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Carbohydrate Mimetics

Multivalent 1,2,3-Triazole-Linked Carbohydrate Mimetics by Huisgen–Meldal-Sharpless Cycloadditions of an Azidopyran

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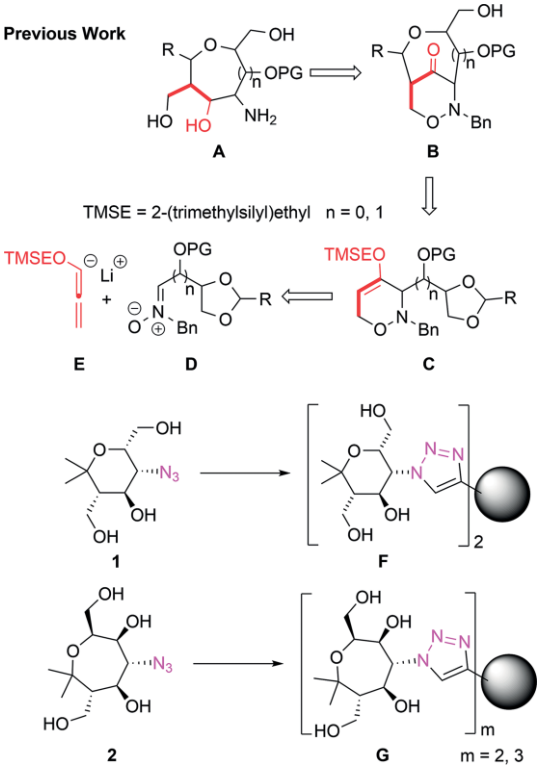
Dedicated to the memory of François Diederich

Abstract: Starting from an enantiopure 3-azido-substituted pyran derivative and various oligo-alkynes a series of multivalent 1,2,3-triazole-linked carbohydrate mimetics was synthesized. The copper-catalyzed Huisgen–Meldal-Sharpless cycloaddition (CuAAC) served as key coupling reaction. Cu/C in the presence of triethylamine proved to be a good catalytic system in most cases. Tri-, tetra-, hexa-, and octavalent compounds with typical rigid or flexible core units were prepared. The most complex compound contains a C_{60}-fullerene center leading to a dodecavalent carbohydrate mimetic. Only a few of the multivalent target compounds could be converted into pure *O*-sulfated derivatives that are required for their evaluation as L- and P-selectin ligands. Nevertheless, preliminary experiments suggest that the dodecavalent C_{60}-derived compound may be a promising ligand of these biologically important proteins with IC_{50} values in the low nanomolar range.

Introduction

Enantiopure aminopyrans and aminooxepanes of general structure **A** are easily available from their bicyclic precursors **B** which result from the Lewis acid-promoted rearrangement of 1,2-oxazine derivatives **C** (Scheme 1).[1] These heterocycles are prepared by a (3+3) cyclization process of lithiated alkoxyallene **E**[2] with carbohydrate-derived nitrones **D**.[3] This route to **A** allows many variations concerning the ring size, the substitution pattern and the stereochemistry that is determined by the configuration of the side chain of nitrones **D**. The polyhydroxylated compounds **A** can be regarded as carbohydrate mimetics – a compound class of high current interest due to their potential biological activities.[4] In preceding publications, we reported the synthesis of divalent compounds **F** and **G** employing 3-azidopyran **1** and 4-azidooxepane **2** which were prepared from the corresponding amino compounds by an efficient diazo transfer reaction.[5] The copper-catalyzed azide-alkyne (3+2) cycloaddition (Huisgen–Meldal-Sharpless cycloaddition, CuAAC)[6] was optimized with respect to the catalyst system applied, and most of the divalent products **F** and **G** were obtained in good yields. The synthesis of a few trivalent compounds derived from azidooxepane **2** was



Scheme 1. Route to amino-substituted pyran and oxepane derivatives **A** starting from lithiated alkoxyallene **E** and nitrones **D**; conversion of azidopyran **1** and azidooxepane **2** to divalent or trivalent carbohydrate mimetics **F** or **G**.

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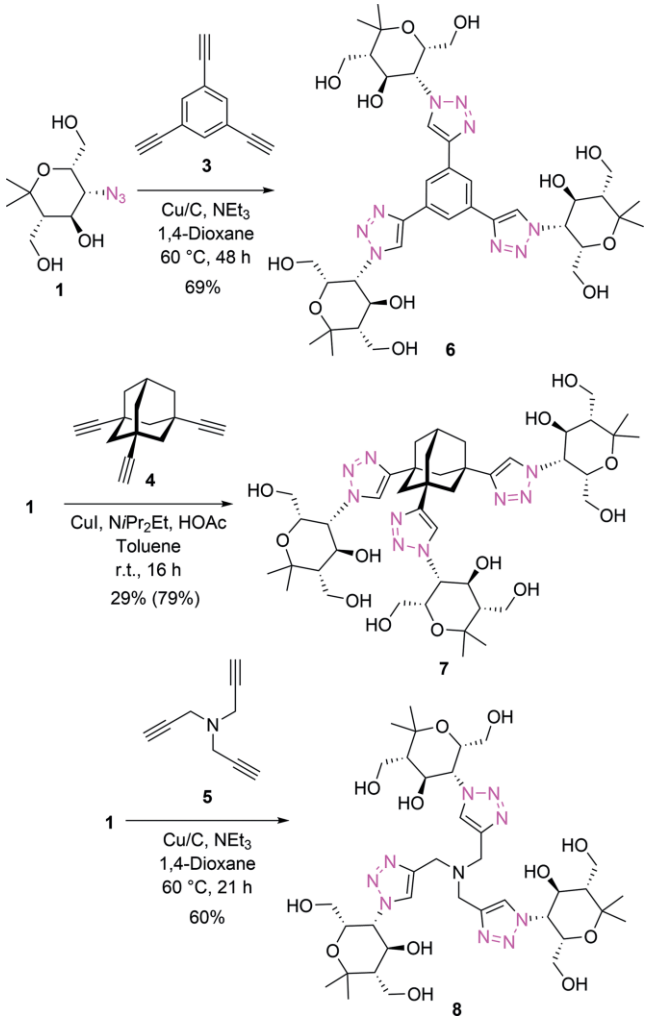
also reported.[7] In the current study, we use easily available compound **1** for the preparation of carbohydrate mimetics with higher valency. Multivalent compounds are well known to enhance the effects of their monovalent ligands in a nonlinear fashion and were therefore broadly utilized in glycoscience.[8] A 3-aminopyran (configured like **1**) was previously connected to gold nanoparticles and after *O*-sulfation this spherical multivalent entity turned out to be an excellent ligand for L-selectin and P-selectin with IC_{50} values in the subnanomolar range.[9] For an understanding of this high activity, an investigation of related compounds with lower valency was therefore of interest, in particular of compounds with a spherical or semi-spherical arrangement of end groups.[7,10]

Results and Discussion

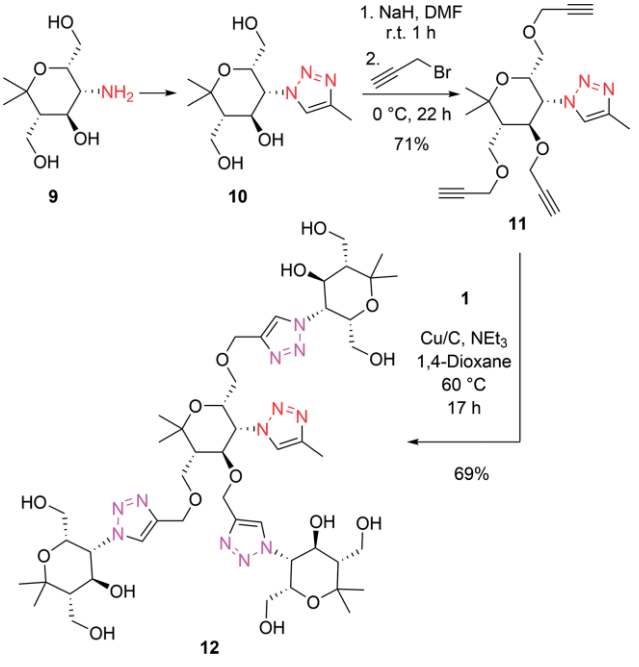
The synthesis of three C_3-symmetric trivalent carbohydrate mimetics[11] by CuAAC is illustrated in Scheme 2. The inexpensive heterogeneous catalyst Cu/C,[12] which worked nicely with most of the divalent systems, was used in presence of triethylamine in the coupling of **1** with the planar and rigid trisalkyne **3**. The



Scheme 2. CuAAC of 3-azidopyran **1** with trisalkynes **3**–**5** to trivalent carbohydrate mimetics **6**–**8**.

(3+2) cycloaddition occurs in the Cu/C matrix thus avoiding the presence of copper in solution and the contamination of the products with the metal. Removal of the catalyst by filtration is also very simple; on the other hand, the method requires heating to 60 °C. Under these established conditions 3-azidopyran **1** and trisalkyne **3** furnished trivalent product **6** in 69 % yield. The adamantanyl core is a fascinating central unit frequently employed as a component of tri- and tetravalent compounds, which were used for host-guest chemistry, for drug delivery, or as the center of glycoclusters.[13,14] Important functionalization methods and applications were reported by the group of Maison,[15] including the synthesis of trisalkyne **4**. With this sterically hindered and rigid compound, the CuAAC with **1** employing the Cu/C method provided only a low yield of **7** (16 % yield). However, a protocol applying homogeneous conditions with CuI, Hünig's base, and acetic acid[16] gave at least 29 % of the desired product **7**; with respect to recovered starting material **4** the yield was calculated to be even 79 %. The Cu/C method worked satisfyingly when flexible and sterically less hindered trisalkyne **5** and 3-azidopyran **1** were coupled affording the expected trivalent compound **8** in 60 % yield.

In order to test the Sakai–Westermann method of triazole synthesis[17] – a valuable metal-free alternative to the CuAAC – we converted 3-aminopyran **9** into triazole derivative **10** (Scheme 3).[5] The three hydroxy groups of this compound were alkylated with propargyl bromide under established conditions and the resulting trisalkyne **11** was subsequently treated with 3-azidopyran **1** in the presence of Cu/C to furnish the unsymmetrical trivalent carbohydrate mimetic **12** in 69 % yield.



Scheme 3. Conversion of triazole derivative **10** into trisalkyne **11** and subsequent CuAAC with 3-azidopyran **1** to unsymmetrical trivalent carbohydrate mimetic **12**.

The Cu/C protocol also worked reasonably well when tetraalkyne **13**, hexaalkyne **14**, and octaalkyne **15** were employed as starting materials (Scheme 4). The flexible and sterically un-

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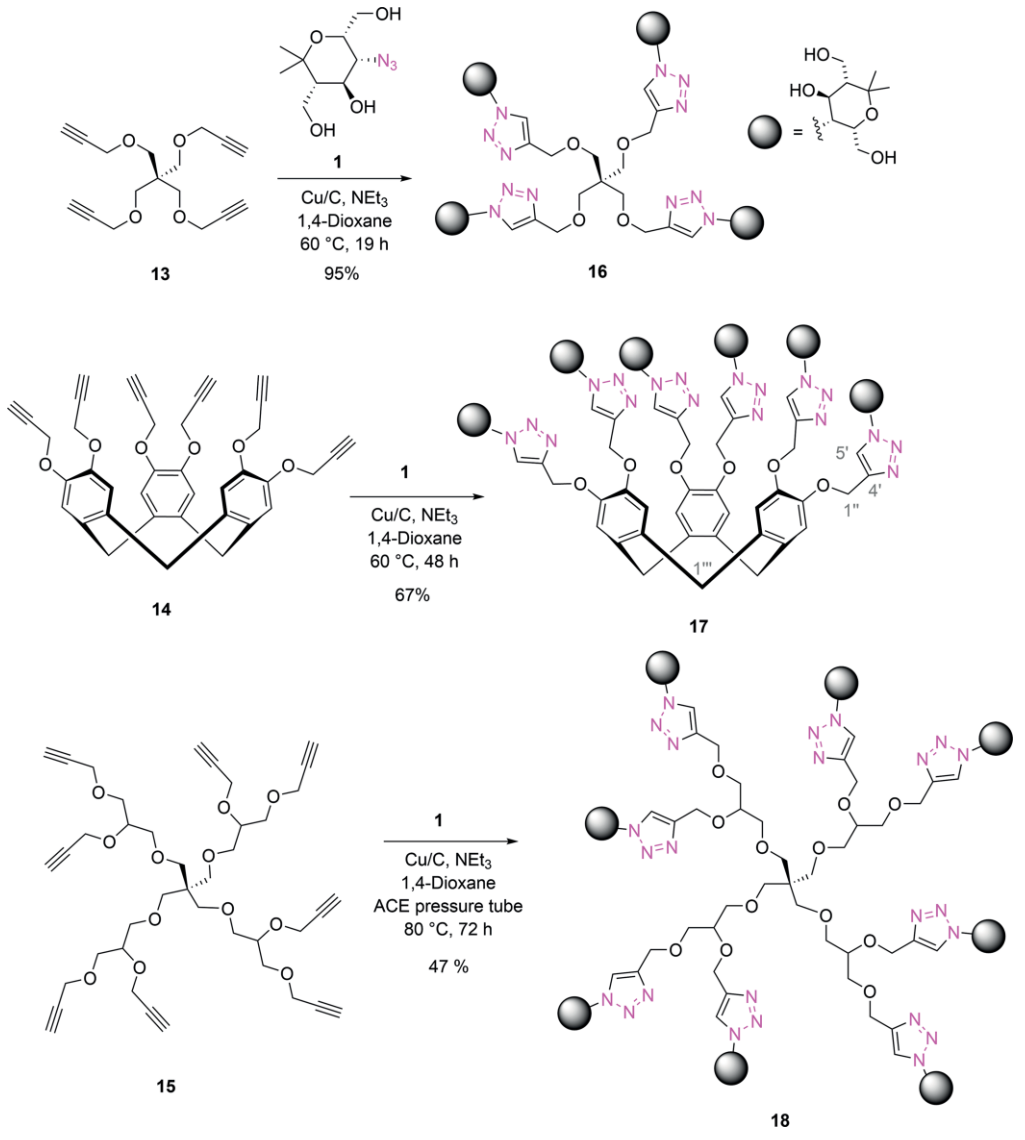

Scheme 4. Synthesis of tetravalent, hexavalent, and octavalent carbohydrate mimetics **16**–**18** by CuAAC of 3-azidopyran **1** with oligoalkynes **13**–**15**.

hindered tetraerythritol-based compound **13**[18] and 3-azidopyran **1** afforded the tetravalent carbohydrate mimetic **16** under standard reaction conditions in excellent 95 % yield. An attempted synthesis of a tetravalent compound with a more rigid *O*-propargyl-substituted calix[4]arene core[19] did not deliver a homogeneous product. However, the sixfold CuAAC of cyclotriveratrylene derivative **14**[20] with **1** proceeds smoothly. After slightly longer reaction times 67 % of the desired hexavalent product **17** were obtained; a small splitting of the signals of the aromatic protons in the ^{1}H-NMR spectrum indicated sterically hindered conformational changes of the compound at room temperature. The synthesis of the octavalent glycomimetic is based on the efficient route to octaalkyne **15** developed by the Haag group.[21] Its CuAAC with 3-azidopyran **1** in the presence of Cu/C and triethylamine was performed at 80 °C (pressure tube) and gave the expected product **18** in 47 % yield (still ca. 90 % yield per cycloaddition).

As a final target compound of this study, we planned to prepare the dodecavalent carbohydrate mimetic **22** with a C_{60}-fullerene as the central unit. Multivalent compounds with this core, in particular carbohydrate clusters, were mainly studied by Nierengarten et al.[22] and many interesting results have been reported by this group[23] and others.[24] The 1,2,3-triazole units in **22** are not derived by cycloaddition to propargyl ethers but to pent-4-yne ester moieties. For spectroscopic comparison, we therefore first prepared the divalent model compound **20** which contains the 1,2,3-triazolyl-substituted alkyl malonate substructure as found in fullerene derivative **22**. The CuAAC of 3-azidopyran with bisalkyne **19**[25] gave the required bistriazole derivative **20** under mild conditions in 60 % yield (Scheme 5).

According to Nierengarten et al.[25] the Bingel-Hirsch reaction[26] of the terminally C-silylated derivative of **19** with C_{60} provided the desired symmetrical hexakis C_{60}-fullerene adduct **21** in sufficient quantities. For the next step, we also followed reported methods[25] and performed the desilylation of **21** and its CuAAC with 3-azidopyran **1** in a one-pot protocol (Scheme 6) employing tetra-*n*-butylammonium fluoride in the presence of copper sulfate, sodium ascorbate in a specific mixture of very

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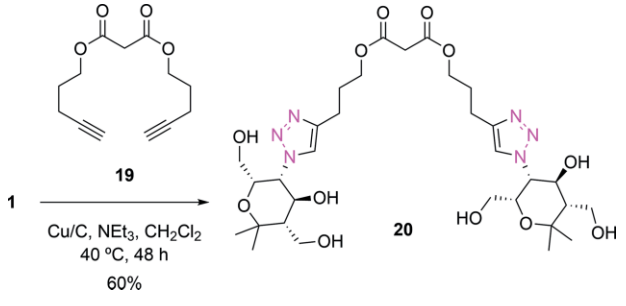
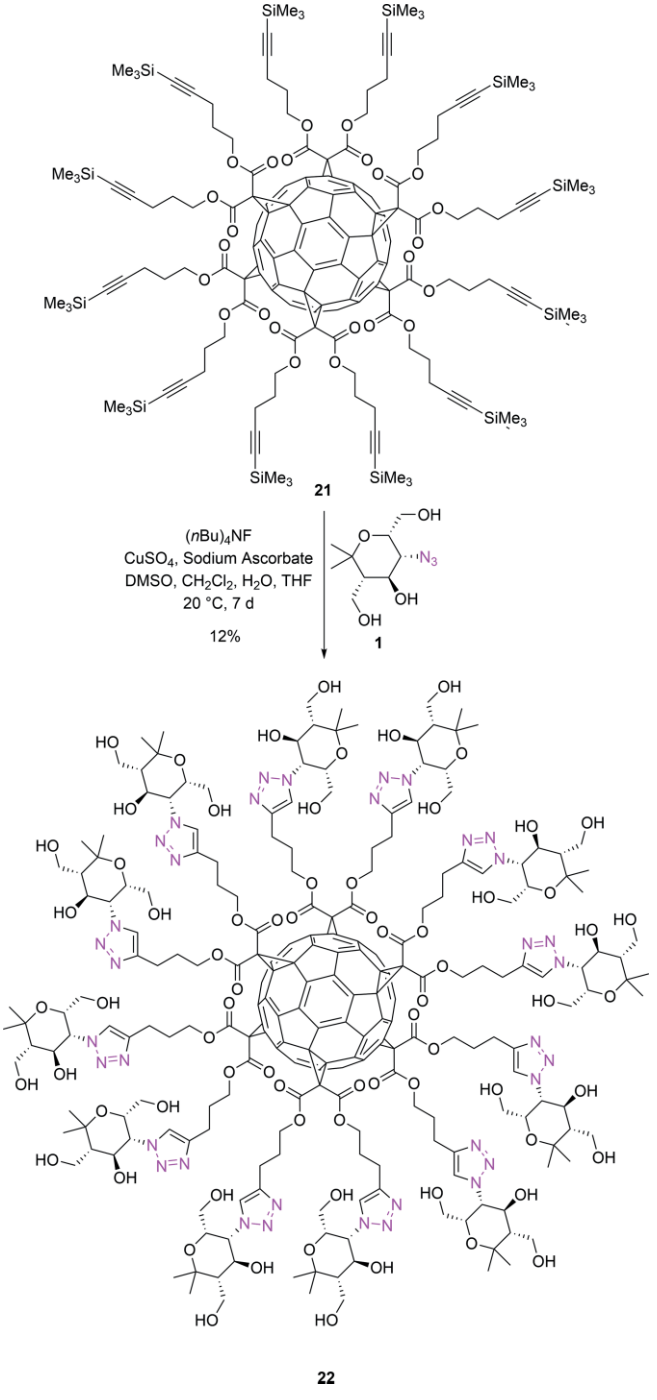
polar and less polar solvents. Stirring for seven days at room temperature and purification by precipitation followed by washing afforded a red solid in ca. 12 % yield. Although this sample could not be fully purified (estimated purity ca. 95 %) it could be identified by spectroscopic means to be the desired dodecavalent carbohydrate mimetic **22**. Its structure was proven by high-resolution mass spectrometry and the NMR spectroscopic data that show one set of the typical pyran signals and those of a symmetric hexakis C_{60} adduct. The typical ^{13}C NMR signals of the fullerene carbons are at 70.7 ppm for the sp^3-hybridized carbons and at 142.7 and 146.9 ppm for the two different sp^2-hybridized carbons. The twelve identical 1,2,3-triazole units of **22** are characterized by a typical proton signal at 7.74 ppm in the ^1H-NMR spectrum and a doublet and a singlet signal at 124.1 ppm and 147.3 ppm for C-5 and C-4, respectively, in the ^{13}C-NMR spectrum. These values match the signals of model compound **20** well.

An *O*-sulfation of our compounds was mandatory for their evaluation as ligands of L- and P-selectins. These lectins are involved in the inflammatory process[27] and compounds inhibiting their activity are therefore of interest as potential therapeutics.[28] Unfortunately, most of the compounds prepared provided mixtures of compounds when we tried their *O*-sulfation. The problems of this process[29] under the established conditions using sulfurtrioxide DMF complex[10d] may in part stem from the rigidity and thus poor solubility of the compounds in [D_7]DMF, which allows the advantageous NMR control of this difficult transformation. Incomplete *O*-sulfation and/or partial decomposition led to inseparable mixtures that could not be purified by dialysis. Due to a lack of material, optimizations were not possible. Among the trivalent compounds only the unsymmetrically substituted and well soluble carbohydrate mimetic **12** gave the desired *O*-sulfated product **23** in quantitative yield and in good purity (Scheme 7). The simple divalent model compound **20** was also successfully *O*-sulfated to ester **24** in 66 % yield. With the little quantity of the C_{60}-fullerene-based dodecavalent carbohydrate mimetic **22** in hand, we also tried its conversion into the desired *O*-sulfated form. Indeed, under the established conditions we observed complete consumption of **22** and received an orange solid, but the isolated material was not pure and certainly contained inorganic salts (sodium sulfate and/or sodium hydrogen carbonate). Its purity can be estimated to be 40–50 %. The NMR spectra of the sample showed broad signals that do not allow a full identification; very likely the material also contains compounds with hydroxy groups that were not sulfated.

The three *O*-sulfated samples obtained were investigated by surface plasmon resonance (SPR) spectroscopy. As earlier found for this type of compound a competitive binding assay was performed.[30] Several of the measurements were executed twice providing slightly differing results (see Supporting Information). For the unsymmetrical trivalent compound **23** we obtained IC_{50} values of 1.1–1.5 μM for L-selectin and 1.1–4.5 μM



Scheme 5. Synthesis of model compound **20** by CuAAC of bisalkyne **19** and 3-azidopyran **1**.



Scheme 6. One-pot desilylation of silylated C_{60} fullerene derivative **21** and CuAAC with 3-azidopyran **1** to dodecavalent carbohydrate mimetic **22**.

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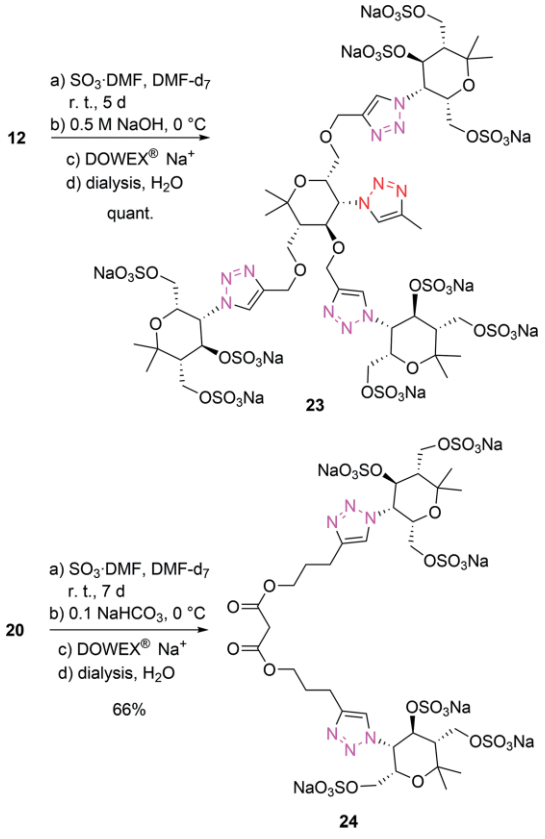

Scheme 7g. *O*-Sulfations of trivalent compound **12** to **23** and of divalent model compound **20** to **24**.

for P-selectin. The divalent model compound **24** gave an IC_{50} value of 30 μM for P-Selectin, but the L-selectin inhibition value could not be determined exactly (1–100 μM). Preliminary measurements of the impure *O*-sulfated dodecavalent C_{60}-fullerene-derived sample showed that the IC_{50} value for L-selectin is in the range of 10–100 nM[31] and that for P-selectin even between 1–5 nM. Considering the fact that this sample was probably containing more than 50 % of inorganic salts these values in the low nanomolar range should be taken only as very crude estimates. A further investigation of the polysulfated fullerene derivative **22** is certainly justified.

Conclusions

A series of multivalent carbohydrate mimetics linked by 1,2,3-triazole moieties was prepared by starting from 3-azidopyran **1** and oligo-alkynes. The copper-catalyzed Huisgen–Meldal-Sharpless (3+2) cycloadditions (CuAAC) proved to be generally applicable. Very good results were obtained in most cases employing Cu/C as a catalyst. Trivalent compounds with flexible and rigid central units were synthesized and typical tetra-, hexa- and octavalent compounds, generally with flexible core units, were obtained in reasonable yields. For the synthesis of the new C_{60}-fullerene-based dodecavalent carbohydrate mimetic **22** we employed methods developed by the group of Nierengarten. Only a few compounds could be successfully *O*-sulfated with the sulfur trioxide-DMF complex and evaluated by SPR as inhibitors of L-selectin and P-selectin. The preliminary IC_{50} value of the impure *O*-sulfated C_{60}-fullerene-derived compound in the nanomolar range indicates that a spherical presentation (diameter ca. 1 nm) of the ligands is a promising arrangement for good inhibition of selectins. The above-mentioned gold nanoparticles with the *O*-sulfated amidopyran decoration (IC_{50} values in picomolar range) are also big spherical entities (diameter ca. 6 or 14 nm). It will be certainly worthwhile to attempt a more efficient preparation of fullerene derivative **22** and to optimize its *O*-sulfation for future investigations.

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 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 analytically 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 GP for the CuAAC: To a solution of 3-azidopyran **1** (1.0 equiv.) in 1,4-dioxane (3 mL/mmol) were added Cu/C (0.1–0.5 equiv.), Et_3N (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.

Trivalent Compound 6: According to **GP**, to a solution of azidopyran **1** (49 mg, 195 μmol) in 1,4-dioxane (1.0 mL) were added Cu/C (183 mg, 86 μmol), NEt_3 (50 μL, 360 μmol), and 1,3,5-triethynylbenzene (**3**) (8 mg, 54 μmol). The reaction mixture was stirred at 60 °C for 21 h. Then another batch of Cu/C (183 mg, 86 μmol), Et_3N (50 μL, 361 μmol), and 1,4-dioxane (1 mL) were additionally added. After stirring for 2 d, 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, 4:1) affording **6** (31 mg, 69 %) as a light yellow solid. M. p. 195–197 °C; $[\alpha]_D^{22}$ = +101.0 (*c* = 0.63 MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 1.35, 1.42 (2 s, 9 H each, Me), 2.12 (td, *J* = 6.2, 12.1 Hz, 3 H, 5-H), 3.12, 3.18 (AB part of ABX system, J_{AB} = 11.5 Hz, J_{AX} = 5.3 Hz, J_{BX} = 7.2 Hz, 3 H each, 2-CH_2), 3.74, 3.97 (2 dd, *J* = 6.2, 11.4 Hz, 3 H each, 5-CH_2), 4.35 (dt, *J* = 5.3, 7.2, Hz, 3 H, 2-H), 4.46 (dd, *J* = 7.2, 12.1 Hz, 3 H, 4-H), 4.84 (dd, *J* = 5.3, 7.2 Hz, 3 H, 3-H), 8.21 (s, 3 H, Ar), 8.41 (s, 3 H, 5′-H) ppm; ^{13}C NMR (CD_3OD, 126 MHz): δ = 23.6, 26.7 (2 q, Me), 49.7 (d, C-5), 61.7 (t, 2-CH_2), 62.4 (t, 5-CH_2), 70.7 (d, C-3), 71.9 (d, C-2), 73.2 (d, C-4), 77.6 (s, C-6), 123.2 (d, C-5′), 123.3 (d, Ar), 133.0 (s, Ar), 147.7 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3365 (OH), 2930 (C–H), 1600 (C=C), 1230 (C–O–C) cm^{-1}; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd. for $C_{39}H_{58}N_9O_{12}$: 844.4206, found 844.4212; *m/z* [M + Na]$^+$ calcd. for $C_{39}H_{57}N_9NaO_{12}$: 866.4025, found 866.4034.

Trivalent Compound 7: To a suspension of azidopyran **1** (80 mg, 0.346 mmol) in toluene (0.2 mL) were added CuI (19 mg, 0.101 mmol), triyne **4** (16 mg, 76 µmol), followed by N*i*Pr_2Et (290 µL, 1.70 mmol) and acetic acid (97.3 µL, 1.70 mmol). The mixture was stirred at room temperature for 16 h and then quenched with 7 N NH_3 in MeOH. 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 (silica gel, CH_2Cl_2/MeOH, 9:1 to 4:1) affording **7** (20 mg, 29 %; based on consumed **4** 79 % yield) as a yellow solid. M. p. 291 °C; $[\alpha]_D^{22}$ = +22.7 (c = 0.45, MeOH); ^{1}H NMR (700 MHz, CD_3OD): δ = 1.29, 1.39 (2 s, 9 H each, Me), 2.05 (td, *J* = 6.3, 12.3 Hz, 3 H, 5-H), 2.10 (d, *J* = 2.1 Hz, 6 H, 3′′-H), 2.23, 2.26 (AB system, J_{AB} = 12.3 Hz, 3 H each, 1′′-H), 2.44–2.47 (m, 1 H, 4′′-H), 2.93, 3.03 (AB part of ABX system, J_{AB} = 11.5, J_{AX} = 4.7 Hz, J_{BX} = 7.6 Hz, 3 H each, 2-CH_2), 3.69, 3.89 (2 dd, *J* = 6.3, 11.3 Hz, 3 H each, 5-CH_2), 4.24–4.28 (m, 3 H, 2-H), 4.31 (dd, *J* = 7.0, 12.3 Hz, 3 H, 4-H), 4.71 (dd, *J* = 5.2, 7.0 Hz, 3 H, 3-H), 7.80 (s, 3 H, 5′-H) ppm; ^{13}C NMR (175 MHz, CD_3OD): δ = 23.5, 26.7 (2 q, Me), 30.6 (d, C-4′′), 35.3 (s, C-2′′), 41.9 (t, C-3′′), 47.5 (t, C-1′′), 49.7 (d, C-5), 61.7 (t, 2-CH_2), 62.3 (t, 5-CH_2), 70.3 (d, C-3), 72.1 (d, C-2), 73.0 (d, C-4), 77.5 (s, C-6), 121.6 (d, C-5′), 157.1 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3400 (OH), 2975 (C–H), 1640 (C=C), 1160 (C–O), 1230 (C–O–C) cm^{-1}; HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd. for $C_{43}H_{67}N_9NaO_{12}$: 924.4801, found 924.4824; $C_{43}H_{67}N_9O_{12}$ (902.0) + 4 H_2O: calcd. C 53.02, H 7.76, N 12.94; found C 53.46, H 7.23, N 11.78.

Trivalent Compound 8: According to **GP**, to a solution of azidopyran **1** (70 mg, 303 µmol) in 1,4-dioxane (1.4 mL) were added Cu/C (481 mg, 227 µmol), NEt_3 (140 µL, 1.01 mmol) and triyne **5** (9.9 mg, 10.7 µL, 75.7 µmol). The mixture was stirred at 60 °C for 21 h and then filtered through a pad of Celite®. After washing with MeOH the solvents were removed in vacuo and the crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 4:1) affording **8** (37 mg, 60 %) as a light pink solid. Melting range: 125–131 °C; $[\alpha]_D^{22}$ = +69.5 (c = 0.71 MeOH); ^{1}H NMR (700 MHz, CD_3OD): δ = 1.30, 1.40 (2 s, 9 H each, Me), 2.07 (td, *J* = 6.2, 12.1 Hz, 3 H, 5-H), 2.99, 3.05 (AB part of ABX system, J_{AB} = 11.4 Hz, J_{AX} = 5.1 Hz, J_{BX} = 7.2 Hz, 3 H each, 2-CH_2), 3.70 (dd, *J* = 6.2, 11.3 Hz, 3 H, 5-CH_2), 3.78 (s, 6 H, NCH_2), 3.90 (dd, *J* = 6.2, 11.3 Hz, 3 H, 5-CH_2), 4.28 (dt, *J* = 5.1, 7.2 Hz, 3 H, 2-H), 4.34 (dd, *J* = 6.9, 12.1 Hz, 3 H, 4-H), 4.75 (dd, *J* = 5.1, 6.9 Hz, 3 H, 3-H), 8.03 (s, 3 H, 5′-H) ppm; ^{13}C NMR (176 MHz, CD_3OD): δ = 23.6, 26.8 (2 q, Me), 48.5 (t, NCH_2), 49.6 (d, C-5), 61.7 (t, 2-CH_2), 62.3 (t, 5-CH_2), 70.4 (d, C-3), 71.9 (d, C-2), 73.1 (d, C-4), 77.5 (s, C-6), 126.0 (d, C-5′), 145.0 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3385 (OH), 2970–2935 (C–H), 1650 (C=C), 1155 (C–O), 1230 (C–O–C) cm^{-1}; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd. for $C_{36}H_{61}N_{10}O_{12}$: 825.4471, found 825.4471; *m/z* [M + Na]$^+$ calcd. for $C_{36}H_{60}N_{10}NaO_{12}$ 847.4296, found 847.4303; $C_{36}H_{60}N_{10}O_{12}$ (824.9) + 4 H_2O: calcd. C 48.20, H 7.64, N 15.62; found C 48.43, H 7.59, N 15.32.

(2*S*,3*R*,4*S*,5*S*)-1-{6,6-Dimethyl-4-(prop-2-ynyloxy)-2,5-bis[(prop-2-ynyloxy)methyl]tetrahydro-2*H*-pyran-3-yl}-4-methyl-1*H*-1′,2′,3′-triazole (11): To a cooled solution of triazole **10** (72 mg, 0.26 mmol) in anhydrous DMF (1 mL), NaH (25 mg, 0.11 mmol) was added. The resulting suspension was stirred at room temperature for 1 h. After cooling to 0 °C, propargyl bromide (1.51 g, 12.7 mmol) was added dropwise. After 22 h of stirring, MeOH (2 mL) was added and the mixture was stirred for 30 min. After removing all volatiles in vacuo, the resulting mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvents were removed in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes/ethyl acetate, 5:1 to 2:1) affording **11** (72 mg, 71 %) as an orange oil. $[\alpha]_D^{22}$ = –4.90 (c = 0.59, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33, 1.36 (2 s, 3 H each, Me), 2.14 (ddd, *J* = 3.8, 7.4, 11.4 Hz, 1 H, 5-H), 2.25 (t, *J* = 2.4 Hz, 1 H, ≡CH), 2.37–2.33 (m, 4 H, CH_3, ≡CH), 2.41 (t, *J* = 2.4 Hz, 1 H, ≡CH), 2.98, 3.11 (AB part of ABX system, J_{AB} = 10.0 Hz, J_{AX} = 6.0 Hz, J_{BX} = 6.5 Hz, 1 H each, 2-CH_2), 3.62–3.69 (m, 2 H, 5-CH_2), 3.85 (dd, *J* = 2.4, 15.7 Hz, 1 H, CH_2C≡), 3.91, 3.94 (AB part of ABX system, J_{AB} = 15.7 Hz, J_{AX} = J_{BX} = 2.4 Hz, 1 H each, CH_2C≡), 4.02–4.14 (m, 3 H, 4-H, CH_2C≡), 4.30 (dt, *J* ≈ 4.4, 6.2 Hz, 1 H, 2-H), 4.84 (dd, *J* = 4.4, 5.4 Hz, 1 H, 3-H), 7.48 (s, 1 H, 5′-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.0, 24.2, 27.2 (3 q, Me), 45.7 (d, C-5), 58.0, 58.4, 58.6 (3 t, CH_2C≡), 66.5 (d, C-3), 67.6 (t, 5-CH_2), 68.2 (t, 2-CH_2), 68.8 (d, C-2), 74.6, 74.7, 74.9 (3 d, C≡*C*H), 76.9 (s, C-6), 77.9 (d, C-4), 78.9, 79.1, 79.5 (3 s, *C*≡CH), 121.4 (d, C-5′), 143.5 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3290 (≡C–H), 3150–3060 (=C–H), 2960–2840 (C–H), 2115 (C≡C), 1550, 1440, 1390, 1360 (C=C) cm^{-1}. HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd. for $C_{21}H_{27}N_3NaO_4$: 408.1894, found 408.1904; $C_{21}H_{27}N_3O_4$ (385.5): calcd. C 65.44, H 7.06, N 10.90; found C 65.84, H 7.06, N 10.26.

Trivalent Compound 12: To a solution of azidopyran **1** (24 mg, 0.104 mmol) in 1,4-dioxane (1 mL) were added Cu/C (165 mg, 77.7 µmol), NEt_3 (50 µL, 0.337 mmol), and trisalkyne **11** (10 mg, 0.26 mmol). The mixture was stirred at 60 °C for 17 h, then filtered through a pad of Celite® and washed with MeOH. Solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 4:1) affording **12** (22 mg, 79 %) as a yellow solid. M. p. 220 °C; $[\alpha]_D^{22}$ = –34.2 (c = 0.58, MeOH); ^{1}H NMR (700 MHz, CD_3OD): δ = 1.28–1.29 (m, 12 H, Me), 1.35 (s, 3 H, Me), 1.38–1.40 (m, 9 H, Me), 2.04–2.09 (m, 3 H, 5-H^B), 2.22 (ddd, *J* = 3.6, 7.7, 11.5 Hz, 1 H, 5-H^A), 2.31 (s, 3 H, Me), 2.90–2.92 (m, 1 H, 2-$CH_2{}^A$), 2.91–2.94, 2.94–2.97, 2.98–3.01 (3 m, 2 H each, 2-$CH_2{}^B$), 3.17 (m_c, 1 H, 2-$CH_2{}^A$), 3.61 (m_c, 1 H, 5-$CH_2{}^A$), 3.67–3.74 (m, 5 H, 5-$CH_2{}^{A,B}$), 3.87–3.95 (m, 2 H, 5-$CH_2{}^B$), 4.12 (dd, *J* = 6.1, 11.5 Hz, 1 H, 4-H^A), 4.24–4.29 (m, 7 H, 2-H^B, 4-H^B, CH_2), 4.36 (s_b, 2 H, CH_2), 4.40 (dd, *J* = 6.2, 11.3 Hz, 1 H, 2-H^A), 4.45 (d, *J* = 12.5 Hz, 1 H, CH_2), 4.57 (s_b, 2 H, CH_2), 4.70–4.75 (m, 3 H, 3-H^B), 4.79–4.81 (m, 1 H, 3-H^A), 7.66, 7.74, 7.87, 8.00 (4 s, 1 H each, 5′-$H^{A,B}$) ppm; ^{13}C NMR (175 MHz, CD_3OD): δ = 10.8, 23.5, 23.6, 24.4, 26.66, 26.68, 26.75, 27.3 (8 q, Me), 47.2, 49.1, 49.3, 49.4 (4 d, C-$5^{A,B}$), 61.57, 61.59, 61.64 (3 t, 2-$CH_2{}^B$), 62.28, 62.38, 62.42 (3 t, 5-$CH_2{}^B$), 64.5, 64.76, 64.84 (3 t, CH_2), 68.4 (d, C-3^A), 68.9 (t, 5-$CH_2{}^A$), 69.3 (t, 2-$CH_2{}^A$), 69.5 (d, C-2^A), 70.3, 70.5, 70.6 (3 d, C-3^B), 71.86, 71.89, 71.96 (3 d, C-2^B), 73.1, 73.2, 73.34 (3 d, C-4^B), 77.49, 77.51, 77.53 (3 s, C-6^B) 78.2 (s, C-6^A), 79.3 (d, C-4^A), 124.2, 125.2, 154.4, 125.6 (4 d, C-5′^{A,B}), 144.4, 145.1, 145.2, 145.4 (4 s, C-4′^{A,B}) ppm; "A" refers to the central pyran ring, "B" to the three external pyran rings, "A′" to the methyl-substituted 1,2,3-triazole unit, "B′" to the three external

1,2,3-triazoles substituted with "B"; a specific assignment of the signals to the three B-rings and to the four triazole units is not possible; IR (ATR): $\tilde{\nu}$ = 3385 (OH), 2970–2850 (C–H), 1650, 1450, 1370 (C=C), 1050 (C–O–C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd. for $C_{48}H_{78}N_{12}NaO_{16}^+$: 1102.1924, found 1102.5881; $C_{48}H_{78}N_{12}O_{16}$ (1079.2) + 3 H_2O: calcd. C 50.87, H 7.74, N 14.83; found C 51.61, H 7.42, N 14.21.

Tetravalent Compound 16: To a solution of azidopyran **1** (31 mg, 0.13 mmol) in 1,4-dioxane (1.5 mL) were added Cu/C (235 mg, 0.111 mmol), NEt_3 (70 µL, 0.50 mmol) and tetrayne **13** (8 mg, 28 µmol). The mixture was stirred at 60 °C for 19 h, then 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, 4:1) affording **16** (32 mg, 95 %) as a yellow solid. M. p. 122–125 °C; $[\alpha]^{22}_D$ = +10.5 (c = 0.12, MeOH); ^1H NMR (700 MHz, CD_3OD): δ = 1.29, 1.39 (2 s, 12 H each, Me), 2.07 (td, *J* = 6.3, 12.0 Hz, 4 H, 5-H), 2.95, 3.03 (AB part of ABX system, J_{AB} = 11.5 Hz, J_{AX} = 4.8 Hz, J_{BX} = 7.5 Hz, 4 H each, 2-CH_2), 3.41 (s, 8 H, 3″-H), 3.70, 3.90 (2 dd, *J* = 6.3, 11.3 Hz, 4 H each, 5-CH_2), 4.28 (dt, *J* ≈ 5.0, 7.5 Hz, 4 H, 2-H), 4.36 (dd, *J* = 7.1, 12.0 Hz, 4 H, 4-H), 4.52, 4.55 (AB system, J_{AB} = 12.7 Hz, 8 H, 1″-H), 4.76 (dd, *J* = 5.2, 7.1 Hz, 4 H, 3-H), 7.97 (s, 4 H, 5′-H) ppm; ^{13}C NMR (175 MHz, CD_3OD): δ = 23.6, 26.7 (2 q, Me), 43.5 (s, C-4″), 49.7 (d, C-5), 61.6 (t, 2-CH_2), 62.3 (t, 5-CH_2), 65.2 (t, C-1″), 69.9 (t, C-3″), 70.3 (d, C-3), 72.0 (d, C-2), 73.0 (d, C-4), 77.7 (s, C-6), 125.6 (d, C-5′), 145.8 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3375 (OH), 2965–2875 (CH), 1650 (C=C), 1230–1055 (C–O–C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd. for $C_{53}H_{88}N_{12}NaO_{20}$: calcd. 1235.6125, found 1235.6102.

Hexavalent Compound 17: To a solution of azidopyran **1** (44 mg, 0.19 mmol) in 1,4-dioxane (1.1 mL) were added Cu/C (116 mg, 18.2 µmol), NEt_3 (160 µL, 30 µmol) and hexayne **14** (9 mg, 15 µmol). After stirring for 2 d at 60 °C the mixture was filtered through a pad of Celite® and washed with MeOH. The solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 4:1) affording **17** (20 mg, 67 %) as a yellow solid. M. p. 137–140 °C; $[\alpha]^{22}_D$ = +18.1 (c = 0.85, MeOH); ^1H NMR (700 MHz, CD_3OD): δ = 1.19, 1.23 (2 s, 6 H each, Me), 1.29 (s_b, 12 H, Me), 1.35, 1.36 (2 s, 6 H each, Me), 1.99–2.07 (m, 6 H, 5-H), 2.87–2.93, 2.96–3.01 (2 m, 6 H each, 2-CH_2), 3.63–3.70 (m, 6 H, 5-CH_2), 3.74–3.79 (m, 2 H, 1‴-H), 3.82–3.89 (m, 6 H, 5-CH_2), 4.10–4.17 (m, 2 H, 1‴-H), 4.21–4.24, 4.25–4.29 (2 m, 6 H each, 4-H, 2-H), 4.30–4.34 (m, 2 H, 1‴-H), 4.67–4.74 (m, 6 H, 3-H), 5.12–5.19 (m, 12 H, 1″-H), 7.15–7.20 (m, 6 H, Ar), 7.99 (s, 6 H, 5′-H) ppm; a small splitting of the signals of the aromatic protons was observed; ^{13}C NMR (175 MHz, CD_3OD): δ = 23.6, 26.8, 30.6, 30.7, 30.8, 33.1 (6 q, Me), 49.5 (d, C-5), 61.6 (t, 2-CH_2), 62.1 (t, 5-CH_2), 62.6 (t, C-1‴), 64.0 (t, C-1″), 70.3 (d, C-3), 72.0 (d, C-2), 73.1 (d, C-4), 77.5 (s, C-6), 118.5, 126.2, 127.7, 130.0, 135.1 (5 d, C-5′, Ar), 144.9 (s, Ar), 148.3 (s, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3370 (OH), 2960–2850 (C–H), 1510, 1455 (C=C), 1260, 1055 (C–O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + 2\ Na]^{2+}$ calcd. for 0.5 ($C_{93}H_{132}N_{18}Na_2O_{30}$): 1013.9586, found 1013.9587; $[M + Na]^+$ calcd. for $C_{93}H_{132}N_{18}NaO_{30}$: 2004.9279, found 2004.9269.

Octavalent Compound 18: According to **GP** but applying 80 °C, to a solution of azidopyran **1** (60 mg, 0.26 mmol) in 1,4-dioxane (2.5 mL) were added Cu/C (460 mg, 259 µmol), NEt_3 (65 µL, 0.47 mmol) and octayne **15** (19 mg, 26 µmol). After stirring for 72 h at 80 °C in an ACE pressure tube, the mixture was diluted with 1,4-dioxane and filtered through a pad of Celite®. After washing with CH_2Cl_2 and MeOH the filtrate was collected in fractions. The last fraction gave product **18** (31.5 mg, 47 %) as an orange oil. $[\alpha]^{22}_D$ = +67.0 (*c* = 0.1, MeOH); ^1H NMR (700 MHz, CD_3OD): δ = 1.30 (s, 24 H, Me), 1.40 (s, 24 H, Me), 2.08 (m_c, 8 H, 5-H), 3.00 (m_c, 8 H, 2-CH_2), 3.06 (A part of an ABX system, J_{AB} = 14.7 Hz, J_{AX} = 7.2 Hz, 8 H, 2-CH_2), 3.42 (m_c, 8 H, 4″-H), 3.49–3.66 (m, 16 H, 2″-H, 5″-H), 3.71 (dd, *J* = 6.1, 11.3 Hz, 8 H, 5-CH_2), 3.80 (m_c, 4 H, 3″-H), 3.91 (dd, *J* = 6.1, 11.3 Hz, 8 H, 5-CH_2), 4.27–4.31 (m, 8 H, 2-H), 4.33–4.37 (m, 8 H, 4-H), 4.62 (s, 8 H, 1″-H), 4.72–4.82 (m, 16 H, 3-H, 7″-H), 8.03 (s, 8 H, 5′-H) ppm; ^{13}C NMR (176 MHz, CD_3OD): δ = 23.5, 26.8 (2 q, Me), 43.5 (s, C-6″), 49.6 (d, C-5), 61.7 (t, 2-CH_2), 62.3 (t, 5-CH_2), 64.4 (t, C-7″), 65.2 (t, C-1″), 70.4 (d, C-3), 71.1 (t, C-4″), 71.6 (t, C-2″), 71.9 (d, C-2), 72.7 (t, C-5″), 73.1 (d, C-3), 77.6 (s, C-6), 78.7 (d, C-3″), 125.7 (d, C-5′), 146.1 (d, C-4′) ppm; IR (ATR): $\tilde{\nu}$ = 3350 (OH), 2930 (C–H), 1450 (C=C), 1060 (C–O–C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + Na + H]^{2+}$ calcd. for 0.5($C_{113}H_{189}N_{24}NaO_{44}$): 1305.1605, found 1305.3090; $[M + H]^+$ calcd. for $C_{113}H_{189}N_{24}O_{44}$: 2587.3318, found 2587.6199.

Divalent Compound 20: According to GP, to a solution of azidopyran **1** (74 mg, 0.32 mmol) in CH_2Cl_2 (2 mL) were added Cu/C (27 mg, 13 µmol), NEt_3 (53 µL, 0.39 mmol), and diyne **19** (30 mg, 0.13 mmol). The mixture was stirred at 40 °C for 2 d, then filtered through a pad of Celite® and washed with CH_2Cl_2 and MeOH. The solvents were removed under reduced pressure and the crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1 to 4:1) affording **20** (55 mg, 60 %) as a colorless wax. $[\alpha]^{20}_D$ = +49.4 (c = 1, MeOH); ^1H NMR (700 MHz, CD_3OD): δ = 1.30 (s, 6 H, Me), 1.40 (s, 6 H, Me), 2.02–2.11 (m, 6 H, 2″-H, 5-H), 2.83 (t, *J* = 7.5 Hz, 4 H, 1″-H), 2.91, 3.06 (AB part of ABX system, J_{AB} = 11.5 Hz, J_{AX} = 4.8 Hz, J_{BX} = 7.5 Hz, 4 H, 2-CH_2), 3.71 (dd, *J* = 6.3, 11.3 Hz, 2 H, 5-CH_2), 3.91 (dd, *J* = 6.1, 11.3 Hz, 2 H, 5-CH_2), 4.21 (m_c, 4 H, 3″-H), 4.26–4.33 (m, 6 H, 2-H, 4-H, 5″-H), 4.72 (dd, *J* = 5.1, 6.9 Hz, 2 H, 3-H), 7.81 (s, 2 H, 5′-H) ppm; ^{13}C NMR (176 MHz, CD_3OD): δ = 22.7 (t, C-1″), 23.5, 26.7 (2 q, Me), 29.3 (t, C-2″), 33.3 (t, C-5″), 49.6 (d, C-5), 61.6 (t, 2-CH_2), 62.3 (t, 5-CH_2), 65.5 (t, C-3″), 70.2 (d, C-3), 72.0 (d, C-2), 73.1 (d, C-4), 77.5 (s, C-6), 123.8 (d, C-5′), 147.7 (s, C-4′), 168.5 (s, C-4″) ppm; IR (ATR): $\tilde{\nu}$ = 3355 (OH), 2965–2895 (C–H), 1725 (C=O), 1550 (C=C), 1220–1025 (C–O–C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd. for $C_{31}H_{51}N_6O_{12}$: 699.3565, found 699.3568; $[M + Na]^+$ calcd. for $C_{31}H_{50}N_6NaO_{12}$ 721.3384, found 721.3391.

Dodecavalent Compound 22: Dodecaalkyne **21** (84 mg, 28 µmol) and azidopyran **1** (83 mg, 0.36 mmol) were dissolved in CH_2Cl_2/DMSO (1 mL each). A solution of $CuSO_4 \cdot 5H_2O$ (4.8 mg, 19.2 µmol) and sodium ascorbate (19 mg, 97 µmol) in water (1 mL), and a solution of tetra-*n*-butylammonium fluoride (1 M in THF, 415 µL, 415 µmol) were subsequently added. After stirring the mixture for 48 h at room temperature, CH_2Cl_2 was added and stirring was continued for 24 h. Then, CH_2Cl_2 was cautiously removed in vacuo and DMSO (1.5 mL) was added and stirring was continued for 96 h. The mixture was concentrated at 40 °C/24 mbar and CH_2Cl_2/DMSO/water (50:10:1) were added causing precipitation of the product as an oil. This oil was washed with a mixture of CH_2Cl_2/DMSO/water (50:10:1) and then with water. After evaporation in ultrahigh vacuum product **22** (16 mg, 12 %) was obtained as a red solid (estimated purity of product ca. 95 %). $[\alpha]^{20}_D$ = +39.9 (c = 0.1, MeOH); ^1H NMR (700 MHz, CD_3OD): δ = 1.27 (s, 36 H, Me), 1.37 (s, 36 H, Me), 2.01–2.10 (m, 36 H, 2″-H, 5-H), 2.72–2.78 (m, 24 H, 1″-H), 2.95, 3.04 (AB part of ABX system, J_{AB} = 11.2 Hz, J_{AX} = 4.3 Hz, J_{BX} = 7.3 Hz, 24 H, 2-CH_2), 3.68 (dd, *J* = 5.8, 10.9 Hz, 12 H, 5-CH_2), 3.89 (dd, *J* = 5.8, 10.9 Hz, 12 H, 5-CH_2), 4.26 (m_c, 12 H, 2-H), 4.34 (m_c, 24 H, 3″-H), 4.37–4.41 (m, 12 H, 4-H), 4.67–4.73 (m, 12 H, 3-H), 7.74 (s, 12 H, 5′-H) ppm; signals that could not be assigned: δ = 1.03 (t, *J* = 7.5 Hz), 1.66 (m_c), 2.16 (s), 2.66 (s), 3.21–3.25 (m) ppm; ^{13}C NMR (176 MHz, CD_3OD): δ = 22.8 (t, C-1″), 23.7, 26.8 (2 q, Me), 29.4 (t, C-2″), 40.4 (s, C-5″), 49.7 (d, C-5), 61.7 (t, 2-CH_2), 62.4 (t, 5-CH_2), 67.5 (t, C-3″), 70.3 (d, C-3), 70.7 (s, C-6″), 72.0 (d, C-2), 73.1 (d, C-4), 77.5

(s, C-6), 124.1 (d, C-5′), 142.7, 146.9 (2 s, C-7′′, C-8′′), 147.3 (s, C-4′), 164.8 (s, C-4′′) ppm; IR (ATR): $\tilde{\nu}$ = 3380 (OH), 2930 (C–H), 1735 (C=O), 1560 (C=C), 1220–1040 (C–O–C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + 2\ Na]^{2+}$ calcd. for 0.5 ($C_{246}H_{288}N_{36}Na_2O_{72}$): 2473.4933, found 2473.4769; $[M + 3\ Na]^{3+}$ calcd. for 1/3 ($C_{246}H_{288}N_{36}Na_3O_{72}$): 1656.3247; found 1656.3151.

General Procedure for *O*-Sulfation: 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. The reaction mixture was cooled to 0 °C and a solution of NaOH or $NaHCO_3$ was added dropwise until the indicated pH value was reached. 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.

***O*-Sulfated Trivalent Compound 23:** Polyol **12** (16 mg, 0.015 mmol), SO_3•DMF (97 %, 64 mg, 0.40 mmol) and [D_7]DMF (0.7 mL) were stirred at room temperature overnight. After ^{1}H-NMR control, the reaction mixture was stirred for 5 d and each day a new portion of SO_3•DMF (64 mg) was added. A 0.5 M aqueous solution of NaOH was added dropwise until pH 9 was reached. The reaction mixture was then 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: 500–1000 Da). The product was filtered through a syringe filter affording **23** (30 mg, quant.) as a colorless solid. M. p. 290 °C (decomposition); $[\alpha]_D^{22}$ = +10.7 (c = 0.09, H_2O); ^{1}H NMR (700 MHz, D_2O): δ = 1.38, 1.48, 1.55, 1.56, 1.57 (5 s, 3 H each, Me), 1.61 (s, 6 H, CH_3), 1.62 (s, 3 H, Me), 2.42–2.48 (m, 1 H, 5-H^A), 2.50 (s, 3 H, CH_3), 2.77–2.84 (m, 3 H, 5-H^B), 3.11 (dd, *J* = 7.6, 10.6 Hz, 1 H, 2-CH_2^A), 3.24 (dd, *J* = 4.4, 10.6 Hz, 1 H, 2-CH_2^A), 3.62–3.64, 3.66–3.67, 3.73–3.75 (3 m, 2 H each, 2-CH_2^B), 3.76–3.78 (m, 1 H, 5-CH_2^A), 3.88 (m_c, 1 H, 5-CH_2^A), 4.29–4.32 (m, 4 H, 5-CH_2^B), 4.47–4.52 (m, 4 H, 2-H, 2-H^B), 4.55–4.66 (m, 4 H, CH_2), 4.83–4.89 (m, 4 H, 4-H, 4-H^B), 5.01–5.10 (m, 2 H, CH_2), 5.10–5.13, 5.23–5.26, 5.26–5.30, 5.30–5.33 (4 m, 1 H each, 3-$H^{A,B}$), 7.83, 7.96, 8.13, 8.26 (4 s, 1 H each, 5′-$H^{A,B}$) ppm; ^{13}C NMR (175 MHz, D_2O): δ = 9.7, 9.8, 22.27, 22.37, 22.42, 26.0, 26.1, 26.2 (8 q, Me), 44.0, 44.2, 44.3, 45.0 (4 d, C-$5^{A,B}$), 63.0, 63.2, 63.4 (3 t, CH_2), 65.7 (d, C-3^A), 66.6, 66.7 (2 t, 5-CH_2^A, 2-CH_2^A), 68.0 (d, C-2 ^{A}), 77.4 (d, C-4 ^{A}), 78.0 (s, C-6 ^{A}), 126.5 (d, C-5′$^{A\ or\ B}$) ppm; C-4′ of A and B and further signals from B-rings could not be assigned; a specific assignment of the signals to the B-rings and to the triazole units is not possible; IR (ATR): $\tilde{\nu}$ = 2960–2855 (C–H), 1465 (C=C), 1250 (C–O), 1130 (C–O–C, SO_3Na) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + 2\ Na]^{2+}$ calcd. for 0.5 ($C_{48}H_{69}N_{12}Na_9O_{43}S_9$): 1020.9963, found 1021.0006.

***O*-Sulfated Divalent Compound 24:** Compound **20** (21.5 mg, 0.031 mmol), SO_3•DMF (97 %, 57 mg, 0.37 mmol) and [D_7]DMF (1.4 mL) were stirred 24 h at room temperature. After ^{1}H-NMR control, SO_3•DMF (57 mg, 0.37 mmol) was added and stirring was continued for 72 h. Another batch of SO_3•DMF (226 mg, 1.48 mmol) was added and the mixture stirred for 72 h. ^{1}H-NMR control showed a homogeneous product. A 0.1 M aqueous solution of $NaHCO_3$ (0 °C, ca. 130 mL) was added under vigorous stirring until pH 7–8 was reached and the resulting mixture was frozen quickly by liquid nitrogen. After freeze-drying, the product was dissolved in water and purified by dialysis. The resulting product was again freeze dried affording **24** (27 mg, 66 %) as a greyish solid. M. p. > 250 °C (decomposition); $[\alpha]_D^{20}$ +8.25 (c = 0.8, H_2O); ^{1}H NMR (700 MHz, D_2O): δ = 1.36 (s, 6 H, Me), 1.41 (s, 6 H, Me), 1.98 (m_c, 4 H, 2′′-H), 2.61 (m_c, 2 H, 5-H), 2.76 (m_c, 4H, 1′′-H), 3.45 (m_c, 2 H, 2-CH_2), 3.49–3.56 (m, 2 H, 2-CH_2), 4.10 (m_c, 4 H, 5-CH_2, 5′′-H), 4.15 (m_c, 4 H, 3′′-H), 4.30 (m_c, 2 H, 5-CH_2), 4.66 (m_c, 2 H, 2-H), 4.87 (m_c, 2 H, 4-H), 5.06 (m_c, 2 H, 3-H), 7.81 (s, 2 H, 5′-H) ppm; signals of impurities that could not be assigned: δ = 1.84 (td, *J* = 6.9, 13.8 Hz), 3.25–3.29 (m), 4.04–4.07 (m); ^{13}C NMR (176 MHz, D_2O): δ = 21.0 (t, C-1′′), 22.3 (q, Me), 26.0 (q, Me), 27.4 (t, C-2′′), 30.9 (t, C-5′′), 44.0 (d, C-5), 65.3 (t, 2-CH_2), 65.5 (t, 5-CH_2), 65.7 (t, C-3′′), 66.5 (d, C-3), 67.9 (d, C-2), 77.2 (d, C-4), 77.9 (s, C-6), 124.4 (d, C-5′), 147.2 (s, C-4′), 169.1 (s, C-4′′) ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd. for $C_{31}H_{44}N_6Na_6NaO_{30}S_6$: 1332.9705, found 1332.9747.

***O*-Sulfation of Fullerene Derivative 22:** Compound **22** (10.0 mg, 2.04 µmol), SO_3•DMF (97 %, 22.5 mg, 147 µmol) and [D_7]DMF (0.7 mL) were stirred for 24 h at room temperature. After ^{1}H-NMR control, SO_3•DMF (22.5 mg, 147 µmol) was added and stirring was continued for 72 h. Another batch of SO_3•DMF (113 mg, 738 µmol) was added and the mixture stirred for 72 h. ^{1}H-NMR control showed a homogeneous product. A 0.1 M aqueous solution of $NaHCO_3$ (0 °C, ca. 130 mL) was added under vigorous stirring until pH 7–8 was reached and the resulting mixture was frozen quickly by liquid nitrogen. After freeze drying the product was dissolved in water and purified by dialysis (72 h). The resulting product was again freeze-dried affording 36 mg of an orange solid (17.5 mg = 100 %), that apparently contains considerable amounts of $NaHCO_3$ and Na_2SO_4. ^{1}H NMR (700 MHz, CD_3OD): δ = 1.36 (s, 36 H, Me), 1.41 (s, 36 H, Me), 1.93–2.12 (m, 36 H, 2′′-H, 5-H), 2.60 (m_c, 12 H, 1′′-H), 2.68–2.82 (m, 12 H, 1′′-H), 3.38–3.45 (m, 12 H, 2-CH_2), 3.55 (m_c, 12 H, 2-CH_2), 4.11 (m_c, 12 H, 5-CH_2), 4.28–4.40 (m, 36 H, 3′′-H, 5-CH_2), 4.67 (m_c, 12 H, 2-H), 4.87 (m_c, 12 H, 4-H), 5.09 (m_c, 12 H, 3-H), 7.87 (s, 12 H, 5′-H) ppm; the ^{13}C-NMR spectrum shows very broad signals (see Supporting Information).

SPR Measurements: Experiments were performed on Biacore X and Biacore X100 instruments (GE Healthcare, Freiburg, Germany) at 25 °C using a sensor chip SA (GE Healthcare). For further details, see Supporting Information.

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