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Carbohydrate Mimetics

Divalent Triazole-Linked Carbohydrate Mimetics: Synthesis by Click Chemistry and Evaluation as Selectin Ligands

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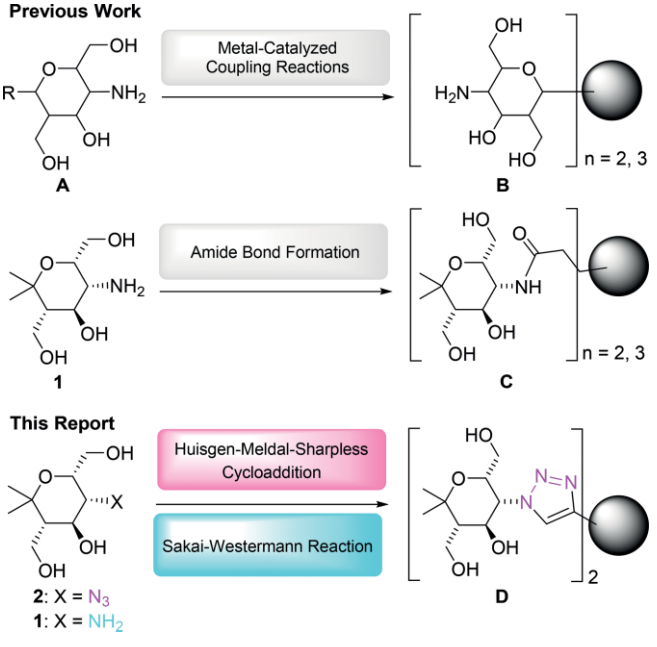
Dedicated to Professor Bernd Giese on the occasion of this 80th birthday.

Abstract: Starting from an enantiopure 3-amino-substituted pyran derivative, the synthesis of a series of divalent 1,2,3-triazole-linked carbohydrate mimetics is described. The preparation of the required 3-azido-substituted pyran proceeds smoothly by copper-catalyzed diazo transfer. Using different conditions for the Huisgen-Meldal-Sharpless cycloaddition, this azide reacts with several diynes to furnish the desired divalent carbohydrate mimetics bearing rigid or flexible linker units. The in situ generation of the 3-azidopyran in the presence of Cu/C as catalyst followed by the reaction with the alkyne allows a direct one-pot transformation from the 3-aminopyran to the desired click products. We also examined the Sakai-Westermann method that transfers primary amines with the aid of α,α-dichlorotosylhydrazones into 1,2,3-triazoles. These copper-free click conditions were applied for the first time to the preparation of a divalent compound. The *O*-sulfation of the carbohydrate mimetics was achieved using the SO_3-DMF complex under careful ^{1}H-NMR control. Five polysulfated compounds could be obtained in pure form and these were tested by surface plasmon resonance spectroscopy as inhibitors of L-selectin giving IC_{50} values between 45 nM and 50 μM.

Introduction

Synthetic C-glycosides and other carbohydrate mimetics are compounds of great interest due to their similarity to carbohydrate structures.[1,2] Their modified properties may influence bioavailability, selectivity, and affinity in important biological processes involving carbohydrates. Our group discovered an alkoxyallene-based[3] straightforward access to enantiopure 3-aminopyrans of general structure **A** and the closely related ring-expanded 4-aminooxepanes (Scheme 1).[4] Among compounds **A**, the 6,6-dimethyl-substituted 3-aminopyran **1** is the most easily available derivative[4a,4b] and hence its properties were investigated in detail.[4e,4f] Most remarkably, the connection of **1** to gold nanoparticles via amide bonds and subsequent *O*-sulfation of the pyran hydroxyl groups provided a multivalent macromolecular species that turned out to be a highly potent inhibitor of L- and P-selectin with IC_{50} values in the picomolar range.[5] L- and P-selectins are crucial components in the inflammatory process[6] and therefore compounds inhibiting their activity are of interest as potential therapeutics.[7] The mentioned aminopyran-decorated gold nanoparticles are densely packed with 1000–1200 ligands. For an understanding of the activity of these multivalent species, we studied analogous compounds that contain only a few of the aminopyrans ligands. Therefore we synthesized divalent and trivalent compounds of general structure **B** employing metal-catalyzed reactions (Scheme 1).[8] We also connected two or three aminopyrans units **1** via amide



Scheme 1. Routes to di- and trivalent carbohydrate mimetics **B**, **C**, and **D**.

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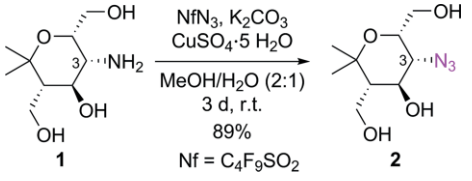
bonds to compounds of general structure **C** with rigid or flexible linker units.[9] Similar compounds could be prepared by reductive amination.[10]

In this report, we employ enantiopure 3-azido-substituted pyran **2** to synthesize the related divalent products **D** that are connected via 1,2,3-triazole units. The well-established Huisgen-Meldal-Sharpless copper-catalyzed azide-alkyne cycloaddition (click reaction)[11,12] has already been successfully used by our group for the reactions of the analogous 4-azidooxepanes.[13] Alternatively, the so-far under-explored Sakai-Westermann method[14,15] was examined to convert 3-aminopyran **1** into **D**. The resulting divalent pyran derivatives **D** were subsequently *O*-sulfated and investigated by surface plasmon resonance (SPR) spectroscopy as L-selectin inhibitors.

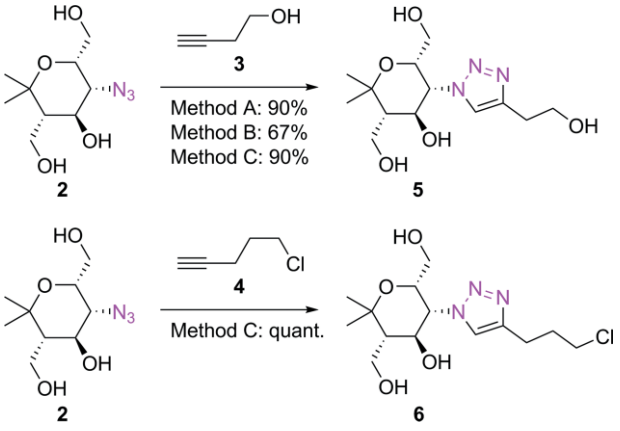
Results and Discussion

The conversion of 3-aminopyran **1** into the required azido-substituted pyran **2** was achieved by a copper sulfate-catalyzed diazo transfer that has previously been established as very effective and easy to perform route to organic azides.[16] In our group, the use of nonafluorobutanesulfonyl azide (NfN_3)[17] was implemented as a safe alternative to the commonly used trifluoromethanesulfonyl azide (TfN_3).[18] NFN_3 is less explosive and volatile than TfN_3 and therefore its handling is much easier and highly recommendable.[19] The copper sulfate-catalyzed reaction of **1** with NfN_3 smoothly furnished the fully deprotected 3-azidopyran **2** in excellent yield and under retention of configuration at C-3 (Scheme 2).



Scheme 2. Conversion of 3-aminopyran **1** into 3-azido-substituted pyran **2** by copper sulfate-catalyzed diazo transfer employing nonafluorobutanesulfonyl azide.

Different reaction conditions were examined for the copper-catalyzed azide-alkyne cycloadditions (CuAAC) of 3-azidopyran **2** with simple terminal alkynes **3** and **4** (Scheme 3). In these model reactions, we applied methods previously employed in our group using either CuI and tris-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-amine (TBTA) as ligand (method A)[4b,13] or an acid/base-catalyzed modification (method B) adapting a recently reported procedure.[20] We were also interested in exploring the efficiency of Cu/C, an inexpensive heterogeneous catalyst for CuAAC reactions (method C).[21] One of the advantages of this method is the fact that the cycloadditions occur in the Cu/C matrix, thus avoiding the presence of copper in solution and preventing contamination of the final products with the metal. Additional advantages are the easy removal of the catalyst by simple filtration through a pad of Celite® and its reusability. On the other hand, this method required a reaction temperature of 60 °C whereas methods A and B were applied at room temperature.



Scheme 3. Model CuAAC of 3-azidopyran **2** with alkynes **3** and **4** leading to 1,2,3-triazoles **5** and **6**. Method A: CuI, TBTA, NEt_3, MeCN, 20 h, r.t.; method B: CuI, $N(iPr)_2Et$, HOAc, toluene, 20 h, r.t.; method C: Cu/C, NEt_3, 1,4-dioxane, 20 h (for **5**) 21 h (for **6**), 60 °C.

The cycloaddition of **2** and **3** proceeded smoothly with methods A and C providing 1,4-disubstituted 1,2,3-triazole derivative **5** in excellent yields, but the purification of the product obtained by method A is not as straightforward due to the presence of the fairly large amounts of the TBTA ligand. Employing the acid/base-catalyzed method B the desired product **5** was obtained with a lower yield of 67 %. Due to the relatively high polarity of 1,2,3-triazole **5** an extraction was not possible and separation of the product from the acid and base was less efficient. For the synthesis of 1,2,3-triazole derivative **6** from alkyne **4** only method C was examined that furnished the desired product quantitatively.

Since we planned to test the prepared carbohydrate mimetics in biological assays, it should be assured that no copper is present in the obtained compounds. The three samples of 1,2,3-triazole derivative **5** obtained by the alternative CuAAC methods A, B, and C depicted in Scheme 3 were submitted to quantitative copper ICP-MS analyses. Values in the range between 4–8 ppb for ^{63}Cu and ^{65}Cu were obtained; these are lower than 15 ppb which is regarded as the sensitivity limit of this method.

For the synthesis of divalent structures diynes **7** and **8** with rigid arene centers and diynes **9** and **10** with flexible aliphatic linker units were chosen (Scheme 4). Alkynes **7**, **8**, and **9** and 3-azidopyran **2** were subjected to method A using CuI and TBTA. Although all desired divalent bis-1,2,3-triazoles **11**–**14** were obtained in good yields, the reactions of alkynes **8** and **9** also provided small amounts of the corresponding mono-1,2,3-triazoles.

The acid/base-catalyzed CuAAC (method B) was examined with diyne **9**. Using toluene as solvent and a mixture of Hünig base/acetic acid led to a fast reaction and a slight improvement of the yield. Apparently, the use of TBTA as additive is not necessary, whose removal is sometimes tedious.[13] Due to the excellent results observed with Cu/C-catalyzed CuAAC (method C) for the synthesis of the model 1,2,3-triazoles and the easy purification of the obtained compounds, these conditions were also applied to the synthesis of divalent compound **14**. The commercially available diyne **10** and 3-azidopyran **2** furnished the corresponding product **14** in a very high yield.

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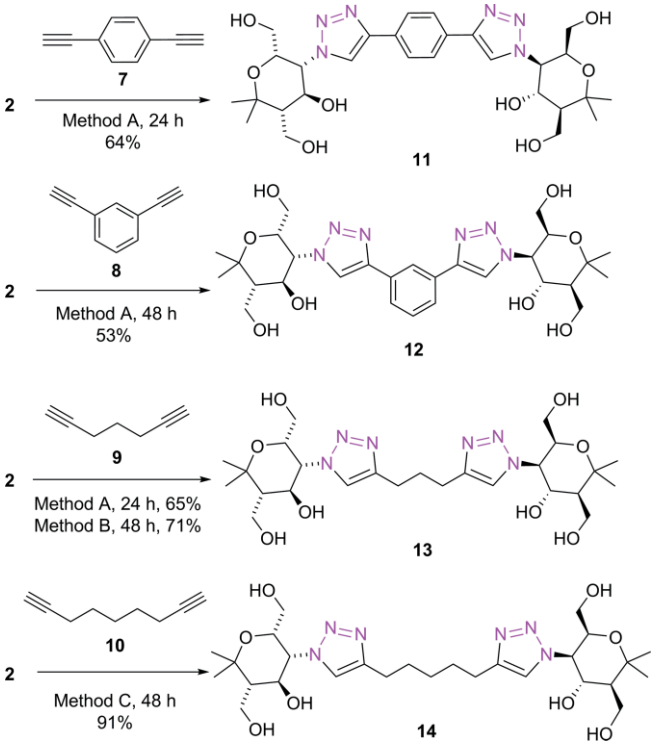
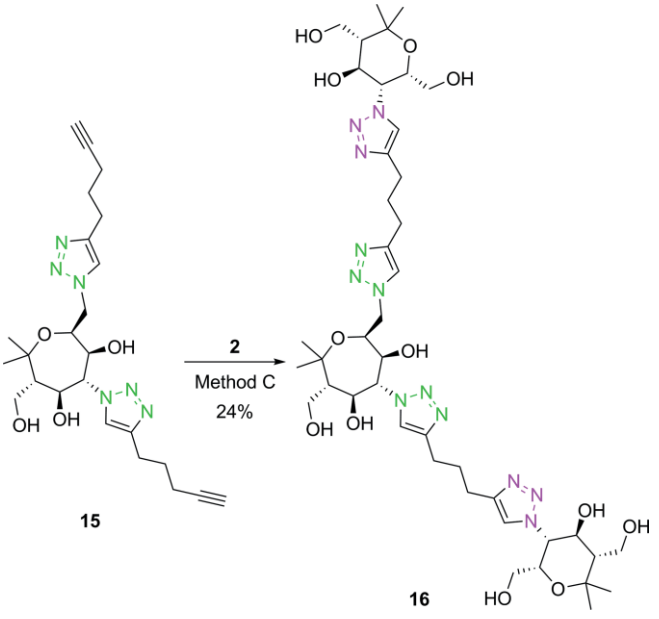


Scheme 4. Synthesis of bis-1,2,3-triazoles **11**–**14** by CuAAC of 3-azidopyran **2** with diynes **7**–**10**. Method A: CuI, TBTA, NEt_3, MeCN, r.t.; method B: CuI, $N(iPr)_2Et$, HOAc, toluene, r.t.; method C: Cu/C, NEt_3, 1,4-dioxane, 60 °C.

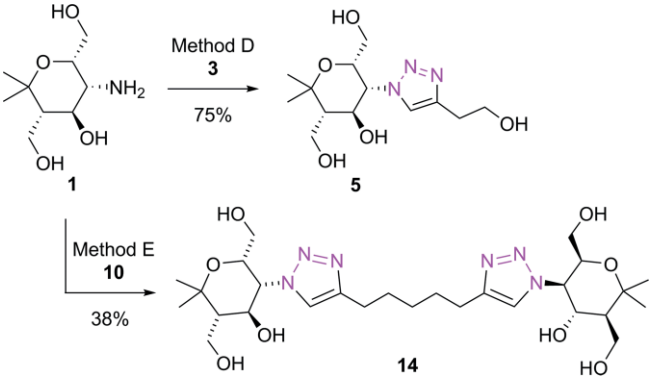
In our study on 4-aminooxepanes we also prepared a bis-(azido)oxepane derivative that underwent a twofold CuAAC with an excess of 1,6-heptadiyne affording an unsymmetrical diyne **15** (Scheme 5).[13] In order to enhance the degree of complexity, compound **15** was treated with 3-azido-substituted pyran **2** employing the approved method C. The reaction proceeded smoothly, but product **16** with three carbohydrate mimicking subunits and four connecting 1,2,3-triazole moieties was extremely polar and hence hard to purify, resulting in a disappointingly low yield of 24 %.

The Cu/C matrix contains copper(I) as well as copper(II) species and therefore the Lipshutz group explored the direct one-pot transformation of amines into the desired 1,2,3-triazoles by in situ generation of the corresponding organic azides employing TfN_3.[22] We tested these reported one-pot conditions for the synthesis of the desired carbohydrate mimetics. It should be possible to start from 3-aminopyran **1** and after in situ generation of the 3-azidopyran **2**, an alkyne can be added and the desired cycloaddition product should be obtained. Lipshutz et al. reported that the method proceeds in dichloromethane as solvent,[22] but we found for our compounds that under these conditions only unchanged 3-aminopyran **1** and 3-azidopyran **2** and no 1,2,3-triazoles were isolated. An optimization revealed that acetonitrile was a suitable solvent and we could successfully apply the one-pot procedure to the syntheses of 1,2,3-triazole **5** and bis-1,2,3-triazole **14** (Scheme 6). For the preparation of the simple 1,2,3-triazole **5** we used the convenient and safe NfN_3 as reagent (method D) and the product was isolated in satisfying 75 % yield. The divalent product **14** was prepared



Scheme 5. Synthesis of unsymmetrical tetrakis-1,2,3-triazole **16** by CuAAC of diyne **15** and 3-azidopyran **2**. Method C: Cu/C, NEt_3, 1,4-dioxane, 72 h, 60 °C.

with TfN_3 as a reagent for the diazo transfer (method E) and the yield was only 38 %; no control experiment with NfN_3 was performed to identify the reason for the lower efficiency in this example. In any case, the two experiments depicted in Scheme 6 indicate that the one-pot procedure for the diazo transfer and CuAAC may be a good alternative to the step-wise route.[23]



Scheme 6. One-pot syntheses of 1,2,3-triazole **5** and of divalent bis-1,2,3-triazole **14** starting from amine **1** using a Cu/C-catalyzed one-pot procedure. Method D: a) Cu/C, $Ba(OH)_2$, NfN_3, MeCN, 15 h, r.t.; b) addition of alkyne **3**, NEt_3, 2 d, 60 °C; method E: a) Cu/C, $Ba(OH)_2$, TfN_3, MeCN, 1 h, r.t.; b) addition of diyne **10**, NEt_3, 4 d, 60 °C.

The methods presented above proved to be very suitable for the (3+2) cycloaddition leading to the desired 1,2,3-triazoles, however, they all require copper as metal catalyst. Orthogonal ligation protocols have been widely used as an alternative for the common CuAAC.[24] A so far less explored possibility for the regioselective preparation of 1,4-disubstituted triazoles employs the Sakai reaction of primary amines with α,α-dichlorotosylhydrazones.[14] In 2012, Westermann et al. reinvestigated and optimized this method for the synthesis of 1,2,3-triazoles

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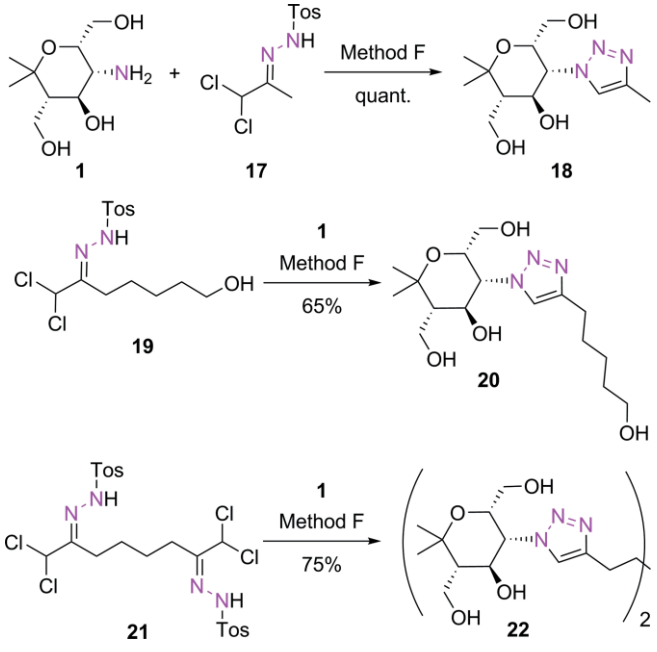
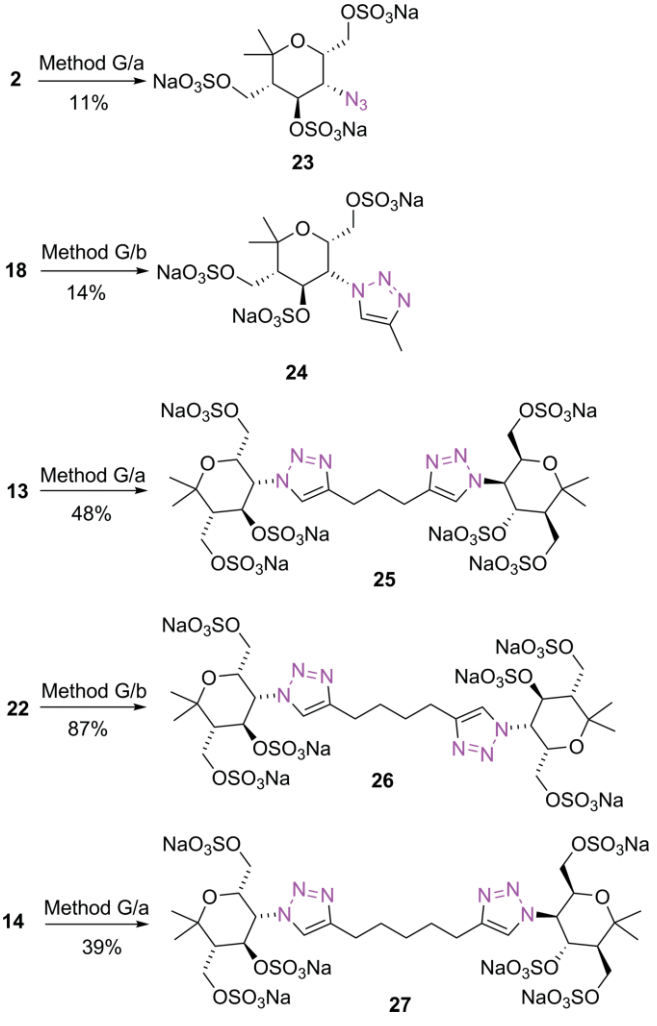
and the modification of biologically significant target compounds.[15] The impressive results prompted us to briefly study the potential of this copper-free alternative for the construction of carbohydrate mimetics starting directly from 3-aminopyran **1**. For the first trial the simple α,α-dichlorotosylhydrazones **17** and **19** were chosen (Scheme 7).[15] Following Westermann's protocol for the Sakai reaction the simple 1,2,3-triazoles **18** and **20** were obtained in excellent or good yield. To further evaluate the efficacy of this procedure, the synthesis of a divalent carbohydrate mimetic was also attempted. For this purpose, the bis(α,α-dichlorotosylhydrazone) **21** was prepared in two steps starting from dimethyl adipate and dichloromethane.[25] The metal-free connection of this compound with 3-aminopyran **1** furnished the bis-1,2,3-triazole **22** in good yield. To the best of our knowledge, this transformation is the first application of the Sakai-Westermann method for the synthesis of a divalent compound. With easily obtained and bench stable starting materials this method proved to be a good alternative for the metal-free direct conversion of primary amines into compounds with 1,2,3-triazole units without the need to generate potentially hazardous azide intermediates.



Scheme 7. Synthesis of 1,2,3-triazoles **18**, **20** and **22** using the Sakai-Westermann method. Method F: KOAc, EtOH, MeCN, 21 h (for **18**), 26 h (for **20**), 20 h (for **22**), 0 °C to r.t.

For the evaluation as selectin ligands the prepared oligohydroxylated compounds had to be converted into the corresponding *O*-sulfated samples which is not a trivial challenge.[26] We recently reported optimizations of the *O*-sulfation step of multivalent carbohydrate mimetics connected with amide bonds and the commercially available sulfur trioxide-DMF complex was found to be the reagent of choice.[9] It was employed in (deuterated) DMF, thus allowing to follow the reaction progress with high-resolution ^{1}H-NMR spectroscopy. Here we present the successful application of this method for the *O*-sulfation of 3-azidopyran **2** and multivalent carbohydrate mimetics bearing 1,2,3-triazole units (Scheme 8). After *O*-sulfation all sulfuric acid monoesters were converted into the corresponding sodium salts using either a 1 M solution of sodium hydroxide (method G/a) or 0.5 M solution of this base (method G/b). The resulting products were finally purified by dialysis. 3-Azidopyran **2** and 1,2,3-triazole **18** were successfully converted into the desired products **23** and **24** (Scheme 8). Only low yields were observed for the two simple compounds due to their low molecular mass that leads to considerable losses of mass during the dialysis purification. Higher yields were observed for the *O*-sulfated divalent compounds **25**–**27**. In agreement with our previous results, method G/b is favorable for the compounds with 1,2,3-triazole substructures. The two divalent compounds **11** and **12** (Scheme 4) with rigid arene linker units were also treated under the approved conditions with the sulfur trioxide-DMF complex and they were completely consumed, but after dialysis high-resolution ^{1}H-NMR spectroscopy revealed that complex mixtures of compounds were formed. To our regret,



Scheme 8. *O*-Sulfation of 3-azidopyran **2**, 1,2,3-triazole **18** and divalent compounds **13**, **22**, and **14** leading to the corresponding *O*-sulfated carbohydrate mimetics **23**–**27**. Method G/a: 1) SO_3-DMF, [D_7]DMF, 2 d (for **2**), 1 d (for **13**), 1 d (for **14**), r.t.; 2) 1 M NaOH, 0 °C; 3) dialysis, H_2O; method G/b: 1) SO_3•DMF, [D_7]DMF, 4 d (for **18**), 3 d (for **22**), r.t.; 2) 0.5 M NaOH, 0 °C, DOWEX® Na^+; 3) dialysis, H_2O.

these interesting compounds could therefore not be investigated further by SPR experiments.

The five *O*-sulfated samples obtained were investigated by surface plasmon resonance (SPR) spectroscopy and as earlier found for this type of compounds a competitive binding assay was applied.[27] The resulting IC_{50} values for binding to L-Selectin are compiled in Figure 1 and should be regarded as preliminary results that need further validation. For the monovalent *O*-sulfated 3-azidopyran **23** the lowest IC_{50} value of 45 nM was found, however, this result has to be regarded with caution since the dose-response curve ascended slightly at higher concentrations. For the four 1,2,3-triazole derivatives **24**–**27** IC_{50} values in the range of 0.6–50 μM were determined. The most potent compound **25** is characterized by the smallest distance between the two *O*-sulfated pyran moieties. The low number of comparable compounds does not allow a sound interpretation of their observed inhibitor properties. At the moment it is pure speculation that fairly close *O*-sulfated pyran moieties as in the divalent compound **25** (and in the multivalent polysulfated pyran-decorated gold nanoparticles mentioned in the introduction) are a prerequisite for high activity of these compounds.

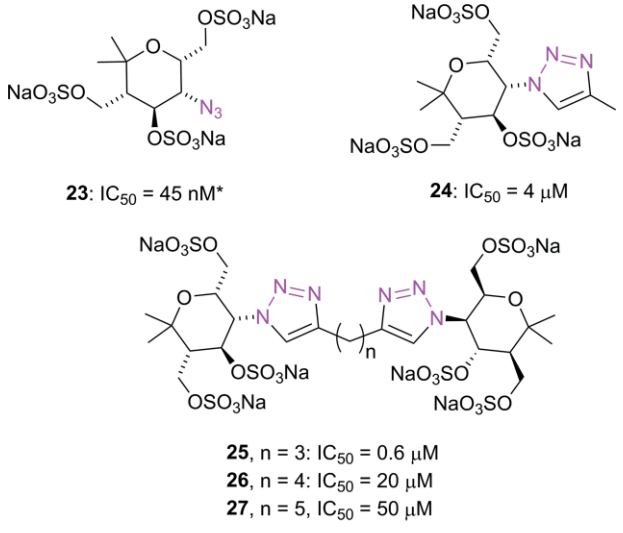


Figure 1. IC_{50} values for L-selectin of *O*-sulfated compounds **23**–**27** determined by surface plasmon resonance spectroscopy (* this value needs re-evaluation since the dose-response curve ascended again at higher concentrations).

Conclusions

A series of divalent carbohydrate mimetics **11**–**14** linked by 1,2,3-triazole moieties was prepared by starting with 3-azidopyran derivative **2**. The Huisgen-Meldal-Sharpless (3+2) cycloadditions with alkynes proved to be generally applicable and very good results were found in particular with Cu/C as catalyst.[28] A one-pot method that allowed direct conversion of 3-aminopyran **1** into 1,2,3-triazoles was also successfully examined. We found that the copper-free Sakai-Westermann protocol allows the efficient transformation of primary amines such as **1** into 1,2,3-triazoles including the divalent carbohydrate mimetic **22**. After *O*-sulfation of the compounds with the sulfur trioxide-DMF complex five products were isolated in sufficient purity. They were investigated by SPR as inhibitors of L-selectin and IC_{50} values between 45 nM and 50 μM were found. These preliminary results need further confirmation and inclusion of more compounds in order to prove or disprove a multivalency effect.[29] In summary, the presented synthetic results show that the azide-alkyne (3+2) cycloadditions and the related methods furnish carbohydrate mimetics with interesting structural features.

Experimental Section

Reactions were generally performed under an inert atmosphere (argon) in flame-dried flasks. Solvents and reagents were added by syringe. Solvents were dried using standard procedures and were purified with a MB SPS-800-dry solvent system. Triethylamine was distilled from CaH_2 and stored with KOH under an argon atmosphere. Commercially available reagents were used as received without further purification unless otherwise stated. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck or MACHEREY-NAGEL) or by ion exchange resin (DOWEX® 50WX8–200 Sigma-Aldrich). DOWEX® Na^+ was freshly prepared by washing DOWEX® with a saturated solution of NaCl. Unless stated otherwise, yields refer to analytical pure samples. TLC analyses were performed on silica gel coated aluminum plates (Merck). Products were detected by UV and by using staining reagents (cerium/molybdenum reagent, $KMnO_4$, and ninhydrin).

NMR spectra were recorded with BRUKER (AV 500, AV 700) and JEOL (ECP 500) instruments. Chemical shifts (δ) are listed in parts per million (ppm) and are reported relative to solvent residual signals: CD_3OD (^1H: δ = 3.31 ppm, ^{13}C: δ = 49.0 ppm), [D_7]DMF (^1H: δ = 2.75 ppm, ^{13}C: δ = 29.8 ppm) or D_2O (^1H: δ = 4.79 ppm). Integrals are in accordance with assignments; coupling constants *J* are given in Hz. All ^{13}C-NMR spectra are proton-decoupled. Multiplicity is indicated as follows: s (singlet), s_b (broad singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), m (multiplet), m_c (centered multiplet). For detailed peak assignments 2D spectra were measured (COSY and HMQC). IR spectra were measured with a JASCO spectrometer (FT/IR-4100 with DLATGS Detector). HRMS analyses were performed with Agilent 6210 (ESI-TOF, 10 μL/min, 1.0 bar, 4 kV) and Varian/Agilent Ionspec QFT-7 (ESI-FTICR, 4 μL/min, 1.0 bar, 4 kV) instruments. Elemental analyses were carried out with PerkinElmer (CHN-Analyzer 2400) and Elementar (Vario, Vario EL, Vario EL III) instruments. Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected.

General Procedure (GP1), CuAAC using TBTA (Method A): 3-Azidopyran **2** (1.0 equiv.) was dissolved in MeCN (40 mL/mmol). Tris-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) (0.23 equiv.) and CuI (0.23 equiv.) were added, followed by the addition of the corresponding alkyne (1.2 equiv.) and NEt_3 (0.23 equiv.). The resulting mixture was stirred at r.t. for the indicated time. The solution was quenched with 7 N NH_3 in MeOH and the resulting mixture was filtered through a short silica gel column and washed with a mixture of CH_2Cl_2/7 N NH_3 in MeOH (10:1). After removing the solvents in vacuo, the crude product was purified by flash column chromatography.

General Procedure (GP2), CuAAC using DIPEA/AcOH (Method B): To a suspension of 3-azidopyran **2** (1.0 equiv.) in toluene (1 mL/mmol) were added CuI (0.4 equiv.), the corresponding alkyne

(1.2 equiv.) and finally diisopropylethylamine (DIPEA) (4.0 equiv.) and HOAc (4.0 equiv.). The reaction mixture was stirred at r.t. during the indicated time. The solution was quenched with 7 N NH_3 in MeOH and the resulting mixture was filtered through a short silica gel column and washed with a mixture of CH_2Cl_2/7 N NH_3 in MeOH (10:1). After removing the solvents in vacuo, the crude product was purified by flash column chromatography.

General Procedure (GP3), CuAAC using Cu/C (Method C): To a solution of 3-azidopyran **2** (1.0 equiv.) in 1,4-dioxane (3 mL/mmol) were added Cu/C (0.1–0.5 equiv.), NEt_3 (1.2–3.0 equiv.) and the corresponding alkyne (1.2 equiv.). The reaction mixture was stirred at 60 °C during the indicated time. The mixture was filtered through a pad of Celite® and washed with MeOH. When indicated, the product was further purified by flash column chromatography.

General Procedure (GP4), One-pot click reaction using Cu/C (Methods D and E): 3-Aminopyran **1** (1.0 equiv.), Cu/C (0.1 equiv.) and $Ba(OH)_2$ (1.0 equiv.) were dissolved in MeCN (1 mL/mmol). TfN_3 or NfN_3 was added dropwise at r.t. under constant stirring. After the diazo transfer was complete (controlled by TLC, CH_2Cl_2/MeOH, 9:1), Cu/C (0.1 equiv.), NEt_3 (5.0 equiv.) and the corresponding alkyne were added and the reaction mixture was stirred at 60 °C. After the total consumption of TfN_3 or NfN_3 (controlled by TLC, CH_2Cl_2/MeOH, 9:1) the mixture was filtered through a pad of Celite® and washed with MeOH. The product was purified by flash column chromatography.

General Procedure (GP5), Metal free triazole synthesis using tosylhydrazones (Method F): To a cooled solution of 3-aminopyran **1** (1.0 equiv.) in EtOH (12 mL/mmol), KOAc (3.0 equiv.) was added and the resulting solution was stirred for 10 min at 0 °C. The corresponding α,α-dichlorotosylhydrazone (1.3 equiv.) was dissolved in MeCN (6 mL/mmol) and added dropwise to the reaction mixture. Stirring was continued at r.t. until the reaction was complete (monitored by TLC). All volatiles were removed in vacuo and the crude product was purified by flash column chromatography.

General Procedure (GP6), *O*-sulfation (Method G): The corresponding polyol (1.0 equiv.) was dissolved in [D_7]DMF (0.6–1.0 mL). The solution was cooled to 0 °C and SO_3-DMF (3.0 equiv. per OH) was added. The reaction mixture was stirred at r.t. during the indicated time. The reaction progress was followed by ^{1}H-NMR spectroscopy (700 MHz). When indicated, additional SO_3-DMF (1.0–3.0 equiv. for each OH group) was added and the reaction mixture was stirred at r.t. for the additional time given until full conversion was observed. The obtained sulfated intermediates were directly converted into the corresponding sodium salts either by *method G/a* or *method G/b*.

Method G/a: The reaction mixture was cooled to 0 °C and an aq. 1 M solution of NaOH was added dropwise until pH 10–12 was reached. The solvents were removed in vacuo and the crude product was purified by dialysis in H_2O.

Method G/b: The reaction mixture was cooled to 0 °C and an aq. 0.5 M solution of NaOH was added dropwise until pH 7–9 was reached. The reaction mixture was filtered through an ion exchange DOWEX® Na^+ column. The solvents were removed in vacuo and the crude product was purified by dialysis in H_2O.

The final products were filtered through a syringe filter (diameter 25 mm; pore size 0.2 µm; PTFE membrane) when indicated.

(2*S*,3*R*,4*S*,5*S*)-(3-Azido-4-hydroxy-6,6-dimethyltetrahydro-2*H*-pyran-2,5-diyl)dimethanol (2): To a solution of 3-aminopyran **1**[4b] (150 mg, 0.73 mmol) in MeOH/H_2O (2:1, 3 mL) at r.t. were added $CuSO_4$·5H_2O (18 mg, 0.073 mmol) and K_2CO_3 (101 mg, 0.73 mmol), followed by slow addition of freshly prepared NfN_3[17] (475 mg, 1.46 mmol). The mixture was stirred for 24 h, then glycine hydrochloride (554 mg, 5.00 mmol) was added and the suspension was stirred for another 24 h. The solution was quenched with 7 N NH_3 in MeOH and the copper salt was filtered off through a short silica gel column. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2 100 %, CH_2Cl_2/MeOH, 95:5 then 90:10) affording **2** (301 mg, 89 %) as a colorless solid. M. p. 121 °C; $[\alpha]_D^{22}$ = –18.4 (c = 0.76, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 1.14, 1.34 (2 s, 3 H each, Me), 1.82 (td, $J \approx$ 6.0, 9.3 Hz, 1 H, 5-H), 3.51 (dd, J = 4.1, 5.5 Hz, 1 H, 3-H), 3.56, 3.63 (AB part of ABX system, J_{AB} = 11.2 Hz, J_{AX} = 5.7 Hz, J_{BX} = 7.0 Hz, 1 H each, 2-CH_2), 3.68, 3.80 (AB part of AB system, J_{AB} = 11.1 Hz, J_{AX} = 5.6 Hz, J_{BX} = 6.6 Hz, 1 H each, 5-CH_2), 3.92 (dd, J = 5.5, 9.3 Hz, 1 H, 4-H), 4.02 (ddd, J = 4.1, 5.7, 7.0 Hz, 1 H, 2-H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ = 24.8, 27.0 (2 q, Me), 49.5 (d, C-5), 62.1, 62.7 (2 t, 2-CH_2, 5-CH_2), 68.2 (d, C-3), 71.3 (d, C-2), 72.3 (d, C-4), 76.4 (s, C-6) ppm; IR (ATR): $\tilde{\nu}$ = 3370 (OH), 2970–2930 (C-H), 2110 (N_3), 1235 (C-O), 1045 (C-O-C) cm^{-1}; HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd. for $C_9H_{17}N_3NaO_4$: 254.1113, found 254.1122; $C_9H_{17}N_3O_4$ (231.3): calcd. C 46.74, H 7.41, N 18.17; found C 46.80, H 7.27, N 18.21.

(2*S*,3*R*,4*S*,5*S*)-{4′-Hydroxy-3-[4′-(2-hydroxyethyl)-1′*H*-1′,2′,3′-triazol-1′-yl]-6,6-dimethyltetrahydro-2*H*-pyran-2,5-diyl}dimethanol (5): According to **GP3**, to a solution of 3-azidopyran **2** (40 mg, 0.17 mmol) in 1,4-dioxane (0.6 mL) were added Cu/C (37 mg, 17 µmol), NEt_3 (70 µL, 0.52 mmol) and 3-butyn-1-ol (**3**) (28 mg, 31 µL, 0.40 mmol). The reaction mixture was stirred at 60 °C for 20 h. The mixture was filtered through a pad of Celite® which was washed with MeOH. The solvents were removed in vacuo and the crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1 to 6:1) affording **5** (47 mg, 0.156 mmol, 90 %) as a colorless solid. M. p. 156–157 °C; $[\alpha]_D^{22}$ = +13.7 (c = 0.98, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 1.28, 1.39 (2 s, 3 H each, Me), 2.06 (td, $J \approx$ 6.2, 12.2 Hz, 1 H, 5-H), 2.92 (t, J = 6.6 Hz, 2 H, CH_2), 2.98, 3.06 (AB part of ABX system, J_{AB} = 11.5 Hz, J_{AX} = 4.9 Hz, J_{BX} = 7.5 Hz, 1 H each, 2-CH_2), 3.69 (dd, J = 6.4, 11.3 Hz, 1 H, 5-CH_2), 3.82 (t, J = 6.6 Hz, 2 H, CH_2), 3.89 (dd, J = 6.0, 11.3 Hz, 1 H, 5-CH_2), 4.24–4.30 (m, 2 H, 2-H, 4-H), 4.70 (dd, J = 5.2, 7.0 Hz, 1 H, 3-H), 7.80 (s, 1 H, 5′-H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ = 23.5, 26.7 (2 q, Me), 29.9 (t, CH_2), 49.5 (d, C-5), 61.6 (t, 2-CH_2), 62.1 (t, CH_2), 62.3 (t, 5-CH_2), 70.2 (d, C-3), 71.9 (d, C-2), 73.2 (d, C-4), 77.5 (s, C-6), 124.2 (d, C-5′), 146.0 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3360 (OH), 3160 (=C-H), 2960–2850 (C-H), 1560, 1370, 1320 (C=C), 1060, 1030 (C-O-C) cm^{-1}; HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd. for $C_{13}H_{23}N_3NaO_5$: 324.1530; found 324.1555; $C_{13}H_{23}N_3O_5$ (301.3): calcd. C 51.82, H 7.69, N 13.94; found C 51.96, H 7.72, N 13.36.

(2*S*,3*R*,4*S*,5*S*)-3-{[4′-(3-Chloropropyl)-1′*H*-1′,2′,3′-triazol-1′-yl]-4-hydroxy-6,6-dimethyltetrahydro-2*H*-pyran-2,5-diyl}dimethanol (6): According to **GP3**, to a solution of 3-azidopyran **2** (24 mg, 0.10 mmol) in 1,4-dioxane (0.3 mL) were added Cu/C (11 mg, 5.20 µmol), NEt_3 (17 µL, 0.13 mmol) and 5-chloro-1-pentyne (**4**) (12.8 mg, 13 µL, 0.13 mmol). The reaction mixture was stirred at 60 °C for 21 h. The mixture was filtered through a pad of Celite® and washed with MeOH. The solvents were removed in vacuo affording **6** (35 mg, quant.) as a pale yellow oil. $[\alpha]_D^{22}$ = +55.9 (c = 1.32, MeOH); ^{1}H NMR (700 MHz, CD_3OD): δ = 1.29, 1.39 (2 s, 3 H each, Me), 2.06 (td, $J \approx$ 6.2, 12.2 Hz, 1 H, 5-H), 2.10–2.17 (m, 2 H, CH_2), 2.86–2.91 (m, 2 H, CH_2), 2.96, 3.04 (AB part of ABX system, J_{AB} = 11.5 Hz, J_{AX} = 4.5 Hz, J_{BX} = 7.5 Hz, 1 H each, 2-CH_2), 3.60 (t, J = 6.5 Hz, 2 H, CH_2), 3.69 (dd, J = 6.3, 11.3 Hz, 1 H, 5-CH_2), 3.89 (dd, J = 6.1, 11.3 Hz, 1 H, 5-CH_2), 4.24–4.31 (m, 2 H, 2-H, 4-H), 4.70 (dd, J = 5.2, 7.0 Hz, 1 H, 3-H), 7.79 (s, 1 H, 5′-H) ppm; ^{13}C NMR (175 MHz, CD_3OD): δ = 23.47 (t, CH_2), 23.50, 26.7 (2 q, Me), 33.3 (t,

CH_2), 44.8 (t, CH_2), 49.4 (d, C-5), 61.6 (t, 2-CH_2), 62.3 (t, 5-CH_2), 70.3 (d, C-3), 72.0 (t, C-2), 73.1 (t, C-4), 77.5 (s, C-6), 123.8 (d, C-5′), 147.4 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3310 (OH), 2960–2850 (C-H), 1440, 1370 (C=C), 1050 (C-O-C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd. for $C_{14}H_{24}ClN_3NaO_4$: 356.1342; found 356.1353; $C_{14}H_{24}ClN_3O_4$ (333.8): calcd. C 50.37, H 7.25, N 12.59; found C 49.92, H 6.97, N 12.12.

Divalent Bis-1,2,3-triazole 11: According to **GP1**, 3-azidopyran **2** (100 mg, 0.432 mmol), TBTA (45.9 mg, 0.086 mmol), CuI (16.5 mg, 0.086 mmol), NEt_3 (12 µL, 0.087 mmol) and 1,4-diethynylbenzene (**7**) (24.8 mg, 0.197 mmol) were dissolved in MeCN (20 mL). The orange colored mixture was stirred at r.t. for 24 h and worked up. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2, CH_2Cl_2/MeOH, 95:5 then 90:1) affording **11** (74 mg, 64 %) as a yellow solid. M. p. 131 °C; $[\alpha]_D^{22}$ = +0.41 (c = 0.5, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 1.33, 1.41 (2 s, 6 H each, Me), 2.10 (dt, $J \approx$ 6.2, 12.2 Hz, 2 H, 5-H), 3.08, 3.14 (AB part of ABX system, J_{AB} = 11.4 Hz, J_{AX} = 5.1 Hz, J_{BX} = 7.3 Hz, 2 H each, 2-CH_2), 3.72 (dd, J = 6.3, 11.3 Hz, 2 H, 5-CH_2), 3.93 (dd, J = 6.1, 11.3 Hz, 2 H, 5-CH_2), 4.33 (m_c, 2 H, 2-H), 4.41 (dd, J = 7.1, 12.0 Hz, 2 H, 4-H), 4.80 (dd, J = 5.3, 7.1 Hz, 2 H, 3-H), 7.94 (s, 4 H, Ar), 8.36 (s, 2 H, 5′-H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ = 22.2, 25.4 (2 q, Me), 48.4 (d, C-5), 60.4 (t, 2-CH_2), 61.0 (t, 5-CH_2), 69.3 (d, C-3), 70.6 (d, C-2), 71.8 (d, C-4), 76.3 (s, C-6), 122.8 (d, C-5′), 127.3 (d, Ar), 131.6 (s, Ar), 148.0 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3335 (OH), 2930 (C-H), 1620 (C=C), 1230–1030 (C-O-C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd. for $C_{28}H_{41}N_6O_8$: 589.2980; found 589.2972; $[M + Na]^+$ $C_{28}H_{40}N_6NaO_8$: 611.2800; found 611.2797.

Divalent Bis-1,2,3-triazole 12: According to **GP1**, 3-azidopyran **2** (181 mg, 0.783 mmol), TBTA (83.1 mg, 0.157 mmol), CuI (29.8 mg, 0.157 mmol), NEt_3 (21.8 µL, 0.157 mmol) and 1,3-diethynylbenzene (**8**) (42.8 mg, 54.1 µL, 0.339 mmol) were dissolved in MeCN (30 mL). The fluorescent yellow mixture was stirred at r.t. for 48 h and worked up. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2, CH_2Cl_2/MeOH, 95:5 then 90:1) affording **12** (105 mg, 53 %) as a colorless solid. In addition, the corresponding monosubstituted product was also isolated (7 mg, 4 %) as a colorless solid. M. p. 171 °C; $[\alpha]_D^{22}$ = +0.34 (c = 0.5, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 1.33, 1.41 (2 s, 6 H each, Me), 2.11 (td, J = 6.3, 12.0 Hz, 2 H, 5-H), 3.08, 3.15 (AB part of ABX system, J_{AB} = 11.4 Hz, J_{AX} = 5.0 Hz, J_{BX} = 7.4 Hz, 2 H each, 2-CH_2), 3.72 (dd, J = 6.3, 11.3 Hz, 2 H, 5-CH_2), 3.93 (dd, J = 6.3, 11.3 Hz, 2 H, 5-CH_2), 4.33 (dt, $J \approx$ 5.1, 7.2 Hz, 2 H, 2-H), 4.41 (dd, J = 7.2, 12.0 Hz, 2 H, 4-H), 4.81 (dd, J = 5.3, 7.1 Hz, 2 H, 3-H), 7.52 (t, J = 7.8 Hz, 1 H, Ar), 7.85 (d, J = 7.8 Hz, 2 H, Ar), 8.32 (s_b, 1 H, Ar), 8.40 (s, 2 H, 5′-H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ = 23.5, 26.7 (2 q, Me), 49.7 (d, C-5), 61.7 (t, 2-CH_2), 62.3 (t, 5-CH_2), 70.6 (d, C-3), 71.9 (d, C-2), 73.1 (d, C-4), 77.6 (s, C-6), 123.0 (d, C-5′), 124.0, 126.4, 130.7 (3 d, Ar), 132.4 (s, Ar), 148.1 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3285 (OH), 2970–2925 (C-H), 1620 (C=C), 1230–1030 (C-O-C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd. for $C_{28}H_{40}N_6NaO_8$: 611.2800; found 611.2777.

Divalent Bis-1,2,3-triazole 13: According to **GP1**, 3-azidopyran **2** (100 mg, 0.432 mmol), TBTA (46.2 mg, 0.087 mmol), CuI (16.6 mg, 0.087 mmol), NEt_3 (12 µL, 0.087 mmol) and 1,6-heptadiyne (**9**) (18.4 mg, 22.9 µL, 0.198 mmol) were dissolved in MeCN (20 mL). The mixture was stirred at r.t. for 24 h and worked up. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2, CH_2Cl_2/MeOH, 95:5 then 90:1) affording **13** (71 mg, 65 %) as a colorless solid. In addition, the corresponding monosubstituted product was also isolated (9 mg, 8 %) as a colorless solid. M. p. 91 °C; $[\alpha]_D^{22}$ = +0.19 (c = 0.5, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 1.29, 1.39 (2 s, 6 H each, Me), 2.05 (m, 4 H, 5-H, CH_2), 2.77 (t, J = 7.5 Hz, 4 H, CH_2), 2.95, 3.05 (AB part of ABX system, J_{AB} = 11.4 Hz, J_{AX} = 4.7 Hz, J_{BX} = 7.5 Hz, 2 H each, 2-CH_2), 3.69 (dd, J = 6.5, 11.3 Hz, 2 H, 5-CH_2), 3.89 (dd, J = 6.0, 11.3 Hz, 2 H, 5-CH_2), 4.23–4.32 (m, 4 H, 2-H, 4-H), 4.67–4.70 (m, 2 H, 3-H), 7.78 (s, 2 H, 5′-H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ = 22.0 (q, Me), 24.3 (t, CH_2), 25.4 (q, Me), 28.9 (t, CH_2), 48.4 (d, C-5), 60.3 (t, 2-CH_2), 61.0 (t, 5-CH_2), 68.9 (d, C-3), 70.7 (d, C-2), 71.8 (d, C-4), 76.2 (s, C-6), 122.4 (d, C-5′), 146.9 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3365 (OH), 2970–2925 (C-H), 1450 (C=C), 1230–1030 (C-O-C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd. for $C_{25}H_{42}N_6NaO_8$: 577.2956; found 577.2954.

Divalent Bis-1,2,3-triazole 14: According to **GP3**, to a solution of 3-azidopyran **2** (70 mg, 0.303 mmol) in 1,4-dioxane (0.8 mL) were added Cu/C (28 mg, 13 µmol), NEt_3 (50 µL, 0.37 mmol) and 1,8-nonadiyne (**10**) (14.2 mg, 19.8 µL, 0.132 mmol). The reaction mixture was stirred at 60 °C for 24 h. Additional Cu/C (28 mg, 13 µmol) and NEt_3 (50 µL, 0.37 mmol) were added and the reaction was stirred at 60 °C for another 24 h. The mixture was filtered through a pad of Celite® and washed with MeOH. The solvents were removed in vacuo and the crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1 to 4:1) affording **14** (71 mg, 91 %) as a pale yellow oil. $[\alpha]_D^{22}$ = +25.9 (c = 1.28, MeOH); ^{1}H NMR (700 MHz, CD_3OD): δ = 1.28, 1.39 (2 s, 6 H each, Me), 1.43 (dd, J = 7.9, 15.3 Hz, 4 H, CH_2), 1.68–1.75 (m, 4 H, CH_2), 2.05 (td, $J \approx$ 6.2, 12.2 Hz, 2 H, 5-H), 2.71 (t, J = 7.5 Hz, 4 H, CH_2), 2.93, 3.04 (AB part of ABX system, J_{AB} = 11.5 Hz, J_{AX} = 4.7 Hz, J_{BX} = 7.5 Hz, 2 H each, 2-CH_2), 3.70 (dd, J = 6.3, 11.4 Hz, 2 H, 5-CH_2), 3.89 (dd, J = 6.0, 11.4 Hz, 2 H, 5-CH_2), 4.24–4.32 (m, 4 H, 2-H, 4-H), 4.69 (dd, J = 5.2, 6.9 Hz, 2 H, 3-H), 7.73 (s, 2 H, 5′-H) ppm; ^{13}C NMR (175 MHz, CD_3OD): δ = 23.5 (q, Me), 26.1 (t, CH_2), 26.7 (q, Me), 29.5, 30.2 (2 t, CH_2), 49.6 (d, C-5), 61.6 (t, 2-CH_2), 62.3 (t, 5-CH_2), 70.2 (d, C-3), 72.0 (d, C-2), 73.1 (d, C-4), 77.5 (s, C-6), 123.4 (d, C-5′), 148.8 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3450 (OH), 2980–2855 (C-H), 1645 (C=C), 1225–1030 (C-O-C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd. for $C_{27}H_{46}N_6NaO_8$: 605.3269; found 605.3270.

Divalent Tetrakis-1,2,3-triazole 16: According to **GP3**, to a solution of 3-azidopyran **2** (31 mg, 0.133 mmol) in 1,4-dioxane (1 mL) were added Cu/C (23 mg, 10.6 µmol), NEt_3 (20 µL, 0.133 mmol) and diyne **15**[13] (25 mg, 53 µmol). The reaction mixture was stirred at 60 °C for 72 h. The mixture was filtered through a pad of Celite® and washed with MeOH. The solvents were removed in vacuo and the crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1 to 4:1) affording **16** (12 mg, 24 %) as a yellow solid. M. p. 235 °C; $[\alpha]_D^{22}$ = –20.3 (c = 0.09, MeOH); ^{1}H NMR (700 MHz, CD_3OD): δ = 0.54, 1.27 (2 s, 3 H each, Me^A), 1.29, 1.39 (2 s, 6 H each, Me^B), 1.93 (m_c, 1 H, 6-H^A), 2.02–2.10 (m, 6 H, CH_2, 5-H^B), 2.75–2.78 (m, 8 H, CH_2), 2.93–2.98, 3.03–3.06 (2 m, 2 H each, 2-CH_2^B), 3.54–3.61 (m, 2 H, 6-CH_2^A), 3.70 (dd, J = 6.4, 11.3 Hz, 2 H, 5-CH_2^B), 3.89 (dd, J = 6.1, 11.3 Hz, 2 H, 5-CH_2^B), 4.23–4.28 (m, 2 H, 4-H^B, 2-H^B), 4.28–4.32 (m, 2 H, 5-H^A, 3-H^A), 4.43–4.46 (m, 2 H, 2-CH_2^A, 3-H^A), 4.52 (B part of ABX system, J_{AB} = 14.3 Hz, J_{BX} = 3.1 Hz, 1 H, 2-CH_2^A), 4.60 (dd, J = 7.4, 9.5 Hz, 1 H, 4-H^A), 4.68–4.72 (m, 2 H, 3-H^B), 7.77 (s, 1 H, 5′-H), 7.77 (s_b, 2 H, 5′-H), 7.79 (s, 1 H, 5′-H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ = 20.1, 23.5 (2 q, Me), 25.47, 25.51, 25.52, 25.6 (4 t, CH_2), 26.7, 26.8 (2 q, Me), 30.1, 30.5 (2 t, CH_2), 30.9, 31.4 (2 q, Me), 49.4 (d, C-5^B), 53.2 (t, 2-CH_2^A), 53.3 (d, C-2^A), 60.3 (d, C-6^A), 61.7 (t, 2-CH_2^B), 62.3 (t, 5-CH_2^B), 63.5 (t, 6-CH_2^A), 69.8 (d, C-3^B), 70.3 (d, C-2^B), 72.0 (d, C-4^B), 73.0 (d, C-5^A), 74.3 (d, C-3^A), 75.1 (d, C-4^A), 77.5, 77.9 (2 s, C-6^B, C-7^A), 123.65, 123.73, 125.3, 125.4 (4 d, C-5′), 148.21, 148.28, 148.29, 148.31 (4 s, C-4′) ppm;* a specific assignment of the signals to one of the two pyran rings and to the four triazole units is not possible. IR (ATR): $\tilde{\nu}$ = 3370 (OH), 2925 (C-H), 1595 (C=C), 1060 (C-O-C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd. for $C_{42}H_{68}N_{12}NaO_{12}$: 955.4966; found 955.5003.

(2*S*,3*R*,4*S*,5*S*)-[4-Hydroxy-6,6-dimethyl-3-(4′-methyl-1*H*-1′,2′,3′-triazol-1′-yl)tetrahydro-2*H*-pyran-2,5-diyl]dimethanol (18): According to **GP5**, to a cooled solution of 3-aminopyran **1** (58 mg, 0.28 mmol) in EtOH (3.3 mL) was added KOAc (83 mg, 0.85 mmol) and the resulting solution was stirred for 10 min at 0 °C. Tosylhydrazone **17**[15] (109 mg, 0.37 mmol) was dissolved in MeCN (2.2 mL) and added dropwise to the reaction mixture. Stirring was continued at r.t. for 21 h. All volatiles were removed in vacuo and the crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1) affording **18** (78 mg, quant.) as a colorless solid. M. p. 176 °C; $[\alpha]_D^{22}$ = +2.68 (c = 0.77, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 1.28, 1.39 (2 s, 3 H each, Me), 2.05 (td, $J \approx$ 6.2, 12.3 Hz, 1 H, 5-H), 2.33 (s, 3 H, Me), 2.95, 3.05 (AB part of ABX system, J_{AB} = 11.5 Hz, J_{AX} = 4.8 Hz, J_{BX} = 7.5 Hz, 1 H each, 2-CH_2), 3.69 (dd, J = 6.4, 11.3 Hz, 1 H, 5-CH_2), 3.89 (dd, J = 6.0, 11.3 Hz, 1 H, 5-CH_2), 4.22–4.28 (m, 2 H, 2-H, 4-H), 4.67 (dd, J = 5.1, 7.0 Hz, 1 H, 3-H), 7.72 (s, 1 H, 5′-H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ = 10.5, 23.5, 26.7 (3 q, Me), 49.6 (d, C-5), 61.6 (t, 2-CH_2), 62.3 (t, 5-CH_2), 70.2 (d, C-3), 71.9 (d, C-2), 73.1 (d, C-4), 77.5 (s, C-6), 123.8 (d, C-5′), 143.9 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3370 (OH), 3150 (=C-H), 2975–2885 (C-H), 1560, 1440, 1390 (C=C), 1055 (C-O-C) cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ calcd. for $C_{12}H_{22}N_3O_4$: 272.1605; found 272.1604; $[M + Na]^+$ calcd. for $C_{12}H_{21}N_3NaO_4$: 294.1424; found 294.1435; $C_{12}H_{21}N_3O_4$ (271.3): calcd. C 53.12, H 7.80, N 15.49; found C 53.27, H 7.80, N 15.52.

(2*S*,3*R*,4*S*,5*S*)-{4-Hydroxy-3-[4′-(5-hydroxypentyl)-1′*H*-1′,2′,3′-triazol-1-yl]-6,6-dimethyltetrahydro-2*H*-pyran-2,5-diyl}dimethanol (20): According to **GP5**, to a cooled solution of 3-aminopyran **1** (26 mg, 0.13 mmol) in EtOH (1.5 mL) was added KOAc (37 mg, 0.38 mmol) and the resulting solution was stirred for 10 min at 0 °C. Tosylhydrazone **19**[15] (60 mg, 0.16 mmol) was dissolved in MeCN (1.2 mL) and added dropwise to the reaction mixture. Stirring was continued at r.t. for 26 h. All volatiles were removed in vacuo and the crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 95:5 then 9:1) affording **20** (28 mg, 65 %) as a yellow oil. $[\alpha]_D^{22}$ = +27.3 (c = 1.29, MeOH); ^{1}H NMR (700 MHz, CD_3OD): δ = 1.29, 1.39 (2 s, 3 H each, Me), 1.40–1.45 (m, 2 H, CH_2), 1.54–1.60 (m, 2 H, CH_2), 1.71 (quint, J = 7.6 Hz, 2 H, CH_2), 2.05 (td, $J \approx$ 6.2, 12.2 Hz, 1 H, 5-H), 2.73 (t, J = 7.6 Hz, 2 H, CH_2), 2.93, 3.04 (AB part of ABX system, J_{AB} = 11.5 Hz, J_{AX} = 4.8 Hz, J_{BX} = 7.6 Hz, 1 H each, 2-CH_2), 3.55 (t, J = 6.5 Hz, 2 H, CH_2), 3.69 (dd, J = 6.4, 11.3 Hz, 1 H, 5-CH_2), 3.89 (dd, J = 6.0, 11.3 Hz, 1 H, 5-CH_2), 4.23–4.31 (m, 2 H, 2-H, 4-H), 4.69 (dd, J = 5.1, 7.0 Hz, 1 H, 3-H), 7.74 (s, 1 H, 5′-H) ppm; ^{13}C NMR (175 MHz, CD_3OD): δ = 23.5 (q, Me), 26.3, 26.4 (2 t, CH_2), 26.7 (q, Me), 30.4, 33.3 (2 t, CH_2), 48.5 (d, C-5), 61.6 (t, 2-CH_2), 62.3 (t, 5-CH_2), 62.8 (t, CH_2), 70.2 (d, C-3), 72.0 (d, C-2), 73.1 (d, C-4), 77.5 (s, C-6), 123.4 (d, C-5′), 148.8 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3355 (OH), 2930–2860 (C-H), 1550 (C=C), 1170–1010 (C-O-C) cm^{-1}; HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd. for $C_{16}H_{29}N_3NaO_5$: 366.1994; found 366.2001.

Divalent Bis-1,2,3-triazole 22: According to **GP5**, to a cooled solution of 3-aminopyran **1** (100 mg, 0.487 mmol) in EtOH (5.7 mL) was added KOAc (147 mg, 1.49 mmol) and the resulting solution was stirred for 10 min at 0 °C. Tosylhydrazone **21**[25] (116 mg, 0.187 mmol) was dissolved in MeCN (3.8 mL) and added dropwise to the colorless solution. The reaction mixture turned bright yellow after 10 min. Stirring was continued at r.t. for 20 h. All volatiles were removed in vacuo and the crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1 to 6:1) affording **22** (80 mg, 75 %) as a colorless solid. M. p. 184 °C; $[\alpha]_D^{22}$ = +33.2 (c = 1.18, MeOH); ^{1}H NMR (700 MHz, CD_3OD): δ = 1.29, 1.39 (2 s, 6 H each, Me), 1.69–1.76 (m, 4 H, CH_2), 2.05 (td, $J \approx$ 6.2, 12.2 Hz, 2 H, 5-H), 2.75 (t, J = 6.4 Hz, 4 H, CH_2), 2.92, 3.03 (AB part of ABX system, J_{AB} = 11.4 Hz, J_{AX} = 4.7 Hz, J_{BX} = 7.5 Hz, 2 H each, 2-CH_2), 3.67–3.72 (m, 2 H, 5-CH_2), 3.89 (dd, J = 6.0, 11.3 Hz, 2 H, 5-CH_2), 4.23–4.30 (m, 4 H, 2-H, 4-H), 4.68 (dd, J = 5.2, 7.0 Hz, 2 H, 3-H), 7.74 (s, 2 H, 5′-H) ppm; ^{13}C NMR (175 MHz, CD_3OD): δ = 23.5 (q, Me), 25.9 (t, CH_2), 26.7 (q, Me), 29.9 (t, CH_2), 49.6 (d, C-5), 61.6 (t, 2-CH_2), 62.3 (t, 5-CH_2), 70.2 (d, C-3), 72.0 (d, C-2), 73.0 (d, C-4), 77.5 (s, C-6), 123.5 (d, C-5′), 148.6 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3370 (OH), 2930 (C-H), 1680 (C=C), 1045 (C-O-C) cm^{-1}; HRMS (ESI-TOF): m/z $[M + H]^+$ calcd. for $C_{26}H_{45}N_6O_8$: 569.3293; found 569.3301; $[M + Na]^+$ calcd. for $C_{26}H_{44}N_6NaO_8$: 591.3107; found 591.3128.

***O*-Sulfated Azidopyran 23:** According to **GP6**, 3-azidopyran **2** (19 mg, 0.082 mmol), SO_3-DMF (47 %, 240 mg, 0.739 mmol) and $[D_7]$DMF (0.8 mL) were stirred overnight. After ^{1}H-NMR spectroscopic control, the reaction mixture was stirred for 2 d and each day a new portion of SO_3-DMF (120 mg) was added. According to *method G/a*, 1 M NaOH solution was added dropwise until pH 12 was reached. The solvents were removed in vacuo and the crude product was purified by dialysis (tube width: 10–16 mm, molecular weight cut off: 100–500 Da). The product was filtered through a syringe filter affording **23** (5 mg, 11 %) as a colorless solid. M. p. 203 °C (decomposition); $[\alpha]_D^{22}$ = +13.5 (c = 0.08, H_2O); ^{1}H NMR (700 MHz, D_2O): δ = 1.28, 1.50 (2 s, 3 H each, Me), 2.41 (dt, J = 4.4, 7.9 Hz, 1 H, 5-H), 4.03–4.06 (m, 1 H, 3-H), 4.11 (dd, J = 7.4, 10.7 Hz, 1 H, 2-CH_2), 4.23 (dd, J = 4.9, 10.7 Hz, 1 H, 2-CH_2), 4.30 (d, J = 7.9 Hz, 2 H, 5-CH_2), 4.46 (ddd, J = 2.5, 4.9, 7.4 Hz, 1 H, 2-H), 4.86–4.87 (m, 1 H, 4-H) ppm; ^{13}C NMR (175 MHz, D_2O): δ = 25.6, 25.7 (2 q, Me), 42.6 (d, C-5), 59.7 (d, C-3), 66.5 (d, C-2), 66.7 (t, 5-CH_2), 67.6 (t, 2-CH_2), 74.2 (d, C-4), 75.3 (s, C-6) ppm; IR (ATR): $\tilde{\nu}$ = 2905 (C-H), 2110 (N_3), 1240 (C-O), 1130 (C-O-C, SO_3Na) cm^{-1}; HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd. for $C_9H_{14}N_3Na_4O_{13}S_3$: 559.9274; found 559.9418.

***O*-Sulfated 1,2,3-Triazole Derivative 24:** According to **GP6**, 1,2,3-triazole **18** (13 mg, 0.048 mmol), SO_3-DMF (97 %, 66 mg, 0.431 mmol) and $[D_7]$DMF (0.8 mL) were stirred overnight. After ^{1}H-NMR spectroscopic control, the reaction mixture was stirred for 4 d and each day a new portion of SO_3-DMF (66 mg) was added. According to *method G/b*, 0.5 M NaOH solution was added dropwise until pH 8 was reached. The reaction mixture was filtered through an ion exchange DOWEX® Na^+ column. The solvents were removed in vacuo and the crude product was purified by dialysis (tube width: 10–16 mm, molecular weight cut off: 100–500 Da). The product was filtered through a syringe filter affording **24** (4 mg, 14 %) as a colorless solid. M. p. 246 °C (decomposition); ^{1}H NMR (700 MHz, D_2O): δ = 1.45, 1.50, 2.34 (3 s, 3 H each, Me), 2.67–2.73 (m, 1 H, 5-H), 3.53 (dd, J = 7.4, 10.7 Hz, 1 H, 2-CH_2), 3.57–3.61 (m, 1 H, 2-CH_2), 4.14–4.25 (m, 1 H, 5-CH_2), 4.38 (dd, J = 4.6, 10.7 Hz, 1 H, 5-CH_2), 4.75 (m, 1 H, 2-H), 4.93–4.96 (m, 1 H, 4-H), 5.07–5.17 (m, 1 H, 3-H), 7.83 (s, 1 H, 5′-H) ppm; ^{13}C NMR (175 MHz, D_2O): δ = 9.6, 22.2, 26.0 (3 q, Me), 44.0 (d, C-5), 65.4 (d, C-3), 65.7 (t, 2-CH_2), 66.5 (t, 5-CH_2), 67.9 (d, C-2), 77.9 (d, C-4), 77.3 (s, C-6), 125.5 (d, C-5′)* ppm; *C-5′ attributed by HMQC; the signal of C-4′ could not be detected unambiguously; IR (ATR): $\tilde{\nu}$ = 1640 (C=C), 1225 (C-O), 1130 (C-O-C, SO_3Na) cm^{-1}; HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd. for $C_{12}H_{18}N_3Na_4O_{13}S_3$: 599.9587; found 599.9661.

***O*-Sulfated Divalent Bis-1,2,3-triazole 25:** According to **GP6**, bis-1,2,3-triazole **13** (15 mg, 0.027 mmol), SO_3-DMF (97 %, 75 mg, 0.49 mmol) and $[D_7]$DMF (0.6 mL) were stirred overnight. After ^{1}H-NMR spectroscopic control, the reaction mixture was stirred for 1 d and each day a new portion of SO_3-DMF (60 mg) was added. According to *method G/a*, 1 M NaOH solution was added dropwise until pH 12 was reached. The solvents were removed in vacuo and the crude product was purified by dialysis (tube width: 10–16 mm, molecular weight cut off: 100–500 Da). The product was filtered

through a syringe filter affording **25** (15 mg, 48 %) as a colorless solid. M. p. 267 °C (decomposition); $[\alpha]_D^{22}$ = +65.2 (c = 0.1, H_2O); ^{1}H NMR (700 MHz, D_2O): δ = 1.46, 1.51 (2 s, 6 H each, Me), 2.04–2.12 (m, 2 H, CH_2), 2.66–2.74 (m, 2 H, 5-H), 2.78 (t, J = 6.7 Hz, 4 H, CH_2), 3.51 (dd, J = 7.7, 11.0 Hz, 2 H, 2-CH_2), 3.65 (dd, J = 4.8, 11.0 Hz, 2 H, 2-CH_2), 4.20 (m_c, 2 H, 5-CH_2), 4.41 (dd, J = 4.4, 10.8 Hz, 2 H, 5-CH_2), 4.74–4.77 (m, 2 H, 2-H), 4.97 (dd, J = 6.5, 12.1 Hz, 2 H, 4-H), 5.16 (m_c, 2 H, 3-H), 7.92 (s, 2 H, 5′-H) ppm; ^{13}C NMR (175 MHz, D_2O): δ = 22.2 (q, Me), 23.7 (t, CH_2), 26.0 (q, Me), 28.0 (t, CH_2), 44.1 (d, C-5), 65.6 (d, C-3), 65.8 (t, 2-CH_2), 66.6 (t, 5-CH_2), 68.1 (d, C-2), 77.3 (d, C-4), 77.9 (s, C-6), 124.5 (d, C-5′), 151.2 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 2950–2850 (C-H), 1640 (C=C), 1220 (C-O), 1130 (C-O-C, SO_3Na) cm^{-1}; HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd. for $C_{25}H_{36}N_6Na_7O_{26}S_6$: 1188.9281; found 1188.9303.

***O*-Sulfated Divalent Bis-1,2,3-triazole 26:** According to **GP6**, bis-1,2,3-triazole **22** (30 mg, 0.053 mmol), SO_3-DMF (97 %, 145 mg, 0.949 mmol) and [D_7]DMF (0.8 mL) were stirred overnight. After ^{1}H-NMR spectroscopic control, the reaction mixture was stirred for 3 d and each day a new portion of SO_3-DMF (145 mg) was added. According to *method G/b*, 0.5 M NaOH solution was added dropwise until pH 8 was reached. The reaction mixture was filtered through an ion exchange DOWEX® Na^+ column. The solvents were removed in vacuo and the crude product was purified by dialysis (tube width: 10–16 mm, molecular weight cut off: 100–500 Da). The product was filtered through a syringe filter affording **26** (54 mg, 87 %) as a colorless solid. M. p. 269 °C (decomposition); $[\alpha]_D^{22}$ = +25.1 (c = 0.06, H_2O); ^{1}H NMR (700 MHz, D_2O): δ = 1.47, 1.52 (2 s, 6 H each, Me), 1.73 (s_b, 4 H, CH_2), 2.68–2.76 (m, 2 H, 5-H), 2.79 (s_b, 4 H, CH_2), 3.51 (dd, J = 7.7, 10.8 Hz, 2 H, 2-CH_2), 3.65 (dd, J = 4.8, 10.8 Hz, 2 H, 2-CH_2), 4.21 (m_c, 2 H, 5-CH_2), 4.41 (dd, J = 4.6, 10.9 Hz, 2 H, 5-CH_2), 4.75–4.77 (m, 2 H, 2-H), 4.99 (dd, J = 6.3, 12.1 Hz, 2 H, 4-H), 5.14–5.19 (m, 2 H, 3-H), 7.90 (s, 2 H, 5′-H) ppm; ^{13}C NMR (175 MHz, D_2O): δ = 22.3 (q, Me), 24.1 (t, CH_2), 26.0 (q, Me), 27.9 (t, CH_2), 44.1 (d, C-5), 65.4 (d, C-3), 65.5 (t, 2-CH_2), 66.6 (t, 5-CH_2), 68.1 (d, C-2), 77.2 (d, C-4), 77.9 (s, C-6), 124.3 (d, C-5′), 148.7 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 2970–2850 (C-H), 1440 (C=C), 1225 (C-O), 1200 (SO_3Na) cm^{-1}; HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd. for $C_{26}H_{38}N_6Na_7O_{26}S_6$: 1202.9438; found 1202.9407.

***O*-Sulfated Divalent Bis-1,2,3-triazole 27:** According to **GP6**, bis-1,2,3-triazole **14** (15 mg, 0.026 mmol), SO_3-DMF (47 %, 151 mg, 0.463 mmol) and [D_7]DMF (0.7 mL) were stirred overnight. After ^{1}H-NMR spectroscopic control, the reaction mixture was stirred for 1 d and each day a new portion of SO_3-DMF (151 mg) was added. According to *method G/a*, 1 M NaOH solution was added dropwise until pH 12 was reached. The solvents were removed in vacuo and the crude product was purified twice by dialysis (tube width: 10–16 mm, molecular weight cut off: 100–500 Da). The product was filtered through a syringe filter affording **32** (12 mg, 39 %) as a colorless solid. M. p. 265 °C (decomposition); $[\alpha]_D^{22}$ = +30.5 (c = 0.08, H_2O); ^{1}H NMR (700 MHz, D_2O): δ = 1.40, 1.47 (2 s, 6 H each, Me), 1.63–1.76 (m, 4 H, CH_2), 2.62–2.67 (m, 2 H, 5-H), 2.67–2.70 (m, 6 H, CH_2), 3.41–3.51 (m, 2 H, 2-CH_2), 3.59 (B part of ABX system, J_{AB} = 10.8 Hz, J_{BX} = 4.9 Hz, 2 H, 2-CH_2), 4.11–4.22 (m, 2 H, 5-CH_2), 4.36 (dd, J = 4.5, 10.7 Hz, 2 H, 5-CH_2), 4.67–4.73 (m, 2 H, 2-H), 4.93 (dd, J = 6.6, 12.1 Hz, 2 H, 4-H), 5.07–5.14 (m, 2 H, 3-H), 7.84 (s, 2 H, 5′-H) ppm; ^{13}C NMR (175 MHz, D_2O): δ = 22.2 (q, Me), 24.4 (t, CH_2), 26.0 (q, Me), 27.7, 28.3 (2 t, CH_2), 44.1 (d, C-5), 65.5 (d, C-3), 65.7 (t, 2-CH_2), 66.6 (t, 5-CH_2), 68.1 (d, C-2), 77.2 (d, C-4), 77.9 (s, C-6), 124.0 (d, C-5′)* ppm; *C-5′ attributed by HMQC; the signal of C-4′ could not be detected unambiguously; IR (ATR): $\tilde{\nu}$ = 2910 (C-H), 1460 (C=C), 1205 (SO_3Na) cm^{-1}; HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd. for $C_{27}H_{40}N_6Na_7O_{26}S_6$: 1216.9600; found 1216.9607.

SPR measurements: Experiments were performed on a BIACORE X instrument (GE Healthcare, Freiburg, Germany) at 25 °C using a sensor chip (sensor chip SA, GE Healthcare). For further details see Supporting Information.

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