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Neoglycopolymer Inhibitors of the Selectins

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Abstract: The selectin class of proteins plays an important role in the inflammatory response. These proteins, which bind saccharide ligands, facilitate the recruitment of leukocytes to the inflamed endothelium. The ring-opening metathesis polymerization (ROMP) has been used to generate synthetic multidentate ligands, which display multiple copies of sulfated saccharide residues. By altering the structure of the appended saccharide residues, multivalent ligands that selectively target one member of the selectin family, P-selectin, were created. The biological activities of materials prepared from the same monomer unit varied, depending on the method of polymer preparation. This result suggests that polymers containing more repeat elements exhibit higher selectin inhibitory activities. © 1997 Elsevier Science Ltd.

Introduction

A number of essential biological processes, such as the inflammatory response, lymphocyte homing, and fertilization depend on protein–carbohydrate recognition.[1] The interaction of proteins with saccharides also facilitates a variety of pathogenic events, including bacterial and viral infection and tumor metastasis. Given the involvement of protein – saccharide complexes in a variety of physiologically and medically important functions, strategies to modulate such interactions are required.[2]

The importance of developing methods to manipulate protein-saccharide interactions was accentuated by the discovery of the selectin family of carbohydrate-binding proteins.[3] The selectins are cell adhesion molecules that assist in mediating the recruitment of leukocytes to the endothelium, a critical step in inflammation.[4] There are three members of the selectin family, E-, P-, and L-selectin (Figure 1), which mediate essential initial steps in both the inflammatory response and the trafficking of lymphocytes between the lymph and the blood. Although they share structural homology, each is regulated differently. As a result, it is not surprising that these proteins fulfill overlapping roles in the inflammmatory response, yet their functions are not identical.[3] The ability to selectively inhibit each of

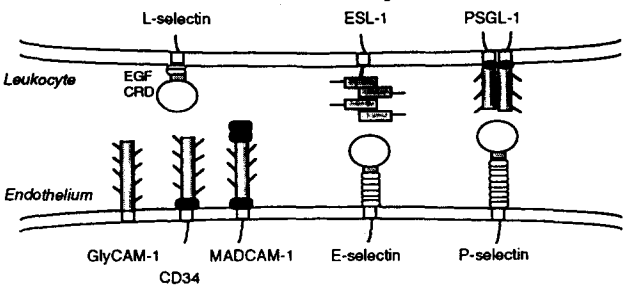


Figure 1. The selectins and their ligands.

the selectins would facilitate the analysis of their separate activities and pave the way for the development of new therapeutic strategies for the treatment of inflammatory conditions.

Although the biologically relevant ligands for the selectins are not known, physiological glycoproteins that bind tightly to the selectins have been identified (Figure 1). Several of these glycoproteins, such as the L-selectin binding protein GlyCAM-1[5,6] and the P-selectin ligand PSGL-1,[7,6b] are decorated with the sialyl Lewis x [sLe^x: NeuNAcα2→3Galβ1→4(Fucα1→3) GlcNAc] epitope **1** (Figure 2). All three of the selectins can bind the tetrasaccharide sLe^x,[8] but they do so weakly. For example, various measurements of the dissociation constant for sLe^x binding to E-selectin place it between 100 μM and 1 mM.[9] The weak interaction between the tetrasaccharide sLe^x and the selectins contrasts with the strong interactions that occur with the physiological selectin ligands. The differences indicate that other features of these glycoprotein ligands also enhance the strength of their interactions with the selectins.

One feature of these physiological ligands that may affect binding is that they present multiple copies of their saccharide determinants to the selectins. In our previous studies of protein – saccharide interactions, we demonstrated that the ring-opening metathesis polymerization (ROMP) can be used to synthesize multivalent saccharide derivatives with high functional affinities.[10-12] Moreover, we found that these multivalent ligands can give rise to both increased functional affinity and increased specificity.[10,11] Here, we have applied those principles to generate selectin inhibitors that selectively target one of the members of this receptor family, P-selectin. In addition, we demonstrate that the method of multivalent ligand preparation significantly affects the inhibitory potencies of the resulting materials.

Design and Preparation of Multivalent Selectin Ligands

Several strategies for generating high affinity selectin inhibitors have been pursued, and these studies indicate that multidentate ligands can effectively block the selectins.[13-15] For example, liposomes with anionic saccharides displayed on their surface were potent inhibitors of P-selectin binding.[13] The anionic groups incorporated into the liposomes were critical for their inhibitory activity against P-selectin; however, the specificity of these liposomes, which can reorganize to create different displays of charge and saccharide spacings to faciliate protein binding, was not reported. Another type of synthetic multivalent selectin ligand consists of acrylamide copolymers bearing sLe^x (**1**, Figure 2) or related saccharides.[14] As in the case of the liposomes, the selectivities of these ligands for targeting particular proteins have not been described. Results from these studies and related studies indicate that effective multivalent selectin inhibitors can be synthesized, but additional information is needed to sort out the mechanism(s) underlying the increased efficacies of multidentate ligands for the selectins.

An alternative method for the synthesis of multivalent saccharide derivatives is ROMP. The application of ROMP to the creation of saccharide arrays is attractive for several reasons. First, ROMP catalysts have been generated that tolerate monomers with unprotected polar functionality.[12,16] This

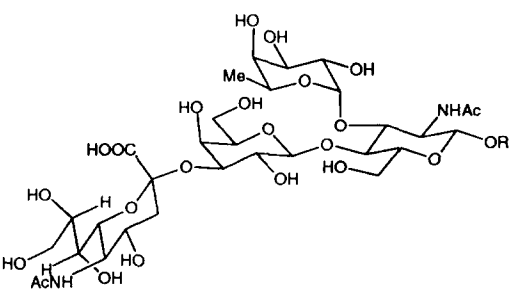


Figure 2. The selectin ligand, sialyl Lewis x: **1**

feature is critical for our purposes because many biologically relevant saccharide determinants contain sulfate groups, which cannot easily be masked. Second, well-defined catalysts, such as $[(Cy)_3P]_2Cl_2Ru{=}CHPh$,[16b] can afford living polymerizations. Living polymerizations are those in which termination does not compete effectively with elongation.[17] For such a process, if the rate of initiation exceeds the rate of propagation, polymers of specific lengths with narrow polydispersities can be generated. Materials of different lengths would be useful for exploring the molecular features of multivalent ligands that give rise to their increased activities. Third, this polymerization process can also be used to generate block copolymers, which could be useful to modulate the immunogenicity of a particular material or to target it to particular cell type. Fourth, with the many metal alkylidene catalysts, specific endlabels can be introduced for detection or immobilization. Thus, we set out to explore the utility of ROMP for the creation of oligomeric molecules that selectively inhibit the selectins.[11]

The design of our monomer targets was guided by the mechanistic features of ruthenium-catalyzed ROMP and information about the saccharide recognition properties of the selectins. For the strained alkene scaffold, norbornene and oxanorbornene templates were selected for their reactivity properties in ROMP. These templates possess complementary features: the norbornene is more reactive and the oxanorbornene generates more hydrophilic materials, so both were examined.[18] In the case of the bicyclo[2.2.1] systems, the *endo* isomer is a less reactive ROMP substrate than the *exo*, an observation that is attributed to chelation of the substituents with the metal center in the propagating species.[17,19] Thus, the templates were designed to bear a saccharide substituent in the *exo* orientation. Our choice for the saccharide recognition elements was influenced by a desire to use residues that possessed important features of naturally occurring ligands and could be readily synthesized in large quantities. The carbohydrates chosen, 3-sulfo galactose and 3,6-disulfo galactose, were inspired by the features of two distinct multivalent selectin ligands: sulfatides[20] and GlyCAM-1[6].

Sulfatides, such as **2**, are glycolipids containing 3-sulfo galactose residues, and these compounds bind to both L- and P-selectin.[20] Because monovalent 3-sulfo galactose derivatives are not effective ligands, sulfatide micelles or other aggregates are the likely selectin-binding species. This analysis led us to hypothesize that polymers possessing multiple 3-sulfogalactose groups might effectively inhibit L- and P-selectin; therefore, compounds **3** and **4** were selected as monomer targets.

Impetus to synthesize the related monomers **5** and **6** was derived from our investigations of the selectin binding properties of the GlyCAM-1 determinant 6'-sulfo sLe^x [NeuNAcα2→3(6-O-SO_3)Galβ1→4(Fucα1→3)GlcNAc] **7** (Figure 3).[21] To determine the importance of sulfation at the 6' position, we synthesized a series of monovalent sulfated Lewis a [Le^a: Galβ1→3 (Fucα1→4)GlcNAc] and Le^x derivatives and evaluated their abilities to inhibit selectin function.[21c,d] One particular member of this series, 3',6'-disulfo Le^a(Glc)-OPr (**8**, Figure 3), displayed a 4-fold increase in potency for P-selectin relative to the monosulfate derivative 3'-sulfo Le^a(Glc)-OPr.[21d] No differences in L-selectin binding were observed when the mono- and disulfate derivatives were compared.[21c,d] Thus, we reasoned that neoglycopolymers displaying the disulfated saccharide substituents might bind with increased specificity to P-selectin.To explore whether multivalent display of a galactose residue containing sulfates at the 3 and 6 positions would provide higher selectivity, we synthesized compounds **5** and **6**. These derivatives contain the 3,6-disulfogalactose residue, which presents anionic groups in a manner similar to that of the GlyCAM-1 capping structure **7**.

The saccharide recognition elements were generated using a strategy that minimized protecting group manipulations.[11] Glycosylation of galactose pentaacetate with azidoethanol furnished the desired β-linked galactose derivative **9** after removal of the acetate protecting

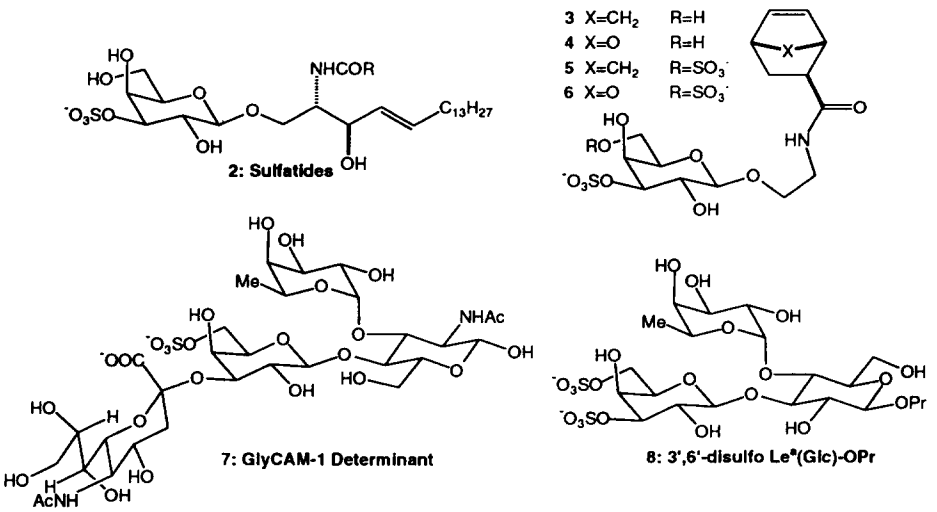


*Figure 3.*The design of monomers **3-6** is based on the charge distribution of the naturally-occuring glycolipid **2** and saccharide epitope **7**

groups. To activate the hydroxyls targeted for sulfation, organostannane complexation was employed. The 3,6-disulfo galactose derivative was generated by stannylation with dibutyltin oxide followed by sulfation with pyridine-sulfur trioxide complex. The sulfation reaction proceeded in high yield, and only the 3,6-disulfo galactose product **10** was obtained. In contrast, the 3-monosulfate **11** could not be prepared by direct reaction of the stannylene acetal with a sulfating reagent; therefore, a variation on the original strategy was employed. Treatment of the tetraol with phenyl boronic acid provided the necessary transient protection through formation of the 4,6 phenylboronate.[22] Subsequent reaction of the alkoxy stannane complex derived from the intermediate boronate with trimethylammonium-sulfur trioxide complex afforded the 3-sulfate **11** in high yield. Reduction of the azide group provided a handle with which to attach the saccharide derivatives to the desired polymerization template.

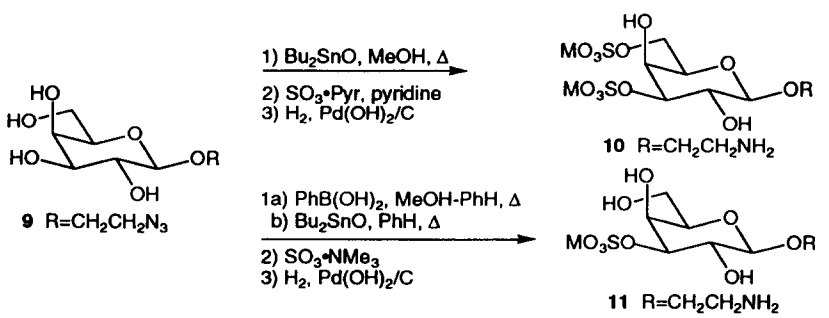


Figure 4. Scheme depicting routes to sulfated galactose derivatives **10** and **11**.

To prepare the bicyclic substrates for ROMP, the scaffolds for carbohydrate attachment were generated from Diels-Alder adducts. In the case of the 7-oxanorbornene system **13**, the desired *exo* adduct was generated by the zinc iodide-catalyzed reaction of furan and methyl

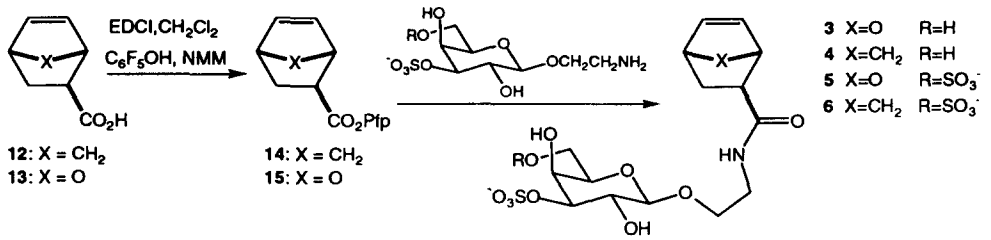


Figure 5. Synthetic route to monomers for ROMP that possess sulfated galactose residues.

acrylate.[23] For the synthesis of the norbornene scaffold, the *endo* isomer derived from reaction of cyclopentadiene with methyl acrylate was epimerized with sodium methoxide to afford an inseparable mixture of isomers (3:2 *exo* to *endo* ratio). Carboxylic acid **12** was isolated after removal of the *endo* adduct facilitated by iodolactonization and subsequent hydrolysis of the *exo* ester group.[24] Attempts to directly couple sulfated aminoglycoside derivatives **10** and **11** to the oxabicyclic acid **13** were unsuccessful, a result that could be attributed to the instability of the activated ester intermediates.[18] Attachment of the amine-substituted saccharide derivative to the template was achieved through the intermediacy of the pentafluorophenol ester.[18] This coupling method was used to generate the monomers **3-6** as a mixture of diastereomers.

Because our studies would benefit from many of the features of controlled ROMP, we opted to explore the reactivity of the defined, reactive ruthenium $[(Cy)_3P]_2Cl_2Ru{=}CHPh$ catalyst[16b] toward sulfated monomers. Our first generation studies applying ROMP to generate saccharide-substituted polymers employed $RuCl_3$;[10] however, many unique features of ROMP, such as the ability to generate polymers of different lengths, can not be accessed using undefined catalysts generated *in situ*. ROMP of sulfated substrates had not been investigated with any type of catalyst. One anticipated difficulty in such polymerization reactions is the solubility differences between the monomer and the catalyst. Consequently, we examined the polymerization reactions under both homogeneous and emulsion conditions.

In our initial investigations using sulfated substrates, we conducted the polymerizations in a mixture of methanol-dichloromethane using the triethylammonium salts of the monomers to solubilize these anionic substrates. A solution of the catalyst in dichloroethane was added to a

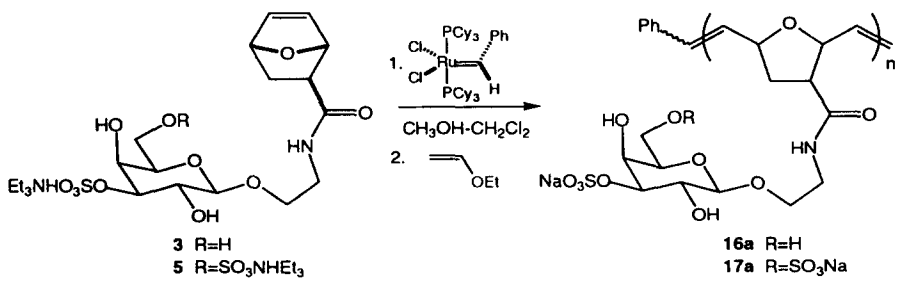
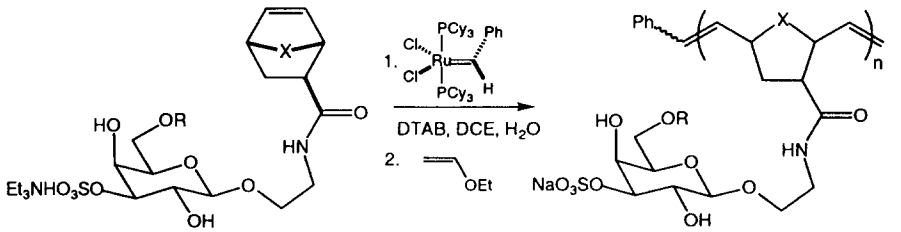


Figure 6. Homogeneous conditions for ROMP using a defined ruthenium carbene catalyst.

mixture of the monomer, and the polymerization reactions were allowed to proceed at 65 °C. Even with extended reaction times, the conversion of monomer to polymer was not complete with substantial amounts of monomer remaining. Despite these difficulties, oxanorbornene-derived polymers **16a** and **17a** were synthesized by this approach. The observation that a solid formed during the course of the reactions provides insight into the factors leading to incomplete polymerization: the growing polymer chains appeared to become increasingly insoluble as the reaction progressed. Because the monomer substrates were not fully consumed in these reactions, the polymerization reactions conducted under these conditions cannot be living. With the concomitant changes in solubility brought about by polymer growth, termination processes appear to compete favorably with elongation steps. Thus, a polymer produced under these conditions is likely to have a broad molecular mass distribution.

The features of the polymerization reactions in organic solutions led us to explore other conditions in our pursuit of a living polymerization process for monomers with anionic saccha-



3 X=O R=H
4 X=CH_2 R=H
5 X=O R=SO_3HNEt_3
6 X=CH_2 R=SO_3HNEt_3

16e X=O R=H
17e X=CH_2 R=H
18e X=O R=SO_3Na
19e X=CH_2 R=SO_3Na

Figure 7. ROMP conducted under emulsion conditions using a defined ruthenium carbene catalyst.

ride residues. The ruthenium carbene-promoted oligomerization of polar uncharged monomers recently had been accomplished using emulsion polymerizations,[16c] providing us with the impetus to examine similar conditions with our substrates. Thus, the triethylammonium salts of the monomers were dissolved in water in the presence of the emulsifier dodecyl trimethylammonium bromide (DTAB), and a solution of the catalyst was added to this mixture. When these emulsion conditions were applied to the synthesis of polymers **16e-19e**, the reactions occurred rapidly with almost complete consumption of the monomer. In contrast to what had been observed in the reactions conducted in mixed organic solvents, no visible precipitation of the polymer occurred. Overall, these reactions were efficient with the isolated yields of the final materials diminished by the challenges of polymer purification.

Selectin Inhibitor Activities of the Neoglycopolymers

The polymers generated from both methods were tested for their ability to block the binding properties of L, P, and E-selectin. The concentration of saccharide residues required to suppress the binding of immobilized recombinant selectin fusion proteins to a myeloid cell line (HL-60) was determined for each of the polymers.[26] To provide an alternative evaluation of polymer activity, the ability of the synthetic materials to prevent the binding of L- or P-selectin derivatized polystyrene beads to immobilized heparin was also tested. Heparin interacts only with P- and L-selectin, and the physiological relevance of these interactions has not been deter-

mined.[27] This latter assay, however, can be used to distinguish specific inhibition of the selectins from non-specific effects on the HL-60 cells. For all new synthetic materials, the relative activities found for P- and L-selectin in the heparin assay were consistent with those obtained in the cell binding assay.[28]

Compound	P-selectin (IC_{50} mM)	L-selectin (IC_{50} mM)	E-selectin (IC_{50} mM)
16a	2.2	75% @ 3.0	2.9
17a	0.084	1.7	90%@ 3.0
sLe^x	3.4 + 0.27	3.5 + 0.18	3.3 +0.17

Table 1. Inhibitory activity of polymers prepared under homogeneous conditions in the HL60 cell assay. In cases in which IC_{50} values are not available, the percent inhibtion at a particular concentration is provided.

Polymers **16a** and **17a**, prepared from reaction under homogeneous conditions, exhibited significant inhibitory activities toward all three selectins. As expected, no selectin inhibitory activity was observed in either assay for monomers **3** or **5**. In contrast, polymer **16a**, which presents 3-sulfated galactose substituents, had significant inhibitory activity with all three of the selectins in the HL60 cell assay (Table 1). The concentration of saccharide residues needed to block 50% of the selectin binding activity was comparable to that obtained for sLe^x. These results indicate that the polymers are more effective on a molar basis than is the monovalent tetrasaccharide sLe^x. This finding is consistent with our expectation that these materials might behave like sulfatides.

Interestingly, polymer **17a**, possessing the 3,6-disulfo galactose residues, was more effective in targeting P-selectin than the other family members. Although this material showed activity toward E- and L-selectin, it was a potent inhibitor of P-selectin.[29] The observation that this compound targets P-selectin is consistent with our predictions. Because 3',6'-disulfo Le^a(Glc)-OPr **8** is a more effective inhibitor of P-selectin than is the corresponding 3'-monosulfate derivative, we expected that a multivalent display of 3,6-disulfated galactose residues might afford a specific P-selectin blocking agent. The activity found for **17a** lends support to this hypothesis. Material **17a** is a not only a more potent inhibitor of P-selectin than the monosulfate analog **16a**, it exhibits a 20-fold preference for binding P- versus L-selectin. These results highlight how information about small changes in monovalent binding specificity can be used to generate more potent and selective ligands for saccharide binding proteins.

Polymers produced under the emulsion conditions, compounds **16e-19e**, showed similar trends in their selectin binding activities; however, these materials were generally less potent than polymers, **16a** and **17a**, generated under homogenous conditions. For example, none of the oligomers produced under emulsion conditions were very effective inhibitors of L- and E-selectin (Table 2). They still displayed, however, reasonable potency toward P-selectin. Although the galactose monosulfate-substituted polymers were only moderate inhibitors of P-selectin, the disulfated polymer was a potent, selective P-selectin inhibitor with an IC_{50} value 500 fold lower than that of sLe^x. Specifically, the disulfated

Compound	P-selectin (IC_{50} mM)	L-selectin (IC_{50} mM)	E-selectin (IC_{50} mM)
16e	7.8	0% @ 20.0	20
17e	1.2	0% @ 20.0	0% @ 20.0
18e	13% @ 20.0	13% @ 20.0	13% @ 20.0
19e	0.17	18	58% @ 20.0

Table 2. Inhibitory activity of polymers prepared under emulsion conditions in the HL60 cell assay. In cases in which IC_{50} values are not available, the percent inhibtion at a particular concentration is provided.

polymers displayed a preference greater than 100-fold for blocking P- over L-selectin (Table 2). It should be noted that the emulsion conditions produced polymers that were more selective in their ability to discriminate between members of the selectin family.

The increased potency of the polymers prepared in organic solution relative to those generated under emulsion conditions is unexpected, and further studies are needed to identify the molecular features responsible for these differences. One potential origin for the differences in efficacies for polymers **16a** and **17a** relative to **16e** and **17e** may lie in the variant populations of polymers produced. Because the polymerizations conducted under homogeneous conditions are not living, the products are likely to be more polydisperse and contain higher molecular weight species. In contrast, the emulsion polymerizations, in which high ratios of catalyst to monomers were employed, are more apt to afford materials of narrower polydispersity and lower average molecular mass. Thus, one interpretation is that higher molecular weight polymers, which were produced by ROMP in organic solvents, are more effective selectin blocking agents. Consequently, the conditions of polymerization can be used to alter the affinity and the specificity of a bio-active material for its target receptor. Further experiments exploring this facet of multivalent interactions in selectin recognition may provide insight into the features governing binding affinity and specificity as well as provide new leads for the generation of agents that target saccharide-binding proteins.

Conclusion

We have demonstrated that ROMP can be used to create biologically active multivalent inhibitors. Selective and potent inhibitors can be generated in a single oligomerization step from simple starting materials. The ability of polymers bearing 3,6-disulfo galactose residues to specifically target P-selectin relative to those bearing a 3-monosulfated galactose determinant indicates that ROMP can be used to generate potent and specific inhibitors of target proteins. Marked differences in the selectin inhibitory activities of oligomers synthesized under different conditions indicate that ROMP can be used to modulate the affinity of a particular ligand for its target. Wide ranging applications for saccharide-derived materials prepared by ROMP include probing of cell surface interactions, blocking medically significant cell adhesion and cell recognition events, and facilitating physiological processes triggered by aggregation of cell surface receptors.

Acknowledgements

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Experimental Materials and Methods

Reactions were carried out in oven-dried glassware under an argon atmosphere, except where otherwise noted. All materials, unless otherwise noted, were obtained from commercial suppliers and used as provided. Reaction solvents were freshly distilled from sodium-benzophenone ketyl (benzene), calcium hydride (dichloromethane, pyridine, triethylamine, dimethylformamide), or magnesium metal (methanol). ACS grade 1,2-dichloroethane and 1,3-

dimethylimidazolidin-2-one were used as purchased. Solvents used in polymerization reactions were deoxygenated with a minimum of three freeze-pump-thaw cycles prior to use, except where otherwise noted. Chromatography solvents were ACS grade; dichloromethane and hexanes were distilled. Analytical thin layer chromatography (TLC) was performed on 0.25 mm precoated silica gel plates (60F-254), and flash chromatography on silica gel-60 (230-400 mesh). DEAE Cellulose anion exchange resin was swelled in 0.5M $Et_3NH_2CO_3$ buffer and rinsed with excess water to remove the buffer prior to use. Sephadex cation exchange resins were prepared by equilibrating in 0.5M NaCl, followed by washing with approximately ten column volumes of water. Ten column volumes of water was used to wash the size exclusion resin prior to use.[30] ^1H and ^{13}C NMR spectra were recorded on Bruker AC-300 (purchased with support by NIH 1S10 RR08389) or AM-500 (purchased with support from NSF CHE-8306121) or on a Varian Unity 300 or 500 spectrometers (supported by NSF CHE-8813550 and NIH 1S10 RR04981, respectively), and chemical shifts are reported downfield from tetramethylsilane in parts per million (δ). ^1H NMR data are assumed to be first order with apparent doublets and triplets reported as d and t, respectively. Resonances that appear broad are designated as br. Infrared spectra were recorded on a Mattson FTIR spectrometer and mass spectra on a VG AutoSpec M (LSIMS) or Kratos MS-80RFA (EI).

(2-Azidoethyl)-3,6-O-disulfo-β-D-galactopyranoside (10)

Tetraol **9** (297 mg, 1.19 mmol) and dibutyltin oxide (329 mg, 1.32 mmol) were combined with anhydrous methanol (12 mL), and the resulting solution was heated to reflux. After the solution became clear (*ca.* 1 h), the methanol was removed under reduced pressure, and the alkoxy stannane was dried overnight under vacuum. Pyridine sulfur trioxide complex (480 mg, 3.02 mmol) and the alkoxy stannane were dissolved in pyridine (12 mL). The mixture was stirred until the starting material appeared to be consumed as judged by TLC (*ca.* 4 h). Excess methanol (*ca.* 1 mL) was added to quench any residual sulfating agent, and the solvent mixture was evaporated under reduced pressure. The crude sulfated product was dissolved in water (10 mL) and purified by anion exchange chromatography [DEAE Cellulose (fast flow), 0 to 0.25 M $Et_3NH_2CO_3$, linear gradient]. Fractions were analyzed by thin layer chromatography. The appropriate fractions were concentrated to afford the triethylammonium salt of the sulfated azidoglycoside (538 mg, 0.854 mmol). A portion of the sulfated azidoglycoside (460 mg, 0.731 mmol; Et_3NH^+ salt) was dissolved in a 1 : 1 mixture of methanol-water, and the resulting solution was subjected to hydrogenation (50 PSI H_2, 20% $Pd(OH)_2$/carbon). The sulfated aminoglycoside was isolated by filtration of the mixture through Celite with a water eluent, and the resulting filtrate was purified by anion exchange chromatography [DEAE Cellulose (fast flow), 0 to 0.25 M $Et_3NH_2CO_3$, linear gradient]. Fractions were monitored by thin layer chromatography. TLC plates were visualized by a ninhydrin stain. The appropriate fractions were concentrated, and the resulting material passed through cation exchange resin (Sephadex-SP C-25, Na^+ form, H_2O eluent) to afford sulfated aminoglycoside **10** (306 mg, 0.716 mmol) as a white solid. Yield: 71%; ^1H NMR (300 MHz, D_2O) δ 4.65 (d, J = 8 Hz, 1 H), 4.45-4.41 (m, 2 H), 4.29 (d, J = 6 Hz, 2 H), 4.22-4.07 (m, 3 H), 3.78 (t, J = 8 Hz, 1 H), 3.39-3.32 (m, 2 H); ^{13}C NMR (75 MHz, D_2O) d 103.4, 80.8, 73.6, 69.8, 68.6, 67.8, 67.4, 40.7; IR (KBr) 3590-2962 (br), 1645, 1598 cm^{-1}; mass spectrum (LSIMS, 3-NBA) *m/z* 382.0 [M^{2-} + H^+, calcd for $C_8H_{16}O_{12}N_1S_2$ 382.0].

Azidoethyl 3-O-sulfo-β-D-galactopyranoside (11)

Phenyl boronic acid (82.2 mg, 0.674 mmol) and tetraol **9** (151 mg, 0.606 mmol) were dissolved in methanol (1 mL), and the resulting solution was diluted with benzene (5 mL). The reaction was fitted with a Dean-Stark apparatus, and the solvent concentrated to *ca.* 1 mL by distillation. An additional portion of benzene was added (5 mL), and the mixture concentrated to *ca.* 1 mL by distillation over an hour. The reaction was then evaporated to dryness under

reduced pressure. To the residue, dibutyltin oxide (167 mg, 0.672 mmol) and benzene (5 mL) were added, and the Dean-Stark apparatus was reattached. After the resulting solution was refluxed for 2 h, the solvent was concentrated to *ca.* 1 mL by distillation. An additional portion of benzene (5 mL) was added, concentrated by distillation to *ca.* 1 mL, and the resulting mixture was concentrated to dryness under reduced pressure to afford the alkoxy stannane derivative. Trimethylamine sulfur trioxide (105 mg, 0.754 mmol) was added to a solution of the alkoxy stannane in 1,3-dimethylimidazolidin-2-one (7.4 mL). After 12 h, the reaction was quenched with methanol (1 mL), diluted with water (5 mL), then extracted with ether (3 x 5 mL). The aqueous layer was purified by anion exchange chromatography [DEAE Cellulose (fast flow), 0 to 0.25 M $Et_3NH_2CO_3$ linear gradient]. Fractions were analyzed by thin layer chromatography. The appropriate fractions were concentrated to afford the sulfated azidoglycoside. The sulfate was dissolved in a 1 : 1 mixture of methanol-water (1 mL), and the resulting solution was subjected to catalytic hydrogenation (50 PSI H_2, 20% $Pd(OH)_2$/carbon). The sulfated aminoglycoside was isolated by filtration of the mixture through Celite with a water eluent, and the filtrate was passed through cation exchange resin (Sephadex-SP C-25, Na^+ form, H_2O eluent) to generate the sodium salt. The sulfated aminoethylglycoside **11** (1.137 g, 3.50 mmol) isolated was a white amorphous solid. Yield: 77 %; ^1H NMR (300 MHz, D_2O) δ 4.58 (d, *J* = 8 Hz, 1 H), 4.35 (dd, *J* = 10, 3 Hz, 1 H), 4.31 (d, *J* = 3 Hz, 1 H), 4.16 (dt, *J* = 12, 5 Hz, 1 H), 3.99 (dt, *J* = 12, 5 Hz, 1 H), 3.83-3.76 (m, 3 H), 3.73 (dd, *J* = 10, 8 Hz, 1 H), 3.29 (t, *J* = 5 Hz, 2 H); ^{13}C NMR (75 MHz, D_2O) d 103.3, 81.1, 75.9, 69.9, 67.9, 66.9, 62.0, 40.6; IR (KBr) 3487 (b), 2933 (b), 2519, 1635 cm^{-1}; mass spectrum (LSIMS, 3-NBA) *m/z* 302.0 [M - Na^+, calcd for $C_8H_{16}O_9N_1S_1$ 302.1].

Bicyclo[2.2.1]hept-5-ene-exo-2-carboxylic acid (12)

Cyclopentadiene (25 mL, 0.304 mmol) and methyl acrylate (30.1 mL, 0.335 mmol) were dissolved in dichloromethane (30 mL), and the solution maintained at reflux for 24 hours. The reaction solvent was concentrated under reduced pressure, and the resulting crude product was dissolved in a sodium methoxide solution (5.3 g Na(s) in 80 mL methanol). This solution was maintained at refluxing temperature, and aliquots of the solution were periodically taken and analyzed by ^1H NMR. Integration of the ester methyl groups indicated a thermodynamic product ratio of 3:2 *exo:endo* isomers was obtained after *ca.* 4 h. Methanol was removed by concentration under reduced pressure. The resulting residue was dissolved in water (50 mL), and the solution was heated to reflux until the methyl ester had been transformed into the acid as judged by TLC. The basic solution was cooled, and extracted with diethyl ether (2 x 25 mL) to remove dicyclopentadiene. The aqueous solution was acidified with 5 N sulfuric acid and extracted with ether (3 x 25 mL). The combined ether extracts were washed with cold water (1 x 25 mL), and dried (Na_2SO_4).

To separate the acid isomers, an iodolactonization reaction was carried out. The acid mixture was dissolved in a solution of sodium bicarbonate (28.8g) in H_2O (460 mL). An addition funnel was attached, and a solution of iodine (25.2 g) and potassium iodide (53.2 g) in H_2O (150 mL) was added dropwise until a dark brown color persisted. The aqueous solution was extracted with diethyl ether (5 x 200 mL) to remove the iodolactone. A 10 % sodium thiosulfate solution was added to the aqueous phase to decolorize the solution (*ca.* 50 mL). The resulting aqueous layer was brought to pH 2 by slow addition of 1 N sulfuric acid. A precipitate was observed that presumably contained sulfur byproducts. The resulting mixture was extracted with diethyl ether (4 x 150 mL), and the aqueous solution was readjusted to pH 2 after each extraction. The diethyl ether extracts were combined, dried (Na_2SO_4), and filtered through Celite. The resulting filtrate was concentrated to afford a pale yellow crystalline solid (18.2 g, 0.132). A portion of the solid was precipitated from cold pentane (-78 °C) to provide pure *exo* acid **12** (7.84 g, 0.0568 mmol) as a white solid. Yield: 43 % (crude); ^1H NMR (300 MHz, $CDCl_3$) δ

6.15-6.11 (m, 2 H), 3.09 (bs, 1 H), 2.92 (bs, 1 H), 2.27-2.22 (m, 1 H), 1.93 (dt, *J* = 12, 4 Hz, 1 H), 1.52 (d, *J* = 10 Hz, 1 H), 1.42-1.35 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) d 182.9, 138.1, 135.7, 46.7, 46.4, 43.2, 41.6, 30.3.

Pentafluorophenyl oxabicyclo[2.2.1]hept-5-ene-exo-2-carboxylate (15)

Carboxylic acid **13** (412 mg, 2.94 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (676 mg, 3.53 mmol) and pentafluorophenol (692 mg, 3.76 mmol) were dissolved in dichloromethane (6 mL) at 0 °C, and the resulting solution was warmed slowly to room temperature overnight. The reaction mixture was filtered through silica gel (30% diethyl ether in hexane). Concentration of the solvent afforded the ester (906 mg, 2.96 mmol) contaminated with pentafluorophenol (detected by ^{19}F NMR) and a retro Diels-Alder product (20:1 ester to retro). The concentrate was crystallized from hexane (-20 °C) to provide pure racemic **15** (540.1 mg, 1.77 mmol) as wooly fibers. Yield: 60 %; ^{1}H NMR (300 MHz, $CDCl_3$) d 6.48 (dd, *J* = 17, 2 Hz, 1 H), 6.46 (dd, *J* = 17, 2 Hz, 1 H), 5.35 (Br s, 1 H), 5.18 (d, *J* = 4 Hz, 1 H), 2.79 (dd, *J* = 8, 4 Hz, 1 H), 2.29 (dt, *J* = 12, 4 Hz, 1 H), 1.75 (dd, *J* = 12, 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) d 170.0, 142.8, 141.1, 139.5, 137.5, 136.1, 134.4, 125.2, 81.0, 78.1, 42.6, 29.6; IR (KBr) 3145, 3100, 3016, 2971, 2871, 2667, 2459, 1778, 1656, 1529 cm^{-1}; mass spectrum (LSIMS, 3-NBA) *m/z* 307.1 [M + H$^+$, calcd for $C_{13}H_8O_3F_5$ 307.0].

Pentafluorophenyl bicyclo[2.2.1]hept-5-ene-exo-2-carboxylate (14)

Carboxylic acid **12** (510 mg, 3.70 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (769 mg, 4.01 mmol) and pentafluorophenol (762 mg, 4.14 mmol) were dissolved in dichloromethane (10 mL) at 0 °C, then 4-dimethylaminopyridine (30.0 mg, 0.246 mmol) was added. The starting material was consumed (as judged by TLC). The reaction mixture was filtered through silica gel (30% diethyl ether/hexane). Concentration of the solvent afforded ester **14** (1.08 g, 3.55 mmol) as a colorless oil. Yield: 96%; ^{1}H NMR (300 MHz, $CDCl_3$) d 6.19 (dd, *J* = 15, 3 Hz, 1 H), 6.17 (dd, *J* = 15, 3 Hz, 1 H), 3.25 (Br s, 1 H), 3.01 (Br s, 1H), 2.57 (ddd, *J* = 9, 4, 1.5 Hz, 1 H), 2.05 (dt, *J* = 12, 4 Hz, 1 H), 1.57-1.44 (m, 3 H).

Aminoethyl 3-O-sulfo-β-D-galactopyranosyl oxabicyclo[2.2.1]hept-5-ene-exo-2-carboxamide (3).

Sulfate **11** (318 mg, 0.913 mmol) and pentafluorophenyl ester **15** (336 mg, 1.10 mmol) were dissolved in amine-free dimethylformamide (3 mL) and *N*-methylmorpholine (200 μL). After stirring for 3 h, the reaction was diluted with water (3 mL), and the aqueous layer was extracted with ethyl acetate (3 x 1 mL) to remove soluble organics. The aqueous phase from the extraction was loaded onto anion exchange resin and purified by anion exchange chromatography [DEAE Cellulose (fast flow), 0 to 0.25 M $Et_3NH_2CO_3$, linear gradient]. The appropriate fractions (detected by TLC, *p*-anisaldehyde stain) were concentrated to afford amide **3** (449 mg, 0.853 mmol) as the triethylammonium salt (yield: 94 %). For characterization purposes, compound **7** was passed through cation exchange resin (Sephadex-SP C-25, Na$^+$ form, H_2O eluent) to generate sodium salt **3** as a white solid. ^{1}H NMR (300 MHz, D_2O) δ 6.00 (dd, *J* = 16, 2, 1 H), 5.99 (dd, *J* = 16, 2 Hz, 1 H), 4.68 (d, *J* = 4 Hz, 1 H), 4.64 (dd, *J* = 2, 1 Hz 1 H), 4.06 (d, *J* = 8 Hz, 1 H), 3.86 (dd, *J* = 10, 3 Hz, 1 H), 4.83 (dd, *J* = 3, 1 Hz, 1 H), 3.57-3.50 9 (m, 1 H), 3.38-3.26 (m, 4 H), 3.22 (dd, *J* = 10, 8 Hz, 1 H), 3.03-2.98 (m, 2 H), 1.98 (dd, *J* = 9, 4 Hz, 1 H), 1.45 (dt, *J* = 12, 4 Hz, 1 H), 1.22 (dd, *J* = 12, 9 Hz, 1 H); ^{13}C NMR (75 MHz, D_2O) d 178.5, 137.9, 135.8, 103.6, 82.3, 81.4, 79.1, 75.8, 69.9, 69.6, 68.0, 62.0, 43.8, 40.4, 30.6; IR (KBr) 3454, 2951, 2891, 2515, 1658, 1541 cm^{-1}; mass spectrum (LSIMS, 3-NBA) *m/z* 424.1 [M$^-$, calcd for $C_{15}H_{22}O_{11}N_1S_1$ 424.1].

Aminoethyl 3,6-O-disulfo-β-D-galactopyranosyl oxabicyclo[2.2.1]hept-5-ene-exo-2-carboxamide (5)

As described for the preparation of **3**, reaction of disulfate **10** (227 mg, 0.532 mmol) and activated ester **15** (161 mg, 0.526 mmol) in dimethylformamide (2.2 mL) and *N*-methylmorpholine (120 μL) provided amide **5** (344 mg, 0.487 mmol) as the triethylammonium salt (yield: 92%) following purification by anion exchange chromatography [DEAE Cellulose (fast flow), 0 to 0.25 M $Et_3NH_2CO_3$, linear gradient]. For characterization purposes, compound **5** was passed through cation exchange resin (Sephadex-SP C-25, Na^+ form, H_2O eluent) to generate sodium salt **5** as a white solid. ^1H NMR (300 MHz, D_2O) δ 6.51-6.45 (m, 2 H), 5.16 (dd, *J* = 4 Hz, 1 H), 5.13 (Br s, 1 H), 4.57 isomer A (d, *J* = 8 Hz, 1 H), 4.56 isomer B (d, *J* = 8 Hz, 1 H), 4.39-4.36 (m, 2 H), 4.26-4.18 (m, 2 H), 4.03-3.96 (m, 2 H), 3.89-3.80 (m, 1 H), 3.73-3.67 (m, 1 H), 3.52-3.47 (m, 2 H), 2.48 (dd, *J* = 9, 4 Hz, 1 H), 1.93 (dt, *J* = 12, 4 Hz, 1 H), 1.72 (ddd, *J* = 12, 9, 1 Hz, 1 H); ^{13}C NMR (75 MHz, D_2O) d 178.5, 137.9, 135.8, 103.5, 82.2, 81.0, 79.1, 73.5, 69.8, 68.3, 67.8, 43.7, 40.5, 30.6; IR (KBr) 3487 (b), 2953, 2877, 2507, 1653, 1259 cm^{-1}; mass spectrum (LSIMS, 3-NBA) *m/z* 526.1 [M^{2-}+ Na^+, calcd for $C_{15}H_{21}O_{14}N_1S_2Na_1$ 526.1].

Aminoethyl 3-O-sulfo-β-D-galactopyranosyl bicyclo[2.2.1]hept-5-ene-exo-2-carboxamide (4)

As described for the preparation of **3**, reaction of sulfate **11** (270 mg, 0.831 mmol) and pentafluorophenyl ester **14** (265 mg, 0.873 mmol) in DMF (2.5 mL) and *N*-methylmorpholine (200 μL) provided amide **4** (429 mg, 0.819 mmol) as the triethylammonium salt (yield: 98%) following purification by anion exchange chromatography [DEAE Cellulose (fast flow), 0 to 0.25 M $Et_3NH_2CO_3$, linear gradient]. For characterization purposes, compound **4** was passed through cation exchange resin (Sephadex-SP C-25, Na^+ form, H_2O eluent) to generate sodium salt **4** as a white solid. ^1H NMR (300 MHz, D_2O) δ 6.25-6.20 (m, 2 H), 4.55 (d, *J* = 8 Hz, 1 H), 4.37-4.31 (m, 2 H), 4.06-3.98 (m, 1 H), 3.86-3.75 (m, 4 H), 3.70 (dd, *J* = 10, 8 Hz, 1 H), 3.51-3.46 (m, 2 H), 2.99-2.96 (m, 2 H), 2.23 (ddd, *J* = 9, 5, 1.7 Hz, 1 H), 1.81-1.74 (m, 1 H), 1.54 (Br d, *J* = 8 Hz, 1 H), 1.46-1.35 (m, 2 H); ^{13}C NMR (75 MHz, D_2O) δ 179.5, 138.2, 136.2, 102.5, 80.2, 74.4, 68.8, 68.5, 66.8, 60.8, 46.4, 45.9, 43.9, 41.3, 39.3, 30.0; mass spectrum (LSIMS, 3-NBA) *m/z* 421.9 [M^-, calcd for $C_{16}H_{24}O_{10}N_1S_1$ 422.1].

Aminoethyl 3,6-O-disulfo-β-D-galactopyranosyl bicyclo[2.2.1]hept-5-ene-exo-2-carboxamide (6)

As described for the preparation of **3**, reaction of sulfate **10** (136 mg, 0.319 mmol) and pentafluorophenyl ester **14** (142 mg, 0.467 mmol) in DMF (2.5 mL) and *N*-methylmorpholine (100 μL) provided amide **6** (194 mg, 0.275 mmol) as the triethylammonium salt (yield: 86%) following purification by anion exchange chromatography [DEAE Cellulose (fast flow), 0 to 0.25 M $Et_3NH_2CO_3$, linear gradient]. For characterization purposes, compound **6** was passed through cation exchange resin (Sephadex-SP C-25, Na^+ form, H_2O eluent) to generate sodium salt **6** as a white solid. ^1H NMR (300 MHz, D_2O) d 6.25-6.20 (m, 2 H), 4.57 (d, *J* = 8 Hz, 1 H), 4.40-4.35 (m, 2 H), 4.27-4.19 (m, 2 H), 4.04-3.97 (m, 2 H), 3.90-3.83 (m, 1 H), 3.74-3.67 (m, 1 H), 3.52-3.46 (m, 2 H), 2.97 (m, 2 H), 2.24 (ddd, *J* = 9, 5, 2 Hz, 1 H), 1.78 (dt, *J* = 9, 3 Hz, 1 H), 1.47-1.35 (m, 2 H); ^{13}C NMR (75 MHz, D_2O) d 179.5, 138.2, 136.2, 102.4, 79.9, 72.3, 68.7, 67.1, 66.6, 46.5, 46.4 45.9, 43.9, 41.3, 39.3, 30.1, 30.0; mass spectrum (LSIMS, 3-NBA) *m/z* 524.1 [M^{2-} + Na^+, calcd for $C_{16}H_{23}O_{13}N_1S_2Na_1$ 524.1].

*Polymerization of aminoethyl 3-O-sulfo-β-D-galactopyranosyl oxabicyclo[2.2.1]hept-5-ene-exo-2-carboxamide (**polymer 16a**)*

Sulfate **3** (38.3 mg, 72.8 μmol)was dissolved in methanol (350 μL) and dichloromethane (350 μL), and the solution was deoxygenated by passing argon through the solution for ten minutes. To this was added a fresh solution (250 μL) of $[(Cy)_3P]_2Cl_2Ru$=CHPh (5.7 mg) in deoxygenated 1,2-dichloroethane (500 μL) with an airtight syringe. The solution changed colors from violet to tan within minutes. The reaction was heated in an oil bath at 65 °C. After two days, the reaction was cooled to room temperature, and ethyl vinyl ether (500 μL) was introduced. To generate the

sodium salt of the resulting material, the crude solution was diluted with water, and then passed through cation exchange resin (Sephadex-SP C-25 , Na^+ form, H_2O eluent). Following concentration of the fractions from cation exchange chromatography, the crude polymer was further purified by gel filtration (Sephacryl S-200 resin, water eluent) to remove unreacted **3**. Fractions containing polymer were collected and then concentrated to afford **16a** (16.8 mg) as a tan solid. Yield: 52 %; ^1H NMR (300 MHz, D_2O) δ 7.64-7.31 (0.20 H), 6.03-5.50 (2 H), 5.12-4.28 (5 H), 4.14-3.27 (8 H), 3.06-2.80 (1 H), 2.59-2.36 (1 H), 2.21-1.99 (1 H).

*Polymerization of aminoethyl 3,6-O-disulfo-β-D-galactopyranosyl oxabicyclo[2.2.1]hept-5-ene-exo-2-carboxamide (**polymer 17a**)*

Disulfate **5** (32.4 mg, 45.8 μmol) was dissolved in methanol (350 μL) and dichloromethane (250 μL), and the resulting solution was deoxygenated by passing argon through the solution for ten minutes. To this was added a fresh solution (250 μL) of $[(Cy)_3P]_2Cl_2Ru$=CHPh (5.0 mg) dissolved in deoxygenated dichloromethane (500 μL) with an airtight syringe. The solution changed appearance from violet to tan within minutes. An oil bath at 65 °C was applied, and the reaction heated. After two days of heating, the reaction was cooled to room temperature, and ethyl vinyl ether (500 μL) was added. To generate the sodium salt of the resulting material, the crude sample was diluted with water, and the resulting solution was passed through cation exchange resin (Sephadex-SP C-25 , Na^+ form, H_2O eluent). After concentration of the relevant fractions, the crude polymer was further purified by gel filtration (Sephacryl S-200 resin, water eluent) to remove unreacted **5**. Fractions containing polymer were collected and then concentrated to afford **17a** (6.5 mg) as a tan solid. Yield: 25%; ^1H NMR (300 MHz, D_2O) δ 7.60-7.33 (0.29 H), 5.92-5.57 (2 H), 5.20-4.51 (3 H), 4.43-4.32 (2 H), 4.27-4.17 (2 H), 4.07-3.94 (2 H), 3.89-3.22 (4 H), 3.02-2.79 (1 H), 2.56-2.32 (1 H), 2.22-1.95 (1 H).

*Polymerization of aminoethyl 3-O-sulfo-β-D-galactopyranosyl oxabicyclo[2.2.1]hept-5-ene-exo-2-carboxamide (**polymer 16e**)*

Sulfate **3** (74.4 mg, 0.142 mmol) and dodecyl trimethylammonium bromide (DTAB; 4.3 mg, 0.014 mmol) were dissolved in deoxygenated water (1.5 mL). To this was added a fresh solution (515 μL) of $[(Cy)_3P]_2Cl_2Ru$=CHPh (14.6 mg) in deoxygenated 1,2-dichloroethane (700 μL) with an airtight syringe. The reaction was stirred at room temperature for 30 minutes, then warmed with a 55 °C sand bath. After 11 hr of stirring, the reaction was cooled to room temperature and treated with ethyl vinyl ether (500 μL). The resulting mixture was stirred under argon for 30 minutes prior to exposure to air overnight. To remove the dark precipitate which had formed and to provide the polymer as the sodium salt, the mixture was passed through a short two-layered column consisting of equal portions of cation exchange resin (Sephadex SP C-25, Na^+ form, H_2O eluent) on the top and gel filtration resin (Sephacryl S-400 HR, H_2O eluent) on the bottom. The effluent was concentrated to dryness, and the polymer dissolved in a minimum volume of water (*ca* 200 μL), then precipitated in absolute ethanol (50 mL) to remove traces of monomer. The fine precipitate was centrifuged to a pellet to afford polymeric **16e** (63.7 mg) as a tan solid. NMR integration estimates the average length of these polymers to be 17 units . Yield: 74%; ^1H NMR (300 MHz, D_2O) δ 7.64-7.31 (0.20 H), 6.03-5.50 (2 H), 5.12-4.28 (5 H), 4.14-3.27 (8 H), 3.06-2.80 (1 H), 2.59-2.36 (1 H), 2.21-1.99 (1 H); ^{13}C NMR (126 MHz, D_2O) d Major signals: 173.9, 173.8, 136.7-126.6 (multiple peaks), 102.5, 82.7, 80.2, 79.3, 78.6, 78.0, 75.2, 74.6, 68.3, 66.8, 60.8, 51.2, 50.5, 39.3, 36.1; Minor signals: 64.4, 70.8, 69.3, 67.3, 42.6, 29.5, 26.2.

*Polymerization of aminoethyl 3,6-O-disulfo-β-D-galactopyranosyl oxabicyclo[2.2.1]hept-5-ene-exo-2-carboxamide (**polymer 18e**)*

As described for the preparation of **16e**, reaction of sulfate **5** (86.8 mg, 0.123 mmol) and DTAB (5.7 mg, 0.019 mmol) in water (1.2 mL) with a solution of $[(Cy)_3P]_2Cl_2Ru$=CHPh (6.8 mg, 0.0083 mmol) in 1,2-dichloroethane (420 μL) at 55 °C for 6.5 hours provided **17e** (21.9 mg) as a

tan solid following purification. The average length of the polymers by NMR integration is 25 units. Yield: 32%; ^{1}H NMR (300 MHz, D_2O) δ 7.60-7.33 (0.29 H), 5.92-5.57 (2 H), 5.20-4.51 (3 H), 4.43-4.32 (2 H), 4.27-4.17 (2 H), 4.07-3.94 (2 H), 3.89-3.22 (4 H), 3.02-2.79 (1 H), 2.56-2.32 (1 H), 2.22-1.95 (1 H); ^{13}C NMR (126 MHz, D_2O) d Major signals: 174.0, 134.0-130.2 (multiple peaks), 102.5, 79.8, 79.4, 78.3, 74.9, 72.2, 68.7, 66.8, 66.5, 51.0, 39.5, 36.4; Minor signals: 101.2, 82.4.

*Polymerization of aminoethyl 3-O-sulfo-β-D-galactopyranosyl bicyclo[2.2.1]hept-5-ene-exo-2-carboxamide (**polymer 17e**)*

As described for the preparation of **16e**, reaction of sulfate **4** (74.4 mg, 0.142 mmol) and DTAB (4.3 mg, 0.014 mmol) in water (1 mL) with a solution of $[(Cy)_3P]_2Cl_2Ru$=CHPh (7.8 mg, 0.0095 mmol) in 1,2-dichloroethane (370 μL) at 40 °C for 6.5 hours provided polymer **18e** 44.3 mg) as a tan solid following purification. NMR integration predicts an average polymer length of 25 units. Yield: 70%; ^{1}H NMR (300 MHz, D_2O)δ 7.56-7.25 (0.15 H), 5.57-5.20 (2 H), 4.51 (1 H), 4.39-4.27 (2 H), 4.10-2.86 (9 H), 2.82-2.40 (2 H), 2.17-1.55 (3 H), 1.39-1.10 (1 H); ^{13}C NMR (126 MHz, D_2O) d Major signals: 178.0, 135.7-130.3 (multiple peaks), 102.5, 80.2, 74.6, 68.8, 68.5, 66.7, 60.7, 51.2, 48.7. 41.1, 39.2, 36.0; Minor signals: 96.3, 75.4, 70.8, 69.3, 67.3, 43.8.

*Polymerization of aminoethyl 3,6-O-disulfo-β-D-galactopyranosyl bicyclo[2.2.1]hept-5-ene-exo-2-carboxamide (**polymer 19e**)*

As described for the preparation of **16e**, reaction of sulfate **6** (104 mg, 147 mmol) and DTAB (4.3 mg, 0.014 mmol) in water (1 mL) with a solution of $[(Cy)_3P]_2Cl_2Ru$=CHPh (8.1 mg, 0.0098 mmol) in 1,2-dichloroethane (280 μL) at 40 °C for 18 hours provided polymer **19e** (51.9 mg) as a tan solid following purification. The average length of these polymers, determined by NMR integration, is 33 units. Yield: 65%; ^{1}H NMR (300 MHz, D_2O) δ 7.55-7.26 (0.20 H), 5.59-5.21 (2 H), 4.59-4.48 (1 H), 4.42-4.30 (2 H), 4.28-4.15 (2 H), 4.05-3.89 (2 H), 3.85-3.64 (2 H), 2.83-2.43 (3 H), 2.18-1.87 (2 H), 1.81-1.53 (1 H), 1.47-1.12 (2 H) ; ^{13}C NMR (126 MHz, D_2O) d Major signals: 178.5, 135.5-130.7 (multiple peaks), 102.6, 80.0, 72.3, 68.8, 66.9, 66.6, 51.4, 48.9, 41.7, 41.2, 39.2, 36.4, 35.3; Minor signals: 68.3, 67.4, 53.0, 48.6, 44.0, 43.9, 40.7, 38.8, 36.0, 35.9.

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