 7.76 (m, 9H, C$\underline{H}$ Triaz), 7.13 (app. s, 15H, H Trt), 4.71 (app. s, 9H, 9 × $H_{1\ Fuc}$), 4.71 (app. s, 4H, 4 × $H_{1\ Gluc}$), 4.64 – 4.46 (m, 18H, 9 × -O-C$\underline{H}_2$-Triaz), 4.43 – 4.20 (m, 18H, 9 × Triaz-C$\underline{H}_2$-C), 3.98 – 2.95 (m, 121H, 12 × -C$\underline{H}_2$-O-, 3 × CONH-C$\underline{H}_2$-, 4 × OC$\underline{H}_3$, 9 × $H_{2\ Fuc}$, 9 × $H_{3\ Fuc}$, 9 × $H_{4\ Fuc}$, 9 × $H_{5\ Fuc}$, 4 × $H_{2\ Gluc}$, 4 × $H_{3\ Gluc}$, 4 × $H_{4\ Gluc}$, 4 × $H_{5\ Gluc}$, 4 × $H_{6\ Gluc}$, 4 × H_7, H_8), 2.13 – 1.87 (br. s, 18H, -C$\underline{H}_2$-), 1.72 – 1.48 (br. s, 6H, -C$\underline{H}_2$-), 1.04 – 0.86 (m, 27H, $H_{6\ Fuc}$). ^{13}C NMR (75 MHz, D_2O) δ 171.76 – 171.70 (4 × $\underline{C}$O amid), 144.33 – 143.96 (Cq ar Trt, 9 × Cq Triaz), 129.11 (6 × Car Trt), 128.15 (6 × Car Trt), 127.17 (3 × Car Trt), 124.81 – 124.59 (9 × $\underline{C}$H Triaz), 98.48 (9 × $C_{1\ Fuc}$), 96.88 (4 × $C_{1\ Gluc}$), 81.07 – 80.91 (4 × $C_{3\ Gluc}$), 79.46 – 79.25 (4 × $C_{2\ Gluc}$), 77.41 – 77.19 (4 × $C_{4\ Gluc}$), 71.66 (9 × C Fuc : C_2 or C_3 or C_4), 69.94 – 69.54 (4 × C_7,12 × -$\underline{C}H_2$-O), 69.44 (9 × C Fuc: C_2 or C_3 or C_4), 69.29 – 69.19 (4 × $C_{5\ Gluc}$), 67.84 (9 × C Fuc: C_2 or C_3 or C_4), 67.18 – 67.15 (4 × $C_{6\ Gluc}$), 66.66 ($C_{5\ Fuc}$), 60.57 (9 × -O-$\underline{C}H_2$-Triaz), 54.88 (4 × O$\underline{C}H_3$), 47.20 – 47.13 (9 × Triaz-$\underline{C}H_2$-C), 36.02 (C_8), 30.84 (C_9), 30.19 – 29.83 (9 × -$\underline{C}H_2$-), 15.21 (9 × $C_{6\ Fuc}$).

Dendrimer IIId: To a solution of **IIIc** (124 mg, 19.71 µmol, 1 equiv.) and **4** (247 mg, 0.6386 mmol, 32.4 equiv.) in dioxane (10 mL) was added a solution of $CuSO_4$, 5 H_2O (66 mg, 0.2661 mmol, 13.5 equiv.) and sodium ascorbate (69 mg, 0.3725 mmol, 18.9 equiv.) in water (2 mL). The reaction was stirred overnight at room temperature and concentrated. A solution of the residue in CH_2Cl_2 (20 mL) was washed with 0.05M aq Na_2EDTA (2× 10 mL), dried over $MgSO_4$, filtered, and concentrated. the residue was purified by column chromatography on silica gel ($CH_2Cl_2$100% then CH_2Cl_2/MeOH 90:10) to give **IIId** (202mg, 61%) as a slightly yellow foam. R_f: 0.50 (CH_2Cl_2/MeOH 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.60 (br s, 27H, HTriaz), 7.35 (d, *J* = 7.7 Hz, 6H, Har Trt), 7.30 – 7.14 (m, 9H, Har Trt), 7.09 – 6.79 (m, 13H, 13H × N$\underline{H}$CO), 5.35 – 5.14 (m, 81H, 27 × $H_{2\ Man}$, 27 × $H_{3\ Man}$, 27 × $H_{4\ Man}$), 4.95 (s, 27H, 27 × $H_{1\ Man}$), 4.88 – 4.75 (m, 54H, 27 × O-C$\underline{H}_{2a}$-Triaz, $H_{1\ Glc}$), 4.73 – 4.58 (m, 27H, O-C$\underline{H}_{2b}$-Triaz), 4.57 – 4.35 (br s, 54H, 27 × Triaz-C$\underline{H}_2$-

C), 4.34 – 4.21 (m, 27H, 27 × $H_{6a\ Man}$), 4.20 – 3.91 (m, 80H, 27 × $H_{5\ Man}$, 27 × $H_{6b\ Man}$, 13 × H_7), 3.90 – 3.48 (m, 104H, 13 × OCH_3, 13 × -CH_2-O-, 13 × $H_{3\ Glc}$, 13 × $H_{6\ Glc}$), 3.48 – 3.07 (m, 54H, 13 × -CONHCH_2-, 13 × $H_{2\ Glc}$, 13 × $H_{4\ Glc}$, H_8), 2.32 – 2.05 (m, 242H, H_9, 39 × -CH_2-, 54 × CH_3 Ac,), 2.03 – 2.00 (br s, 81H, 27 × CH_3 Ac), 1.96 – 1.94 (br s, 81H, 27× CH_3 Ac). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.71 – 169.71 (108 × CO Ac, 13 × NHCO), 144,61 (Cq ar Trt), 143.44 (Cq Triaz), 129.56 – 123.30 (Car), 97.25 (13 × $C_{1\ Glc}$), 96.91 (27 × $C_{1\ Man}$), 81.46 (13 × $C_{3\ Glc}$), 80.58 (13 × $C_{2\ Gluc}$), 77.92 (13 × $C_{4\ Glc}$), 70.81 – 69.74 (39 × O-CH_2-, 13 × $C_{5\ Glc}$,13 × $C_{6\ Glc,}$ 13 × C_7), 69.40 (27× $C_{2\ Man}$), 69.11 (27× $C_{3\ Man}$), 68.73 (27 × $C_{5\ Man}$), 66.95 (Cq Trt), 66.02 (27 × $C_{4\ Man}$), 62.38 (27 × $C_{6\ Man}$), 60.93 (27 × O-CH_2-Triaz), 55.30 (13× OCH_3), 47.52 – 47.28 (27 × Triaz-CH_2-C), 37.72 (C_8), 36.66 – 36.38 (12 × -CONHCH_2-), 31.17 – 30.78 (39 × -CH_2-), 20.92 – 20.74 (108 × CH_3 Ac).

Dendrimer IIIg: To a solution of **IIIc** (20.0 mg, 1.20 µmol) in MeOH (1.30 mL) was added 1M aq sodium hydroxide (1.30 mL). The reaction was stirred for 48 hours at room temperature and neutralized with 1M aq HCl (1.30 mL) and concentrated. The residue was purified by column chromatography on Sephadex G25 to obtain after lyophilisation **IIIg** (7.2 mg, 50%).

DC-SIGN ECD production and purification: DC-SIGN extracellular domain (DC-SIGN ECD) construct was produced and purified as described previously [21]

Surface Plasmon Resonance Experiments: Surface plasmon resonance experiments were performed on a Biacore 3000 using a CM4 chip, functionalized at 5 μL/min. BSA or BSA-Man were immobilized on flow cells using amine-coupling method. Fc1 was prepared as reference surface. Flow cell (Fc) 1, 2, 3 and 4 were activated with 50 μL of a 0.2 M EDC/ 0.05 M NHS mixture. After this step, Fc1 was functionalized with bovine serum albumine (BSA). While Fc2, Fc3 and Fc4 were functionalized with mannosylated bovine serum albumine (BSA-(Manα1-3(Manα1-6)Man), 12 trimannose residues on average) from Dextra laboratories. Then remaining activated groups of both cells were blocked with 30 μL of 1 M ethanolamine. After blocking, the four Fc were treated with 5 μL of 10 mM HCl to remove unspecific bound protein and 5 μL of 50 mM Na_2EDTA to expose surface to regeneration protocol. Finally, 2381 RU of BSA was immobilized on Fc1. The Fc2, Fc3 and Fc4 were respectively immobilized with 1664, 1376, 1847 RU of BSA-Man. For inhibition studies, 20 µM of DC-SIGN ECD mixed with increasing concentrations of inhibiting compounds were prepared in a running buffer composed of 25 mM Tris pH 8, 150 mM NaCl, 4 mM $CaCl_2$, 0.005% P20 surfactant, and 13 µL of each sample was injected onto the surfaces at 5 µL/min flow rate. The resulting sensorgrams were reference surface corrected.

$$y = R_{hi} - \frac{R_{hi} - R_{lo}}{1 + \left(\frac{Conc}{A_1}\right)^{A_2}} \quad (1) \qquad IC_{50} = A_1 \cdot \left(\left(\frac{R_{hi} - R_{lo}}{R_{hi} - 50} \right)^{\frac{1}{A_2}} - 1 \right) \quad (2)$$

The lectin binding responses were extracted from sensorgrams, converted to percent residual activity values (y) with respect to lectin alone binding, and plotted against corresponding compound concentration. The 4-parameter logistic model (eq, 1) was fitted to the plots, and the IC_{50} values were calculated, from equation 2, using the values of fitted parameters (R_{hi}, R_{lo}, A_1 and A_2).

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Supplementary Material

Spectral data are available in supplementary document.

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