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Bacterial Inhibition

Inhibitory Effect of Multivalent Rhamnobiosides on Recombinant Horseshoe Crab Plasma Lectin Interactions with *Pseudomonas aeruginosa* PAO1

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Abstract: To evaluate the molecular interaction of recombinant horseshoe crab plasma lectin (rHPL) with *Pseudomonas aeruginosa* PAO1, multivalent rhamnobioside derivatives were designed. Eight rhamnoclusters with three or four α(1–3)-rhamnobiosides attached to different central cores, such as methyl gallate, pentaerythritol, and *N*-Boc Tris, through either an ethylene glycol or a tetraethylene glycol linker, were assembled in two consecutive azide–alkyne cycloaddition click reactions. The synthetic method embraced the preparation of two α(1–3)-rhamnobiosides with different linker arms and their conjugation, in stoichiometric or sub-stoichiometric amounts, to propargyl ether-functionalized tri- or tetravalent scaffolds. A divalent derivative and two self-assembling rhamnobiosides were also prepared. The different architectures and valences of the rhamnoclusters provided an opportunity to evaluate the impact of topology and valency on the binding properties toward rHPL. Inhibitory ELISA data showed that all covalently linked rhamnoclusters could inhibit *P. aeruginosa* PAO1 recognition activity of rHPL with high efficacy. Trivalent rhamnobiosides showed a stronger inhibitory effect on *P. aeruginosa* PAO1 binding, and the more flexible clusters on a pentaerythritol or a Tris core were superior to the less flexible methyl gallate-based clusters. Interestingly, the length of the linker arms had a very low impact on the binding ability of the rhamnoclusters. Herein, the two trivalent derivatives on an *N*-Boc protected Tris central core were the best inhibitors. The self-assembling amphiphilic rhamnobioside derivatives were found to display no multivalent effect.

Introduction

A horseshoe crab plasma lectin (HPL), *Tachypleus* plasma lectin 2 derived from Taiwanese *Tachypleus tridentatus*, has been found to recognize certain lipopolysaccharides (LPS) on Gram-negative bacteria.[1] In 2014, pure recombinant HPL (rHPL) was successfully obtained in a soluble and functional form in an *E. coli* expression system. This rHPL is demonstrated to bind selectively to certain bacteria, such as Gram-negative bacterium *Pseudomonas aeruginosa* PAO1 and Gram-positive bacterium *Listeria monocytogenes*. Interestingly, its bacterial recognition activities occur through specific molecular recognition of L-rhamnose in pathogen-associated molecular patterns (PAMPs) on the bacterial surface.[2] L-Rhamnose is a 6-deoxyhexose commonly found in the cell walls and capsules of many pathogenic bacteria. In addition, rhamnose is an important unit in PAMPs and plays crucial roles in fundamental aspects of bacterial physiology, such as antibiotic resistance.[3]

The interaction between rHPL and pathogenic bacteria can be exploited for diagnostic and therapeutic applications. Therefore, further characterization of the glycan-binding specificity of rHPL by using potent carbohydrate inhibitors are of great importance. Because the lectin–glycan interaction at the monovalent level is weak,[4] multivalent rhamnoside derivatives were examined for potentially enhanced binding.

In a preliminary inhibitory ELISA study with α(1–2)- and α(1–3)-rhamnobioses (Figure S1) and higher rhamnooligosaccharides, we have found that the α(1–3)-linked rhamnobiose could inhibit the interaction between rHPL and bacteria with the highest efficacy (Figure S2). Thus, this disaccharide was used for the synthesis of multivalent derivatives. Multivalency is known to increase the affinity of carbohydrate ligands for lectins through the cluster effect,[5,6] however, proper spacing and

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orientation of the monovalent ligands are required to produce an effective multivalent interaction. Many parameters, including the valency, the structure of the multivalent scaffold, and the size and nature of the linker arm, can influence the binding process.[7,8]

Towards this goal, we prepared two sets of multivalent rhamnobiosides in which the sugar residue was attached to different central cores through either an ethylene glycol or a tetraethylene glycol linker (Figure 1). Ethylene glycol oligomers have found widespread use as spacer arms for multivalent glycoconjugates because they are inexpensive, water soluble, biostable, and their transformation into heterobifunctionalized, click-reaction compatible derivatives is well documented.[9–11] The assembly of rhamnoclusters from the structural elements was envisaged by two consecutive 1,3-dipolar azide–alkyne cycloaddition click reactions. To obtain tri- and tetravalent derivatives of various architectures, simple tri- and tetraols, such as methyl gallate, pentaerythritol, and *N*-Boc-protected tris(hydroxymethyl)aminomethane (Tris) equipped with propargyl moieties (**2**–**4**), were chosen as the multivalent platforms. Tris derivative **4** has the advantage of also having an additional functional group that, after deprotection, provides an opportunity for further functionalization of the multivalent derivatives.

Over the past few years, self-assembly has emerged as an alternative to covalent scaffold synthesis to organize multiple ligands.[12] We also planned to prepare self-assembling derivatives by conjugation of sugar epitope **1** to a decyl chain (**5**) through the aforementioned linkers. We have found previously that this type of amphiphile forms nanoscale aggregates in water[13,14] and provides self-assembled multivalent presentation of the sugar unit.

Herein, we present the preparation of di-, tri-, and tetravalent clusters and derivatives of linker structures that contain α(1–3)-rhamnobioside for self-assembly and evaluation of their inhibitory effects on the interaction of rHPL with *P. aeruginosa* PAO1.

Results and Discussion

The synthesis of glycosyl donor and acceptor building blocks for clickable rhamnobioside **1** started from tetra-*O*-acetyl-L-rhamnopyranose **6**[15] (Scheme 1). Anomeric deacetylation of **6** with benzylamine afforded hemiacetal **7**, which was transformed into trichloroacetimidate donor **8**[16] in 81% yield in two steps. In a parallel reaction path, compound **6** was coupled to propargyl alcohol in the presence of $BF_3{\cdot}Et_2O$ and the product (**9**)[17] was deacetylated under Zemplén conditions to provide known triol **10**.[18] Differentiation of the free hydroxyls of **10** was achieved in three steps: cyclic orthoacetate formation on the 2,3-*cis*-diol, acetylation of the 4-OH group, and regioselective opening of the orthoester by mild acid hydrolysis to give acceptor **11**, which exposes a free hydroxyl group at position C3 for a glycosylation reaction.

Condensation between donor **8** and acceptor **11** upon trimethylsilyl triflate promotion proceeded with complete conversion and full stereoselectivity and provided α-linked disaccharide **1** in 99% yield. The required α-selectivity of the glycosylation was ensured by the C2 acetyl participating group of

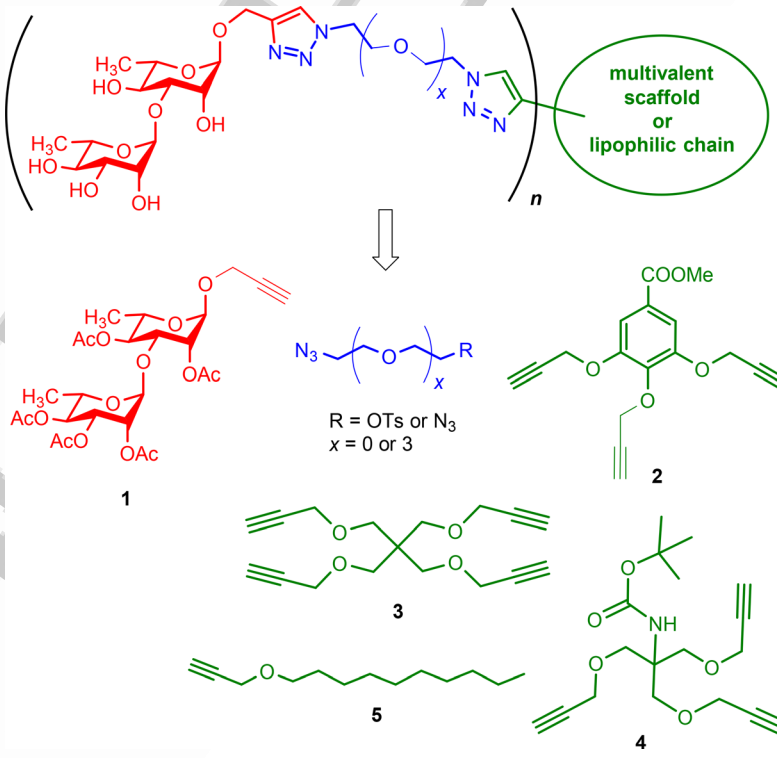

Figure 1. Structure and building blocks for the designed rhamnoclusters.

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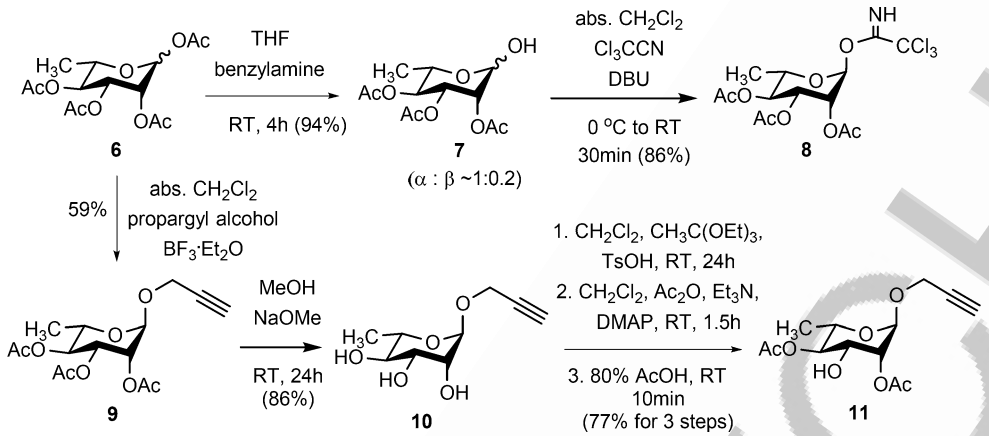
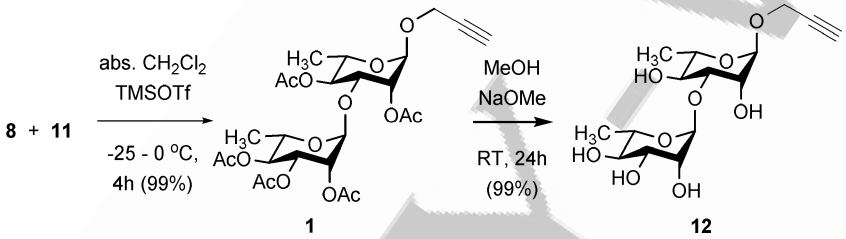


Scheme 1. Synthesis of rhamnosyl donor **8** and rhamnosyl acceptor **11**.



Scheme 2. Synthesis of propargylated α(1–3)-rhamnobioside building block **1** and its transformation to reference compound **12**.

the donor (Scheme 2)■■scheme 2 ok?■■. Compound **1** served as the bioactive building unit for synthesis of the multivalent derivatives. Zemplén deacetylation of **1** by using a catalytic amount of NaOMe in methanol afforded rhamnobioside **12**, which was used in the lectin-binding studies as a reference compound.

The tetraethylene glycol linker arm was attached to the sugar epitope by a Cu^{I}-catalyzed azide–alkyne cycloaddition reaction[19,20] between **1** and diazido derivative **13**[9] with copper(I) iodide as the Cu^{I} source in the presence of triethylamine (Scheme 3). It is known from the literature that CuI and CuBr require at least an amine base to form Cu–acetylide complexes because these copper salts initially occur in stable clusters and require a certain concentration of acetylide anion before the reactive complex can form.[20] Similarly, in our previous experiments[13,14,21] we have found that triethylamine (TEA) mediates the azide–alkyne click reaction efficiently. The application of **13** and **1** in a 2.5:1 ratio had the advantage of giving clickable linker-armed **14** and bivalent **15** in one step. For the biological studies, both derivatives were deacetylated to give **16** and **17** in 76 and 81% yields, respectively. For the large-scale synthesis of **14**, we attempted to drive the reaction to the formation of the monovalent derivative by changing the ratio of reactants **13** and **1** to 6:1. However, the isolated yield of **14** only increased slightly. Then, compound **1** was reacted with readily available heterobifunctionalized tetraethylene glycol derivative **18**,[10] and the tosyl end-group of product **19** was converted to an azido moiety. Fortunately, this transformation provided **14** in 71% yield in two steps. Compound **22** with the ethylene glycol linker arm was prepared analogously from **1** and **20**[11] via **21**, and deacetylation of **22** provided **23** as a further reference compound for lectin-binding studies.

With the azido-functionalized linker-armed carbohydrates in hand, conjugation of **14** and **22** was performed by a Cu^{I}-catalyzed azide–alkyne cycloaddition (CuAAC) with propargylated multivalent scaffolds **2** and **3** to afford tri- and tetravalent rhamnoclusters (Scheme 4). First, disaccharide **14** was reacted with methyl gallate derivative **2**[22] at room temperature in acetonitrile with a 1:1 azide/alkyne ratio and 10 mol% of catalyst relative to the alkyne moieties. Zemplén deacetylation of product **24** gave **25** with three rhamnobioside units attached to the methyl gallate core through long and flexible linkers. Similarly, CuAAC of **2** with rhamnobioside **22** with a short linker arm provided acetylated derivative **26**, and removal of the acetate groups gave desired trivalent cluster **27** with a more compact structure than that of **25**. Tetravalent derivatives **29** and **31** were prepared in an analogous way by using tetra-*O*-propargyl pentaerythritol **3**[23] as the central core. The CuAAC reactions proceeded with high efficacy except for the reaction of **3** with **22**. Our attempts to improve the yield of this reaction by changing the solvent to DMF■■please define■■ and heating the reaction mixture were unsuccessful. After studying how the amount of catalyst affected the reaction, we have found that low equivalents of Cu^{I} were beneficial, and decreas-

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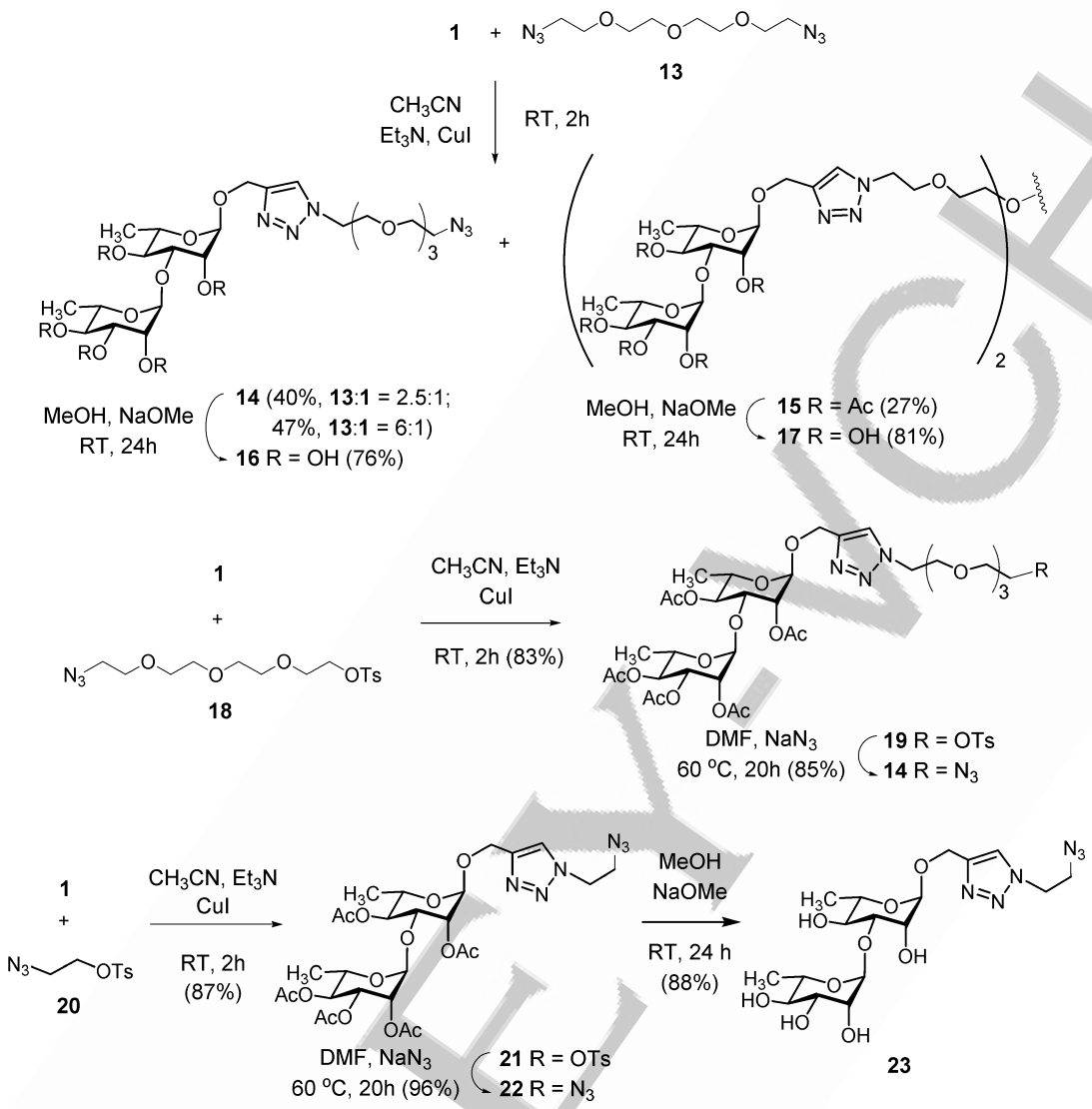

Scheme 3. Functionalization of rhamnobioside **1** with the azido-functionalized linker arms.

ing the catalyst to 2.5 mol% (alkyne units)$^{-1}$ resulted in a two-fold increase in the yield of **30**.

Next, conjugation of a sub-stoichiometric amount of **14** and **22** (2.5–3 equiv for four propargylic groups) to core **3** under click-chemistry conditions led to the formation of **32** and **34**, respectively, which were deacetylated to provide trivalent clusters **33** and **35** (Scheme 5). These derivatives, which differ in architecture from **25** and **27** and in valency from **29** and **31**, can be used to evaluate the impact of the topology and valency of glycoclusters on binding properties. In addition, the untouched propargyl function of compounds **33** and **35** allows further functionalization or multiplication of the glycoclusters.

Unfortunately, the sub-stoichiometric derivatization of tetravalent scaffold **3** proceeded with low efficacy (33% for **32** and 31% for **34**). Therefore, tri-*O*-propargyl derivative **4**[24] was used as the core compound to produce, by using CuAAC followed by deacetylation, trivalent derivatives **37** and **39**. Compounds **37** and **39** have the same advantages as **33** and **35** and could be prepared in significantly higher yields.

Finally, conjugations of **14** and **22** were performed by using CuAAC with propargylated decyl chain **5**[25] to afford **40** and **42** in yields of 86 and 91%, respectively. Deprotection of the acetate esters under Zemplén conditions provided amphiphilic derivatives **41** and **43** (Scheme 6).

The self-assembly of **41** and **43** into multivalent aggregates was studied by using dynamic light scattering (DLS). At the concentration used in the inhibitory ELISA assay, the dimensions of assemblies that resulted from these amphiphiles in water ranged from approximately 9 to 36 nm. The effective diameter of the aggregates was 22.6 nm for **41** and 8.8 nm for **43** at a concentration of 2 mM and 35.7 nm for **41** and 8.9 nm for **43** at a concentration of 4 mM.

rHCPL has been previously reported to recognize bacteria *P. aeruginosa* PAO1; this interaction can be inhibited by the presence of L-rhamnose but not other monosaccharides, which indicates that rHPL recognizes bacteria through the L-rhamnose moiety on the bacterial surface.[2] Here, 2 mM synthetic multivalent rhamnobiosides with different rhamnose contents

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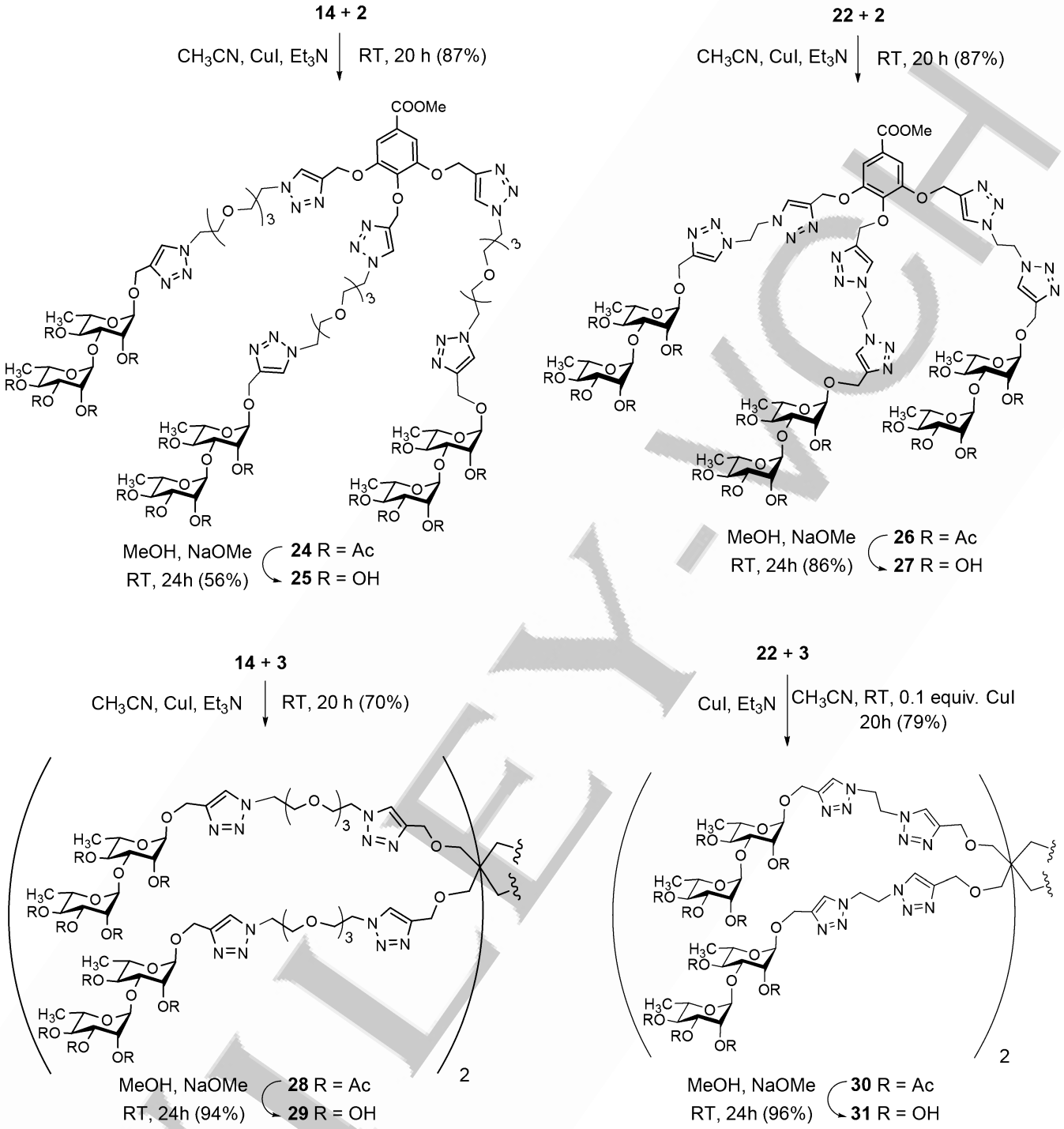

Scheme 4. Conjugation of linker-armed rhamnobiosides **14** and **22** to tri- and tetravalent central cores by an azide–alkyne cycloaddition click reaction.

were used to inhibit binding between 0.5 μM rHPL and *P. aeruginosa* PAO1 and compared with L-rhamnose monosaccharide treatment (Figure 2).

As expected, addition of L-rhamnose (2 mM) could only reduce the binding activity of rHPL to *P. aeruginosa* PAO1 to (92.2±4.4)%, and 10 mM L-rhamnose could decrease the binding to (78.7±8.8)%. For reference, for rhamnobiose **12** with two consecutive terminal rhamnose groups, the rHPL–bacteria interaction was inhibited to (68.4±8.5)%, which indicated stronger effects than the L-rhamnose monosaccharide. Rhamnobiosides **16** and **23**, with triazole-containing linker arms, displayed even stronger inhibitory effects and resulted in rHPL binding of (40.8±11.3) and (42.0±11.8)%, respectively, to *P. aeruginosa* PAO1. For multivalent rhamnobiosides with a tetraethylene glycol linker, compounds **17** (four rhamnose groups), **25** (six rhamnose groups), and **29** (eight rhamnose groups) could reduce the binding between rHPL and *P. aeruginosa* PAO1 to (43.5±5.7), (36.4±15.3), and (18.1±2.2)%, re-

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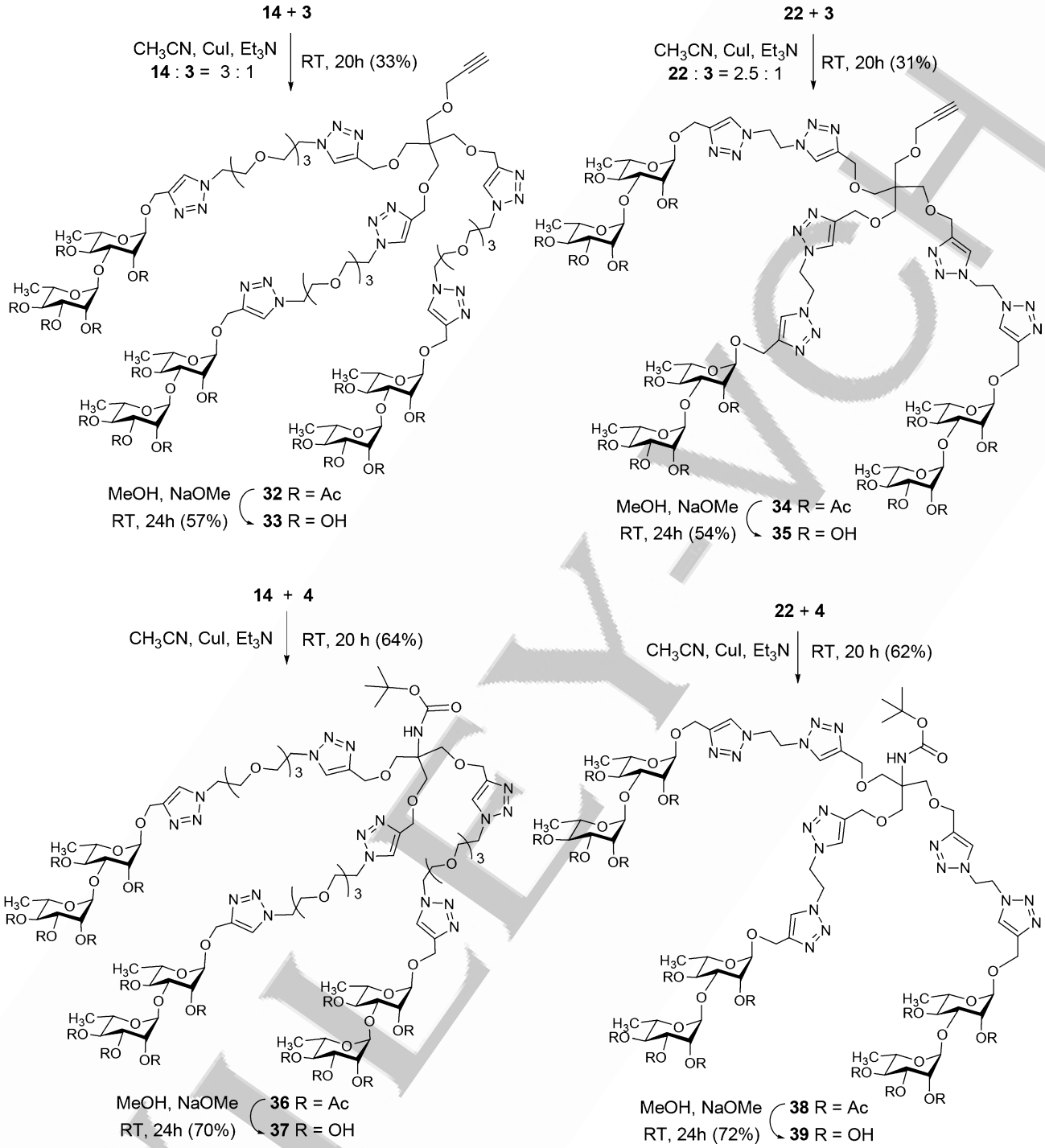

Scheme 5. Synthesis of trivalent rhamnoclusters with an additional functional group.

spectively, which clearly suggests that multiple rhamnose units exerted a stronger inhibitory effect. For multivalent rhamnobiosides with an ethylene glycol linker, compound **27** (six rhamnose groups) and **31** (eight rhamnose groups) could reduce the binding between rHPL and PAO1 to (25.6 ± 11.0) and (22.7 ± 2.5) %, respectively. Conversely, compounds **33** and **35**, trivalent rhamnobiosides with a tetra-*O*-propargyl pentaerythritol **3** core, showed decreased binding between rHPL and *P. aeruginosa* PAO1 of (6.6 ± 1.3) and (3.5 ± 1.2) %, respectively. The other set of trivalent rhamnobiosides, **37** and **39**, with a tri-*O*-propargyl Tris core **4** and a *N*-*tert*-butoxycarbonyl protective group, showed dramatically inhibitory effects on the rHPL–bacteria interaction, and the binding was decreased to (1.4 ± 0.7) and (1.5 ± 0.6) %, respectively. For the self-assembling rhamnobiosides, compounds **41** and **43** reduced the rHPL–bacteria binding to (71.8 ± 12.3) and (65.4 ± 17.7) %, respectively. The parameters for the inhibitory effects of multivalent rhamnobiosides on the rHPL–bacteria interaction are listed

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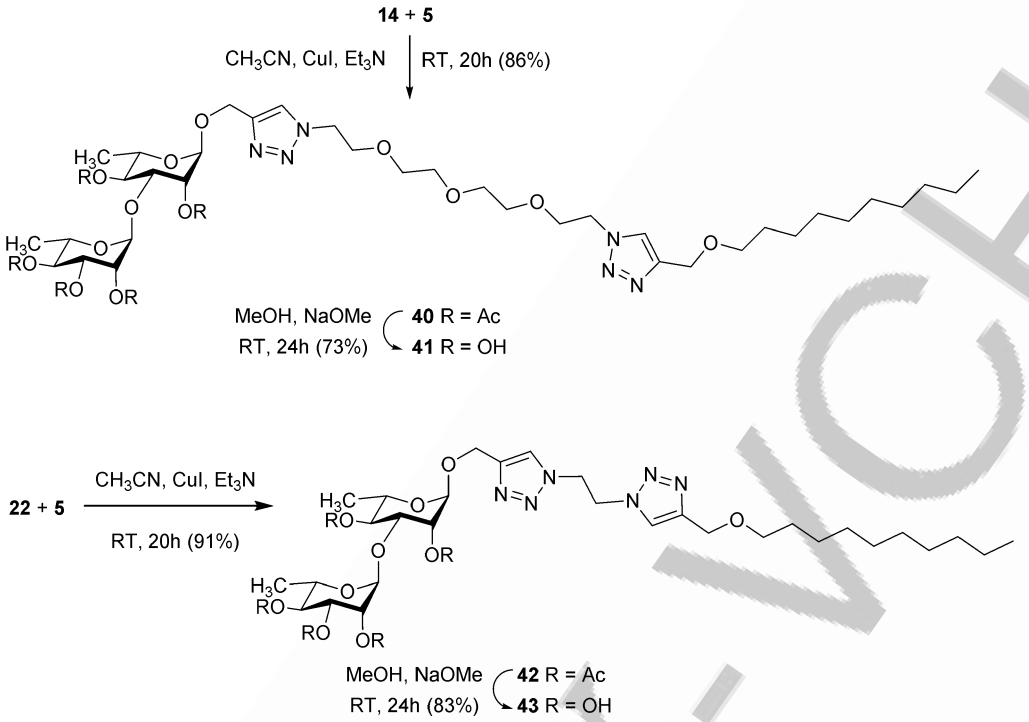

Scheme 6. Synthesis of self-assembling rhamnobioside derivatives by conjugation of **14** and **22** to a lipophilic chain.

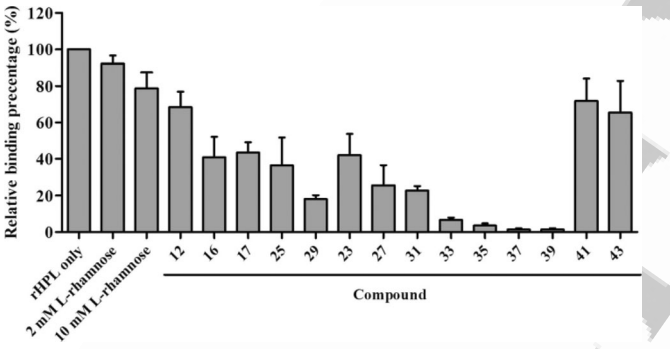

Figure 2. The inhibitory effect of multivalent rhamnobiosides on the rHPL–bacteria interaction. *P. aeruginosa* PAO1 (5×10^7 cells) was coated on 96-well microplates. L-Rhamnose or multivalent rhamnobiosides (initial: 4 mM; final: 2 mM) were incubated with 1 μM rHPL (final: 0.5 μM) and then added to the microplates. Anti-His (1:5000) was used to detect rHPL binding to the bacterial cells. rHPL only refers to microplate wells with buffer and rHPL instead of glycans and rHPL. The values are the mean ± SD from three experiments.

in Table S1. These results suggested that all our synthetic rhamnobioside derivatives could inhibit the binding of rHPL to PAO1, and a higher rhamnose content in the rhamnosides led to a stronger inhibitory effect on the bacterial recognition activity of rHPL. In addition, trivalent rhamnobiosides **33**, **35**, **37**, and **39**, with different architecture to **25** and **27**, showed the strongest inhibitory effect on the rHPL–bacteria interaction. However, rhamnoside derivatives that contained two rhamnoses, compounds **16** and **23**, with a tetraethylene glycol or an ethylene glycol linker, respectively, showed a stronger inhibitory effect than reference compound **12** with no addition of linker, which suggests that the linker region might also affect bacterial recognition of rHPL, possibly by forming noncovalent interactions (most probably by hydrogen bonding) with rHPL.

Conclusion

Eight rhamnoclusters with three or four α(1–3)-rhamnobiosides were assembled by using a propargyl rhamnobioside, two heterobifunctionalyzed linkers of different lengths, and three different clusters (methyl gallate, pentaerythritol, and *N*-Boc Tris), as the building elements. The straightforward synthetic route, which included two consecutive CuAAC reactions, in which CuI served as the catalyst in the presence of triethylamine, proved to be very efficient. A divalent derivative and two self-assembling rhamnobiosides were also prepared by using this route. Different architectures and valences of rhamnoclusters provided an opportunity to evaluate the impact of topology and valency on the binding properties of rHPL. Inhibitory ELISA data showed that L-rhamnose monosaccharide and synthetic rhamnobioside derivatives could inhibit the *P. aeruginosa* PAO1 recognition activity of rHPL. As expected, the multivalent rhamnobioside derivatives showed stronger inhibitory effects on *P. aeruginosa* PAO1 binding than L-rhamnose monosaccharide; in particular, derivative pairs **33**/**37** and **35**/**39** showed significant inhibitory effects, presumably due to a multivalent effect. Compounds **33**, **35**, **37**, and **39**, which contained six rhamnoses and pentaerythritol or *N*-Boc Tris as the central core, showed a stronger inhibitory effect on rHPL binding to bacteria than compounds **25** and **27** (with the same valency but different scaffolds) and compounds **29** and **31** (with higher valency but different scaffolds). These results indicated that compounds

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33, **35**, **37**, and **39** were more suitable for further characterization of rHPL–rhamnose binding specificity. In addition, regardless of the linker structure, synthetic compounds with eight rhamnoses (**29** and **31**) showed inhibition that was at least twofold stronger than compounds with two rhamnoses (**12**, **16**, **23**, **41**, and **43**). Moreover, rhamnoside derivatives with either tetraethylene glycol or ethylene glycol linkers showed a similar inhibitory effect on *P. aeruginosa* PAO1 recognition activity. However, of the rhamnoside derivatives with two rhamnoses, **12**, **41**, and **43** showed similar inhibitory effects on the rHPL–bacteria interaction and a 20 to 30% weaker inhibitory effect than **16** (with triazole and tetraethylene glycol linkers) and **23** (with triazole and ethylene glycol linkers), which strongly indicated that these linkers might play a role in the inhibitory effect, possibly due to noncovalent interactions between the linker and rHPL.

Although multivalent ligands often increase binding by glycan-binding proteins (GBPs), the improvement is not strictly according to the valency number, so the fact that rHPL does not bind tetravalent ligands as well as trivalent ligands is not an exception. If a tetravalent ligand has certain structural features that do not favor binding, it can be a poorer ligand than the trivalent one. For example, compounds **25** and **29** differ not only in valency, but also in the parts that form branches. Similarly compounds **27** and **31** differ in their branching structures. Moreover, compounds **37** and **39** are far better ligands than **25** and **27** due to their structural differences in the branching device. Also, note that monovalent binding can also have a multivalence effect. A good example is the binding of polyvalent folate in the form of dendrimers by the folate receptor.[26]

P. aeruginosa is a Gram-negative opportunistic nosocomial pathogen that causes a wide range of infections, such as pneumonia, urinary tract infections, skin and soft tissue infections, and septic shock,[27] and presents high rates of morbidity and mortality associated with the possibility of development of drug resistance during therapy.[28] These synthetic multivalent rhamnoside derivatives can help us further understand the molecular interactions between rHPL and *P. aeruginosa*, which in turn may lead to the development of novel rHPL-based strategies for infection diagnosis and even therapy.

Experimental Section

General Information

Optical rotations were measured at RT by using a Perkin–Elmer 241 automatic polarimeter. TLC analysis was performed by using Kieselgel 60 F_{254} (Merck) silica-gel plates, with visualization performed by immersion in a sulfuric acid solution (5% in EtOH) followed by heating. Column chromatography was performed with silica gel 60 (Merck 0.063–0.200 mm) and Sephadex LH-20 (Sigma–Aldrich, bead size: 25–100 mm). Organic solutions were dried over $MgSO_4$ and concentrated under vacuum. ^{1}H and ^{13}C NMR spectroscopy (^{1}H: 360 and 400 MHz; ^{13}C: 90.54 and 100.28 MHz) were performed by using Bruker DRX-360 and Bruker DRX-400 spectrometers at 25 °C. Chemical shifts were referenced to $SiMe_4$ or sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS, $\delta = 0.00$ ppm for ^{1}H nuclei) and to residual solvent signals ($CDCl_3$: $\delta = 77.00$ ppm, CD_3OD: $\delta = 49.15$ ppm for ^{13}C nuclei). MALDI-TOF MS analyses of the compounds were carried out in the positive reflectron mode by using a BIFLEX III mass spectrometer (Bruker, Germany) equipped with delayed-ion extraction. 2,5-Dihydroxybenzoic acid (DHB) was used as a matrix and $F_3CCOONa$ as the cationizing agent in DMF. ESI-TOF MS spectra were recorded by using a micro-TOF-Q type QTOFMS mass spectrometer (Bruker) in the positive-ion mode and with MeOH as the solvent. Elemental analysis was performed by using an Elementar Vario MicroCube instrument.

Dynamic Light Scattering (DLS) Experiments

For the DLS experiments, a Brookhaven light scattering instrument equipped with a BI-9000 digital correlator and temperature-controlled goniometer was used. The light source was a solid-state vertically polarized laser operated at $\lambda = 533$ nm. Experiments were performed in water at final concentrations of 2 and 4 mM for the amphiphiles. By using cumulant methods, the effective diameters (d_{eff}) of the aggregates were determined from the characteristic decay rate (Γ) of the autocorrelation function of the scattered light at 90°. The particle-size distribution was determined at a 90° scattering angle and evaluated by using the nonnegative constraint least-squares (NNLS) method.

Material and Method for Inhibitory ELISA

E. coli Rosetta (DE3) transformed with pET23a–rHPL was used to express recombinant protein rHPL with an *N*-terminal 6His-tag. The pET23a-rHPL/Rosetta (DE3) in Luria–Bertani (LB) broth (1 L) was induced with 0.1 mM isopropyl-β-■-1-thiogalactopyranoside (IPTG) at 16 °C for 16 h, and the overexpressed rHPL was purified by using nickel Sepharose (GE Healthcare) according to the manufacturer's instructions. Inhibition of the binding between rHPL and *P. aeruginosa* PAO1 by various rhamnosides was assayed by using an ELISA, as described previously.[2] Briefly, a suspension of bacteria (5×10^7 cells well^{-1}) in coating buffer (0.1 M sodium carbonate/bicarbonate buffer, pH 9.6) was added to flat-bottom 96-well microplates (Thermo Scientific, USA) and incubated at 4 °C overnight. After blocking with 3% bovine serum albumin (BSA) in phosphate-buffered saline■■ok?■■ (PBS) that contained 0.05% Tween 20 (PBST) at 37 °C for 2 h, the plates were washed four times with PBST. Next, rHPL (25 μL, 1 μM) and a twofold indicated concentration of L-rhamnose (25 μL; Sigma–Aldrich, USA) or synthetic rhamnosides were first incubated at 37 °C for 30 min, then the mixture was added to the bacteria in the wells and kept at 37 °C for a further 1 h. Finally, monoclonal anti-His (1:5000; Clontech) in PBST was added and the cells were incubated at 37 °C for 1 h, then horseradish-peroxidase-conjugated anti-mouse IgG■■please define■■ (1:5000; Jackson Lab) in PBST was added. The wells were washed with PBST between each incubation. After washing four times with PBST, 3,3′,5,5′-tetramethylbenzidine substrate (100 μL) was added to each well and incubated at 37 °C for exactly 15 min, then the reaction was terminated by the addition of H_2SO_4 (100 μL, 2 N). The OD_{450} was recorded by using a Bio-Rad iMark Microplate Absorbance Reader. Bacteria with only Tris buffer (Tris-HCl (20 mM), NaCl (200 mM), and EDTA (1 mM), pH 7.4) added was used as a blank, and bacteria with rHPL incubated with Tris buffer added was set as 100% binding. All ELISA experiments were individually performed at least three times. The values are indicated as the mean ± SD.

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General Method A for the Azide–Alkyne Click Reaction

CuI (0.1 equiv/alkyne) and triethylamine (1 equiv/alkyne) were added to a stirred solution of alkyne (0.2 mmol) and azide in acetonitrile (≈10 mL/1 mmol sugar derivative) under an argon atmosphere. The reaction mixture was stirred for 2 or 20 h at RT (2 h for **19** and **21**; 20 h for **24**, **26**, **28**, **30**, **32**, **34, 36**, **38**, **40**, and **42**) and monitored by using TLC. After complete or satisfactory conversion of the sugar reactant, the mixture was concentrated in vacuo and the crude product was purified by using column chromatography.

General Method B for the Zemplén Deacetylation

A catalytic amount of $NaOCH_3$ (≈0.2 equiv, pH ≈9) was added to a solution of the acetylated compound (0.2 mmol) in MeOH (2.5 mL). The reaction mixture was stirred for 24 h at RT and monitored by using TLC. After complete conversion of the starting material, the mixture was neutralized by using Amberlite IR-120 (H^+) resin, filtered, and concentrated, then the crude product was purified by using column chromatography.

2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranose (7)

Benzylamine (9.87 mL, 90.33 mmol, 5 equiv) was added to a stirred solution of **6**[15] (6.0 g, 18.07 mmol) in THF (190 mL) at RT. When the TLC (*n*-hexane/acetone 6:4) indicated complete disappearance of the starting material (5 h), the reaction was quenched by addition of 1 M HCl (110 mL), the mixture was extracted with EtOAc (3× 150 mL), and the organic phase was dried and concentrated. The crude product was purified by using column chromatography (CH_2Cl_2/acetone 9:1) to give **7** as a colorless syrup (5.0 g, 94%). $[\alpha]_D = -24.3$ ($c = 0.21$, $CHCl_3$); $R_f = 0.50$ (*n*-hexane/acetone 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.37$ (dd, $J = 3.2$ Hz, $J = 10.1$ Hz, 1H), 5.26 (s, 1H), 5.16 (s, 1H), 5.08 (t, $J = 9.9$ Hz, 1H), 4.17–4.12 (m, 1H; H5), 3.77 (s, 1H; O*H*), 2.16, 2.06, 2.00 (3×s, 9H; 3×Ac-C*H*$_3$), 1.22 ppm (d, $J = 6.2$ Hz, 3H; C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 170.5, 170.4, 170.3 (3C; 3×Ac-*C*O), 92.2, (1C; C1), 71.3, 70.5, 69.0, 66.4 (4C; C2, C3, C4, C5), 21.0, 20.9, 20.8 (3C; 3×Ac-*C*H$_3$), 17.5 ppm (1C; *C*H$_3$); ESI-TOF MS: *m/z* calcd for $C_{12}H_{18}NaO_8$: 313.0894 $[M+Na]^+$; found: 313.0862.

2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate (8)[16]

A solution of **7** (780 mg, 2.69 mmol) in dry CH_2Cl_2 (27.5 mL) was cooled to 0 °C, then trichloroacetonitrile (4.04 mL) and DBU (82 μL) were added and the mixture was allowed to warm to RT over 30 min. After completion of the reaction, the mixture was concentrated in vacuo. The crude product was purified by using column chromatography (*n*-hexane/EtOAc 1:1) to give **8** as a colorless syrup (1.16 g, 86%). $[\alpha]_D = -50.4$ ($c = 0.17$, $CHCl_3$), literature data: $[\alpha]_D = -52.0$ ($c = 1.0$ $CHCl_3$);[16] $R_f = 0.70$ (*n*-hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.74$ (s, 1H; N*H*), 6.20 (s, 1H; H1), 5.46 (d, $J = 1.8$ Hz, 1H; H2), 5.37 (dd, $J = 10.2$ Hz, $J = 3.3$ Hz, 1H; H4), 5.18 (t, $J = 10.0$ Hz, 1H; H3), 4.09 (dt, $J = 12.6$ Hz, $J = 6.5$ Hz, 1H; H5), 2.19, 2.07, 2.01 (3×s, 9H; 3×Ac-C*H*$_3$), 1.27 ppm (d, $J =$ 6.2 Hz, 3H; C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.0$, 169.9 (3C; 3×Ac-*C*O), 160.1 (1C; *C*NH), 94.8 (1C; C1), 70.4, 69.4, 68.9, 68.2 (4C; C2, C3, C4, C5), 20.9, 20.8, 20.7 (3C; 3×Ac-*C*H$_3$), 17.6 ppm (1C; *C*H$_3$); ESI-TOF MS: *m/z* calcd for $C_{14}H_{18}Cl_3NNaO_8$: 455.9990 $[M+Na]^+$; found: 455.9951.

Propargyl-2,3,4-tri-*O*-acetyl-α-L-rhamnopyranoside (9)[17]

A solution of **6** (10 g, 30.0 mmol) in dry CH_2Cl_2 (50 mL) was cooled to 0 °C, propargyl alcohol (4.46 mL, 75.3 mmol, 2.5 equiv) and BF_3·Et_2O (11.1 mL, 90.3 mmol, 3.0 equiv) were added and the mixture was stirred at 0 °C for 24 h. When the TLC (*n*-hexane/acetone 6:4) indicated complete disappearance of the starting material, the reaction was diluted with CH_2Cl_2 (200 mL) and neutralized by using saturated aqueous $NaHCO_3$. The organic phase was washed with water, dried, and concentrated. The residue was purified by crystallization from EtOH to give **9** as white crystals (9.87 g, 59%). M.p.: 62–65 °C; $[\alpha]_D = -79.5$ ($c = 0.11$, $CHCl_3$); $R_f = 0.48$ (*n*-hexane/acetone 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.31$–5.26 (m, 2H), 5.08 (t, $J =$ 9.7 Hz, 1H), 4.95 (d, $J = 1$ Hz, 1H; H1), 4.26 (d, $J = 2.4$ Hz, 2H; C*H*$_2$ propargyl), 3.94–3.89 (m, 1H; H5), 2.49 (t, $J = 2.3$ Hz, 1H; C*H* propargyl), 2.16, 2.05, 1.99 (3×s, 9H; 3×Ac-C*H*$_3$), 1.23 ppm (d, $J =$ 6.3 Hz, 3H; C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.9$, 171.8, 171.7 (3C; 3×Ac-*C*O), 98.0 (1C; C1), 80.1 (1C; *C*H propargyl), 77.2 (1C; C$_q$ propargyl), 72.8, 71.5, 70.8, 68.8 (4C; C2, C3, C4, C5), 56.6 (1C; C*H*$_2$ propargyl), 22.8, 22.7, 22.6 (3C; 3×Ac-*C*H$_3$), 19.2 ppm (1C; *C*H$_3$); ESI-TOF MS: *m/z* calcd for $C_{15}H_{20}NaO_8$: 351.1050 $[M+Na]^+$; found: 351.1014.

Propargyl-α-L-rhamnopyranoside (10)[18]

NaOMe (50 mg, 0.92 mmol) was added to a solution of compound **9** (4.35 g, 13.3 mmol) in MeOH (40 mL), and the reaction mixture was stirred for 24 h at RT. The reaction was quenched by addition of Amberlite IR-120 (H^+) resin (3.0 g), then after filtration the reaction mixture was concentrated in vacuo. The residue was purified by crystallization from EtOH to give **10** as white crystals (2.68 g, 86%). M.p.: 105–108 °C; $[\alpha]_D = -102.8$ ($c = 0.18$, $CHCl_3$); $R_f = 0.36$ (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 4.89$ (d, $J_{1,2} =$ 1.4 Hz, 1H; H1), 4.79 (s, 3H; 3×O*H*), 4.25 (d, $J = 2.4$ Hz, 1H; C*H*$_2$ propargyl), 3.83 (dd, $J_{2,3} = 3.4$ Hz, $J_{1,2} = 1.6$ Hz, 1H; H2), 3.64 (dd, $J_{3,4} = 9.5$ Hz, $J_{2,3} = 3.4$ Hz, 1H; H3), 3.59 (ddd, $J = 12.4$ Hz, $J = 7.9$ Hz, $J = 4.7$ Hz, 1H; H5), 3.40 (t, $J_{3,4} = J_{4,5} = 9.5$ Hz, 1H; H4), 2.87 (t, $J =$ 2.4 Hz, 1H; *CH* propargyl), 1.28 ppm (d, $J = 6.2$ Hz, 3H; C*H*$_3$); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 99.9$ (1C; C1), 80.0 (1C; *C*H propargyl), 75.9 (1C; C$_q$ propargyl), 73.6, 72.1, 71.8, 70.1 (4C; C2, C3, C4, C5), 54.9 (1C; C*H*$_2$ propargyl), 17.9 ppm (1C; *C*H$_3$); ESI-TOF MS: *m/z* calcd for $C_9H_{14}NaO_5$: 225.0733 $[M+Na]^+$; found: 225.0696.

Propargyl-2,4-di-*O*-acetyl-α-L-rhamnopyranoside (11)

Triethyl orthoacetate (27.35 mL, 149.2 mmol) and TsOH (352 mg) were added to a solution of compound **10** (3.75 g, 18.5 mmol) in CH_2Cl_2 (41.2 mL), and the reaction mixture was stirred for 24 h at RT. When the TLC (*n*-hexane/acetone 6:4; $R_f = 0.62$) indicated complete disappearance of the starting material, the reaction was quenched by addition of TEA (4.5 mL) and all volatiles were evaporated. The crude product (5.05 g) was dissolved in CH_2Cl_2 (37.5 mL), then Ac_2O (3.52 mL), TEA (7.79 mL), and DMAP■ ■please define■ ■ (229 mg) were added. When the TLC (*n*-hexane/acetone 6:4; $R_f = 0.63$) indicated complete disappearance of the starting material (1 h), the reaction mixture was diluted with CH_2Cl_2 (150 mL), washed with saturated aqueous $NaHCO_3$ (2×50 mL) and water (2× 50 mL), and the organic phase was dried, filtered, and concentrated. The crude product was dissolved in 80% AcOH (17.5 mL) and the mixture was vigorously stirred for 10 min. When the TLC (*n*-hexane/acetone 6:4; $R_f = 0.48$) indicated complete disappearance of the starting material, the reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with saturated aqueous $NaHCO_3$ (2× 50 mL) and water (2×50 mL), then the organic phase was dried, fil-

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tered, and concentrated. The crude product was purified by crystallization from a mixture of *n*-hexane and EtOAc to give **11** as white crystals (4.08 g, 77% for three steps). M.p.: 60–65 °C; $[\alpha]_D = -60.4$ ($c = 0.13$, $CHCl_3$); $R_f = 0.48$ (*n*-hexane/acetone 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.09$ (dd, $J_{2,3} = 3.6$ Hz, $J_{1,2} = 1.6$ Hz, 1H; H2), 4.96 (d, $J_{1,2} = 1.3$ Hz, 1H; H1), 4.88 (t, $J = 9.8$ Hz, 1H; H4), 4.24 (dd, $J = 2.4$ Hz, $J = 0.8$ Hz, 2H; CH_2 propargyl), 4.03 (ddd, $J = 9.8$ Hz, $J = 8.4$ Hz, $J = 3.6$ Hz, 1H; H3), 3.84 (dq, $J = 9.9$ Hz, $J = 6.2$ Hz, 1H; H5), 2.60 (d, $J = 7.4$ Hz, 1H; O*H*), 2.49 (t, $J = 2.4$ Hz, 1H; C*H* propargyl), 2.17, 2.12 (2×s, 6H; 2×Ac-CH_3), 1.21 ppm (d, $J = 6.3$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.4$, 170.7 (2C; 2×Ac-*C*O), 96.2 (1C; C1), 78.4 (1C; C_q propargyl), 75.2 (1C; *C*H propargyl), 74.4 (1C; C4), 72.5 (1C; C2), 68.3 (1C; C3), 66.6 (1C; C5), 54.9 (1C; CH_2 propargyl), 21.1, 21.0 (2C; 2×Ac-*C*H_3), 17.3 ppm (1C; CH_3); ESI-TOF MS: *m/z* calcd for $C_{13}H_{18}NaO_8$: 309.0945 $[M+Na]^+$; found: 309.0910.

Propargyl-2,4-di-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (1)

Molecular sieves (4 Å, 2.0 g) were added to a solution of acceptor **11** (2.6 g, 9.08 mmol) and donor **8** (5.09 g, 13.63 mmol, 1.5 equiv) in dry CH_2Cl_2 (240 mL). After 30 min, the mixture was cooled to −40 °C and a solution of TMSOTf■■please define■■ (616 μL, 3.407 mmol, 0.25 equiv) in dry CH_2Cl_2 (5.0 mL) was added. After stirring for 4 h at −20 °C, TLC analysis showed complete consumption of the donor. The reaction mixture was neutralized by using TEA (1.5 mL), diluted with CH_2Cl_2 (500 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (2×150 mL) and water (2×150 mL), then dried, filtered, and concentrated. The crude product was purified by using column chromatography on silica gel (*n*-hexane/EtOAc 65:35) to give compound **1** as a colorless syrup (4.88 g, 99%). $[\alpha]_D = -53.1$ ($c = 0.14$, $CHCl_3$); $R_f = 0.24$ (*n*-hexane/EtOAc 65:35); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.22$ (dd, $J_{2,3} = 3.3$ Hz, $J_{1,2} = 1.6$ Hz, 1H; H2), 5.16 (dd, $J_{3',4'} = 10.2$ Hz, $J_{2',3'} = 3.3$ Hz, 1H; H3′), 5.10 (t, $J = 9.9$ Hz, 1H; H4), 5.04 (t, $J = 9.8$ Hz, 1H; H4′), 5.03 (dd, $J_{2',3'} = 3.2$ Hz, $J_{1',2'} = 1.9$ Hz, 1H; H2′), 4.92 (d, $J_{1,2} = 1.2$ Hz, 1H; H1), 4.89 (d, $J_{1',2'} = 1.3$ Hz, 1H; H1′), 4.24 (d, $J = 2.3$ Hz, 2H; CH_2 propargyl), 4.10 (dd, $J_{3,4} = 9.9$ Hz, $J_{2,3} = 3.4$ Hz, 1H; H3), 3.92–3.88 (m, 1H; H5′), 3.83–3.79 (m, 1H; H5), 2.51 (t, $J = 2.4$ Hz, 1H; C*H* propargyl), 2.21, 2.14, 2.13, 2.06, 1.98 (5×s, 15H; 5×Ac-CH_3), 1.21 (d, $J = 6.4$ Hz, 3H; CH_3), 1.19 ppm (d, $J = 6.3$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.4$, 170.1, 169.7 (5C; 5×Ac-*C*O), 98.7 (1C; C1′), 96.2 (1C; C1), 78.4 (1C; C_q propargyl), 75.3 (1C; *C*H propargyl), 74.6 (1C; C3), 72.4 (1C; C4), 71.0 (1C; C2′), 70.8 (1C; C2), 70.3 (1C; C4′), 68.5 (1C; C3′), 67.3, 67.2 (2C; C3, C3′), 54.8 (1C; CH_2 propargyl), 21.0, 20.9, 20.8, 20.7, 20.7 (5C; 5×Ac-CH_3), 17.4 ppm (2C; 2×CH_3); ESI-TOF MS: *m/z* calcd for $C_{25}H_{34}NaO_{14}$: 581.1841 $[M+Na]^+$; found: 581.1908.

Propargyl-3-*O*-(α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (12)

Compound **1** (100 mg, 0.179 mmol) was deacetylated according to general method B. The crude product was purified by using column chromatography to give **12** (61 g, 99%) as a white solid. $[\alpha]_D = -406.3$ ($c = 0.03$, $CHCl_3$); $R_f = 0.42$ (CH_2Cl_2/MeOH 8:2); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 4.91$ (d, $J = 1.0$ Hz, 1H; H1), 4.77 (d, $J = 1.4$ Hz, 1H; H1′), 4.15 (d, $J = 2.2$ Hz, 1H; CH_2 propargyl), 3.88 (dd, $J = 3.1$ Hz, $J = 1.5$ Hz, 1H), 3.78 (dd, $J = 3.0$ Hz, $J = 1.8$ Hz, 1H), 3.69–3.65 (m, 2H), 3.62 (dd, $J = 9.6$ Hz, $J = 3.3$ Hz, 1H), 3.54–3.50 (m, 1H), 3.41 (t, $J = 9.5$ Hz, 1H), 3.30 (t, $J = 9.5$ Hz, 1H), 2.78 (t, $J = 2.3$ Hz, 1H; C*H* propargyl), 1.17 ppm (2×d, $J_1 = J_2 = 6.2$ Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 104.0$, 100.0 (2C; C1, C1′), 80.0 (1C; C_q propargyl), 76.0 (1C; *C*H propargyl), 79.4, 74.0, 73.0, 72.1, 72.0, 71.9, 70.5, 70.0 (8C; skeleton carbons), 55.0 (1C; CH_2 propargyl), 17.9, 17.8 ppm (2C; 2×CH_3); ESI-TOF MS: *m/z* calcd for $C_{15}H_{24}NaO_9$: 371.1313 $[M+Na]^+$; found: 371.1303.

Compounds 14 and 15

CuI (11 mg, 0.062 mmol, 0.1 equiv) and TEA (86 μL, 0.619 mmol, 1 equiv) were added to a solution of compound **13**[9] (378 mg, 1.548 mmol, 2.5 equiv) and disaccharide **1** (345 mg, 0.619 mmol, 1 equiv) in acetonitrile (7.0 mL). The reaction mixture was stirred at RT and monitored by using TLC. After 2 h, TLC revealed the complete disappearance of starting material **1**. The mixture was concentrated in vacuo and the crude product was purified by using column chromatography to give **14** as a colorless syrup (200 mg, 40%) and **15** as a colorless syrup (133 mg, 27%).

Alternate Routes to 14

Compound **14** was also prepared by reacting **13** and **1** in a 6:1 ratio as follows: CuI (4 mg, 0.062 mmol, 0.1 equiv) and TEA (17 μL, 0.2 mmol, 1 equiv) were added to a solution of compound **13** (315 mg, 1.290 mmol, 6 equiv) and disaccharide **1** (120 mg, 0.215 mmol, 1 equiv) in acetonitrile (3.0 mL), and the reaction mixture was stirred for 2 h at RT and monitored by using TLC. After complete disappearance of compound **1**, the mixture was concentrated in vacuo. The crude product was purified by using column chromatography to give **14** (81 mg, 47%).

Compound **14** was also prepared from compound **19** as follows: NaN_3 (84 mg, 1.288 mmol) was added to a solution of compound **19** (240 mg, 0.258 mmol) in dry DMF (3.0 mL) and the reaction mixture was stirred for 20 h at 60 °C. The reaction was quenched by addition of water (0.5 mL) and the mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (150 mL) and washed with water (3×25 mL), then the organic phase was dried, filtered, and concentrated. The crude product was purified by using column chromatography to give **14** (173 mg, 85%).

Data for 14

$[\alpha]_D = -31.9$ ($c = 0.11$ $CHCl_3$); $R_f = 0.37$ (*n*-hexane/acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$ (s, 1H; C*H* triazole), 5.19 (dd, $J = 3.0$ Hz, $J = 1.4$ Hz, 1H; H2), 5.15 (dd, $J = 10.2$ Hz, $J = 3.3$ Hz, 1H; H3), 5.10 (d, $J = 9.9$ Hz, 1H; H4), 5.05–5.00 (m, 2H; H2′, H4′), 4.86 (s, 2H; H1, H1′), 4.81 (d, $J = 12.2$ Hz, 1H; CH_2a propargyl), 4.64 (d, $J = 12.2$ Hz, 1H; CH_2b propargyl), 4.57 (t, $J = 5.0$ Hz, 2H; CH_2 TEG), 4.09 (dd, $J = 9.9$ Hz, $J = 3.4$ Hz, 1H; H3), 3.91–3.83 (m, 4H; CH_2 TEG, H5, H5′), 3.69–3.64 (m, 10H; CH_2 TEG), 3.40–3.38 (m, 2H; CH_2 TEG), 2.19, 2.12, 2.05, 1.97 (4×s, 15H; 4×CH_3 acetyl), 1.21, 1.16 ppm (2×d, $J = 6.2$ Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.6$, 170.3, 170.2, 169.8 (5C; 5×CO acetyl), 143.6 (1C; *C*=CH triazole), 124.3 (1C; C=*C*H triazole), 98.8, 96.7 (2C; C1, C1′), 75.1, 72.4, 71.2, 70.9, 70.3, 68.6, 67.3, 66.9 (8C; skeleton carbons), 70.8, 70.7, 70.2, 69.5 (6C; CH_2 TEG), 60.7 (1C; CH_2 propargyl), 50.7, 50.4 (2C; 2×NCH_2 TEG), 21.1, 21.0, 20.9, 20.8, 20.7 (5C; 5×CH_3 acetyl), 17.5, 17.4 ppm (2C; 2×CH_3); ESI-TOF MS: *m/z* calcd for $C_{33}H_{50}N_6NaO_{17}$: 825.3125 $[M+Na]^+$; found: 825.3146.

Data for 15

$[\alpha]_D = -42.4$ ($c = 0.15$ $CHCl_3$); $R_f = 0.14$ (*n*-hexane/acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (s, 2H; 2×C*H* triazole), 5.19–5.00 (m, 10H; 2×H2, H4, H2′, H3′, H4′), 4.86 (s, 4H; 2×H1, H1′), 4.81–4.62 (m, 4H; 2×CH_2 propargyl), 4.57 (s, 4H; 2×CH_2 TEG), 4.08 (dd, $J = 9.8$ Hz, $J = 2.8$ Hz, 2H; 2×H3), 3.91–3.83 (m, 8H; 2×H5, H5′, 2×

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CH_2 TEG), 3.63–3.58 (m, 8H; 4×CH_2 TEG), 2.19, 2.12, 2.05, 1.98 (4× s, 30H; CH_3 acetyl), 1.21 (d, J=6.1 Hz, 6H; 2×CH_3), 1.16 ppm (d, J=6.1 Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.4, 170.1, 170.0, 169.6 (10C; 10×CO acetyl), 129.7 (2C; 2×C=CH triazole), 98.7, 96.5 (4C; 2×C1, 2×C1′), 75.1, 72.3, 71.1, 70.7, 70.1, 68.4, 67.2, 66.7 (16C; 2×skeleton carbons), 70.5, 70.4, 69.4 (6C; 6×CH_2 TEG), 60.5 (2C; 2×CH_2 propargyl), 50.3 (2C; 2×NCH_2 TEG), 20.9, 20.8, 20.7, 20.6 (10C; 10×CH_3 acetyl), 17.4, 17.3 ppm (4C; 4×CH_3); ESI-TOF MS: m/z calcd for $C_{58}H_{84}N_6NaO_{31}$: 1383.5073 $[M+Na]^+$; found: 1383.5146.

Compound 16

Compound **14** (67 mg, 0.084 mmol) was deacetylated according to general method B. The crude product was purified by using column chromatography to give **16** as a white solid (38 mg, 76%). $[\alpha]_D$=−69.1 (c=0.14 MeOH); R_f=0.51 (CH_2Cl_2/MeOH 8:2); ^{1}H NMR (400 MHz, D_2O): δ=8.13 (s, 1H; CH triazole), 5.02 (s, 1H), 4.83 (d, J=12.6 Hz, 1H; CH_2a propargyl), 4.75 (d, J=12.6 Hz, 1H; CH_2b propargyl), 4.66 (t, J=4.5 Hz, 2H; CH_2 TEG),4.06 (s, 1H), 4.01–3.99 (m, 3H), 3.85–3.79 (m, 3H), 3.71–3.64 (m, 12H), 3.56–3.43 (m, 4H), 1.29–1.25 ppm (m, 6H; 2×CH_3); ^{13}C NMR (100 MHz, D_2O): δ=142.7 (1C; C=CH triazole), 124.5 (1C; C=CH triazole), 101.4, 98.6 (2C; C1, C1′), 77.1, 71.0, 70.4, 69.2, 69.1, 68.9, 68.1, 67.9 (8C; skeleton carbons), 68.7, 68.6, 68.5, 68.3, 67.8 (6C; 6×CH_2 TEG), 59.1 (1C; CH_2 propargyl), 49.2, 49.1 (2C; 2×NCH_2 TEG), 15.6 ppm (2C; 2×CH_3); ESI-TOF MS: m/z calcd for $C_{23}H_{40}N_6NaO_{12}$: 615.2596 $[M+Na]^+$; found: 615.2597.

Compound 17

Compound **15** (120 mg, 0.088 mmol) was deacetylated according to general method B. The crude product was purified by using column chromatography to give **17** as a white solid (67 mg, 81%). $[\alpha]_D$=−73.1 (c=0.23 MeOH); R_f=0.55 (CH_2Cl_2/MeOH/H_2O 7:5:1); ^{1}H NMR (400 MHz, D_2O): δ=8.10 (s, 2H; 2×CH triazole), 5.02 (d, J=2.1 Hz, 2H), 4.88 (d, J=2.1 Hz, 2H), 4.82–4.78 (m, 2H; 2×CH_2a propargyl), 4.71 (dd, J=12.7 Hz, J=2.5 Hz, 2H; CH_2b propargyl), 4.67–4.65 (m, 4H; CH_2 TEG), 4.06–3.97 (m, 8H; CH_2 TEG), 3.86–3.77 (m, 6H), 3.70–3.62 (m, 6H), 3.56–3.43 (m, 8H), 1.28–1.25 ppm (m, 12H; 4×CH_3); ^{13}C NMR (100 MHz, D_2O): δ=144.8 (2C; 2×C=CH triazole), 126.6 (2C; 2×C=CH triazole), 103.5, 100.8 (4C; 2×C1, 2×C1′), 79.3, 73.2, 72.5, 71.4, 71.3, 71.1, 70.2, 70.1 (16C; 2×skeleton carbons), 70.8, 70.7, 69.9, 68.3 (6C; 6×CH_2 TEG), 61.2 (2C; 2×CH_2 propargyl), 51.2 (2C; 2×NCH_2 TEG), 17.8 ppm (4C; 4×CH_3); ESI-TOF MS: m/z calcd for $C_{38}H_{64}N_6NaO_{21}$: 963.4017 $[M+Na]^+$; found: 963.4015.

Compound 19

Disaccharide **1** (200 mg, 0.358 mmol) and compound **18**[10] (134 mg, 0.358 mmol) were converted to **19** according to general method A. The crude product was purified by using column chromatography to give **19** as a colorless syrup (280 mg, 83%). $[\alpha]_D$=−28.0 (c=0.32 $CHCl_3$); R_f=0.34 (*n*-hexane/acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.79 (d, J=8.3 Hz, 2H; arom.), 7.76 (s, 1H; CH triazole), 7.34 (d, J=8.1 Hz, 2H; arom), 5.18 (dd, J=3.2 Hz, J=1.5 Hz, 1H; H2), 5.15 (dd, J=10.2 Hz, J=3.4 Hz, 1H; H3′), 5.10 (t, J=9.9 Hz, 1H; H4), 5.05–5.00 (m, 2H; H2′, H4′), 4.85 (s, 2H; H1, H1′), 4.78 (d, J=12.2 Hz, 1H; CH_2a propargyl), 4.62 (d, J=12.2 Hz, 1H; CH_2b propargyl), 4.56 (t, J=5.5 Hz, 2H; CH_2 TEG), 4.16–4.14 (m, 2H; CH_2 TEG), 4.08 (dd, J=9.9 Hz, J=3.4 Hz, 1H; H3), 3.90 (t, J=5.0 Hz, 2H; CH_2 TEG), 3.87–3.83 (m, 2H; H5, H5′), 3.70–3.68 (m, 2H; CH_2 TEG), 3.63–3.56 (m, 8H; CH_2 TEG), 2.45 (s, 3H; CH_3 tosyl), 2.19, 2.12, 2.04, 1.97 (4×s, 15H; 5×CH_3 acetyl), 1.20 (d, J=6.2 Hz, 3H; CH_3), 1.15 ppm (d, J=6.2 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.5, 170.3, 170.2, 170.1, 169.7 (5C; 5×CO acetyl), 145.0 (1C; C=CH triazole), 143.5 (1C; C_q tosyl), 129.9, 128.0 (4C; arom.), 124.3 (1C; C=CH triazole), 98.8, 96.7 (2C; C1, C1′), 75.1 (1C; C3), 72.4 (1C; C4), 71.2 (1C; C2), 70.9, 70.2 (2C; C2′, C4′), 68.6 (1C; C3′), 67.2, 66.9 (2C; C5, C5′), 70.8, 70.6, 70.5, 69.5, 69.3, 68.8 (7C; 7×CH_2 TEG), 60.6 (1C; CH_2 propargyl), 50.4 (1C; NCH_2 TEG), 21.7 (1C; CH_3 tosyl), 21.1, 21.0, 20.9, 20.8, 20.7 (5C; 5×CH_3 acetyl), 17.5, 17.4 ppm (2C; 2×CH_3); ESI-TOF MS: m/z calcd for $C_{40}H_{57}N_3NaO_{20}S$: 954.3148 $[M+Na]^+$; found: 954.3619.

Compound 21

Disaccharide **1** (695 mg, 1.245 mmol) was treated with compound **20**[11] (300 mg, 1.245 mmol) according to general method A. The crude product was purified by using column chromatography to give **21** as a colorless syrup (863 mg, 87%). $[\alpha]_D$=−33.1 (c=0.13 $CHCl_3$); R_f=0.38 (*n*-hexane/acetone 1:1); ^{1}H NMR (360 MHz, $CDCl_3$): δ=7.70 (d, J=8.3 Hz, 2H; arom.), 7.67 (s, 1H; CH triazole), 7.35 (d, J=8.0 Hz, 2H; arom.), 5.20 (dd, J=3.2 Hz, J=1.5 Hz, 1H; H2), 5.15 (dd, J=10.2 Hz, J=3.2 Hz, 1H; H3′), 5.11 (t, J=9.9 Hz, 1H; H4), 5.06–5.00 (m, 2H; H2′, H4′), 4.87 (d, J=1.1 Hz, 1H; H1), 4.86 (d, J=1.1 Hz, 1H; H1′), 4.78 (d, J=12.2 Hz, 1H; CH_2a propargyl), 4.67 (t, J=5.1 Hz, 2H; CH_2 ethylene glycol), 4.62 (d, J=12.3 Hz, 1H; CH_2b propargyl), 4.42 (t, J=5.1 Hz, 2H; CH_2 ethylene glycol), 4.09 (dd, J=9.9 Hz, J=3.4 Hz, 1H; H3), 3.86 (ddd, J=13.7 Hz, J=9.7 Hz, J=6.4 Hz, 2H; H5, H5′), 2.46 (s, 3H; CH_3 tosyl), 2.20, 2.12, 2.11, 2.05, 1.98 (5×s, 15H; 5×CH_3 acetyl), 1.22 (d, J=6.2 Hz, 3H; CH_3), 1.16 ppm (d, J=6.2 Hz, 3H; CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ=170.4, 170.2, 170.1, 170.0, 169.7 (5C; 5×CO acetyl), 145.5 (1C; C=CH triazole), 143.8 (1C; C_q tosyl), 130.1, 127.8 (4C; arom.), 124.9 (1C; C=CH triazole), 98.7, 96.6 (2C; C1, C1′), 74.9, 72.3, 71.1, 70.8, 70.1, 68.5, 67.2, 66.9 (8C; skeleton carbons), 67.6 (1C; CH_2 ethylene glycol), 60.4 (1C; CH_2 propargyl), 49.1 (1C; NCH_2 ethylene glycol), 21.6 (1C; CH_3 tosyl), 20.9, 20.8, 20.7, 20.6 (5C; 5×CH_3 acetyl), 17.4, 17.3 ppm (2C; 2×CH_3); ESI-TOF MS: m/z calcd for $C_{34}H_{45}N_3NaO_{17}S$: 822.2362 $[M+Na]^+$; found: 822.2366.

Compound 22

NaN_3 (671 mg, 10.322 mmol) was added to a solution of compound **21** (1.65 g, 2.064 mmol) in dry DMF (20 mL), and the reaction mixture was stirred for 20 h at 60 °C. The reaction was quenched by addition of water (5 mL) and the mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (350 mL) and washed with water (3×75 mL), then the organic phase was dried, filtered, and concentrated. The crude product was purified by using column chromatography to give **22** as a colorless syrup (1.323 mg, 96%). $[\alpha]_D$=−32.6 (c=0.35 $CHCl_3$); R_f=0.29 (*n*-hexane/acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.68 (s, 1H; CH triazole), 5.19–5.01 (m, 5H; H2, H4, H2′, H3′, H4′), 4.86 (s, 2H; H1, H1′), 4.82 (d, J=12.4 Hz, 1H; CH_2a propargyl), 4.66 (d, J=12.3 Hz, 1H; CH_2b propargyl), 4.53 (t, J=5.5 Hz, 2H; CH_2 ethylene glycol), 4.09 (dd, J=9.9 Hz, J=3.0 Hz, 1H; H3), 3.90–3.82 (m, 4H; CH_2 ethylene glycol, H5, H5′), 2.19, 2.12, 2.05, 1.98 (4×s, 15H; 5×CH_3 acetyl), 1.22 (d, J=6.2 Hz, 3H; CH_3), 1.17 ppm (d, J=6.2 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.6, 170.2, 170.1, 169.7 (5C; 5×CO acetyl), 144.1 (1C; C=CH triazole), 123.8 (1C; C=CH triazole), 98.8, 96.7 (2C; C1, C1′), 75.0, 72.4, 71.2, 70.8, 70.2, 68.5, 67.3, 67.0 (8C; skeleton carbons), 60.7 (1C; CH_2 propargyl), 50.8, 49.5 (2C; 2×NCH_2 ethylene glycol), 21.0, 20.9, 20.8, 20.7 (5C; 5×CH_3 acetyl), 17.5, 17.4 ppm (2C; 2×CH_3); ESI-TOF MS: m/z calcd for $C_{27}H_{38}N_6NaO_{14}$: 693.2338 $[M+Na]^+$; found: 693.2339.

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Compound 23

Compound **22** (73 mg, 0.109 mmol) was deacetylated according to general method B. The crude product was purified by using column chromatography to give **23** (44 mg, 88%) as a white solid. $[\alpha]_D = -82.6$ ($c = 0.12$ MeOH); $R_f = 0.27$ (CH_2Cl_2/MeOH 8:2); ^{1}H NMR (400 MHz, D_2O): $\delta = 8.17$ (s, 1H; C*H* triazole), 5.02 (s, 1H), 4.89 (s, 1H), 4.86–4.04 (m, 1H; CH_2a propargyl), 4.77 (d, $J = 12.7$ Hz, 1H; CH_2b propargyl), 4.68–4.65 (m, 2H; CH_2 ethylene glycol), 4.07 (s, 1H), 4.01 (s, 1H), 3.85–3.79 (m, 5H), 3.71–3.66 (m, 1H), 3.54 (t, $J = 9.6$ Hz, 1H), 3.46 (t, $J = 9.6$ Hz, 1H), 1.27 ppm (t, $J = 6.1$ Hz, 6H; 2×CH_3); ^{13}C NMR (100 MHz, D_2O): $\delta = 143.9$ (1C; *C*=CH triazole), 125.5 (1C; C=*C*H triazole), 102.2, 99.3 (2C; C1, C1′), 77.9, 71.8, 71.2, 70.0, 69.9, 69.7, 68.9, 68.8 (8C; skeleton carbons), 59.8 (1C; CH_2 propargyl), 50.3, 49.5 (2C; 2×NCH_2 ethylene glycol), 16.4 ppm (2C; 2×CH_3); ESI-TOF MS: *m/z* calcd for $C_{17}H_{28}N_6NaO_9$: 483.1810 $[M+Na]^+$; found: 483.1815.

Compound 24

Compound **14** (379 mg, 0.472 mmol) and compound **2**[22] (31 mg, 0.104 mmol) were converted to **24** according to general method A. The crude product was purified by using column chromatography to give **24** as a colorless syrup (245 mg, 87%). $[\alpha]_D = -37.7$ ($c = 0.10$ $CHCl_3$); $R_f = 0.28$ (EtOAc/MeOH 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.95$ (s, 3H; 3×C*H* triazole), 7.74 (s, 3H; 3×C*H* triazole), 7.44 (s, 2H; arom.), 5.22–5.02 (m, 15H; 3×H2, H4, H2′, H3′, H4′), 4.86 (s, 6H; 3×H1, H1′), 4.79–4.54 (m, 24H; 6×CH_2 propargyl, 6×CH_2 TEG), 4.13–4.07 (m, 3H; 3×H3), 3.90–3.87 (m, 21H; 3×H5, H5′, 6×CH_2 TEG, COOCH_3), 3.57 (m, 24H; 12×CH_2 TEG), 2.19, 2.12, 2.05, 1.97 (4×s, 45H; 15×CH_3 acetyl), 1.20 (d, $J = 5.1$ Hz, 9H; 3×CH_3), 1.15 ppm (d, $J = 5.7$ Hz, 9H; 3×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 170.5, 170.2, 170.1, 169.7 (15C; 15×CO acetyl), 166.3 (1C; *C*OOCH$_3$), 152.1, 125.7 (4C; 4×C_q arom.), 109.3 (2C; arom.), 98.8, 96.6 (6C; 3×C1, 3×C1′), 75.1, 72.4, 71.2, 70.8, 70.2, 68.5, 67.2, 66.8 (24C; 3×skeleton carbons), 70.5, 70.4, 69.4 (18C; 18×CH_2 TEG), 60.5, 60.4 (6C; 6×CH_2 propargyl), 52.4 (1C; COOCH_3), 50.3 (6C; 6×NCH_2 TEG), 21.0, 20.9, 20.8, 20.7 (15C; 15×CH_3 acetyl), 17.4, 17.3 ppm (6C; 6×CH_3); ESI-TOF MS: *m/z* calcd for $C_{116}H_{164}N_{18}NaO_{56}$: 2729.647 $[M+Na]^+$; found: 1376.0022 $[M+2Na]^{2+}$.

Compound 25

Compound **24** (235 mg, 0.086 mmol) was converted to **25** according to general method B. The crude product was purified by using column chromatography to give **25** as a white solid (100 mg, 56%). $[\alpha]_D = -55.6$ ($c = 0.11$ MeOH); $R_f = 0.32$ (CH_2Cl_2/MeOH/H_2O 7:5:0.5); ^{1}H NMR (400 MHz, D_2O): $\delta = 8.18$ (s, 2H; 2×C*H* triazole), 8.07 (s, 3H; 3×C*H* triazole), 7.92 (s, 1H; C*H* triazole), 7.45 (s, 2H; arom.), 5.05 (s, 3H; 3×H1), 4.90 (s, 3H; 3×H1′), 4.79–4.57 (m, 24H; 6×CH_2 propargyl, 6×CH_2 TEG), 4.11 (s, 3H), 4.05 (s, 3H), 3.98–3.80 (m, 24H), 3.70–3.68 (m, 3H; 3×H3), 3.60–3.50 (m, 27H; 3×H5, H5′, 11×CH_2 TEG, COOCH_3), 3.41 (s, 3H), 1.30–1.26 ppm (m, 18H; 6×CH_3); ^{13}C NMR (100 MHz, D_2O): $\delta = 166.6$ (1C; *C*OOCH$_3$), 150.4 (2C; 2×C_q arom.), 141.8 (6C; 6×C_q triazole), 124.4 (1C; C_q arom.), 124.2 (6C; C*H* triazole), 108.0 (2C; arom.), 101.3, 98.5 (6C; 3×C1, 3×C1′), 77.2, 71.0, 70.3, 69.1, 68.9, 67.9, 67.8 (24C; 3×skeleton carbons), 68.7, 68.5, 68.4, 67.7, 67.6 (18C; 18×CH_2 TEG), 58.9 (6C; 6×CH_2 propargyl), 51.8 (1C; COOCH_3), 48.9 (6C; 6×NCH_2 TEG), 15.6 ppm (6C; 6×CH_3); MALDI-TOF MS: *m/z* calcd for $C_{86}H_{134}N_{18}NaO_{41}$: 2097.885 $[M+Na]^+$; found: 2097.889 $[M+Na]^+$; elemental analysis calcd (%) for $C_{86}H_{134}N_{18}O_{41}$: C 49.75, H 6.51; found: C 49.81, H 6.63.

Compound 26

Compound **22** (180 mg, 0.265 mmol) and compound **2** (20 mg, 0.067 mmol) were converted to **26** according to general method A. The crude product was purified by using column chromatography to give **26** as a colorless syrup (137 mg, 88%). $[\alpha]_D = -37.3$ ($c = 0.12$ $CHCl_3$); $R_f = 0.56$ (EtOAc/EtOH 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.83–7.34$ (m, 8H; 6×C*H* triazole, 2×arom.), 5.18–4.96 (m, 33H; 3×H2, H4, H2′, H3′, H4′, 3×CH_2 ethylene glycol, 6×CH_2 propargyl), 4.86 (s, 3H; 3×H1), 4.80 (s, 3H; 3×H1′), 4.74–4.53 (m, 6H; 3×CH_2 ethylene glycol), 4.07–4.04 (m, 3H; 3×H3), 3.90 (s, 3H; COOCH_3), 3.88–3.77 (m, 6H; 3×H5, H5′), 2.17, 2.12, 2.05, 1.97 (4×s, 45H; 15×CH_3 acetyl), 1.19–1.13 ppm (m, 18H; 6×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.4$, 170.1, 170.0, 169.9, 169.6 (15C; 15×CO acetyl), 166.0 (1C; *C*OOCH$_3$), 151.6 (2C; 2×C_q arom.), 143.9 (6C; C_q triazole), 141.2 (1C; C_q arom.), 125.7 (1C; C_q arom.), 124.9, 124.1 (6C; 6×C*H* triazole), 108.8 (2C; arom), 98.6, 96.3 (6C; 3×C1, 3×C1′), 75.0, 72.1, 71.0, 70.6, 70.0, 68.4, 67.1, 66.2 (24C; 3×skeleton carbons), 60.1 (6C; 6×CH_2 propargyl), 52.4 (1C; COOCH_3), 49.5, 49.3 (6C; 6×NCH_2 ethylene glycol), 20.9, 20.8, 20.7, 20.6 (15C; 15×CH_3 acetyl), 17.4, 17.3 ppm (6C; 6×CH_3); ESI-TOF MS: *m/z* calcd for $C_{98}H_{128}N_{18}NaO_{47}$: 2331.8071 $[M+Na]^+$; found: 1177.8861 $[M+2Na]^{2+}$.

Compound 27

Compound **26** (125 mg, 0.024 mmol) was converted to **27** according to general method B. The crude product was purified by using column chromatography to give **27** as a white solid (78 mg, 86%). $[\alpha]_D = -63.3$ ($c = 0.10$ MeOH); $R_f = 0.19$ (CH_2Cl_2/MeOH/H_2O 7:5:0.5); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.93$ (s, 2H; 2×C*H* triazole), 7.81 (s, 1H; C*H* triazole), 7.75 (s, 2H; 2×C*H* triazole), 7.70 (s, 1H; C*H* triazole), 7.28 (s, 2H; arom.), 5.05–4.42 (m, 30H; 3×H1, 3×H1′, 6×CH_2 propargyl, 6×CH_2 ethylene glycol), 3.86 (s, 3H), 3.77 (s, 6H), 3.67–3.58 (m, 7H), 3.51–3.46 (m, 3H), 3.42–3.37 (m, 3H), 3.29–3.20 (m, 6H), 1.13–1.06 ppm (m, 18H; 6×CH_3); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 167.8$ (1C; *C*OOCH$_3$), 153.2 (2C; 2×C_q arom), 142.6 (6C; 6×C_q triazole), 126.9 (1C; C_q arom.), 126.2 (6C; C*H* triazole), 110.4 (2C; arom.), 104.0, 100.6 (6C; 3×C1, 3×C1′), 79.7, 74.0, 73.1, 72.2, 72.1, 71.9, 70.3, 70.1 (24C; 3×skeleton carbons), 60.5 (6C; 6×CH_2 propargyl), 53.0 (1C; COOCH_3), 51.0, 50.9, 50.8 (6C; 6×NCH_2 ethylene glycol), 18.1 ppm (6C; 6×CH_3); MALDI-TOF MS: *m/z* calcd for $C_{68}H_{98}N_{18}NaO_{32}$: 1701.649 $[M+Na]^+$; found: 1701.649 $[M+Na]^+$; elemental analysis calcd (%) for $C_{68}H_{98}N_{18}O_{32}$: C 48.63, H 5.88; found: C 48.72, H 7.94.

Compound 28

Compound **14** (553 mg, 0.690 mmol) and compound **3**[23] (40 mg, 0.138 mmol) were converted to **28** according to general method A. The crude product was purified by using column chromatography to give **28** as a colorless syrup (339 mg, 70%). $[\alpha]_D = -28.4$ ($c = 0.11$ $CHCl_3$); $R_f = 0.21$ (EtOAc/EtOH 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.77$, 7.74 (2×s, 8H; 8×C*H* triazole), 5.18–5.00 (m, 20H; 4×H2, H4, H2′, H3′, H4′), 4.86 (s, 8H; 4×H1, 4×H1′), 4.78 (d, $J = 12.2$ Hz, 8H; 8×CH_2a propargyl), 4.63 (d, $J = 12.2$ Hz, 8H; 8×CH_2b propargyl), 4.55–4.53 (m, 16H; 8×CH_2 TEG), 4.09–4.07 (m, 4H; 4×H3), 3.90–3.83 (m, 24H; 12×CH_2 TEG), 3.60–3.58 (m, 32H; 4×H5, H5′, 12×CH_2 TEG), 3.46 (s, 8H; 4×CH_2 pentaerythritol), 2.19, 2.12, 2.05, 1.98 (4×s, 60H; 20×CH_3 acetyl), 1.21–1.15 ppm (m, 24H; 8×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.2$, 169.9, 169.8, 169.5 (20C; 20×CO acetyl), 144.8, 143.2 (8C; C_q triazole), 123.9, 123.5 (8C; C*H* triazole), 98.5, 96.4 (8C; 4×C1, 4×C1′), 74.8, 72.1, 70.9, 70.5, 70.0, 68.3, 67.0, 66.6 (32C; 4×skeleton carbons), 70.5, 69.2, 69.1, (28C; 24×

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CH_2 TEG, 4×CH_2 pentaerythritol), 64.7, 60.3 (8C; 8×CH_2 propargyl), 50.0, 49.9 (8C; 8×NCH_2 TEG), 45.1 (1C; C_q pentaerythritol), 20.7, 20.6, 20.5, 20.4 (20C; 20×CH_3 acetyl), 17.2, 17.1 ppm (8C; 8×CH_3); ESI-TOF MS: *m/z* calcd for $C_{149}H_{220}N_{24}NaO_{72}$: 3520.4184 $[M+Na]^+$; found: 1772.2025 $[M+2Na]^{2+}$, 1189.1164 $[M+3Na]^{3+}$.

Compound 29

Compound **28** (260 mg, 0.074 mmol) was converted to **29** according to general method B. The crude product was purified by using column chromatography to give **29** as a white solid (185 mg, 94%). $[\alpha]_D=-52.0$ ($c=0.12$ MeOH); $R_f=0.62$ (CH_2Cl_2/MeOH/H_2O 7:5:0.5); ^{1}H NMR (400 MHz, CD_3OD): $\delta=8.04$, 7.97 (2×s, 8H; 8×*CH* triazole), 4.98, 4.78 (2×s, 8H; 4×H1, 4×H1′), 4.75–4.48 (m, 40H; 8×CH_2 propargyl, 4×CH_2 pentaerythritol, 8×CH_2 TEG), 3.97 (s, 4H; 4×H3), 3.88–3.86 (m, 24H; 12×CH_2 TEG), 3.67–3.29 (m, 52H; 4×H2, H2′, H3′, H4, H4′, H5, H5′, 12×CH_2 TEG), 1.27–1.19 ppm (m, 24H; 8×CH_3); ^{13}C NMR (100 MHz, CD_3OD): $\delta=144.2$ (8C; C_q triazole), 126.0 (8C; *CH* triazole), 104.0, 100.8 (8C; 4×C1, 4×C1′), 79.7, 74.0, 73.0, 72.1, 72.0, 71.8, 70.3, 70.0 (32C; 4×skeleton carbons), 71.3, 70.2 (24C; 24×CH_2 TEG), 65.4 (4C; 4×CH_2 pentaerythritol), 60.8 (8C; 8×CH_2 propargyl), 51.3 (8C; 8×NCH_2 TEG), 46.4 (1C; C_q pentaerythritol), 18.1 ppm (8C; 8×CH_3); MALDI-TOF MS: *m/z* calcd for $C_{109}H_{180}N_{24}NaO_{52}$: 2680.207 $[M+Na]^+$; found: 2680.208 $[M+Na]^+$; elemental analysis calcd (%) for $C_{109}H_{180}N_{24}O_{52}$: C 49.24, H 6.82; found: C 49.32, H 6.93.

Compound 30

Method I

Compound **22** (233 mg, 0.347 mmol) and compound **3** (20 mg, 0.069 mmol) were converted to **30** according to general method A. The crude product was purified by using column chromatography to give **30** as a colorless syrup (82 mg, 40%).

Method II

CuI (4.0 mg, 0.02 mmol, 0.4 equiv) and TEA (29 μL, 0.208 mmol, 4 equiv) were added to a solution of compound **22** (147 mg, 0.219 mmol, 4 equiv) and compound **3** (15 mg, 0.052 mmol, 1 equiv) in DMF (3.0 mL). The reaction mixture was stirred for 20 h at 50 °C and monitored by using TLC. After complete disappearance of the starting material, the mixture was concentrated in vacuo. The crude product was purified by using column chromatography to give **30** as a colorless syrup (50 mg, 32%).

Method III

CuI (1.0 mg, 0.005 mmol, 0.1 equiv) and TEA (29 μL, 0.208 mmol, 4 equiv) were added to a solution of compound **22** (150 mg, 0.224 mmol) and compound **3** (15 mg, 0.052 mmol) in acetonitrile (3.0 mL). The reaction mixture was stirred for 20 h at RT and monitored by using TLC. After complete disappearance of the starting material, the mixture was concentrated in vacuo. The crude product was purified by using column chromatography to give **30** as a colorless syrup (123 mg, 79%). $[\alpha]_D=-33.8$ ($c=0.11$ $CHCl_3$); $R_f=0.27$ (CH_2Cl_2/MeOH 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.56$, 7.53 (2×s, 8H; 8×*CH* triazole), 5.16–4.98 (m, 36H; 4×H2, H4, H2′, H3′, H4′, 8×CH_2 ethylene glycol, 4.86 (d, $J=1.2$ Hz, 4H; 4×H1), 4.81 (s, 4H; 4×H1′), 4.73 (d, $J=12.4$ Hz, 4H; 4×CH_2a propargyl), 4.59 (d, $J=12.4$ Hz, 4H; 4×CH_2b propargyl), 4.49 (s, 8H; 4×CH_2 propargyl), 4.05 (dd, $J=9.9$ Hz, $J=3.4$ Hz, 4H; 4×H3), 3.88–3.79 (m, 8H; 4×H5, H5′), 3.37 (m, 8H; 4×CH_2 pentaerythritol), 2.18, 2.13, 2.12, 2.05, 1.98 (5×s, 60H; 20×CH_3 acetyl), 1.19 (d, $J=6.2$ Hz, 12H; 4×CH_3), 1.15 ppm (d, $J=6.3$ Hz, 12H; 4×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.5$, 170.2, 170.1, 169.8 (20C; 20×CO acetyl), 143.9 (8C; 8×C_q triazole), 124.2 (8C; 8×*CH* triazole), 98.7, 96.4 (8C; 4×C1, 4×C1′), 75.1, 72.2, 71.1, 70.7, 70.2, 68.5, 67.2, 66.9 (32C; 4×skeleton carbons), 69.2, 64.6 (4C; 4×CH_2 pentaerythritol), 60.2 (8C; 8×CH_2 propargyl), 49.5, 49.3 (8C; 8×NCH_2 ethylene glycol), 21.0, 20.9, 20.8, 20.7 (20C; 20×CH_3 acetyl), 17.5, 17.4 ppm (8C; 8×CH_3); ESI-TOF MS: *m/z* calcd for $C_{125}H_{172}N_{24}NaO_{60}$: 2993.848 $[M+Na]^+$; found: 1508.0374 $[M+2Na]^{2+}$, 1013.0180 $[M+3Na]^{3+}$.

Compound 31

Compound **30** (70 mg, 0.024 mmol) was converted to **31** according to general method B. The crude product was purified by using column chromatography to give **31** as a white solid (48 mg, 96%). $[\alpha]_D=-66.2$ ($c=0.12$ MeOH); $R_f=0.37$ (CH_2Cl_2/MeOH/H_2O 7:5:1); ^{1}H NMR (400 MHz, CD_3OD): $\delta=7.78$ (s, 4H; 4×*CH* triazole), 7.77 (s, 4H; 4×*CH* triazole), 4.89–4.63 (m, 24H; 4×H1, 4×H1′, 8×CH_2 ethylene glycol), 4.60 (d, $J=12.4$ Hz, 4H; 4×CH_2a propargyl), 4.48 (d, $J=12.4$ Hz, 4H; 4×CH_2a propargyl), 4.37 (s, 8H; 4×CH_2 propargyl), 3.88 (s, 4H), 3.77 (s, 4H), 3.68–3.65 (m, 8H), 3.60 (dd, $J=9.3$ Hz, $J=3.0$ Hz, 4H; 4×H3), 3.52–3.47 (m, 4H), 3.40 (t, $J=9.5$ Hz, 4H), 3.31–3.25 (m, 12H), 1.15 (d, $J=6.0$ Hz, 12H; 4×CH_3), 1.15 ppm (d, $J=6.2$ Hz, 12H; 4×CH_3); ^{13}C NMR (100 MHz, CD_3OD): $\delta=146.4$, 145.4 (8C; 8×C_q triazole), 126.0, 125.6 (8C; 8×*CH* triazole), 104.0, 100.6 (8C; 4×C1, 4×C1′), 79.7, 74.0, 73.1, 72.2, 72.1, 71.9, 70.3, 70.1 (32C; 4×skeleton carbons), 69.9, 65.2 (4C; 4×CH_2 pentaerythritol), 60.5 (8C; 8×CH_2 propargyl), 50.9 (8C; 8×NCH_2 ethylene glycol), 46.3 (1C; C_q pentaerythritol), 18.1 ppm (8C; 8×CH_3); MALDI-TOF MS: *m/z* calcd for $C_{85}H_{132}N_{24}NaO_{40}$: 2151.892 $[M+Na]^+$; found: 2151.893 $[M+Na]^+$; elemental analysis calcd (%) for $C_{85}H_{132}N_{24}O_{40}$: C 47.93, H 6.25; found: C 48.09, H 6.36.

Compound 32

Compound **14** (83 mg, 0.104 mmol, 3 equiv) and compound **3** (10 mg, 0.034 mmol) were converted to **32** according to general method A. The crude product was purified by using column chromatography to give **32** as a colorless syrup (31 mg, 33%). $[\alpha]_D=-27.2$ ($c=0.11$ $CHCl_3$); $R_f=0.39$ (EtOAc/MeOH 7:3); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.74$ (s, 6H; 6×*CH* triazole), 5.18–5.00 (m, 15H; 3×H2, H4, H2′, H3′, H4′), 4.85 (s, 6H; 3×H1, 3×H1′), 4.78 (d, $J=11.7$ Hz, 3H; 3×CH_2a propargyl), 4.64–4.56 (m, 21H; 3×CH_2b propargyl, 3×CH_2 propargyl, 6×CH_2 TEG), 4.13–4.07 (m, 6H; 3×CH_2 TEG), 3.89–3.85 (m, 18H), 3.60–3.49 (m, 31H), 2.46 (s, 1H; *CH* propargyl), 2.19, 2.12, 2.04, 1.97 (5×s, 45H; 15×CH_3 acetyl), 1.20 (d, $J=5.7$ Hz, 9H; 3×CH_3), 1.15 ppm (d, $J=6.0$ Hz, 9H; 3×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.6$, 170.3, 170.2, 169.8 (15C; 15×CO acetyl), 98.8, 96.7 (6C; 3×C1, 3×C1′), 75.2, 72.4, 71.2, 70.9, 70.3, 68.6, 67.3, 67.0 (24C; 3×skeleton carbons), 70.6, 70.5, 69.6 (18C; 18×CH_2 TEG), 60.6 (6C; 6×CH_2 propargyl), 50.4 (6C; 6×NCH_2 TEG), 21.1, 21.0, 20.9, 20.8, 20.7 (15C; 15×CH_3 acetyl), 17.5, 17.4 ppm (6C; 6×CH_3); ESI-TOF MS: *m/z* calcd for $C_{116}H_{170}N_{18}NaO_{55}$: 2719.6962 $[M+Na]^+$; found: 1371.0253 $[M+2Na]^{2+}$, 921.6772 $[M+3Na]^{3+}$.

Compound 33

Compound **32** (31 mg, 0.011 mmol) was converted to **33** according to general method B. The crude product was purified by using column chromatography to give **33** as a white solid (13 mg, 57%). $[\alpha]_D=-35.1$ ($c=0.08$ MeOH); $R_f=0.09$ (CH_2Cl_2/MeOH/H_2O 7:5:0.5); ^{1}H NMR (400 MHz, CD_3OD): $\delta=8.03$, 7.97 (2×s, 6H; 6×*CH* triazole), 4.97 (d, $J=1.2$ Hz, 3H; 3×H1), 4.77 (d, $J=1.3$ Hz, 3H; 3×H1′), 4.74

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(d, J=12.3 Hz, 3H; 3×CH_2a propargyl), 4.61 (d, J=12.4 Hz, 3H; 3×CH_2b propargyl), 4.56 (t, J=4.8 Hz, 12H; 6×CH_2 TEG), 4.51 (s, 6H; 3×CH_2 propargyl), 4.03 (d, J=2.4 Hz, 2H), 3.96–3.95 (m, 3H), 3.88–3.86 (m, 6H; 3×CH_2 TEG), 3.77–3.30 (m, 59H), 2.83 (t, J=2.2 Hz, 1H; C*H* propargyl), 1.26 (d, J=6.1 Hz, 9H; 3×CH_3), 1.21 ppm (d, J=6.2 Hz, 9H; 3×CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ=146.0, 145.2 (6C; 6×C_q triazole), 126.1, 125.7 (6C; 6×C*H* triazole), 104.1, 101.0 (6C; 3×C1, 3×C1′), 79.8, 74.1, 73.2, 72.2, 72.1, 72.0, 70.4, 70.1 (24C; 3×skeleton carbons), 76.0 (1C; C*H* propargyl), 71.5 (18C; OCH_2 TEG), 70.4, 70.3 (4C; 4×CH_2 pentaerythritol), 61.0 (6C; 6×CH_2 propargyl), 59.5 (1C; CH_2 propargyl), 51.4 (6C; 6×NCH_2 TEG), 46.4 (1C; C_q pentaerythritol), 18.1 ppm (6C; 6×CH_3); MALDI-TOF MS: *m/z* calcd for $C_{86}H_{140}N_{18}NaO_{40}$: 2089.140 $[M+Na]^+$; found: 2089.130 $[M+Na]^+$; elemental analysis calcd (%) for $C_{86}H_{140}N_{18}O_{40}$: C 49.99, H 6.83; found: C 50.12, H 6.98.

Compound 34

Compound **22** (116 mg, 0.173 mmol, 2.5 equiv) and compound **3** (20 mg, 0.069 mmol) were converted to **34** according to general method A. The crude product was purified by using column chromatography to give **34** as a colorless syrup (50 mg, 31%). $[\alpha]_D$=−28.6 (c=0.10 $CHCl_3$); R_f=0.41 (EtOAc/EtOH 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.69–7.46 (m, 6H; 6×C*H* triazole), 5.15–4.44 (m, 53H; 3×H1, H1′, H2, H4, H2′, H3′, H4′, 6×CH_2 ethylene glycol, 6×CH_2 propargyl, 4×CH_2 pentaerythritol), 4.05 (d, J=9.5 Hz, 3H; 3×H3), 3.88–3.79 (m, 6H; 3×H5, 3×H5′), 3.37 (s, 2H; CH_2 propargyl), 2.73 (d, J=8.1 Hz, 1H; C*H* propargyl), 2.18, 2.12, 2.04, 1.97 (5×s, 45H; 15×CH_3 acetyl), 1.20 (d, J=5.5 Hz, 9H; 3×CH_3), 1.15 ppm (d, J=5.1 Hz, 9H; 3×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.5, 170.2, 170.1, 169.7 (15C; 15×CO acetyl), 143.9 (6C; 6×C_q triazole), 124.2 (6C; 6×CH triazole), 98.8, 96.5 (6C; 3×C1, 3×C1′), 76.4 (1C; C_q propargyl), 75.2, 72.2, 71.1, 70.8, 70.2, 68.5, 67.3, 67.0 (24C; 3×skeleton carbons), 68.9 (1C; CH_2 propargyl), 64.7 (4C; 4×CH_2 pentaerythritol), 60.6 (6C; 6×CH_2 propargyl), 49.4 (6C; 6×NCH_2 ethylene glycol), 47.2 (1C; C_q pentaerythritol), 21.0, 20.9, 20.8, 20. 7 (15C; 15×CH_3 acetyl), 17.5, 17.4 ppm (6C; 6×CH_3); ESI-TOF MS: *m/z* calcd for $C_{98}H_{134}N_{18}NaO_{46}$: 2321.8592 $[M+Na]^+$; found: 1171.9091 $[M+2Na]^{2+}$.

Compound 35

Compound **34** (100 mg, 0.039 mmol) was converted to **35** according to general method B. The crude product was purified by using column chromatography to give **35** as a white solid (34 mg, 52%). $[\alpha]_D$=−44.7 (c=0.17 MeOH); R_f=0.48 (CH_2Cl_2/MeOH/H_2O 6:5:0.5); ^{1}H NMR (400 MHz, CD_3OD): δ=7.78–7.76 (m, 6H; 6×C*H* triazole), 4.89–4.42 (m, 38H; 3×H1, H1′, 6×CH_2 ethylene glycol, 6×CH_2 propargyl, 4×CH_2 pentaerythritol), 3.90 (s, 3H; 3×H3), 3.79–3.22 (m, 24H), 1.24–1.13 ppm (m, 18H; 6×CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ=146.4, 145.5, 145.4 (6C; 6×C_q triazole), 126.0, 125.6 (6C; 6×CH_2 triazole), 103.9, 100.6 (6C; 3×C1, 3×C1′), 79.6, 73.9, 73.0, 72.0, 71.9, 71.7, 70.3, 70.1 (24C; 3×skeleton carbons), 65.1 (1C; CH_2 propargyl), 60.6 (6C; 6×CH_2 propargyl), 50.9 (6C; 6×NCH_2 ethylene glycol), 18.0 ppm (6C; 6×CH_3); MALDI-TOF MS: *m/z* calcd for $C_{68}H_{104}N_{18}NaO_{31}$: 1691.701 $[M+Na]^+$; found: 1690.548 $[M+Na]^+$; elemental analysis calcd (%) for $C_{68}H_{104}N_{18}O_{31}$: C 48.92, H 6.28; found: C 49.11, H 6.34.

Compound 36

Compound **14** (144 mg, 0.179 mmol) and compound **4**[24] (15 mg, 0.045 mmol) were converted to **36** according to general method A. The crude product was purified by using column chromatography to give **36** as a colorless syrup (80 mg, 64%). $[\alpha]_D$=−28.4 (c=0.09 $CHCl_3$); R_f=0.40 (EtOAc/MeOH 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.74–7.72 (m, 6H; 6×C*H* triazole), 5.18–5.00 (m, 16H; N*H*, 3×H2, H4, H2′, H3′, H4′), 4.85 (s, 6H; 3×H1, 3×H1′), 4.78 (d, J=12.1 Hz, 3H; 3×CH_2a propargyl), 4.64–4.54 (m, 21H; 3×CH_2b propargyl, 3×CH_2 propargyl, 6×CH_2 TEG), 4.08 (dd, J=9.8 Hz, J=3.1 Hz, 3H; 3×H3), 3.89–3.83 (m, 18H), 3.75–3.72 (m, 6H; 3×CH_2 Tris), 3.60–3.58 (m, 25H), 3.47 (s, 8H), 2.19, 2.12, 2.05, 1.97 (5×s, 45H; 15×CH_3 acetyl), 1.39 (s, 9H; 3×CH_3 *t*Bu), 1.20 (d, J=6.1 Hz, 9H; 3×CH_3), 1.16 ppm (d, J=6.2 Hz, 9H; 3×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.5, 170.2, 170.1, 169.7 (15C; 15×CO acetyl), 124.2 (6C; 6×CH triazole), 98.8, 96.6 (6C; 3×C1, 3×C1′), 75.1, 72.4, 71.2, 70.8, 70.2, 68.5, 67.2, 66.9 (24C; 3×skeleton carbons), 70.5 (18C; 18×CH_2 TEG), 69.5 (3C; 3×CH_2 Tris), 64.8, 60.6 (6C; 6×CH_2 propargyl), 58.5 (1C; C_q Tris), 50.3, 50.2 (6C; 6×NCH_2 TEG), 29.7 (1C; C_q *t*Bu), 28.4 (3C; 3×CH_3 *t*Bu), 21.0, 20.9, 20.8, 20.7 (15C; 15×CH_3 acetyl), 17.5, 17.4 ppm (6C; 6×CH_3); MALDI-TOF MS: *m/z* calcd for $C_{117}H_{175}N_{19}NaO_{56}$: 2766.75 $[M+Na]^+$; found: 2767.69 [*M*+Na]■■missing $^+$?■■; elemental analysis calcd (%) for $C_{117}H_{175}N_{19}O_{56}$: C 51.22, H 6.43; found: C 51.29, H 6.51.

Compound 37

Compound **36** (60 mg, 0.022 mmol) was converted to **37** according to general method B. The crude product was purified by using column chromatography to give **37** as a white solid (32 mg, 70%). $[\alpha]_D$=−48.8 (c=0.10 MeOH); R_f=0.52 (CH_2Cl_2/MeOH/H_2O 7:5:0.5); ^{1}H NMR (400 MHz, CD_3OD): δ=8.04, 7.98 (2×s, 6H; 6×C*H* triazole), 4.98 (s, 3H; 3×H-1), 4.85–4.73 (m, 6H; 3×CH_2a propargyl, 3×H1′), 4.63–4.55 (m, 21H; 3×CH_2b propargyl, 3×CH_2 propargyl, 6×CH_2 TEG), 3.97 (s, 3H), 3.89–3.85 (m, 16H), 3.78–3.69 (m, 13H), 3.66–3.48 (m, 32H), 3.40–3.31 (m, 12H), 1.38 (s, 9H; 3×CH_3 *t*Bu), 1.27 (d, J=6.1 Hz, 9H; 3×CH_3), 1.21 ppm (d, J=6.2 Hz, 9H; 3×CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ=145.7, 145.2 (66C, 6×C_q triazole), 126.1, 125.8 (6C; 6×CH triazole), 104.1, 100.9 (6C; 3×C1, 3×C1′), 79.7, 74.1, 73.1, 72.2, 72.1, 72.0, 70.4, 70.1 (24C; 3×skeleton carbons), 71.5 (18C; 18×CH_2 TEG), 70.3 (3C; 3×CH_2 Tris), 65.3, 60.8 (6C; 6×CH_2 propargyl), 60.1 (1C; C_q Tris), 51.4 (6C; 6×NCH_2 TEG), 28.8 (3C; 3×CH_3 *t*Bu), 18.1 ppm (6C; 6×CH_3); MALDI-TOF MS: *m/z* calcd for $C_{87}H_{145}N_{19}NaO_{41}$: 2136.20 $[M+Na]^+$; found: 2136.73 [*M*+Na]■■missing $^+$?■■; elemental analysis calcd (%) for $C_{87}H_{145}N_{19}O_{41}$: C 49.45, H 6.92; found: C 49.49, H 6.97.

Compound 38

Compound **22** (160 mg, 0.239 mmol) and compound **4** (20 mg, 0.060 mmol) were converted to **38** according to general method A. The crude product was purified by using column chromatography to give **38** as a colorless syrup (87 mg, 62%). $[\alpha]_D$=−35.1 (c=0.09 $CHCl_3$); R_f=0.11 (EtOAc/acetone 6:4); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.5, 170.2, 170.1, 169.7 (15C; 15×CO acetyl), 154.8 (1C; C_q Boc), 144.0 (6C; 6×C_q triazole), 124.1, 123.9 (6C; 6×CH triazole), 98.8, 96.5 (6C; 3×C1, 3×C1′), 75.2, 72.3, 71.2, 70.9, 70.2, 68.6, 67.3, 67.0 (24C; 3×skeleton carbons), 69.3 (3C; 3×CH_2 Tris), 64.6, 60.3 (6C; 6×CH_2 propargyl), 58.4 (1C; C_q Tris), 49.5, 49.4 (6C; 6×NCH_2 ethylene glycol), 29.7 (1C; C_q *t*Bu), 28.4 (3C; 3×CH_3 *t*Bu), 21.0, 20.9, 20.8, 20.7, 20.6 (15C; 15×CH_3 acetyl), 17.5, 17.4 ppm (6C; 6×CH_3); MALDI-TOF MS: *m/z* calcd for $C_{99}H_{139}N_{19}NaO_{47}$: 2370.3 $[M+Na]^+$; found: 2370.4 $[M+Na]^+$; elemental analysis calcd (%) for $C_{99}H_{139}N_{19}O_{47}$: C 50.66, H 5.97; found: C 50.71, H 6.09.

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Compound 39

Compound **38** (60 mg, 0.026 mmol) was converted to **39** according to general method B. The crude product was purified by using column chromatography to give **39** as a white solid (32 mg, 72%). $[\alpha]_D = -63.1$ ($c = 0.11$ MeOH); $R_f = 0.27$ (CH_2Cl_2/MeOH/H_2O 6:5:0.5); ^{1}H NMR (360 MHz, CD_3OD): $\delta = 7.96$ (s, 6H; 6×*CH* triazole), 5.08 (s, 15H; 3×H-1, 6×CH_2 ethylene glycol), 4.82–4.80 (m, 6H; 3×CH_2a propargyl, 3×H1′), 4.71–4.64 (m, 9H; 3×CH_2b propargyl, 3×CH_2 propargyl), 4.08 (s, 3H), 3.97 (s, 3H), 3.88–3.85 (m, 6H), 3.81 (dd, $J = 9.5$ Hz, $J = 2.7$ Hz, 3H; 3×H3), 3.73–3.69 (m, 9H), 3.63–3.58 (m, 3H), 3.51–3.42 (m, 4H), 1.51 (s, 9H; 3×CH_3 *t*Bu), 1.36 (d, $J = 6.0$ Hz, 9H; 3×CH_3), 1.33 ppm (d, $J = 6.2$ Hz, 9H; 3×CH_3); ^{13}C NMR (90 MHz, CD_3OD): $\delta = 163.6$ (1C; C_q Boc), 146.2, 145.6 (6C; 6×C_q triazole), 125.9, 125.6 (6C; 6×*CH* triazole), 104.1, 100.7 (6C; 3×C1, 3×C1′), 79.8, 74.1, 73.2, 72.3, 72.2, 71.9, 70.4, 70.1 (24C; 3×skeleton carbons), 69.9 (3C; 3×CH_2 Tris), 65.2, 60.6 (6C; 6×CH_2 propargyl), 59.9 (1C; C_q Tris), 50.9 (6C; 6×NCH_2 ethylene glycol), 28.8 (3C; 3×CH_3 *t*Bu), 18.1 ppm (6C; 6×CH_3); MALDI-TOF MS: *m/z* calcd for $C_{69}H_{109}N_{19}NaO_{32}$: 1739.74 $[M+Na]^+$; found: 1739.36 $[M+Na]^+$ missing ?; elemental analysis calcd (%) for $C_{69}H_{109}N_{19}O_{32}$: C 48.28, H 6.40; found: C 48.31, H 6.42.

Compound 40

Compound **14** (100 mg, 0.125 mmol) and compound **5**[25] (29 mg, 0.150 mmol) were converted to **40** according to general method A. The crude product was purified by using column chromatography to give **40** as a colorless syrup (107 mg, 86%). $[\alpha]_D = -28.9$ ($c = 0.15$ $CHCl_3$); $R_f = 0.22$ (CH_2Cl_2/acetone 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.73$, 7.71 (2×s, 2H; 2×*CH* triazole), 5.19–5.00 (m, 5H; H2, H4, H2′, H3′, H4′), 4.86 (s, 2H; H1, H1′), 4.79 (d, $J = 12.2$ Hz, 1H; CH_2a propargyl), 4.64–4.62 (m, 3H; CH_2b propargyl, CH_2 propargyl), 4.57–4.53 (m, 4H; 2×CH_2 TEG), 4.08 (dd, $J = 9.9$ Hz, $J = 3.4$ Hz, 1H; H3), 3.90–3.81 (m, 6H; H5, H5′, 2×CH_2 TEG), 3.62–3.57 (m, 8H; 4×CH_2 TEG), 3.51 (t, $J = 6.7$ Hz, 2H; OCH_2 decyl), 2.19, 2.12, 2.05, 1.98 (5×s, 15H; 5×CH_3 acetyl), 1.60–1.55 (m, 2H; CH_2 decyl), 1.26–1.15 (m, 20H; 2×CH_2, 7×CH_2 decyl), 0.88 ppm (t, $J = 6.7$ Hz, 3H; CH_3 decyl); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.2$, 170.1, 169.7 (5C; 5×CO acetyl), 143.8 (2C; 2×C_q triazole), 124.1 (2C; 2×*CH* triazole), 98.9, 96.7 (2C; C1, C1′), 75.2, 72.5, 71.3, 70.9, 70.3, 68.6, 67.3, 67.0 (8C; skeleton carbons), 71.0, 70.6, 70.5, 69.6, 69.5 (7C; 6×CH_2 TEG, OCH_2 decyl), 64.4, 60.7 (2C; 2×CH_2 propargyl), 50.4, 50.3 (2C; 2×NCH_2 TEG), 32.0, 29.8, 29.7, 29.6, 26.3, 22.7 (8C; 8×CH_2 decyl), 21.0, 20.9, 20.8, 20.7 (5C; 5×CH_3 acetyl), 17.5, 17.4 (2C; 2×CH_3), 14.2 ppm (1C; CH_3 decyl); MALDI-TOF MS: *m/z* calcd for $C_{46}H_{74}N_6NaO_{18}$: 1021.5 $[M+Na]^+$; found: 1021.1 $[M+Na]^+$, 522.1 $[M+2Na]^{2+}$; elemental analysis calcd (%) for $C_{46}H_{74}N_6O_{18}$: C 55.30, H 7.47; found: C 55.38, H 7.52.

Compound 41

Compound **40** (100 mg, 0.100 mmol) was converted to **41** according to general method B. The crude product was purified by using column chromatography to give **41** as a white solid (59 mg, 75%). $[\alpha]_D = -51.0$ ($c = 0.59$ MeOH); $R_f = 0.33$ (CH_2Cl_2/MeOH 85:15); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.95$, 7.91 (2×s, 2H; 2×*CH* triazole), 4.89 (d, $J = 1.2$ Hz, 1H; H1), 4.69 (d, $J = 1.3$ Hz, 1H; H1′), 4.65 (d, $J = 12.3$ Hz, 1H; CH_2a propargyl), 4.52 (d, $J = 12.3$ Hz, 1H; CH_2b propargyl), 4.51–4.46 (m, 6H; CH_2 propargyl, 2×CH_2 TEG), 3.87 (dd, $J = 3.2$ Hz, $J = 1.6$ Hz, 1H), 3.79 (t, $J = 5.0$ Hz, 6H), 3.69–3.61 (m, 3H), 3.56–3.53 (m, 1H), 3.51–3.39 (m, 10H), 3.28 (t, $J = 9.5$ Hz, 1H), 1.51–1.44 (m, 2H; CH_2 decyl), 1.26–1.12 (m, 20H; 2×CH_3, 7×CH_2 decyl), 0.80 ppm (t, $J = 6.8$ Hz, 3H; CH_3 decyl); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 145.2$ (2C; 2×C_q triazole), 125.8 (2C; 2×*CH* triazole), 104.1, 100.8 (2C; C1, C1′), 79.7, 74.0, 73.1, 72.1, 72.0, 71.9, 70.3, 70.0 (8C; skeleton carbons), 71.6, 71.4, 70.3 (7C; 6×CH_2 TEG, OCH_2 decyl), 64.6, 60.8 (2C; 2×CH_2 propargyl), 51.4 (2C; 2×NCH_2 TEG), 33.0, 30.7, 30.6, 30.5, 30.4, 27.2, 23.7 (8C; 8×CH_2 decyl), 18.1 (2C; 2×CH_3), 14.4 ppm (1C; CH_3 decyl); MALDI-TOF MS: *m/z* calcd for $C_{36}H_{64}N_6NaO_{13}$: 811.44 $[M+Na]^+$; found: 811.49 $[M+Na]^+$; elemental analysis calcd (%) for $C_{36}H_{64}N_6O_{13}$: C 54.81, H 8.18; found: C 54.89, H 8.23.

Compound 42

Compound **22** (100 mg, 0.149 mmol) and compound **5** (24 mg, 0.124 mmol) were converted to **42** according to general method A. The crude product was purified by using column chromatography to give **42** as a colorless syrup (117 mg, 91%). $[\alpha]_D = -32.7$ ($c = 0.18$ $CHCl_3$); $R_f = 0.44$ (CH_2Cl_2/acetone 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$, 7.39 (2×s, 2H; 2×*CH* triazole), 5.15–4.93 (m, 9H; H2, H4, H2′, H3′, H4′, 2×CH_2 ethylene glycol), 4.86 (s, 1H; H1), 4.80 (s, 1H; H1′), 4.74 (d, $J = 12.4$ Hz, 1H; CH_2a propargyl), 4.60–4.56 (m, 3H; CH_2b propargyl, CH_2 propargyl), 4.05 (dd, $J = 9.9$ Hz, $J = 3.4$ Hz, 1H; H3), 3.84 (ddd, $J = 23.2$ Hz, $J = 9.7$ Hz, $J = 6.3$ Hz, 2H; H5, H5′), 3.47 (t, $J = 6.7$ Hz, 2H; OCH_2 decyl), 2.18, 2.12, 2.05, 1.97 (4×s, 15H; 5×CH_3 acetyl), 1.58–1.55 (m, 2H; CH_2 decyl), 1.26 (s, 14H; 7×CH_2 decyl), 1.20 (d, $J = 6.2$ Hz, 3H; CH_3), 1.16 (d, $J = 6.2$ Hz, 3H; CH_3), 0.88 ppm (t, $J = 6.7$ Hz, 3H; CH_3 decyl); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.4$, 170.1, 170.0, 169.9, 169.6 (5C; 5×CO acetyl), 145.9, 143.9 (2C; 2×C_q triazole), 124.1, 123.6 (2C; 2×*CH* triazole), 98.7, 96.4 (2C; C1, C1′), 75.0, 72.2, 71.0, 70.7, 70.1, 68.5, 67.2, 66.8 (8C; skeleton carbons), 70.9 (1C; OCH_2 decyl), 64.0, 60.2 (2C; 2×CH_2 propargyl), 49.5, 49.4 (2C; 2×NCH_2 ethylene glycol), 31.8, 29.6, 29.5, 29.4, 29.2, 26.0, 22.6 (8C; 8×CH_2 decyl), 20.9, 20.8, 20.7, 20.6 (5C; 5×CH_3 acetyl), 17.4, 17.3 (2C; 2×CH_3), 14.1 ppm (1C; CH_3 decyl); ESI-TOF MS: *m/z* calcd for $C_{40}H_{62}N_6NaO_{15}$: 889.4165 $[M+Na]^+$; found: 889.4143 $[M+Na]^+$.

Compound 43

Compound **42** (107 mg, 0.123 mmol) was converted to **43** according to general method B. The crude product was purified by using column chromatography to give **43** as a white solid (67 mg, 83%). $[\alpha]_D = -58.4$ ($c = 0.11$ MeOH); $R_f = 0.53$ (CH_2Cl_2/acetone 8:2); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.76$, 7.74 (2×s, 2H; 2×*CH* triazole), 4.88–4.87 (m, 5H; H1, 2×CH_2 ethylene glycol), 4.62, 4.60 (m, 2H; H1′, CH_2a propargyl), 4.49 (d, $J = 12.4$ Hz, 1H; CH_2b propargyl), 4.43 (s, 2H; CH_2 propargyl), 3.87 (s, 1H), 3.77 (s, 1H), 3.69–3.65 (m, 2H), 3.61 (dd, $J = 9.5$ Hz, $J = 3.0$ Hz, 1H), 3.53–3.49 (m, 1H), 3.42 (d, $J = 9.5$ Hz, 1H), 3.36 (t, $J = 6.6$ Hz, 2H), 3.28 (t, $J = 9.5$ Hz, 1H), 1.47–1.44 (m, 2H; CH_2 decyl), 1.19–1.12 (m, 20H; 7×CH_2 decyl, 2×CH_3), 0.80 ppm (t, $J = 6.7$ Hz, 3H; CH_3 decyl); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 145.6$, 144.8 (2C; 2×C_q triazole), 126.0, 125.1 (2C; 2×*CH* triazole), 104.0, 100.6 (2C; C1, C1′), 79.7, 74.0, 73.1, 72.0, 72.0, 71.9, 70.3, 70.0 (8C; skeleton carbons), 71.6 (1C; OCH_2 decyl), 64.5, 60.5 (2C; 2×CH_2 propargyl), 50.8 (2C; 2×NCH_2 ethylene glycol), 33.0, 30.6, 30.5, 30.4, 27.2, 23.7 (8C; 8×CH_2 decyl), 18.0 (2C; 2×CH_3), 14.4 ppm (1C; CH_3 decyl); ESI-TOF MS: *m/z* calcd for $C_{30}H_{52}N_6NaO_{10}$: 679.3637 $[M+Na]^+$; found: 679.3571 $[M+Na]^+$.

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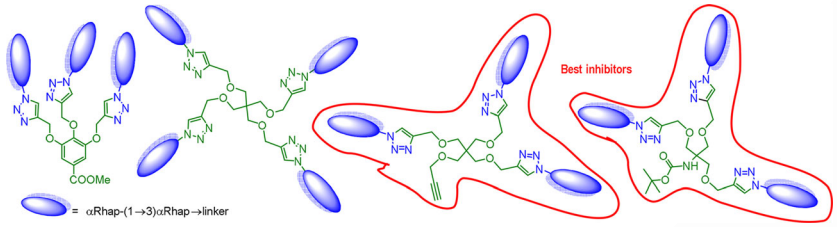

Less is sometimes more: Two sets of glycoclusters with up to four α(1–3)-rhamnobiosides were prepared to study their inhibitory effect on recombinant horseshoe crab plasma lectin (rHPL)–bacteria interactions. Trivalent rhamnobiosides on a pentaerythritol or a Tris central core showed a stronger inhibitory effect on *P. aeruginosa* PAO1 binding than either the corresponding tetravalent derivatives or the less flexible methyl gallate-based trivalent clusters (see figure).■■TOC graphic too big, removed the scheme ok? TOC graphic size should be 11x3 cm■■

Bacterial Inhibition

Mihály Herczeg, Erika Mező, Nikolett Molnár, Sim-Kun Ng, Yuan-Chuan Lee, Margaret Dah-Tsyr Chang,* Anikó Borbás**

■■–■■

Inhibitory Effect of Multivalent Rhamnobiosides on Recombinant Horseshoe Crab Plasma Lectin Interactions with *Pseudomonas aeruginosa* PAO1

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