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ARTICLE TYPE

Adaptable synthesis of *C*-lactosyl glycoclusters and their binding properties with galectin-3

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We report here the syntheses of mono- to tetravalent glycoclusters containing 1-methylene-*C*-β-lactose. The 1-methylene-*C*-β-lactose moiety has been synthesized from octa-acetyl-β-lactose using the key carbonyl insertion reaction and linked to a series of alkynlated scaffolds via CuAAC reaction to afford mono- to tetravalent glycoclusters. The binding affinities of final products to galectin-3 were found in the range of 10-100 μM.

Introduction

Carbohydrate-protein recognition is essential for numerous biological processes, including cell migration, activation of immune system, virus and bacteria infections and toxin adhesion to cells.[1] However, the binding affinity of an individual monosaccharide to a protein is weak with K_D value in the mM range.[2] Preparation of multivalent glycoclusters has been shown to be an effective approach for enhancing the "carbohydrate-protein" affinity, which can be used as efficient inhibitors of many crucial lectins and enzymes. With the advanced tools of structural biology, the interactions between sugar and proteins have been well understood. [3d] Theoretical calculation has been used in drug design utilizing both the conformations of the ligand molecules and the three-dimensional structure of the ligand-receptor complex.[3d, 4] However, it is difficult to design glycoclusters based on theoretical calculation due to equilibrium of a number of conformations, especially for those possessing flexible scaffolds. Synthesis of structurally diverse glycoclusters is still a powerful tool to search for more effective ligands for lectins.[5, 6]

O-glycosides, which are the most common glycosides in nature, are labile to chemical and enzymatic degradation. *C*-glycosyl compounds are therefore prepared because of their higher stability. [2, 7] Although the synthetic methods and strategies had been improved, [8] synthesis of *C*-alkyl-glycosyl compounds in regioselective and stereoselective way was still a challenge[8i]. Moreover, attempts have been made to construct the *C*-glycosyl glycoclusters but the interactions of *C*-glycosyl glycoclusters with lectins are less explored.

Galectin-3 is a member of the β-galactose-binding protein family and it is involved in numerous biological functions, including initiating the adhesion of human breast and prostate cancer cells to the endothelium by specifically interacting with the cancer associated carbohydrates,[9a] anti-apoptotic activity[9b-c] in several tumor cell types, and the regulation of kidney, lung and liver fibrosis.[9d] Attempts have been made to find efficient ligand interacting with galectin-3,[9e-j] and glycoclusters are one of the most effective derivatives.[5, 9h, 9j]

Herein, we report the synthesis of *C*-β-lactosyl glycoclusters. A precursor containing an azido group was constructed, which was coupled to the alkynlated scaffolds via CuAAC reaction. A molecular library of *C*-lactosyl glycoclusters was constructed, which included mono-, di-, tri- and tetravalent glycoclusters. In order to evaluate their binding properties to lectins, the binding affinities (representing in K_D value) of all synthesized glycoclusters with galectin-3 were determined using Surface Plasmon Resonance (SPR) assay. Their K_D values were in the range of 10 μM to 100 μM. Structure activity relationship (SAR) of these *C*-lactosyl glycocluster is also summarized.

Results and discussion

Synthesis of *C*-lactosyl glycoclusters

Methodologies have been developed for the formation of *C*-glycosyl compounds. Most of the methods are focused on establishing aromatic *C*-glycosyl derivatives[10a-b], whereas few methods are developed for the synthesis of alkyl *C*-glycosyl compounds[10c-f]. Compared with the aromatic *C*-glycosyl compounds, alkyl *C*-glycosyl compounds can provide the flexibility to potentially enhance the interactions between sugar and proteins. However, the synthesis of alkyl *C*-glycosyl compounds often need multiple steps and is limited by the relative poor stereoselectivity at anomeric center[10c, 10e]. To meet the needs of constructing a glycocluster library for biological screening, a quick, efficient and low cost strategy should be developed, which also should allow the introduction of unique functional groups that can be coupled to the scaffold. The system of $Co_2(CO)_8$/Silane/CO developed by Murai S. and co-workers[11] has been successively used to synthesize methylene *C*-glycosyl compounds from a variety of glycoacetates. The formation of siloxymethyl group on the anomeric center via mild conditions allows the introduction of functionalized linkers. In this study, the low cost and readily available octa-*O*-acetyl-β-lactose **1** was

chosen as the starting material (Scheme 1). As shown in Table 1, the reaction conditions including the amount of $Co_2(CO)_8$, substrate scale, temperature, the equivalent of Et_3SiH and solvent were optimized.

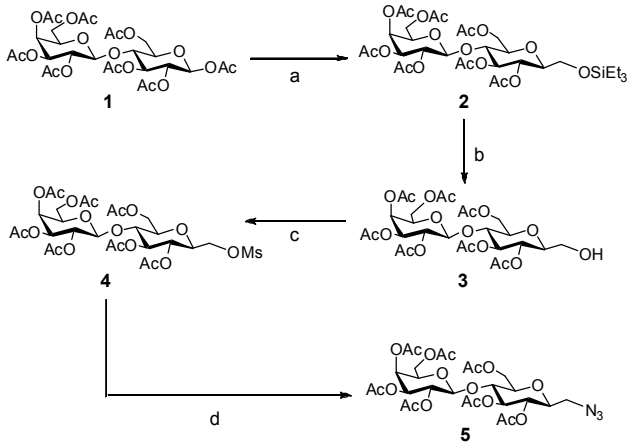
In this work, Et_3SiH was used as an alternative to Me_3SiH and Et_2MeSiH for its lower price and easy handling[11,12]. Under the conditions of using 0.04 eq. $Co_2(CO)_8$ (Table 1, entry 1-3) that was utilized previously by Spak *et al* and Murai *et al* [11,12], only trace amount of product was observed by TLC within 36 h, even after increasing reaction temperature, adding equivalent Et_3SiH, and changing solvent. Most of the starting material **1** was not consumed. With increasing equivalent of $Co_2(CO)_8$ (entry 4), desired product **2** was obtained in 35% yield in DCM at RT, with nearly 50% of the starting material **1** recovered. Further increasing the amount of $Co_2(CO)_8$ to 0.40 eq. (entry 7) did not enhance the yield, but induced a complex mixture of products, which gave **2** in 33% yield. Improved yield was achieved when the reaction was heated at 50°C in benzene with 0.2 eq. $Co_2(CO)_8$. At the scale of 600 mg (entry 6), desired compound **2** was obtained in 71% yield, while increasing the substrate scale to 11 g (entry 5) caused only a slight decrease in the yield (69%), which indicated the reaction was amenable to larger scale synthesis. ^1H NMR analysis indicated the *C*-glycosyl linkage of **2** was β (H-3, 5.20 ppm, $J_{2,3} = J_{3,4} = 9.2$ Hz), confirming no *C*-α-isomer was formed under the conditions (entry 5).

Table 1. Optimization of the synthesis of *C*-lactosyl derivative **2**

Entry	$Co_2(CO)_8$ (equiv.)	Et_3SiH (equiv.)	Temp (°C)	Solvent	Yield (%)[a,d]
1	0.04	6	RT	DCM	trace
2	0.04	10	reflux	DCM	trace
3	0.04	10	reflux	benzene	trace
4	0.20	10	RT	DCM	31
5[b]	**0.20**	**12**	**50**	**benzene**	**69**
6[c]	0.20	12	50	benzene	71
7	0.40	12	50	benzene	33

[a] Isolated yield; [b] Substrate **1** was 11.0g; [c] Substrate **1** was 600mg; [d] The reaction was stopped at 36h by adding pyridine; DCM = dichloromethane.

To avoid the use of toxic HF-pyridine complex or tetra-n-butylammonium fluoride (TBAF) that is hard to remove, a simple and mild mixture of HOAc/THF/H_2O was used to cleave the triethylsilyl group at the temperature from 0°C to RT (Scheme 1). The proton of the newly formed –OH group of **3** appeared as *dd* peaks at 2.34 ppm ($J_{H\text{-}1a,\ OH} = 8.1$ Hz, $J_{H\text{-}1b,\ OH} = 5.7$ Hz), indicating no acetyl migration during the de-silylation process. Notably, compound **3** could be stored as solid on bench top for at least 1 month at ambient temperature without acetyl migration as detected by ^1H NMR spectroscopy (see supplementary data). With the *C*-lactosyl derivative **3** in hand, several strategies could be applied to construct the glycoclusters, because the hydroxyl group could be easily converted to azide, allyl, alkynyl and other groups which could be linked to the scaffold through a number of methods. The efficient synthesis of multivalent glycoclusters requires a chemoselective and high yielding method since a number of saccharide building blocks have to be linked to the scaffold at the same time. Among the numerous strategies[13] that have been applied in the synthesis of multivalent glycoclusters, Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, also called click reaction,[14] is one of the most powerful methods.[6] In the present study, the hydroxyl group of **3** was converted to azide group ($-N_3$), which was conjugated to alkynlated scaffolds.[5]



Scheme 1. Synthesis of *C*-lactosyl azido derivative **5** a: $Co_2(CO)_8$(0.2 eq.), Et_3SiH(12 eq.), CO(balloon pressure), benzene, 36h, 69%; b: HOAc, THF, H_2O, 0°C-RT., overnight; c: MsCl, Et_3N, CH_2Cl_2, 0°C, 30min, 87% from **2**; d: TBAH, NaN_3, n-butanol, H_2O, reflux, 24h, 91%. MsCl = methyl sulfonyl chloride, TBAH = tert-n-butylammonium hydrogen sulfate.

Without chromatographic isolation, compound **3** was directly converted to the corresponding methyl sulfonyl ester **4** using methyl sulfonyl chloride (MsCl) in dichloromethane in 87% yield for two steps from **2**. After treating **4** with sodium azide (NaN_3) in a two-phase reaction consisting of n-butanol and water along with phase transfer catalyst tert-n-butylammonium hydrogen sulfate (TBAH), *C*-lactosyl azidomethane **5** was obtained in 91% yield after stirring for 24 h at refluxing temperature. No desired product was isolated in the absence of TBAH, indicating the necessity of the phase transfer catalyst. A conventional method utilizing sodium azide in dry DMF at 70°C only gave **5** in 30% yield, while using tert-n-butylammonium iodine (TBAI) as promoter did not enhance the yield. Affected by the newly formed azido group, proton H-1a and H-1b of compound **5** appeared at higher field (3.29, 3.24 ppm) in ^1H NMR spectra. In summary, *C*-lactosyl azidomethane **5,** which can be directly coupled to alkynlated scaffold, has been synthesized in 55% overall yield from the simple starting material **1** in four steps.

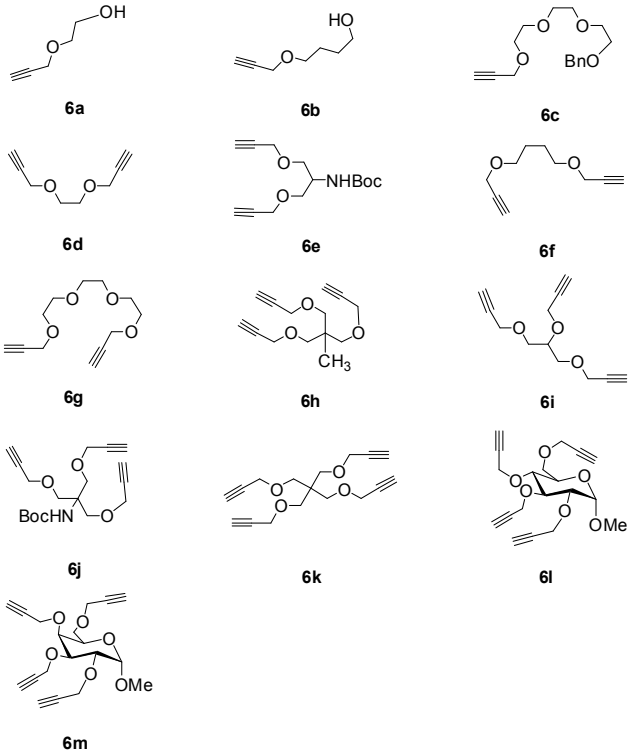


Figure 1. Alkynlated scaffolds **6a-m.**

The binding properties of glycoclusters must be compared with monovalent species to determine the cluster effect[5]. The nature of scaffolds[15, 16], valency, shape, topological aspects[17, 18], and spacer rigidification[19] can greatly influence the binding affinities to lectins. Thus, a series of alkynlated scaffolds were prepared according to the general propargylation method using base/propargyl bromide or other literature procedure[20] (Figure.1).

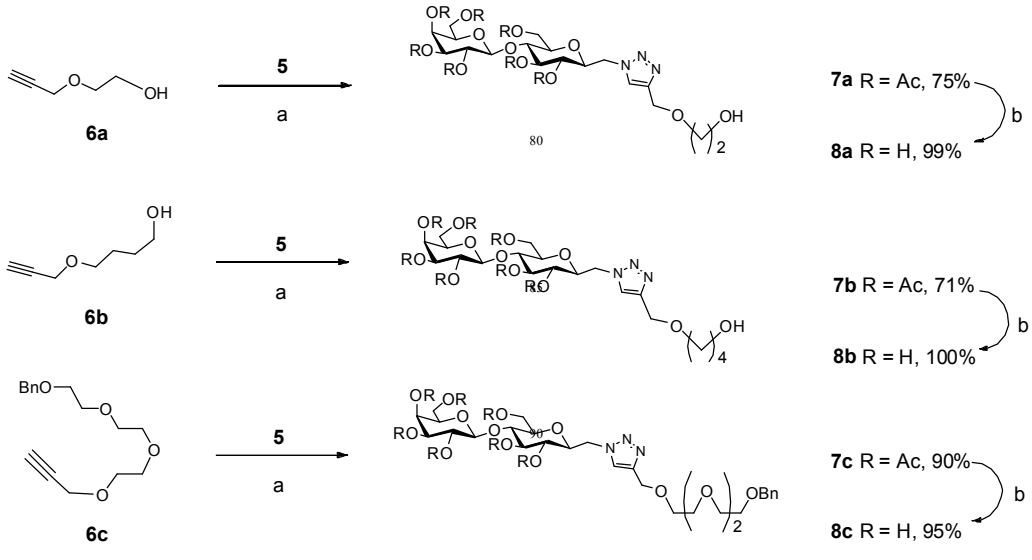
Coupling of the alkynlated scaffolds to azido saccharide **5** was conducted by CuAAC reaction with $CuSO_4$ and sodium ascorbate in a mixture of chloroform, ethanol and water at 40°C.[21] In a model reaction of **5** with divalent scaffold **6g**, protected divalent glycocluster **7g** was obtained in 91% yield. Notably, a slightly lower yield of **7g** was observed when THF/H_2O and DMF/H_2O were used as the solvents, or CuI in toluene was employed at RT. The CuAAC reactions for coupling azido saccharide **5** with alkynlated scaffolds **6a-m** afforded glycocluster **7a-m** in 71-91% yields (Scheme 2, 3 and 4). Fully protected glycoclusters **7a-m** were simply purified by silica gel column chromatography, and the trace amounts of byproducts were successfully removed.

Increasing the length of the linkage between the saccharides is an effective way to improve the "cluster-effect". In order to construct a longer linker, compound **7b** was first converted to the methyl sulfonyl ester using the same method as the synthesis of **4**, which was then transformed to the corresponding azido saccharide **7n** in 87% yield (Scheme 5). Tri- and tetravalent alkynlated scaffolds **6h** and **6k** were both coupled to **7n** through CuAAC reaction under the same conditions, and the tri- and tetravalent *C*-lactosyl glycoclusters **7o** and **7p** were obtained in 80% and 79% yield, respectively. (Scheme 6).

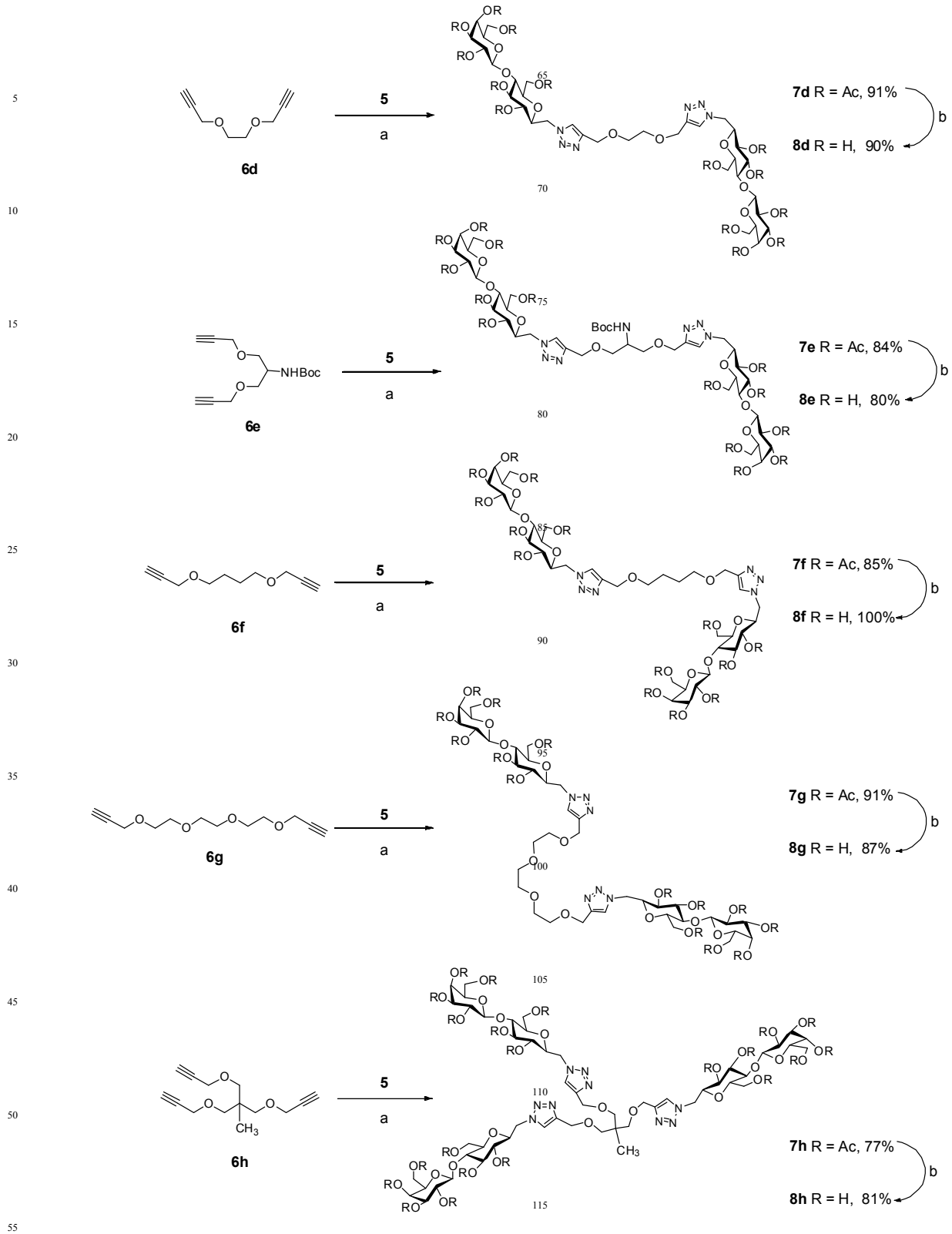
The acetyl protecting groups were successfully removed with catalytic amount of CH_3ONa in MeOH through Zemplèn process at room temperature (Scheme 2, 3, 4 and 6), and the crude products were purified by size-exclusion chromatography, yielding the *C*-lactosyl glycoclusters **8a-m, 8o-p** in 80-100% yield. Furthermore, glycocluster **7e** was treated with dH_2O under refluxing temperature for 2 days to cleave the *NH*-Boc group[22], affording the free amine **8q** (Scheme 7). The structures of the final compounds **8a-m, 8o-q** were confirmed by HRMS, 1D NMR and/or 2D NMR. Clean ^1H NMR spectra were obtained for all products which were used in the SPR binding assay.

Evaluation of the binding affinity to galectin-3 by Surface Plasmon Resonance (SPR)

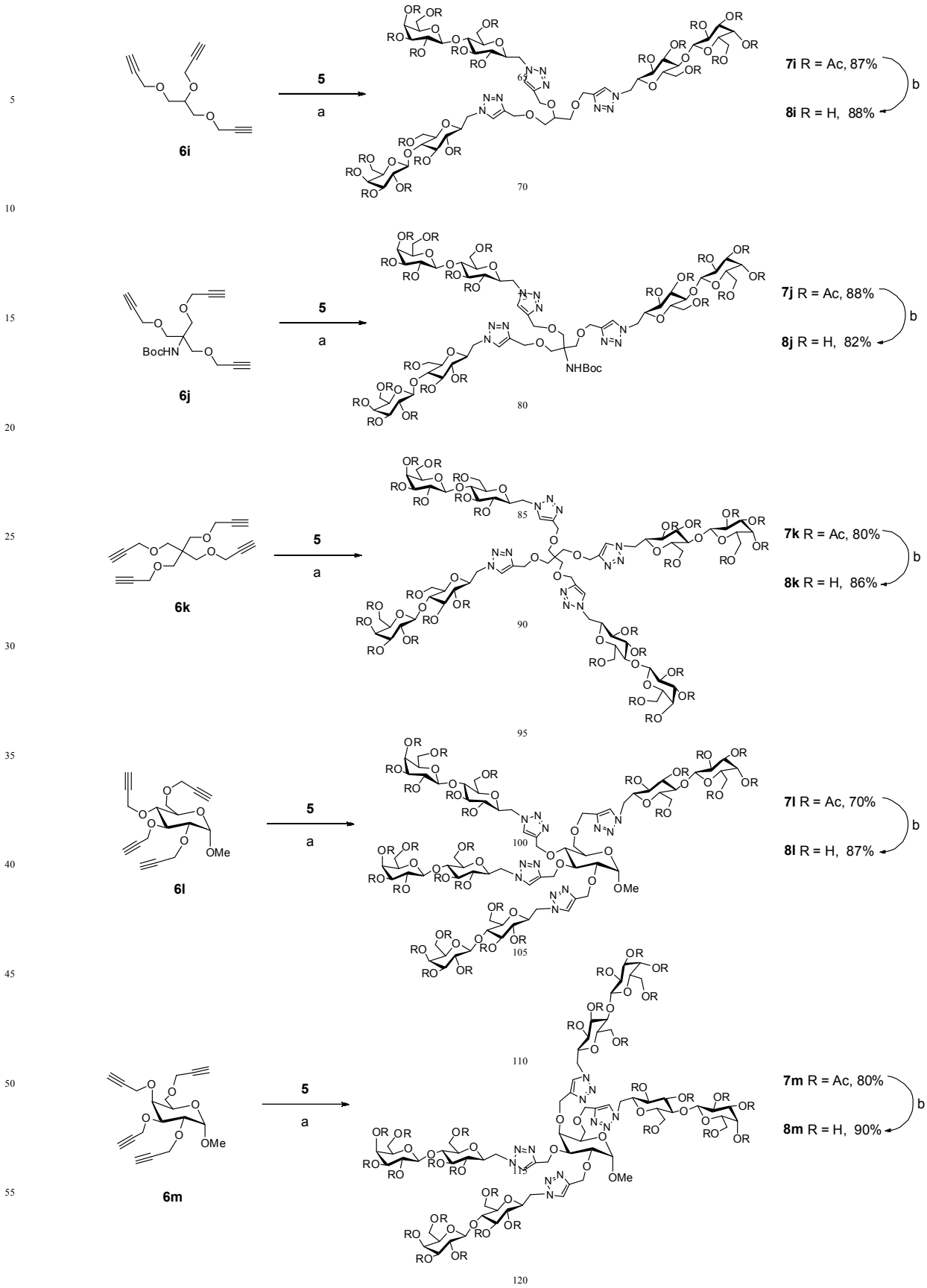
In order to examine the binding properties and the "cluster effect" of the synthesized glycoclusters **8**, a direct-binding assay on a BIAcore 3000 instrument was firstly established in which



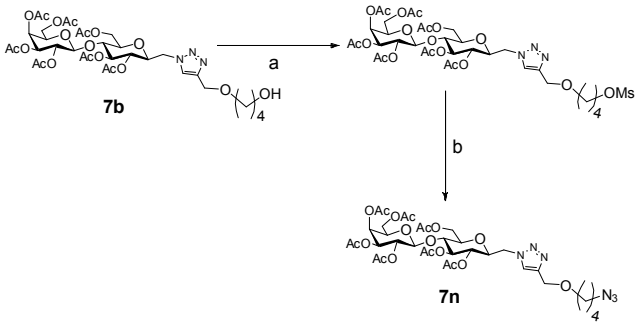
Scheme 2. Synthesis of monovalent *C*-lactosyl derivatives **7a-c, 8a-c.** a: $CuSO_4$, Na ascorbate, EtOH:H_2O:$CHCl_3$ = 1:1:2, 40°C, 24h; b: MeONa, MeOH, RT.,



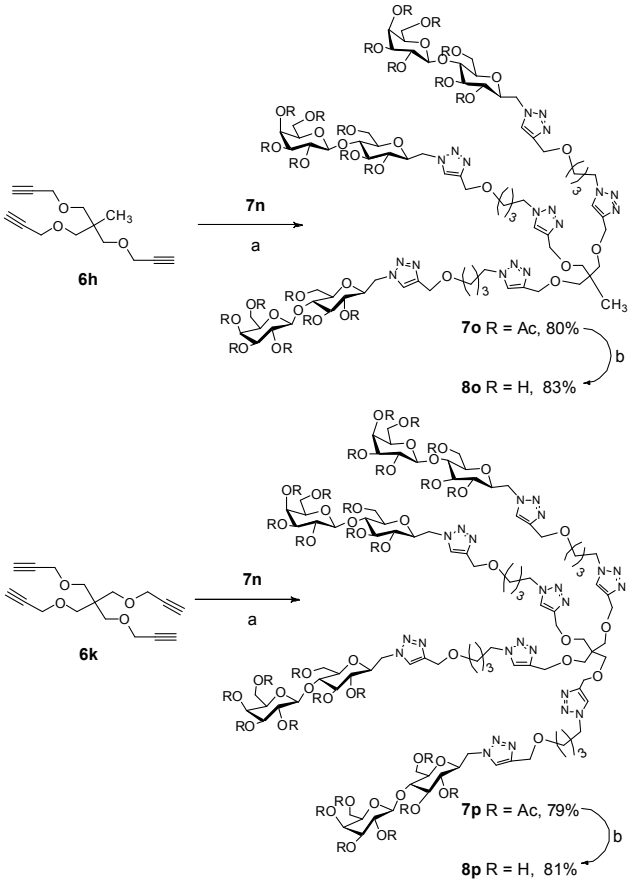
Scheme 3 Synthesis of *C*-lactosyl derivatives **7a-h, 8a-h.** a: $CuSO_4$, Na ascorbate, EtOH:H_2O:$CHCl_3$ = 1:1:2, 40°C, 24h; b: MeONa, MeOH, RT., overnight



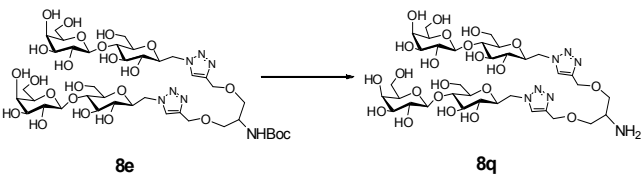
Scheme 4 Synthesis of *C*-lactosyl derivatives **7i-m, 8i-m.** a: $CuSO_4$, Na ascorbate, EtOH:H_2O:$CHCl_3$ = 1:1:2, 40°C, 24h; b: MeONa, MeOH, H_2O, RT., overnight



Scheme 5 Synthesis of azido derivatives **7n**. a: MsCl, Et_3N, CH_2Cl_2, 0°C, 30min; b: TBAH, NaN_3, n-butanol, H_2O, reflux, 24h, 87% from **7b**. MsCl = methyl sulfonyl chloride; TBAH = tert-n- butylammonium hydrogen sulfate.



Scheme 6. Synthesis of tri- and tetravalent *C*-lactosyl glycoclusters **7o, 7p, 8o** and **8p**. a: $CuSO_4$, Na ascorbate, $CHCl_3$/EtOH/H_2O = 2:1:1, 40°C, 24h; b: CH_3ONa (Cat.), MeOH, H_2O, RT, overnight.



Scheme 7. Synthesis of amino derivatives **8q**. Condition: dH_2O, reflux, 2d. 95%.Boc = tert-butyl dicarbonate.

the commercially available *His*-tagged galectin-3 was immobilized onto the surface of the CM 5 chip. Increasing concentrations of the glycoclusters were then injected and flew over the chip surface. The determined dissociation constants (K_D) of the reference compound lactose and other glycoclusters **8**, the potency (β) and the potency per lac-residue (β/N) of each compound are listed in Table 2. Affected by the small molecular weight and low binding affinity, the dissociation constants of lactose, monovalent glycoclusters **8a-c**, divalent glycocluster **8d**, **8e** and trivalent glycocluster **8h** could not be determined properly using BIAcore 3000 instrument, which showed undetectable response enhancement in concentrations up to 2.5 mM. However, using BIAcore T200 instrument which presented a much weaker noise signal of 0.03RU (0.6RU for BIAcore 3000), the dissociation constants of lactose, **8a**, **8e** and **8h** were successfully determined by steady state analysis, but the kinetic analysis was not reliable due to the rapid association and dissociation during the interaction process between the analytes and galectin-3. Except for **8g**, **8f** and **8i** whose K_D values could not be determined reliably by steady state analysis, K_D values of other analytes were determined by steady state analysis. The K_D values of **8g**, **8f** and **8i** were determined by kinetic analysis using Langmuir 1:1 binding model.

Table 2. Binding affinity (K_D μM) of mono-, bi-, tri-, tetravalent *C*-lactosyl glycocluster with galectin-3

Ligand	K_D [a] (μM)	Valency (*N*)	Potency [c] (*β*)	Potency per residue(*β/N*)
lactose	342[a]	1	1	1
8a	1970[a]	1	0.17	0.17
8b	n.d.	1	-	-
8c	n.d.	1	-	-
8d	n.d.	2	-	-
8e	176[a]	2	1.94	0.9
8f	69.3[b]	2	4.94	2.5
8g	306[b]	2	1.12	0.6
8q	15.8[a]	2	21.6	10.8
8h	239[a]	3	1.43	0.5
8i	40.2[b]	3	8.51	2.8
8j	65.9[a]	3	5.19	1.7
8o	38.5[b]	3	8.88	3.0
8k	53.1[a]	4	6.44	1.6
8l	28.0[a]	4	12.2	3.1
8m	41.3[a]	4	8.28	2.1
8p	32.1[a]	4	10.6	2.7

a. K_D value was determined by steady state analysis.
b. K_D value was determined by kinetic analysis fitting to a Langmuir 1:1 binding model.
c. The potency (β) was calculated using lactose as a reference.
n.d. not determined.

As shown in Table 2, K_D value of lactose with galectin-3 was 342 μM which was similar to that reported in the previous works using other methods[23]. To the best of our knowledge, our measurement constitutes the first direct binding assay using SPR for the interaction between immobilized galectin-3 and free lactose, and this experiment mimics the interaction between lactose and cell surface galectin-3 more closely. For the

monovalent species **8a**, a nearly 6 times weaker binding affinity than lactose was found, indicating the adverse effect on binding affinity to galection-3 by the introduction of a methylene triazole ring at the reducing end of lactose.

As reported by Gouin *et al*, the length of the linker does not greatly influence the binding affinity of lactose glycoclusters to galectin-3. [24] In this work, trivalent glycoclusters **8i** and **8o**, tetravalent glycoclusters **8l** and **8p** showed similar binding affinities. While in the case of divalent glycoclusters, **8g** which has a similar length of scaffold as **8o** and **8p**, presented a much weaker binding activity than **8e.** We think this phenomenon can be possibly explained by the global shape of the whole molecule that was greatly affected by the scaffold. In the cases of **8o** and **8p**, in spite of the long linkage between each lac-residue, the lactose units can stay close to each other in three-dimension space and it was supported by the potency per residue, which were 3.0 and 2.7 for **8o** and **8p** respectively. The existence of cluster effect indicates a shorter distance between lac-residues in 3D space. However, in the case of **8g**, no cluster effect was observed (0.6 for potency per residue), indicating the two lac-residues were far apart and behaved like two free lactoses.

The comparison of K_D for the divalent glycoclusters **8e**, **8f** and **8q** shows the influence of the scaffold on the galectin-3 binding activity. These compounds contained the same length linkers between the lactose residues but differed in the functional groups on the linkers. When a –NHBoc group was present on the scaffold (**8f**), the binding activity increased nearly 3 times comparing with the unsubstituted scaffold (**8e**). When –NHBoc was converted to an amino group, the binding affinity increased further as presented by **8q**. These results possibly attributed to the interactions between the amino acid residues of galectin-3 and the substituted groups, for the amino group of **8q** and the amide bond in –NHBoc of **8f** can be hydrogen bond donor and/or acceptor. This conclusion can be partly confirmed by the binding affinities represented by the trivalent glycoclusters, for **8j** with –NHBoc substituted scaffold showed increased binding activity comparing with **8h** containing the methyl substituted scaffold. However, **8i** with unsubstituted scaffold was found to bind to galectin-3 in much stronger affinity than **8j**, and this can be attributed to the hindrance by the lactose epitope, which reduce the chance for the –NHBoc group to interact with galectin-3.

The cluster effect of the glycoclusters is presented as the potency per residue in Table 2. The best result was obtained in **8q** (10.8 β/N)**,** while the cluster effect was much weaker in other compounds that ranged from 0.5 to 3.1 β/N. Nevertheless, our results show that the multivalent *C*-lactosyl glycoclusters are stronger ligands in binding with galectin-3 than the monovalent counterparts.

Conclusion

An efficient and optimized synthetic route was developed for the synthesis of *C*-alkyl-lactosyl glycoclusters from low-cost, readily obtained octa-*O*-acetate-*β*-lactose **1**. This convenient synthesis route allowed the preparation of the *C*-glycoside glycoclusters as promising molecules for biological studies. Binding assay using SPR method indicated these compounds exhibited moderate to high binding with galectin-3. Further studies on the synthesis and biological activity of similar glycoclusters are in progress.

Experimental section

I. Synthesis of *C*-lactosyl glycoclusters

General Procedure

All chemicals were purchased as reagent grade and used without further purification unless otherwise noted. Dry dichloromethane and dry triethylamine were distilled over calcium hydride prior to use. Dry benzene, dry THF and dry toluene were distilled over sodium prior to use. Dry DMF (Extra dry) was purchased from Acros Co. Et_3SiH was dried over freshly activated 4Å molecule sieves for at least 48h, and then degassed with dry Argon. $Co_2(CO)_8$ (containing 1-5% hexane) was weighted under argon atmosphere. CO gas was purchased at a purity of 99.95%. The boiling range of petroleum ether (PE) used as fluent in column chromatography was 65-80°C. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum supported plate (layer thickness 0.2 mm) with solvent system given in each case. Visualization of the spots was achieved by exposure to UV light (254nm) and/or charring with a solution of 5 % (v/v) sulfuric acid in EtOH, then gently heated by a heating-gun. Column chromatography on SiO_2 was carried out with silica gel (200-300 mesh), and size-exclusion chromatography was carried out with Sephadex LH-20. High resolution mass spectra (HRMS) were obtained by Electro Spray Ionization (ESI). For ^1H nuclear magnetic resonance (NMR) spectra, chemical shifts were reported in parts per million (ppm) calibrated with tetramethylsilane (δ = 0. 00 ppm) in $CDCl_3$ and HOD (δ=4.79 ppm) in D_2O, respectively. ^{13}C NMR spectra were calibrated with tetramethylsilane (δ = 0.0 ppm) in $CDCl_3$. Coupling constants (*J*) were given in Hertz (Hz). Except for compounds **2, 3, 4, 5, 7a, 8a, 7b, 8b, 7c, 8c, 7l, 8l, 7m, 8m** and **7n**, the optical rotary values of other compounds could not be measured properly at the concentration range from 0.2 g/100 mL to 2 g/100 mL, which possibly induced by the symmetric scaffold containing in the molecule.

General method for the synthesis of alkynlated scaffolds (method a):

Alkynlated scaffolds **6a**, **6b** and **6f-m** are known compounds and were synthesized under the conditions reported in the literatures listed in [ref. 20]. For new compound **6c**, **6d** and **6e**, the synthesis method was the same as that for **6f**, **6f** and **6j** [ref. 20] using corresponding alcohol, respectively. The corresponding data: yield, R_f value, NMR data, HRMS and NMR spectrum of **6c** and **6e** were given in detail.

General method for CuAAC reaction (method b):

Selected propargyl-containing scaffolds (0.10 mmol) and azido-saccharide **5** (1.10 mol per mol of reacting alkynyl group) were dissolved in a mixture of $CHCl_3/H_2O$/Ethanol (2:1:1, 4 mL). $CuSO_4$ (0.10 mol per mol of reacting alkynyl group) and sodium ascorbate (1.00 mol per mol of reacting alkynyl group) were added. The mixture was stirred in an oil bath at 40°C for 24 h. The mixture was then diluted with $CHCl_3$ and the organic phase was washed with water, brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. Crude product was purified by flash chromatography (solvent systems were shown in each case).

General method for *O*-deacetylation (method c):

The corresponding acetylated glycoclusters (0.06 mmol) were dissolved in MeOH (1.5 mL). CH_3ONa (1 M in MeOH) was added dropwise to adjust the pH to 9. The mixture was stirred at

RT. until TLC indicated the complete consumption of the starting material (for some tetravalent glycoclusters, dH_2O was added when precipitate occurred). HCl (1M aqueous solution) was then added to neutralize the base solution until the pH became 7. Solvent was removed under vacuum. The residue was purified by size-exclusion chromatography eluted with dH_2O, and then lyophilized to dryness.

1-*C*-(2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl) triethylsiloxymethane (2)

$Co_2(CO)_8$ (1.06 g, 3.10 mmol, 0.19 eq.) was added into a 250mL flame-dried flask under CO (balloon pressure) atmosphere. Et_3SiH (38 mL, 0.24 mol, 15 eq.) was then added and the mixture was stirred at RT for 1.5h. A solution of pre-dried octa-*O*-acetyl-β-lactose (11.00 g, 16.2 mmol, 1.0 eq.) in dry benzene (110 mL) was degassed (freeze–pump–thaw procedure) and added using a syringe. After the addition was completed, the flask was evacuated and refilled (×3) with CO gas (The gas was added below the level of the solution). The reaction was stopped after 36h with stirring at 55°C in an oil bath under CO (balloon pressure) atmosphere. The cobalt complex was precipitated by the dropwise addition of pyridine (1.5 mL). Solvent was removed *in vacuo* and the residue was filtered through a silica gel column that was eluted with EtOAc. The filtrate was evaporated and the residue was purified by flash chromatography (EtOAc/PE = 0.2→0.8) to afford **2** (8.51 g, 69%) as white solid. m.p. 70.2-71.5 °C; $[\alpha]^{25}_D$ -16 (*c* 1.0, $CHCl_3$); R_f = 0.47 (SiO_2, PE/EtOAc = 2/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (dd, *J* = 3.3, 0.7 Hz, 1H), 5.19 (dd, *J* = *J* = 9.2 Hz, 1H), 5.11 (dd, *J* = 10.4, 7.9 Hz, 1H), 4.98- 4.93 (m, 2H), 4.50-4.45 (m, 2H), 4.17-4.04 (m, 3H), 3.87 (dt, *J* = 0.7, 6.8 Hz ,1H), 3.75 (t, *J* = 9.5 Hz, 1H), 3.69 (dd, *J* = 11.7, 2.5Hz, 1H), 3.63 (dd, *J* = 11.7, 5.2 Hz, 1H), 3.57 (ddd, *J* = 9.8, 5.0, 1.8 Hz, 1H), 3.49 (ddd, *J* = 9.8, 5.1, 2.5 Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.04 (s, 6H), 2.01 (s, 3H), 1.96 (s, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.57 (q, *J* = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.3, 169.2, 169.1, 169.0, 168.7, 168.1, 100.1, 77.6, 75.5, 75.3, 73.5, 70.0, 69.6, 68.1(C×2), 65.6, 61.4, 61.4, 59.8, 19.9, 19.8, 19.7, 19.6, 19.6(C×2), 19.5, 5.6, 3.4 ppm; HRMS (ESI) *m/z* calcd for $C_{33}H_{53}O_{18}Si$ $[M + H]^+$ 765.2996, found 765.2978; $C_{33}H_{52}NaO_{18}Si$ $[M + Na]^+$ 787.2815, found 787.2796.

1-*C*-(2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methanol (3)

Compound **2** (2.0 g, 2.62 mmol, 1.0 eq.) was dissolved in THF (6.8 mL). H_2O (2.0 mL) was added and then the mixture was cooled to 0°C. HOAc (3.0 mL) was added dropwise and the mixture was stirred at 0°C for 10 h then at RT for 1h. The mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (260 mL). The organic layer was washed with saturated $NaHCO_3$ solution, phosphate buffer (pH = 7.0), brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography (PE/EtOAc = 1/2) to afford **3** as white solid. m.p. 81.1-82.7 °C; $[\alpha]^{25}_D$ -16 (*c* 1.0, $CHCl_3$); R_f = 0.14 (SiO_2, PE/EtOAc = 1/2) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (dd, *J* = 3.3, 0.7 Hz, 1H), 5.25 (t, *J* = 9.2 Hz, 1H), 5.11 (dd, *J* = 10.4, 7.9 Hz, 1H), 4.96 (dd, *J* = 10.4, 3.5 Hz, 1H), 4.96 (dd, *J* = 9.6, 9.6 Hz, 1H), 4.50-4.47 (m, 2H), 4.16-4.06 (m, 3H), 3.88 (m, 1H), 3.76 (m, 1H), 3.70 (m, 1H), 3.62 (ddd, *J* = 9.9, 5.2, 1.8 Hz, 1H), 3.54 (m, 1H), 3.48 (m, 1H), 2.34 (dd, *J* = 8.1, 5.7 Hz, 1H), 2.16 (s, 3H), 2.12(s, 3H), 2.07 (s, 3H), 2.06 (s, 6H), 2.05 (s, 3H), 1.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.4(C×2), 169.2, 169.1, 168.9, 168.1, 100.1, 76.9, 75.6, 75.4, 72.9, 69.9, 69.7, 68.1, 67.9, 65.6, 61.3, 60.6, 59.8, 19.9, 19.8, 19.6, 19.6(C×3), 19.5 ppm; HRMS (ESI) *m/z* calcd for $C_{27}H_{42}NO_{18}$ $[M + NH_4]^+$ 668.2396, found 668.2395.

(2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methyl methanesulfonate (4)

Crude product of **3** (without purification by chromatography) from **2** (2.0 g, 2.62 mmol, 1.0 eq.) was dissolved in dry CH_2Cl_2 (13mL), and cooled to 0°C. Dry Et_3N (1.8 mL, 13.1 mmol, 5.0 eq.) and MsCl (0.8 mL, 7.9 mmol, 3.0 eq.) were added dropwise. The mixture was stirred at 0°C for 30 min and diluted by CH_2Cl_2 (260 mL). The organic layer was washed with water, brine, dried over Na_2SO_4, filtered, then concentrated *in vacuo* and purified by silica gel flash chromatography (PE/EtOAc = 1/2) to afford 4 (1.67 g, 87%) as white solid. $[\alpha]^{25}_D$ -16 (*c* 1.0, $CHCl_3$); R_f = 0.31 (SiO_2, PE/EtOAc = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (dd, *J* = 3.3, 0.8 Hz, 1H), 5.21 (t, *J* = 9.2 Hz, 1H), 5.11 (dd, *J* = 10.4, 7.9 Hz, 1H), 4.99-4.94 (m, 2H), 4.51 - 4.48 (m, 2H), 4.25 - 4.26 (d, *J* = 3.7 Hz, 2H), 4.06-4.16 (m, 3H), 3.85-3.89 (t, *J* = 6.9 Hz, 1H), 3.71-3.80 (m, 2H), 3.62 (ddd, *J* = 9.9, 5.2, 1.8 Hz, 1H), 3.03 (s, 3H), 2.15 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.05 (s, 3H), 2.05 (s, 3H), 1.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.2(C×2), 169.1, 169.0, 168.8, 168.1, 100.1, 75.8, 75.0, 74.3, 72.9, 69.9, 69.7, 68.1, 67.3, 66.2 65.6, 60.9, 69.7, 36.6, 19.8(C×2), 19.6(C×4), 19.5 ppm; HRMS(ESI) *m/z* calcd for $C_{28}H_{41}O_{20}S$ $[M + H]^+$ 729.1906, found 729.1902, calcd for $C_{28}H_{44}NO_{20}S$ $[M + NH_4]^+$ 746.2172, found 746.2152.

1-azido-1-(2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methane (5)

Compound **4** (1.63 g, 2.2 mmol, 1.0 eq.) was dissolved in 1-butanol (13.4 mL) followed by the addition of NaN_3 (2.18 g, 33.5 mmol, 15 eq.), $Bu_4N^+HSO_4^-$ (832.3 mg, 2.46 mmol, 1.1 eq.) and H_2O (2.7 mL). The mixture was stirred at 80°C in an oil bath for 22h and then cooled to RT. The mixture was diluted with EtOAc (240 mL), carefully washed with saturated $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered, then concentrated *in vacuo* and purified by silica gel flash chromatography (PE/EtOAc = 5/7) to afford 5 (1.36 g, 91%) as white solid. m.p. 77.1-79.0 °C; $[\alpha]^{25}_D$ -8 (*c* 1.0, $CHCl_3$), R_f = 0.51(SiO_2, PE/EtOAc = 1/3); ^{1}H NMR(400 MHz, $CDCl_3$) δ 5.35 (dd, *J* = 3.4, 0.7 Hz, 1H), 5.20 (dd, *J* = 9.2, 9.2 Hz, 1H), 5.12 (dd, *J* = 10.4, 7.9 Hz, 1H), 4.97 (t, *J* = 9.6 Hz, 1H), 4.96 (dd, *J* = 10.4, 3.7 Hz, 1H), 4.50 (d, *J* = 8.0 Hz, 1H), 4.49 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.16-4.06 (m, 3H), 3.88 (dt, *J* = 7.0, 0.7 Hz, 1H), 3.78 (dd, *J* = *J* = 9.6, 9.6 Hz, 1H), 3.68-3.61(m, 2H), 3.29 (dd, *J* = 13.6, 2.7 Hz, 1H), 3.24 (dd, *J* = 13.5, 5.9 Hz, 1H), 2.15 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.97 (s, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ 169.5, 169.3, 169.1, 169.1, 168.9, 168.7, 168.1, 100.1, 76.1, 75.5, 75.3, 72.9, 69.9, 69.7, 68.5, 68.1, 65.6, 61.0, 59.8, 49.8, 19.8, 19.8, 19.6(C×3), 19.6, 19.5; HRMS(ESI) *m/z* calcd for $C_{27}H_{41}N_4O_{17}$ $[M + NH_4]^+$ 693.2461, found 693.2456.

1-phenyl-2,5,8,11-tetraoxatetradec-13-yne (6c)

Synthesis was performed using the same procedure as **6f** described in method a, Yield 75%; pale yellow oil; R_f = 0.58 (SiO_2, PE : EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.34-7.33 (m, 5H), 4.57 (s, 2H), 4.19 (d, 2H, *J* = 2.4 Hz), 3.70-3.62 (m, 12H), 2.42 (t, 1H, *J* = 2.4 Hz); ^{13}C NMR (100MHz, $CDCl_3$) : δ 138.3, 128.4, 127.7, 127.6, 79.7, 74.5, 73.2, 70.7, 70.6(C×2), 70.4,

69.5, 69.1, 58.4; HRMS(ESI) m/z calcd for $C_{16}H_{23}O_4$ $[M + H]^+$ 279.1591, found 279.1594, $C_{16}H_{22}NaO_4$ $[M + Na]^+$ 301.1410, found 301.1413.

1,2-di-propargyloxylethane (6d)

Synthesis was performed using the same procedure as **6f** described in method a, Yield 90%; pale yellow oil; R_f = 0.21 (SiO_2, PE : EtOAc=8:1); ^{1}H NMR(400 MHz, $CDCl_3$) δ 4.22 (d, J = 2.4 Hz, 4H), 3.74 (s, 4H), 2.44 (t, J = 2.4 Hz, 2H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 79.6, 74.8, 68.9, 58.6; HRMS(ESI) m/z calcd for $C_8H_{10}NaO_2$ $[M+Na]^+$ 161.0573, found 161.0573.

***N*-(tert-Butyloxycarbonyl) bis [(propargyloxy)methyl] aminomethane (6e)**

Synthesis was performed using the same procedure as **6j** described in method a. Yield 83%; pare yellow oil; R_f= 0.32(SiO_2, CH_2Cl_2: EtOAc=15:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (br s, 1H), 4.16 (d, J = 2.4 Hz, 4H), 3.98-3.88 (m, 1H), 3.64 (dd, J = 9.4, 4.4 Hz, 2H), 3.58 (dd, J = 9.1, 5.8 Hz, 2H), 2.44 (t, J = 2.4 Hz, 2H), 1.45 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 79.5, 74.6, 68.6, 58.5, 49.4, 28.4 ppm; HRMS (ESI) *m/z* calcd for $C_{14}H_{21}NNaO_4$ $[M + Na]^+$ 290.1363, found 290.1362.

2-{[1-((2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}ethan-1-ol (7a)

Synthesis was performed as described in method b. Solvent system CH_2Cl_2/MeOH=20/1; White solid; Yield 75%; m.p. 100.2-101.8 °C; $[\alpha]^{25}_D$ -8 (*c* 1.0, $CHCl_3$); R_f = 0.31 (SiO_2, CH_2Cl_2/MeOH=15/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 5.35 (dd, J = 3.3, 0.7 Hz, 1H), 5.20 (dd, J = J = 9.2 Hz), 5.11 (dd, J = 10.4, 7.9 Hz), 4.97 (dd, J = 10.4, 3.4 Hz, 1H), 4.77(t, J = 9.7 Hz), 4.70(s, 2H), 4.63 (dd, J = 12.0, 2.0 Hz, 1H), 4.61(dd, J = 14.5, 2.3 Hz, 1H), 4.52(d, J = 7.9 Hz, 1H), 4.26 (dd, J = 14.5, 8.2 Hz, 1H), 4.14(dd, J = 11.0, 6.2 Hz, 1H), 4.10-4.05 (m, 2H), 3.89 (dt, J = 6.2, 0.7 Hz, 1H), 3.80-3.75 (m, 4H), 3.70-3.67 (m, 2H), 3.52 (ddd, J = 9.9, 4.7, 2.0 Hz, 1H), 2.67 (br s, 1H, O-H), 2.16(s, 3H), 2.13(s, 3H), 2.11(s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03(s, 3H), 1.97(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.3, 170.1, 170.1, 169.9, 169.7, 168.9, 145.4, 124.2, 101.0, 76.9, 75.9(C×2), 73.7, 72.1, 70.9, 70.7, 69.8, 69.1, 66.6, 64.7, 61.8, 61.2, 60.7, 50.8, 20.9, 20.8, 20.7, 20.6, 20.6(C×2), 20.5 ppm; HRMS(ESI) *m/z* calcd for $[M + H]^+$ $C_{32}H_{46}N_3O_{19}$ 776.2720, found 776.2727.

4-{[1-((2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}butan-1-ol (7b)

Synthesis was performed as described in method b. White solid; Yield 71%; m.p. 104.7-106.3 °C; $[\alpha]^{25}_D$ -8 (*c* 1.0, $CHCl_3$); R_f = 0.21 (SiO_2, CH_2Cl_2:MeOH=15:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 5.35 (dd, J = 3.3, 0.7 Hz, 1H), 5.20 (t, J = 9.2 Hz, 1H), 5.10 (dd, J = 10.4, 7.9 Hz, 1H), 4.96 (dd, J = 10.4, 3.4 Hz, 1H), 4.76 (t, J = 9.7 Hz, 1H), 4.63 (s, 2H), 4.60 (dd, J = 14.9, 2.5 Hz, 1H), 4.55 (dd, J = 12.0, 1.8 Hz, 1H), 4.50 (d, J = 7.9 Hz, 1H), 4.29 (dd, J = 14.6, 8.0 Hz, 1H), 4.14 (dd, J = 11.1, 6.3 Hz, 1H), 4.11-4.05 (m, 2H), 3.89 (dt, J = 6.8, 0.7 Hz, 1H), 3.82-3.75(m, 2H), 3.65-3.58 (m, 4H), 3.55 (dd, J = 10.0, 5.3, 1.9 Hz, 1H), 2.32(br s, 1H), 2.16 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.97 (s, 3H), 1.74-1.62 (m, 4H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ 169.4, 169.3, 169.1, 169.1, 168.9, 168.7, 168.0, 144.3, 123.0, 100.0, 75.7, 75.0, 75.0, 72.7, 69.9, 69.7(C×2), 68.6, 68.1, 65.5, 63.2, 61.5, 60.6, 59.7, 49.8, 28.9, 25.3, 19.8, 19.8, 19.7, 19.6(C×2), 19.6, 19.5 ppm; HRMS(ESI) *m/z* calcd for $C_{34}H_{50}N_3O_{19}$ $[M + H]^+$ 804.3033, found 804.3058.

1-{[1-((2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]}-2,5,8,11-tetraoxa-12-phenyldodecane (7c)

Synthesis was performed as described in method b. Solvent system: CH_2Cl_2/MeOH = 18/1; White solid; Yield 90%; m.p. 103.4-105.1 °C; $[\alpha]^{25}_D$ +8 (*c* 1.0, $CHCl_3$); R_f = 0.44 (SiO_2, CH_2Cl_2/MeOH = 12/1); ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.34-7.26 (m, 5H), 5.34 (dd, J = 3.1, 0.7 Hz, 1H), 5.20 (t, J = 9.2 Hz, 1H), 5.10 (dd, J = 10.3, 7.9 Hz, 1H), 4.96 (dd, J = 10.4, 3.4 Hz, 1H), 4.78 (t, J = 9.8 Hz, 1H), 4.67 (s, 2H), 4.59-4.49 (m, 5H), 4.26 (dd, J = 14.4, 8.1 Hz, 1H), 4.16-4.05 (m, 3H), 3.88 (t, J = 6.6 Hz, 1H), 3.80-3.62 (m, 14H), 3.54 (ddd, J = 9.8, 5.2, 1.4 Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.96 (s, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ 170.3, 170.2, 170.1, 169.9, 169.8, 169.7, 168.9, 145.2, 138.3, 128.3, 127.7, 127.5, 124.1, 100.9, 76.7, 76.1, 75.9, 73.7, 73.1, 70.9, 70.7, 70.6, 70.6, 70.6, 70.5, 69.8, 69.7, 69.4, 69.1, 66.6, 64.6, 61.6, 60.8, 50.8, 20.7(C×2), 20.7, 20.6(C×2), 20.6, 20.5 ppm; HRMS(ESI) *m/z* calcd for $C_{43}H_{60}N_3O_{21}$ $[M + H]^+$ 954.3714, found 954.3722.

1,2-di-{[1-((2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}ethane (7d)

Synthesis was performed as described in method b. Solvent system: CH_2Cl_2/MeOH = 20/1; White solid; Yield 91%; m.p. 115.0-117.9 °C; R_f = 0.50 (SiO_2, CH_2Cl_2/MeOH = 15/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 2H), 5.35 (dd, J = 3.3, 0.7 Hz, 2H), 5.21 (t, J = 9.3 Hz, 2H), 5.11 (dd, J = 10.4, 7.9 Hz, 2H), 4.98 (dd, J = 10.4, 3.4 Hz, 2H), 4.77 (t, J = 9.8 Hz, 2H), 4.66 (s, 4H), 4.59 (dd, J = 14.6, 2.2 Hz, 2H), 4.53-4.50 (m, 4H), 4.29 (dt, J = 14.1, 8.5 Hz, 2H), 4.16-4.05 (m, 6H), 3.89 (dt, J = 7.2, 0.7 Hz, 2H), 3.81 (ddd, J = 10.1, 8.1, 2.1 Hz, 2H), 3.76 (t, J = 9.7 Hz, 2H), 3.72 (s, 4H), 3.55 (ddd, J = 9.9, 5.3, 1.9 Hz, 2H), 2.16 (s, 6H), 2.10 (s, 6H), 2.09 (s, 6H), 2.06 (s, 6H), 2.05 (s, 6H), 2.03 (s, 6H), 1.97 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.3, 170.1, 170.1, 169.9, 169.7, 169.0, 145.1, 124.2, 101.0, 76.7, 76.1, 75.9, 73.7, 70.9, 70.7, 69.7, 69.1, 66.6, 64.6, 61.6, 60.7, 50.8, 20.8, 20.8, 20.7, 20.6(C×2), 20.6, 20.5 ppm; HRMS(ESI) *m/z* calcd for $[M + H]^+$ $C_{62}H_{85}N_6O_{36}$ 1489.4999, found 1489.4974.

***N*-(tert-butyloxycarbonyl)-1,1-di-{{[1-((2,2',3,3',4',6,6'-hepta-O-acetyl-β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy} methyl}aminomethane (7e)**

Synthesis was performed as described in method b. Solvent system: CH_2Cl_2/Acetone = 3/2 → 1/1; White solid; m.p. 114.8-116.3 °C; Yield 84%; R_f = 0.18 (SiO_2, CH_2Cl_2/MeOH = 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.66 (s, 1H), 5.34 (dd, J = 2.8, 0.7 Hz, 2H), 5.21 (t, J = 9.2 Hz, 2H), 5.16 (br s, 1H), 5.11 (dd, J = 10.5, 7.9 Hz, 2H), 4.97 (dd, J = 10.5, 3.4 Hz, 2H), 4.78 (td, J = 9.7, 3.3 Hz, 2H), 4.65-4.54 (m, 8H), 4.52 (d, J = 7.9 Hz, 2H), 4.25 (ddd, J = 14.5, 8.2, 2.8 Hz, 2H), 4.16-4.05 (m, 6H), 3.90-3.87 (m, 3H), 3.83-3.74 (m, 4H), 3.64 (ddd, J = 9.8, 5.4, 1.7 Hz, 2H), 3.59-3.52 (m, 4H), 2.15 (s, 6H), 2.11 (s, 12H), 2.06 (s, 6H), 2.05 (s, 6H), 2.03 (s, 3H), 2.03 (s, 3H), 1.97 (s, 6H), 1.42 (s, 9H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ 170.3, 170.3, 170.3, 170.1, 170.1, 169.9, 169.7, 169.0, 155.4, 145.0, 145.0, 124.3, 101.0, 76.8, 76.7, 76.1, 76.0, 75.9, 73.7, 70.9, 70.7, 69.8, 69.1, 68.9, 66.6, 64.6, 64.6, 61.4, 60.7, 50.8, 49.6, 28.4, 20.8, 20.7,

20.7, 20.6(C×2), 20.6, 20.5 ppm; HRMS(ESI) *m/z* calcd for $C_{40}H_{68}N_7O_{24}$ $[M + H]^+$ 1030.4310, found 1030.4304.

1,4-di-{[1-((2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methyoxy}butane (7f)

Synthesis was performed as described in method b. Solvent system CH_2Cl_2/MeOH = 21/1; White solid; Yield 85%; m.p. 114.7-116.0 °C; R_f = 0.37 (SiO_2, CH_2Cl_2/MeOH = 15/1); ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.66 (s, 2H), 5.35 (dd, J = 3.3, 0.7 Hz, 2H), 5.21 (t, J = 9.23 Hz, 2H), 5.11 (dd, J = 10.4, 7.9 Hz, 2H), 4.97 (dd, J = 10.4, 3.4 Hz, 2H), 4.78 (t, J = 9.8 Hz, 2H), 4.62-4.59 (m, 6H), 4.54-4.50 (m, 4H), 4.28 (dd, J = 14.2, 8.7 Hz, 2H), 4.16-4.05 (m, 6H), 3.89 (dt, J = 6.8, 0.7 Hz, 2H), 3.83-3.73 (m, 4H), 3.57-3.54 (m, 6H), 2.16 (s, 6H), 2.10 (s, 12H), 2.06 (s, 6H), 2.05 (s, 6H), 2.03 (s, 6H), 1.67-1.66 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.2, 169.1, 169.0, 168.9, 168.7, 168.0, 144.4, 123.0, 100.0, 75.7, 75.1, 75.0, 72.7, 69.9, 69.7, 69.5, 68.7, 68.1, 65.6, 63.2, 60.6, 59.8, 49.8, 25.2, 19.8, 19.8, 19.7, 19.6(C×2), 19.6, 19.5 ppm; HRMS(ESI) *m/z* calcd for $C_{64}H_{89}N_6O_{36}$ $[M + H]^+$ 1517.5313, found 1517.5349; calcd for $C_{64}H_{88}N_6NaO_{36}$ $[M + Na]^+$ 1539.5132, found 1539.5170.

1,12-di{[1-((2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]}-2,5,8,11-tetraoxadodecane (7g)

Synthesis was performed as described in method b. Solvent system CH_2Cl_2/MeOH = 13/1; White solid; Yield 91%; m.p. 121.6-122.6 °C; R_f = 0.35 (SiO_2, CH_2Cl_2/MeOH = 10/1); ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.61 (s, 2H), 5.27 (dd, J = 2.8, 0.7 Hz, 2H), 5.13 (t, J = 9.2 Hz, 2H), 5.03 (dd, J = 10.4, 7.9 Hz, 2H), 4.90 (dd, J = 10.4, 3.4 Hz, 2H), 4.71 (t, J = 9.7 Hz, 2H), 4.59 (s, 4H), 4.52 (dd, J = 14.5, 2.0 Hz, 2H), 4.47-4.41 (m, 4H), 4.21 (dd, J = 14.5, 8.1 Hz, 2H), 4.09-3.98 (m, 6H), 3.82 (ddd, J = 10.1, 8.1, 2.1Hz, 2H), 3.76-3.66 (m, 4H), 3.65-3.54 (m, 12H), 3.48 (ddd, J = 9.8, 5.4, 1.7 Hz, 2H), 2.08 (s, 6H), 2.03 (s, 6H), 2.03 (s, 6H), 1.98 (s, 6H), 1.97 (s, 6H), 1.96 (s, 6H), 1.89 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.24, 169.1, 169.0, 168.9, 168.8, 168.0, 144.2, 123.2, 100.0, 75.8, 75.1, 75.0, 72.7, 69.9, 69.8, 69.6, 69.5, 68.9(C×2), 68.2, 65.7, 63.6, 60.7, 59.9, 49.9, 19.8(C×2), 19.7, 19.6(C×2), 19.6, 19.5 ppm; HRMS(ESI) *m/z* calcd for $C_{66}H_{93}N_6O_{38}$ $[M + H]^+$ 1577.5524, found 1577.5546.

1,1,1-tri-{{[1-((2, 2', 3, 3', 4', 6, 6'-hepta-*O*-acetyl-β-lactosyl) methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}ethane (7h)

Synthesis was performed as described in method b. Solvent system PE/Acetone = 10/13; White solid; Yield 77%; m.p. 125.4-126.1 °C; R_f = 0.45 (SiO_2, EtOAc/MeOH = 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 3H), 5.35 (dd, J = 3.3, 0.7 Hz, 3H), 5.22 (t, J = 9.1 Hz, 3H), 5.10 (dd, J = 10.1, 8.1 Hz, 3H), 4.97 (dd, J = 10.4, 3.1 Hz, 3H), 4.79 (t, J = 9.6 Hz, 3H), 4.60-4.51 (m, 15H), 4.26 (dd, J = 14.6, 8.3 Hz, 3H), 4.16-4.05 (m, 9H), 3.89 (t, J = 6.8 Hz, 3H), 3.82 (td, J = 6.8, 0.7 Hz, 3H), 3.77 (t, J = 9.3 Hz, 3H), 3.56 (ddd, J = 9.8, 5.4, 1.7 Hz, 3H), 3.37 (s, 6H), 2.16 (s, 9H), 2.10 (s, 9H), 2.09 (s, 9H), 2.06 (s, 9H), 2.05 (s, 9H), 2.03 (s, 9H), 1.97 (s, 9H), 0.92 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.2, 169.1, 169.0, 168.9, 168.7, 168.0, 144.4, 123.1, 100.0, 75.7, 75.1, 74.9, 72.7, 71.9, 69.9, 69.7, 68.8, 68.1, 65.6, 63.9, 60.6, 59.7, 49.8, 39.8, 19.8, 19.8, 19.7, 19.6(C×2), 19.6, 19.5, 16.5 ppm; HRMS(ESI) *m/z* calcd for $C_{95}H_{130}N_9O_{54}$ $[M + H]^+$ 2260.7698, found 2260.7700.

1,3-di-{{[1-((2, 2', 3, 3', 4', 6, 6'-hepta-*O*-acetyl-β-lactosyl) methyl)-1*H*-1,2,3-triazol-4-yl]methoxy} methyl}-2-{[1-((2, 2', 3, 3', 4', 6, 6'-hepta-*O*-acetyl-β-lactosyl) methyl)- 1*H* -1,2,3-triazol- 4-yl]methoxy}propane (7i)

Synthesis was performed as described in method b. Solvent system CH_2Cl_2/Acetone = 6/5; White solid; Yield 87%; m.p. 122.2-123.8 °C; R_f = 0.29 (SiO_2, CH_2Cl_2/MeOH = 15/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.71 (s, 1H), 7.70 (s, 1H), 5.35 (d, J = 3.1 Hz, 3H), 5.22 (t, J = 9.3 Hz, 3H), 5.10 (dd, J = 10.5, 7.9 Hz, 3H), 4.97 (dd, J = 10.4, 3.4 Hz, 3H), 4.80-4.73 (m, 5H), 4.62-4.56 (m, 7H), 4.53-4.48 (m, 6H), 4.36-4.26 (m, 3H), 4.16-1.05 (m, 9H), 3.91-3.88 (m, 3H), 3.86-3.81 (m, 4H), 3.77 (t, J = 9.3 Hz, 3H), 3.68-3.52 (m, 7H), 2.16 (s, 9H), 2.10 (s, 9H), 2.09 (s, 6H), 2.08 (s, 3H), 2.06 (s, 9H), 2.04 (s, 9H), 2.03 (s, 9H), 1.97 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.3, 170.2, 170.1, 170.1, 169.9, 169.7, 169.0, 145.4, 145.0, 144.9, 124.4, 124.3, 101.0, 76.7, 76.2, 76.1, 75.9, 73.7, 70.9, 70.7, 70.3, 70.2, 69.8, 69.1, 66.6, 64.7, 63.8, 61.7, 61.6, 60.7, 50.8, 29.3, 20.8, 20.8, 20.7, 20.6, 20.6, 20.5 ppm; HRMS(ESI) *m/z* calcd for $C_{93}H_{126}N_9O_{54}$ $[M + H]^+$ 2232.7384, found 2232.7368.

***N*-(tert-butyloxycarbonyl)-1,1,1-tri-{{[1-((2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}aminomethane (7j)**

Synthesis was performed as described in method b. Solvent system: CH_2Cl_2/Acetone = 14/10→10/11; White solid; Yield 88%; m.p. 127.6-128.9 °C; R_f = 0.24 (SiO_2, CH_2Cl_2/MeOH = 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 3H), 5.35 (dd, J = 3.3, 0.7 Hz, 3H), 5.22 (t, J = 9.2 Hz, 3H), 5.10 (dd, J = 10.5, 8.0 Hz, 3H), 5.06 (s, 1H), 4.97 (dd, J = 10.4, 3.3 Hz, 3H), 4.80 (t, J = 9.7 Hz, 3H), 4.61-4.50 (m, 15H), 4.26 (dd, J = 14.6, 8.3 Hz, 3H), 4.16-4.05 (m, 9H), 3.89 (t, J = 6.8 Hz, 3H), 3.82 (td, J = 6.8, 0.7 Hz, 3H), 3.79-3.73 (m, 9H), 3.54 (ddd, J = 9.8, 4.9, 1.8 Hz, 3H), 2.15 (s, 9H), 2.10 (s, 9H), 2.09 (s, 9H), 2.06 (s, 9H), 2.04 (s, 9H), 2.02 (s, 9H), 1.96 (s, 9H), 1.39 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.2, 170.1, 170.1, 170.0, 169.7, 169.0, 154.8, 144.9, 124.4, 101.0, 76.7, 76.1, 75.9, 73.7, 70.9, 70.7, 69.9, 69.1, 66.6, 64.8, 61.5, 60.7, 58.6, 50.8, 28.4, 20.9, 20.8, 20.7, 20.7(C×2), 20.6, 20.5 ppm; HRMS(ESI) *m/z* calcd for $C_{99}H_{138}N_{10}O_{56}$ $[M + 2H]^{2+}$ 1181.4124, found 1181.4122.

Tetra-{{[1-((2, 2', 3, 3', 4', 6, 6'-hepta-*O*-acetyl-β-lactosyl) methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}methane (7k)

Synthesis was performed as described in method b. Solvent system: CH_2Cl_2/MeOH = 20/1; White solid; Yield 80%; m.p. 128.9-130.3 °C; R_f = 0.36 (SiO_2, CH_2Cl_2/MeOH = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 4H), 5.35 (dd, J = 3.3, 0.7 Hz, 4H), 5.22 (t, J = 9.0 Hz, 4H), 5.10 (dd, J = 10.4, 7.9 Hz, 4H), 4.97 (dd, J = 10.4, 3.3 Hz, 4H), 4.79 (t, J = 9.7 Hz, 4H), 4.59-4.50 (m, 20H), 4.24 (dd, J = 14.5, 8.3 Hz, 4H), 4.16-4.05 (m, 12H), 3.90 (t, J = 6.9 Hz, 4H), 3.84 (dt, J = 6.8, 0.7 Hz, 4H), 3.77 (t, J = 9.3 Hz, 4H), 3.56 (ddd, J = 9.8, 5.4, 1.7 Hz, 4H), 3.47 (s, 8H), 2.15 (s, 12H), 2.09 (s, 12H), 2.07 (s, 12H), 2.05 (s, 12H), 2.04 (s, 12H), 2.02 (s, 12H), 1.96 (s, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.2, 169.1, 169.0, 168.9, 168.7, 168.0, 144.3, 123.2, 100.0, 75.6, 75.1, 74.8, 72.7, 69.9, 69.6, 68.9, 68.1, 68.0, 65.6, 63.8, 60.6, 59.7, 49.8, 44.3, 19.8, 19.8, 19.7, 19.6(C×3), 19.5 ppm; HRMS(ESI) *m/z* calcd for $C_{125}H_{170}N_{12}O_{72}$ $[M + 2H]^{2+}$ 1495.5000, found 1495.4997.

Methyl{2,3,4,6-tetra-*O*-{[1-((2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methyl}}-α-D-

glucopyranoside (7l)

Synthesis was performed as described in method b. Solvent system CH_2Cl_2/Acetone = 1/1; White solid; Yield 70%; m.p. 140.3-141.8 °C; $[\alpha]^{25}_D$ +32 (*c* 1.0, $CHCl_3$); R_f = 0.24 (SiO_2, $CHCl_3$/MeOH = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.90 (s, 1H), 7.80 (s, 1H), 7.72 (s, 1H), 5.35 (d, *J* = 3.2 Hz, 4H), 5.26-5.20 (m, 4H), 5.12-5.06 (m, 4H), 5.02-4.95 (m, 5H), 4.91-4.71 (m, 10H), 4.64-4.41 (m, 14H), 4.33-4.23 (m, 4H), 4.16-4.05 (m, 12H), 3.91-3.85 (m, 8H), 3.83-3.73 (m, 6H), 3.69-3.66 (m, 2H), 3.57-3.47 (m, 6H), 3.37 (s, 3H), 2.15 (s, 12H), 2.11 (s, 3H), 2.10 (s, 6H), 2.09 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.05 (s, 15H), 2.04 (s, 9H), 2.04 (s, 3H), 2.02 (s, 3H), 2.02 (s, 3H), 2.02(s, 3H), 2.01 (s, 3H), 2.01 (s, 3H), 1.96 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3-169.0 (C×28, *C*OCH$_3$), 145.2, 144.8(C×2), 144.6, 125.0, 124.8(C×2), 124.6, 101.0(C×4), 97.6, 81.5, 79.6, 76.7-76.6 (C×4), 76.2, 76.1, 76.1, 76.0, 75.9, 75.9, 75.8, 75.8, 73.8, 73.8, 73.7 (C×2), 70.9 (C×4), 70.7 (C×2), 70.6 (C×2), 69.9 (C×4), 69.1 (C×4), 66.6 (C×4), 64.6 (C×2), 64.5 (C×2), 61.6-61.5(C×4), 60.7(C×4), 55.1, 53.8, 50.9(C×4), 20.9-20.5(CO*C*H$_3$) ppm; HRMS(ESI) *m/z* calcd for $C_{127}H_{172}N_{12}O_{74}$ $[M + 2H]^{2+}$ 1524.5027, found 1524.5048.

Methyl{2,3,4,6-tetra-*O*-{[1-((2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methyl}}-α-D-galactopyranoside (7m)

Synthesis was performed as described in method b. Solvent system CH_2Cl_2/Acetone = 1.5/1.0-1.0/1.2; White solid; Yield 80%; m.p. 141.1-143.3 °C; $[\alpha]^{25}_D$ +28 (*c* 1.0, $CHCl_3$); R_f = 0.30 (SiO_2, $CHCl_3$/MeOH = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.68 (s, 1H), 5.35-5.33 (m, 4H), 5.27-5.19 (m, 4H), 5.12-5.06 (m, 4H), 4.99-4.95 (m, 5H), 4.92-4.86 (m, 2H), 4.84-4.71 (m, 8H), 4.63-4.57 (m, 5H), 4.53-4.40 (m, 8H), 4.36-4.25 (m, 4H), 4.16-4.05 (m, 13H), 3.97 (dd, *J* = 9.8, 3.2 Hz, 2H), 3.93-3.72 (m, 14H), 3.63-3.45 (m, 6H), 3.35 (s, 3H, -OMe), 2.15-1.96 (84H, -COC*H*$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3-169.0 (C C×28, *C*OCH$_3$), 145.2(C×2), 145.1, 144.8, 124.8(C×2), 124.7, 124.5(C×2), 101.0(C×4), 98.3, 81.9, 78.8, 76.7-76.5 (C×4), 76.2-75.9 (C×8), 73.8 (C×4), 70.9 (C×4), 70.7 (C×2), 69.9 (C×2), 69.8 (C×4), 69.1 (C×4), 66.6 (C×4), 65.1 (C×2), 64.3 (C×2), 61.6 (C×4), 60.7(C×4), 55.1, 53.8, 50.9(C×4), 20.8-20.5(CO*C*H$_3$) ppm; HRMS(ESI) *m/z* calcd for $C_{127}H_{172}N_{12}O_{74}$ $[M + 2H]^{2+}$ 1524.5027, found 1524.5028.

1-azido-4-[1-((2,2',3,3',4',6,6'-hepta-*O*-acetyl-β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl] methoxybutane (7n)

Compound **7b** (581 mg, 0.72 mmol, 1.0 eq.) was co-evaporated with dry toluene for twice then dissolved in dry CH_2Cl_2 (3.6 mL) and cooled on an ice-water bath. MsCl (0.11 mL, 1.44 mmol, 2.0 eq.) and dry Et_3N (0.30 mL, 2.16 mmol, 3.0 eq.) were added dropwise. The mixture was stirred for 35min at 0°C under argon atmosphere and then evaporated *in vacuo*. n-butanol (3.6 mL), H_2O (0.9 mL), NaN_3 (702 mg, 10.8 mmol, 15.0 eq.), and $Bu_4N^+HSO_4^-$ (268 mg, 0.79 mmol, 1.1 eq.) were then added and the mixture was stirred at 75°C in an oil bath for 12h. EtOAc (150 mL) was added to dilute the mixture then carefully washed by sat. $NaHCO_3$ aqueous, water and brine. Organic layer was dried over Na_2SO_4, then filtered and evaporated *in vacuo*. Crude product was purified by flash chromatography (CH_2Cl_2/Acetone = 4/1) to give **7n** (524 mg, 87% for two steps from **7b**) as white solid. m.p. 68.3-69.8 °C; $[\alpha]^{25}_D$ -16 (*c* 1.0, $CHCl_3$); R_f = 0.55 (SiO_2, CH_2Cl_2/Acetone = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 5.35 (dd, *J* = 3.3, 0.7 Hz, 1H), 5.20 (t, *J* = 9.3 Hz, 1H), 5.10 (dd, *J* = 10.4, 7.9 Hz, 1H), 4.97 (dd, *J* = 10.4, 3.4 Hz, 1H), 4.78 (t, *J* = 9.6 Hz, 1H), 4.81 (s, 2H), 4.60 (dd, *J* = 14.5, 2.3 Hz, 1H), 4.54 (dd, *J* = 12.1, 1.8 Hz, 1H), 4.50 (d, *J* = 7.9 Hz, 1H), 4.27 (dd, *J* = 14.7, 8.2 Hz, 1H), 4.14 (dd, *J* = 11.2, 6.3 Hz, 1H), 4.10-4.05 (m, 2H), 3.88 (t, *J* = 7.1 Hz, 1H), 3.82-3.73 (m, 2H), 3.58-3.52 (m, 3H), 3.29 (m, 2H), 2.15(s, 3H), 2.11 (s, 3H), 2.10(s, 3H), 2.05(s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.97 (s, 3H), 1.70-1.67 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.2, 170.1, 170.1, 169.9, 169.7, 169.0, 145.4, 124.1, 101.0, 76.9, 76.1, 76.1, 73.7, 70.9, 70.8, 70.1, 69.8, 69.2, 66.6, 64.3, 61.6, 60.8, 51.3, 50.9, 26.8, 25.8, 20.8(C×2), 20.7, 20.6(C×2), 20.6, 20.5 ppm; HRMS(ESI) *m/z* calcd for $C_{34}H_{49}N_6O_{18}$ $[M + H]^+$ 829.3098, found 829.3075.

1,1,1-tri-{{[1-(4-((((2, 2', 3, 3', 4', 6, 6'-hepta-*O*-acetyl-β-lactosyl)methyl)-*1H*-1,2,3-triazol-4-yl)methoxy)butyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}ethane (7o)

Synthesis was performed as described in method b. Solvent system CH_2Cl_2/Acetone = 2/3; White solid; Yield 80%; m.p. 103.1-104.5 °C; R_f = 0.25 (SiO_2, CH_2Cl_2/Acetone = 2/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 3H), 7.56 (s, 3H), 5.35 (dd, *J* = 3.3, 0.7 Hz, 3H), 5.20 (t, *J* = 9.2 Hz, 3H), 5.11 (dd, *J* = 10.5, 8.0 Hz, 3H), 4.97 (dd, *J* = 10.5, 3.4 Hz, 3H), 4.77 (t, *J* = 9.6 Hz, 3H), 4.62-4.51 (m, 21H), 4.37 (t, *J* = 7.3 Hz, 6H), 4.28 (dd, *J* = 14.6, 8.3 Hz, 3H), 4.16-4.05 (m, 9H), 3.90 (t, *J* = 7.0 Hz, 3H), 3.82-3.74 (m, 6H), 3.58-3.53 (m, 9H), 3.36 (s, 6H), 2.15 (s, 9H), 2.10 (s, 9H), 2.09 (s, 9H), 2.05 (s, 9H), 2.04 (s, 9H), 2.03 (s, 9H), 2.02-1.99 (m, 6H), 1.97 (s, 9H), 1.66-1.59 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.2, 170.1, 170.1, 169.9, 169.7, 169.0, 145.4, 145.1, 124.2, 122.4, 101.0, 76.8, 76.0, 75.9, 73.7, 73.0, 70.9, 70.7, 69.7, 69.1, 66.6, 65.1, 64.2, 61.5, 60.7, 53.8, 50.8, 50.0, 40.7, 31.7, 29.3, 27.3, 26.5, 20.8, 20.8, 20.7, 20.6, 20.6(C×2), 20.5, 17.5 ppm; HRMS(ESI) *m/z* calcd for $C_{116}H_{163}N_{18}O_{57}$ $[M + H]^+$ 2720.0404, found 2720.0309.

Tetra-{{[1-(4-((((2, 2', 3, 3', 4', 6, 6'-hepta-*O*-acetyl-β-lactosyl) methyl)-1*H*-1,2,3-triazol-4-yl)methoxy)butyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}ethane (7p)

Synthesis was performed as described in method b. Solvent system: CH_2Cl_2/MeOH = 15/1; White solid; Yield 79%; m.p. 107.1-108.9 °C; R_f = 0.21 (SiO_2, CH_2Cl_2/MeOH = 15/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 4H), 7.60 (s, 4H), 5.35 (dd, *J* = 3.3, 0.7 Hz, 4H), 5.20 (t, J = 9.0 Hz, 4H), 5.10 (dd, *J* = 10.6, 7.9 Hz, 4H), 4.97 (dd, *J* = 10.4, 3.4 Hz, 4H), 4.77 (t, *J* = 9.7 Hz, 4H), 4.62-4.51 (m, 28H), 4.36 (t, *J* = 7.1 Hz, 8H), 4.28 (dd, *J* = 14.5, 8.3 Hz, 4H), 4.16-4.05 (m, 12H), 3.90 (t, *J* = 7.0 Hz, 4H), 3.80 (td, *J* = 6.8, 0.7 Hz, 4H), 3.76 (t, *J* = 9.3 Hz, 4H), 3.57-3.52 (m, 12H), 3.46 (s, 8H), 2.15 (s, 12H), 2.09 (s, 12H), 2.09 (s, 12H), 2.05 (s, 12H), 2.04 (s, 12H), 2.02 (s, 12H), 2.00-1.97 (m, 8H), 1.96 (s, 12H), 1.66-1.59 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.2, 170.1, 170.0, 169.9, 169.7, 169.0, 145.3, 145.1, 124.2, 122.5, 101.0, 76.8, 76.0, 75.9, 73.7, 70.9, 70.7, 69.8, 69.1, 66.6, 65.0, 64.2, 61.6, 60.7, 50.8, 50.0, 45.2, 29.3, 27.2, 26.5, 20.8, 20.8, 20.7, 20.6(C×3), 20.5 ppm; HRMS(ESI) *m/z* calcd for $C_{153}H_{214}N_{24}O_{76}$ $[M + 2H]^{2+}$ 1801.6804, found 1801.6765.

2-[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxyethan-1-ol (8a)

Synthesis was performed as described in method c. White solid; Yield 99%; m.p. 127.1-128.5 °C; $[\alpha]^{25}_D$ +8 (*c* 1.0, dH_2O); R_f =

0.61 (SiO_2, n-butanol/H_2O/EtOH=1/1/1); ^1H NMR (400 MHz, D_2O) δ 8.09 (s, 1H), 4.83 (dd, J = 14.8, 2.4 Hz, 1H), 4.69 (s, 2H), 4.63 (dd, J = 14.9, 7.1 Hz, 1H), 4.41 (d, J = 7.60 Hz, 1H), 3.90 (d, J = 3.3 Hz, 1H), 3.87 (dd, J = 12.5, 2.3 Hz, 1H), 3.79-3.67 (m, 7H), 3.66-3.62 (m, 4H), 3.59-3.45 (m, 3H), 3.17 (t, J = 9.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 143.9, 126.2, 102.8, 78.3, 78.1, 76.9, 75.7, 75.3, 72.5, 71.0, 70.9, 70.4, 68.5, 62.9, 61.0, 60.3, 60.0, 51.0 ppm; HRMS(ESI) *m/z* calcd for $C_{18}H_{32}N_3O_{12}$ [M + H]$^+$ 482.1981, found 482.1982,$C_{18}H_{31}N_3NaO_{12}$ [M + Na]$^+$ 504.1800, found 504.1802.

4-[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxybutan-1-ol (8b)

Synthesis was performed as described in method c. White solid; Yield 100%; m.p. 129.1-130.1 °C; $[\alpha]^{25}_D$ +4 (*c* 1.0, dH_2O); R_f = 0.67 (SiO_2, n-butanol/H_2O/EtOH=1/1/1); ^1H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 4.83 (dd, J = 14.8, 2.4 Hz, 1H), 4.62 (s, 2H), 4.62 (dd, J = 14.7, 7.1 Hz, 1H), 4.38 (d, J = 7.8 Hz, 1H), 3.89 (d, J = 3.3 Hz, 1H), 3.85 (dd, J = 12.4, 2.1 Hz, 1H), 3.78-3.66 (m, 5H), 3.65-3.60 (m, 2H), 3.58-3.48 (m, 6H), 3.45 (ddd, J = 9.3 , 4.6, 2.0 Hz, 1H), 3.15 (t, J = 9.2 Hz, 1H), 1.63-1.49 (m, 4H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 143.9, 126.2, 102.8, 78.2, 78.1, 76.9, 75.7, 75.3, 72.5, 70.9, 70.3, 69.9, 68.5, 62.5, 61.3, 61.0, 60.0, 51.0, 27.9, 25.1 ppm; HRMS(ESI) *m/z* calcd for $C_{20}H_{36}N_3O_{12}$ [M + H]$^+$ 510.2294, found 510.2296, $C_{20}H_{35}N_3NaO_{12}$ [M + Na]$^+$ 532.2113, found 532.2116.

1-{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]}-2,5,8,11-tetraoxa-12-phenyldodecane (8c)

Synthesis was performed as described in method c. White amorphous solid; Yield 95%; m.p. 118.3-119.5 °C; $[\alpha]^{25}_D$ +4 (*c* 1.0, dH_2O); R_f = 0.75 (SiO_2, 1-butanol/H_2O/EtOH=1/1/1); ^1H NMR (400 MHz, D_2O) δ 8.04 (s, 1H), 7.38-7.34 (m, 5H), 4.77 (dd, J = 14.8, 2.3 Hz, 1H), 4.64 (s, 2H), 4.59-4.54 (m, 3H), 4.37 (d, J = 7.8 Hz, 1H), 3.88 (d, J = 3.3 Hz, 1H), 3.83 (dd, J = 12.4, 2.1 Hz, 1H), 3.78-3.59 (m, 20H), 3.55-3.49 (m, 2H), 3.40 (ddd, J = 9.3, 4.5, 2.0 Hz, 1H), 3.15 (t, J = 9.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 143.8, 137.2, 128.7, 128.4, 128.2, 126.2, 102.8, 78.2, 78.1, 76.9, 75.7, 75.3, 72.8, 72.5, 70.9, 70.4, 69.6, 69.5, 68.9, 68.8, 68.5, 63.0, 61.0, 60.0, 51.0 ppm; HRMS(ESI) *m/z* calcd for $C_{29}H_{46}N_3O_{14}$ [M + H]$^+$ 660.2974, found 660.2984 , $C_{29}H_{45}N_3NaO_{14}$ [M + Na]$^+$ 682.2793, found 682.2790.

1,2-di-{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}ethane (8d)

Synthesis was performed as described in method c. White solid; Yield 90%; m.p. 142.1-144.3 °C; R_f = 0.61 (SiO_2, n-butanol/H_2O/EtOH=1/1/1); ^1H NMR (400 MHz, D_2O) δ 8.06 (s, 2H), 4.81 (dd, J = 14.8, 2.3 Hz, 2H), 4.64-4.58 (m, 6H), 4.39 (d, J = 7.8 Hz, 2H), 3.89 (d, J = 3.3 Hz, 2H), 3.84 (dd, J = 12.5, 2.0 Hz, 2H), 3.78-3.60 (m, 18H), 3.57-3.48 (m, 4H), 3.44 (ddd, J = 9.4, 4.5, 2.0 Hz, 2H), 3.16 (t, J = 9.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 143.7, 126.2, 102.8, 78.2, 78.1, 76.9, 75.7, 75.3, 72.5, 70.9, 70.4, 68.7, 68.5, 62.9, 61.0, 60.0, 51.0 ppm; HRMS(ESI) *m/z* calcd for $C_{34}H_{57}N_6O_{22}$ [M+H]$^+$ 901.3520, found 901.3527, $C_{34}H_{56}N_6NaO_{22}$ [M + Na]$^+$ 923.3340, found 923.3331.

***N*-(tert-butyloxycarbonyl)-1,1-di-{{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}aminomethane (8e)**

Synthesis was performed as described in method c. White solid; Yield 80%; m.p. 155.2-156.8 °C; R_f = 0.69 (SiO_2, n-butanol/H_2O/EtOH = 1/1/1); ^1H NMR (400 MHz, D_2O) δ 8.06 (s, 2H), 4.83 (dd, J = 14.9, 2.2 Hz, 2H), 4.63-4.58 (m, 6H), 4.40 (d, J = 7.5 Hz, 2H), 3.90 (d, J = 3.3 Hz, 2H), 3.86 (dd, J = 12.5, 2.6 Hz, 2H), 3.85 (br s, 1H), 3.80-3.69 (m, 10H), 3.66-3.62 (m, 4H), 3.60-3.50 (m, 8H), 3.44 (ddd, J = 9.1, 4.8, 1.8 Hz, 2H), 3.20 (t, J = 9.2 Hz, 2H), 1.37 (s, 9H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 157.6, 143.8, 126.1, 102.9, 81.0, 78.2, 78.1, 77.0, 75.7, 75.3, 72.5, 70.9, 70.4, 68.9, 68.5, 63.2, 61.0, 60.0, 51.1, 49.7, 27.6 ppm; HRMS(ESI) *m/z* calcd for $C_{40}H_{68}N_7O_{24}$ [M + H]$^+$ 1030.4310, found 1030.4304.

1,4-di-{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methyoxy}butane (8f)

Synthesis was performed as described in method c. White solid; Yield 100%; m.p. 143.4-146.7 °C; R_f = 0.31 (SiO_2, n-butanol/H_2O/EtOH=3/3/2); ^1H NMR (400 MHz, D_2O) δ 8.05 (s, 2H), 4.81 (dd, J = 14.8, 2.3 Hz, 2H), 4.63-4.58 (m, 6H), 4.37 (d, J = 7.8 Hz, 2H), 3.87 (d, J = 3.3 Hz, 2H), 3.84 (dd, J = 12.5, 2.0 Hz, 2H), 3.77-3.64 (m, 10H), 3.63-3.59 (m, 4H), 3.56-3.47 (m, 8H), 3.42 (ddd, J = 9.5, 4.5, 2.1 Hz, 2H), 3.14 (t, J = 9.3 Hz, 2H), 1.59-1.51 (m, 4H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 144.0, 126.2, 102.8, 78.2, 78.1, 76.9, 75.7, 75.3, 72.5, 70.9, 70.3, 69.8, 68.5, 62.5, 61.0, 60.0, 51.0, 25.1 ppm; HRMS(ESI) *m/z* calcd for $C_{36}H_{61}N_6O_{22}$ [M + H]$^+$ 929.3833, found 929.3826.

1,12-di{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]}-2,5,8,11-tetraoxadodecane (8g)

Synthesis was performed as described in method c. White solid; Yield 87%; m.p. 141.0-142.5 °C; R_f = 0.17 (SiO_2, n-butanol/H_2O/EtOH=3/3/2); ^1H NMR (400 MHz, D_2O) δ 8.10 (s, 2H), 4.84 (dd, J = 14.9, 2.4 Hz, 2H), 4.69 (s, 4H), 4.63 (dd, J = 14.8, 7.0 Hz, 2H), 4.42 (d, J = 7.7 Hz, 2H), 3.92 (d, J = 3.3 Hz, 2H), 3.88 (dd, J = 12.4, 2.1 Hz, 2H), 3.81-3.63 (m, 26H), 3.60-3.51 (m, 4H), 3.47 (ddd, J = 9.5, 4.5, 2.1 Hz, 2H), 3.20 (t, J = 9.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 143.8, 126.2, 102.8, 78.3, 78.1, 77.0, 75.7, 75.3, 72.3, 70.9, 70.4, 69.5, 69.5, 68.8, 68.5, 63.0, 61.0, 60.0, 51.0 ppm; HRMS(ESI) *m/z* calcd for $C_{38}H_{65}N_6O_{24}$ [M + H]$^+$ 989.4045, found 989.4023.

1,1,1-tri-{{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}ethane (8h)

Synthesis was performed as described in method c. White solid; Yield 81%; m.p. 164.3-165.8 °C; R_f = 0.61 (SiO_2, n-butanol/H_2O/EtOH=1/1/1); ^1H NMR (400 MHz, D_2O) δ 8.01 (s, 3H), 4.80 (dd, J = 14.9, 2.2 Hz, 3H), 4.58 (dd, J = 14.7, 7.2 Hz, 3H), 4.51 (s, 6H), 4.38 (d, J = 7.8 Hz, 3H), 3.88 (d, J = 3.3 Hz, 3H), 3.83 (dd, J = 12.5, 2.1 Hz, 3H), 3.78-3.59 (m, 21H), 3.57-3.48 (m, 6H), 3.41 (ddd, J = 9.4, 4.4, 2.1 Hz, 3H), 3.02 (s, 6H), 3.17 (t, J = 8.3 Hz, 3H), 0.78 (s, 3H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 144.0, 126.1, 102.8, 78.2, 78.1, 77.0, 75.7, 75.3, 72.5, 72.1, 70.9, 70.4, 68.5, 63.4, 61.0, 60.0, 51.0, 39.9, 16.8 ppm; HRMS(ESI) *m/z* calcd for $C_{53}H_{88}N_9O_{33}$ [M + H]$^+$ 1378.5479, found 1378.5496.

1,3-di-{{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}-2-{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}propane (8i)

Synthesis was performed as described in method c. White solid; Yield 88%; m.p. 167.9-169.3 °C; R_f = 0.45 (SiO_2, n-butanol/H_2O/EtOH=2/1/2); ^1H NMR (400 MHz, D_2O) δ 8.07 (s, 3H), 4.85-4.82 (m, 3H), 4.70 (s, 2H), 4.64-4.57 (m, 7H), 4.40 (d,

J = 7.8 Hz, 3H), 3.90 (d, *J* = 3.3 Hz, 3H), 3.86-3.83 (m, 4H), 3.80-3.50 (m, 31H), 3.45-3.40 (m, 3H), 3.22-3.17 (m, 3H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 144.0, 126.5, 102.9, 78.2, 78.2, 77.0, 76.5, 75.7, 75.3, 72.5, 70.9, 70.4, 68.9, 68.8, 68.5, 63.3, 62.1, 61.0, 60.0, 51.1 ppm; HRMS(ESI) *m/z* calcd for $C_{51}H_{83}N_9NaO_{33}$ $[M + Na]^+$ 1372.4986, found 1372.5018.

N-(tert-butyloxycarbonyl)-1,1,1-tri-{{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}aminomethane (8j)

Synthesis was performed as described in method c. White solid; Yield 82%; m.p. 171.2-173.3 °C; R_f = 0.58 (SiO_2, n-butanol/H_2O/EtOH=1/1/1); ^{1}H NMR (400 MHz, D_2O) δ 8.02 (s, 3H), 4.82-4.81 (m, 3H), 4.59-4.55 (m, 9H), 4.39 (d, *J* = 7.9 Hz, 3H), 3.89 (d, *J* = 3.3 Hz, 3H), 3.83 (dd, *J* = 12.4, 1.9 Hz, 3H), 3.78-3.49 (m, 33H), 3.41 (ddd, *J* = 9.2, 4.1, 2.1 Hz, 3H), 3.20 (t, *J* = 9.2 Hz, 3H), 1.29 (s, 9H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 156.1, 143.8, 126.2, 102.9, 78.2, 78.2, 77.1, 75.8, 75.3, 72.5, 70.9, 70.5, 68.6, 67.7, 63.4, 61.0, 60.1, 58.3, 51.1, 27.6 ppm; HRMS(ESI) *m/z* calcd for $C_{57}H_{95}N_{10}O_{35}$ $[M + H]^+$ 1479.5956, found 1479.5926.

Tetra-{{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}methane (8k)

Synthesis was performed as described in method c. White amorphous solid; Yield 86%; m.p. 178.1-180.2 °C; R_f = 0.61 (SiO_2, n-butanol/H_2O/EtOH=1/1/1); ^{1}H NMR (400 MHz, D_2O) δ 8.01 (s, 1H), 4.83 (dd, *J* = 14.8, 2.1 Hz, 1H), 4.59 (dd, *J* = 14.8, 7.4 Hz, 1H), 4.51 (s, 2H), 4.42 (d, *J* = 7.8 Hz, 1H), 3.92 (d, *J* = 3.3 Hz, 1H), 3.85 (dd, *J* = 12.5, 2.1 Hz, 1H), 3.82-3.52 (m, 9H), 3.43 (ddd, *J* = 9.4, 4.3, 2.1 Hz, 1H), 3.38 (s, 2H), 3.23 (dd, *J* = *J* = 9.13 Hz, 1H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 144.0, 126.1, 102.9, 78.2, 78.1, 77.0, 75.7, 75.3, 72.5, 70.9, 70.4, 68.5, 68.0, 63.4, 61.0, 60.0, 51.1, 44.5 ppm; HRMS(ESI) *m/z* calcd for $C_{69}H_{113}N_{12}O_{44}$ $[M + H]^+$ 1813.6968, found 1813.6990.

Methyl {2,3,4,6-tetra-*O*-{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methyl}}-α-D-glucopyranoside (8l)

Synthesis was performed as described in method c. White solid; Yield 87%; m.p. 197.0-199.0 °C; $[\alpha]^{25}_D$ = +18 (*c* 0.8, dH_2O); R_f = 0.34 (SiO_2, n-butanol/H_2O/EtOH=1/1/1); ^{1}H NMR (400 MHz, D_2O) δ 8.09 (m, 2H), 8.03 (brs, 1H), 7.99 (br s, 1H), 4.83-4.75 (m, 8H), 4.68-4.47 (m, 8H), 4.41-4.35 (m, 4H), 3.90-3.88 (m, 4H), 3.84-3.47 (m, 46H), 3.44-3.36 (m, 5H), 3.34 (s, 3H), 3.24-3.13 (m, 4H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 143.5 (C×4), 126.4 (C×4), 102.9 (C×4), 97.1, 80.4, 78.9, 78.3, 78.3, 78.2 (C×4), 77.1, 77.0, 77.0, 76.9, 76.3, 75.7(C×4), 75.3 (C×4), 72.5 (C×4), 70.9 (C×4), 70.5, 70.5, 70.4, 70.4, 69.1, 68.5 (C×4), 67.5, 65.2, 64.7, 63.2, 63.1 (C×3), 61.0 (C×4), 60.0 (C×4), 55.0(O*C*H$_3$), 51.2, 51.1, 51.1(C×2) ppm; HRMS(ESI) *m/z* calcd for $C_{71}H_{115}N_{12}O_{46}$ $[M + H]^+$ 1871.7023, found 1871.6979.

Methyl{2,3,4,6-tetra-*O*-{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methyl}}-α-D-galactopyranoside (8m)

White solid; Yield 90%; m.p. 195.8-196.6 °C; $[\alpha]^{25}_D$ = +28 (*c* 0.2, dH_2O); R_f = 0.34 (SiO_2, 1-butanol/H_2O/EtOH=1/1/1); ^{1}H NMR (400 MHz, D_2O) δ 8.09 (s, 1H), 8.07 (s, 1H), 8.05 (s, 2H), 4.85-4.75 (m, 8H), 4.65-4.53 (m, 8H), 4.40-4.35 (m, 4H), 4.08 (s, 1H), 3.96 (dd, J = J = 4.0 Hz， 1H)，3.90-3.48 (m, 50H), 3.46-3.36 (m, 5H), 3.29 (s, 3H), 3.25-3.15 (m, 4H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 143.9-143.6 (C×4), 126.5, 126.3 (C×3), 102.9 (C×4), 97.6, 78.2 (C×4), 78.2 (C×4), 77.4, 77.1, 77.0, 76.9, 75.7 (C×4), 75.5, 75.3 (C×4), 74.4, 72.5 (C×4), 70.9 (C×4), 70.5, 70.4 (C×3), 68.7, 68.5 (C×4), 68.3, 64.6, 63.4, 63.2 (C×2), 62.9, 61.0 (C×4), 60.0 (C×4), 55.1, 51.2, 51.1 (C×3) ppm; HRMS(ESI) *m/z* calcd for $C_{71}H_{114}N_{12}NaO_{46}$ $[M + Na]^+$ 1893.6842, found 1893.6828.

1,1,1-tri-{{[1-(4-((((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl)methoxy)butyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}ethane (8o)

Synthesis was performed as described in method c. White solid; Yield 83%; m.p. 120.0-121.9 °C; R_f = 0.45 (SiO_2, n-butanol/H_2O/EtOH=3/1/3); ^{1}H NMR (400 MHz, D_2O) δ 8.03 (s, 3H), 7.91 (s, 3H), 4.81-4.79 (m, 3H), 4.58 (dd, *J* = 14.7, 7.2 Hz, 3H), 4.54 (s, 6H), 4.47 (s, 6H), 4.39 (d, *J* = 7.8 Hz, 3H), 4.36 (t, *J* = 6.9 Hz, 6H), 3.89 (d, *J* = 3.3 Hz, 3H), 3.83 (dd, *J* = 12.5, 2.1 Hz, 3H), 3.79-3.47 (m, 33H), 3.41 (ddd, *J* = 9.4, 4.4, 2.0 Hz, 3H), 3.27 (s, 6H), 3.16 (t, *J* = 9.3 Hz, 3H), 1.90-1.83 (m, 6H), 1.51-1.44 (m, 6H), 0.76 (s, 3H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 144.0 (C×2), 126.1, 124.7, 102.6, 78.2, 78.2, 77.0, 75.7, 75.3, 72.5, 72.1, 70.9, 70.4, 69.3, 68.5, 63.5, 62.6, 61.0, 60.0, 51.0, 50.0, 39.9, 26.2, 25.5, 16.7 ppm; HRMS(ESI) *m/z* calcd for $C_{74}H_{121}N_{18}O_{36}$ $[M + H]^+$ 1837.8185, found 1837.8173.

Tetra-{{[1-(4-((((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl)methoxy)butyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}methane (8p)

Synthesis was performed as described in method c. White amorphous solid; Yield 81%; m.p. 129.3-131.5 °C; R_f = 0.41(SiO_2, n-butanol/H_2O/EtOH=3/1/3); ^{1}H NMR (400 MHz, D_2O) δ 8.03 (s, 4H), 7.89 (s, 4H), 4.80-4.77 (m, 4H), 4.57 (dd, *J* = 14.8, 7.1 Hz, 4H), 4.53 (s, 8H), 4.48-4.39 (m, 12H), 4.33 (dd, *J* = *J* = 7.1 Hz, 4H), 3.90 (d, *J* = 3.3 Hz, 4H), 3.83 (dd, *J* = 12.3, 1.7 Hz, 4H), 3.79-3.45 (m, 44H), 3.41 (ddd, *J* = 9.3, 4.2, 2.0 Hz, 4H), 3.31 (s, 8H), 3.17 (dd, *J* = *J* = 9.3 Hz, 4H), 1.84 (m, 8H), 1.46 (m, 8H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 144.3(C×2), 126.1, 124.8, 102.9, 78.2, 78.2, 77.0, 75.7, 75.3, 72.5, 70.9, 70.4, 69.3, 68.5, 68.0, 63.5, 62.6, 61.0, 60.0, 51.1, 50.0, 44.5, 26.2, 25.5 ppm; HRMS(ESI) *m/z* calcd for $C_{97}H_{158}N_{24}O_{48}$ $[M + 2H]^{2+}$ 1213.5325, found 1213.5324.

{{[1-((β-lactosyl)methyl)-1*H*-1,2,3-triazol-4-yl]methoxy}methyl}amino methane (8q)

Compound **8e** (20 mg, 0.019 mmol) was dissolved in dH_2O (3 mL) and then stirred at refluxing temperature until TLC indicated the complete consumption of the starting material. The mixture was then cooled, concentrated *in vacuo* and purified by size-exclusion chromatography (eluent by dH_2O) then lyophilized to give **8q** as white solid (17 mg, 95%). m.p. 167.1-168.9 °C; R_f = 0.15 (SiO_2, n-butanol/H_2O/EtOH =2/2/3); ^{1}H NMR (400 MHz, D_2O, TFA salt) δ 8.11 (s, 2H), 4.83 (d, *J* = 14.6 Hz, 2H), 4.67-4.60 (m, 6H), 4.38 (d, *J* = 7.8 Hz, 2H), 3.88 (d, *J* = 3.0 Hz, 2H), 3.85 (d, *J* = 12.1 Hz, 2H), 3.78-3.60 (m, 19H), 3.57-3.48 (m, 4H), 3.47-3.41 (m, 2H), 3.18 (t, *J* = 9.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, D_2O, TFA salt) δ 144.2, 126.5, 102.8, 78.3, 78.2, 76.9, 75.7, 75.3, 72.5, 70.9, 70.4, 68.5, 66.6, 63.2, 61.0, 60.1, 51.3, 50.6 ppm; HRMS(ESI) *m/z* calcd for $C_{35}H_{60}N_7O_{22}$ $[M + H]^+$ 930.3786, found 930.3779.

2. Binding affinity (K_D value) measurement using SPR assay

General procedure

Surface Plasmon Resonance (SPR) measurements were carried out on BIAcore 3000 instrument (for compounds: **8f, 8g and 8h-j, 8l-m 8o-q**) and BIAcore T200 (for compounds: lactose, **8a-e** and **8h**) using carboxymethylated sensor chips (CM5, *GE tech*.) at 25°C. Recombinant *His*-tagged human galectin-3 (Ala2-Ile250) was purchased from R&D system (Catalog # 1154-GA-050/CF). PBS (0.01 M, pH = 7.4, without calcium and magnesium) was chosen as running buffer. Solutions of analytes in buffer were filtered through a 0.22 μM micro membrane and degassed before injected. Data were analyzed by using BIAevaluation software version 4.1. or version 2.0.

Method for immobilizing galectin-3

The flow cell (Fc 4) of carboxymethylated sensor chip (CM 5) was first activated by injecting a freshly prepared mixture of EDC(0.2 M) /NHS(0.05 M) 45 μL at a flow rate of 5 μL/min which gave a 280RU and 200RU enhancement of response on BIAcore 3000 and BIAcore T200 respectively. Galectin-3 (100μg/mL) in sodium acetate buffer (pH = 4.5) 50 μL was then injected at a flow rate of 5 μL/min. Ethanolamine (1 M, pH = 8.0) was utilized to block the rest of the unreacted positions by repeated injection into the flow cell (7 min, 10 min, 10 min at flow rate of 20 μL/min, 30 μL/min and 30 μL/min, respectively), and then buffer was allowed to run for another 2.5 h at 5 μL/min to achieve a stable baseline. The final response reached 11000RU and 12000RU in BIAcore3000 and BIAcore T200 respectively. A controlled flow cell (Fc 3) was established by injecting the mixture of EDC/NHS then blocked by ethanolamine.

Method for the SPR direct-binding assay:

Samples were dissolved in PBS at a series of concentrations (listed in supplementary data) and then injected into the flow cell at a flow rate of 40 μL/min for 180 s. Dissociation process was continued for at least 145 s. In the case of **8f**, 0.2% SDS in dH_2O was injected (8-15 μL) to regenerate the chips. *Note: After the injection of SDS, 120μL PBS should be injected for at least 3 times into the flow cell to confirm no SDS was present in the flow cell.*

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Notes and references

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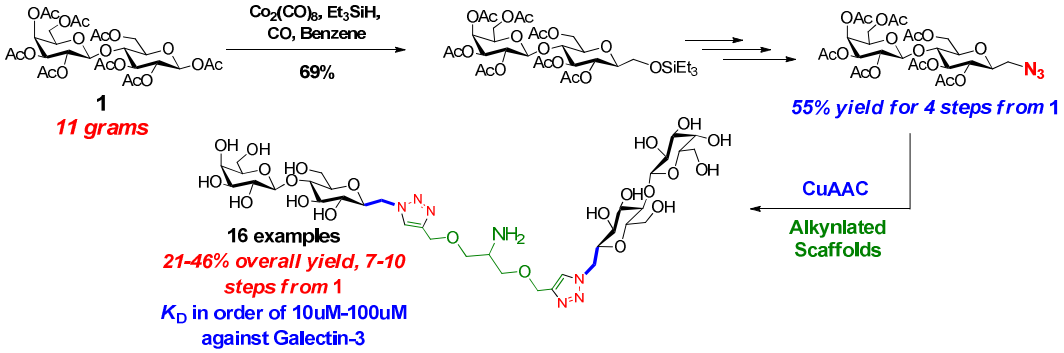

The synthesis of mono- to tetravalent *C*-β-lactosyl glycoclusters has been achieved in good yield. The K_D values of glycoclusters against galectin-3 were tested by SPR assay, and the structure activity relationship has been summarized in detail.