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Synthesis of Sialyl Lewis^X Mimetics with E- and P-Selectin Binding Properties and Immunosuppressive Activity

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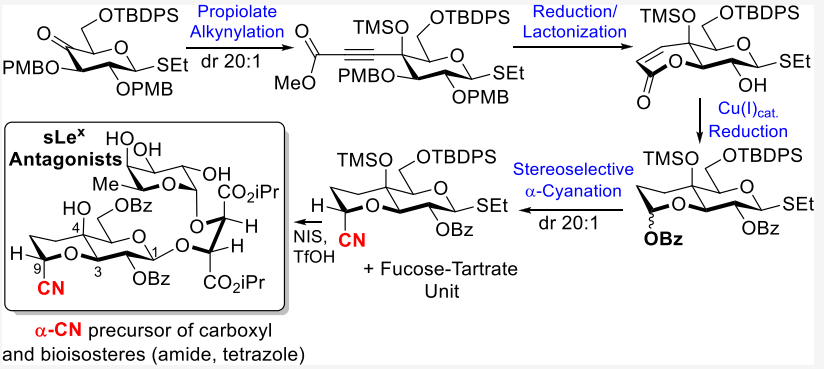

ABSTRACT: E- and P-selectins are adhesion proteins implicated in immune cell recruitment at sites of infection, making them important drug targets for diseases involving excessive and uncontrolled inflammation. In this study, we developed an efficient strategy to synthesize bicyclic galactopyranosides through a key stereoselective equatorial C4-propiolate addition and TMSCN axial C-glycosidation. The nitrile group can then be converted to the carboxyl and different bioisosteres at a late stage in the synthesis, allowing for various derivatizations to potentially enhance biological activity. The sialyl Lewis^X glycomimetic featuring this rigidified bicyclic galactopyranoside moiety prevents neutrophil adhesion to endothelial cells *in vitro* by binding to both E- and P-selectins. We show here that the axial carboxyl analogue blocks immune cell recruitment *in vivo*, demonstrating its potential as an immunomodulator.

INTRODUCTION

Inflammatory disorders often lead to immune response dysfunction, which is characterized by an excessive influx of immune cells.[1] Therapeutic intervention is often crucial to ensure host survival in pathologies such as ischemia−reperfusion injury,[2,3] pancreatitis,[4] acute respiratory distress syndrome (ARDS),[5,6] and vaso-occlusive crises in sickle cell disease patients.[7,8] Extensive research has been conducted to elucidate the function of selectins in inflammatory diseases.[9,10] Importantly, the interactions of endothelial P- and E-selectin with their ligands, P-selectin glycoprotein ligand-1 (PSGL-1), E-selectin ligand-1 (ESL-1), and CD-44 (HCELL) among others, were discovered to govern a vast array of adhesive, intercellular signaling, and homing functions.

The development of glycomimetics, small molecule therapeutics that imitate complex glycan structures to induce or attenuate glycoprotein function, presents an interesting strategy to overcome inflammatory diseases in which vascular homeostasis dysfunction is a problem.[11] The timely administration of a selectin antagonist to attenuate leukocyte recruitment is the premise behind several promising clinical candidates.[11−13] The aim of this work was to improve the synthesis and evaluate the *in vivo* potency of a new class of sialyl Lewis^X (sLe^X) glycomimetics (Figure 1) competing with both P- and E-selectin adhesion processes to PSGL-1.

Previously, we reported a first generation of analogues bearing tartrate diester tethers as promising P- and E-selectin antagonists (**2**, Figure 1).[14,15] The tunable tartrate acyclic tether was central to their design, which aimed to modulate the spatial arrangement of the fucose and galactose units. Early studies by our group demonstrated that tartrate esters induce a conformation that orients these two critical pharmacophores in the gauche arrangement imposed by the GlcNAc residue in sialyl Lewis^X.[16] The presence of di-isopropyl esters on the tartrate, a phenyl lactic acid at C3, and hydroxyl at C4 of the

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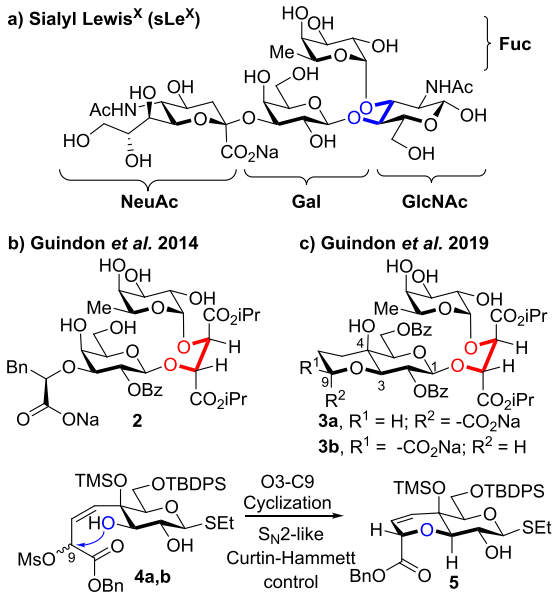
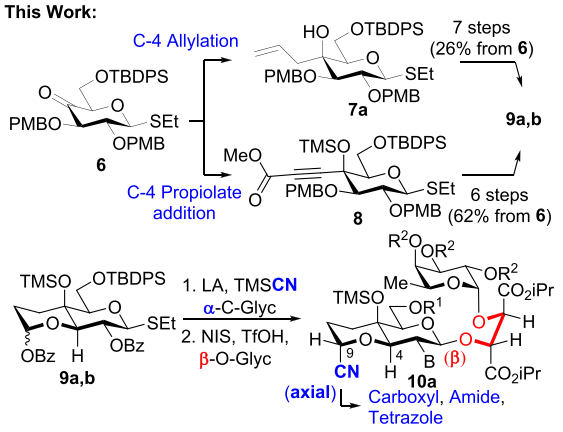


Figure 1. Sialyl Lewis^X and glycomimetic analogues.

galactose were the important structural features leading to high potencies relative to sialyl Lewis^X (Figure 1b). Pre-organization of the carboxylate moiety with a rigidified bicyclic 3-*O*,4-*C*-fused galactopyranoside scaffold to increase binding affinity was next explored (Figure 1c). The overlap of PSGL-1-bound sLe^X with bicyclic galactopyranoside scaffolds led us to suggest that the axially configured carboxylate group, as seen in analogue **3a**, would be oriented in a favorable position for binding to selectins. A first stereoselective synthesis provided access to both axial and equatorial carboxylate diastereomers **3a** and **3b** via O3-C9 cyclization of mesylates **4a** and **4b** under S$_N$2 Curtin–Hammett control.[17] The initial biological investigations indicated that both **3a** and **3b** exhibited better binding to P-selectin compared to sLe^X in a cell-based assay.[17] However, under flow conditions, **3a** was significantly more effective than **3b** in preventing human neutrophil rolling and firm adhesion to immobilized primary umbilical endothelial cells expressing P-selectin following histamine activation.[17]

We present here an optimized synthetic route for the bicyclic galactoside that improves both the yield and number of steps involved to facilitate the production of sufficient materials for *in vivo* studies. The two synthetic routes depicted in Scheme 1 utilize three-carbon nucleophilic additions at C4 to access the key bicyclic galactoside donors **9a** and **9b**. The stereoselective axial cyanation step produces a nitrile group that can be easily transformed into a carboxylic acid or bioisosteric functional groups such as tetrazoles or amides. The immunomodulatory properties of **3a** and **3b** were investigated using an *in vivo* peritonitis model of inflammation. Significant immunosuppression could be clinically relevant for hospitalized patients suffering from severe hyperinflammation. The synergistic effect of E- and P-selectin inhibition has never fully been tested due to the lack of potent molecules active against both proteins. Most selectin antagonists reported thus far target E-selectin (Rivipansel) or are coupled to other pharmaceutical effectors (e.g., GMI-1359, a CXCR4 antagonist).[18]

Scheme 1. Synthetic Route Developed for the Formation of Bicyclic Galactoside Scaffolds



RESULTS AND DISCUSSION

The first synthetic route explored to prepare the key bicyclic intermediates **9a** and **9b**, which can be orthogonally glycosidated at C1 or C9, involved the allylmagnesium alkylation of ketone **6**. The latter is obtained by an Albright–Goldman oxidation of the tri-protected thiogalactoside **11**[17] (Scheme 2). The allylation was carried out at −40 °C in THF and resulted in 9:1 dr (**7a**:**7b**) favoring the equatorially configured product. This isomer was separated by chromatography before TMS protection of the C4-OH group and the hydroboration in the presence of hindered 9-BBN to give the

Scheme 2. Synthesis of Bicyclic Galactoside Donors 9a and 9b through a Stereoselective Allylmagnesium Addition and Stereoselective Lithium Propiolate Addition

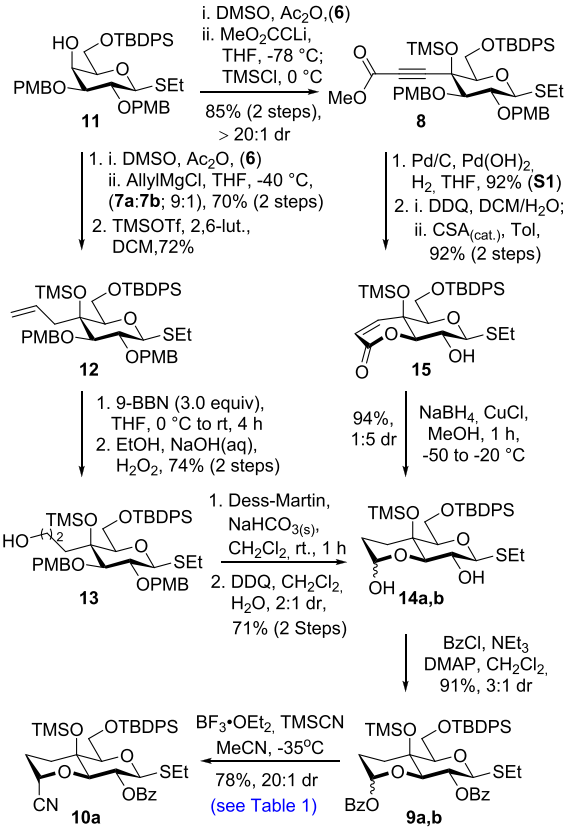


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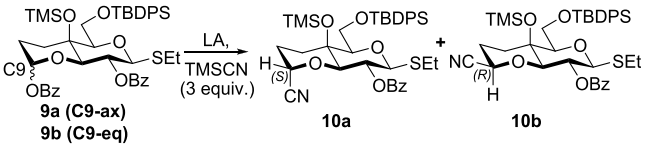
Table 1. C-Glycosidation of Galactopyranosides 9a and 9b



	conditions: LA[a] (equiv), solvent, time	S.M.	temp (°C)	product **10a**:**10b**[b]	yield[c] (%)
1	TMSOTf (0.2), DCM, 4 h	**9a**:**9b** (1:3)	−78		S.M.
2	TMSOTf (0.5), DCM, 1 h	**9a**:**9b** (1:3)	rt		decomp.
3	$BF_3{\cdot}OEt_2$ (2.0), DCM, 5 min	**9b**	0	6:1	61
4	$BF_3{\cdot}OEt_2$ (2.0), DCM, 4 h	**9b**	−40	4:1	62[d]
5	$BF_3{\cdot}OEt_2$ (2.0), DCM, 4 h	**9a**	−40	5:1	97
6	$BF_3{\cdot}OEt_2$ (2.0), **MeCN**, 5 min	**9b**	0	>20:1	65
7	$BF_3{\cdot}OEt_2$ (2.0), **MeCN**, 4 h	**9b**	−35	>20:1	85
8	$BF_3{\cdot}OEt_2$ (2.0), **MeCN**, 4 h	**9a**	−35	17:1	82
9	$BF_3{\cdot}OEt_2$ (2.0), **MeCN**, 1 h	**9a**:**9b** (1:3)	−35	20:1	78
10	$BF_3{\cdot}OEt_2$ (2.0), **$MeNO_2$**, 1 h	**9b**	−30	15:1	63

[a]Conditions: solvent (0.1 M), TMSCN, Lewis acid. [b]Product ratio determined by ^1H NMR analysis of the crude mixture. [c]Isolated yield. [d]10% of unreacted starting material in the crude mixture.

primary alcohol **13**. The latter was oxidized to an aldehyde, and the PMB ethers were cleaved with DDQ to give lactol intermediates **14a** and **14b**. The corresponding 2,9-di-*O*-benzoylated thiogalactosides were then formed using BzCl, NEt_3, and DMAP in dichloromethane in 91% yield (Scheme 2).

The addition of lithium propiolate to ketone **6** was then studied to introduce another functionalizable three-carbon extension at C4 with equatorial selectivity (Scheme 2). In contrast to allylmagnesium reagents, which are highly reactive and prone to undergoing less controlled additions near diffusion rate limits, alkynyllithium reagents add to ketones with higher diastereoselectivity.[19−21] This is consistent with the exclusive formation of the equatorially oriented alkynyl ester **8** in an excellent yield by treatment of cyclohexanone **6** with methyl lithiopropiolate, followed by addition of TMSCl to capture the intermediate lithium alkoxide. Alkyne **8** was then hydrogenated with a 1:1 mixture of Pd/C and $Pd(OH)_2$ in THF.[22] The α,β-unsaturated ester was next subjected to PMB deprotection with DDQ, and the crude mixture was heated with a catalytic amount of CSA in toluene to afford bicyclic unsaturated lactone **15**. Sequential 1,4- and 1,2-reduction developed by Matsumoto and Yonaga, using a catalytic amount of CuCl in the presence of $NaBH_4$ and MeOH, provided lactols **14a** and **14b**.[23]

After benzoylation of lactols **14a** and **14b** to form **9a** and **9b**, the *C*-glycosidation reaction was optimized to introduce an axially configured nitrile at C9 (Table 1 and Scheme 2). Initial attempts with TMSOTf in the presence of TMSCN in DCM resulted only in the recovery of the starting material or decomposition at higher temperatures (entries 1 and 2, Table 1). At this point, flash chromatography conditions were found to separate the two anomers (**9a**:**9b**) to ensure that they reacted with similar stereoselectivity. Activation of **9b** with $BF_3{\cdot}OEt_2$ at 0 °C afforded the desired C-glycosides **10a** and **10b** with a 6:1 ratio in moderate yield due to partial deprotection of the silyl groups (entry 3). The reaction was therefore studied at −40 °C. The deprotection of the silyl groups was avoided with equatorial benzoate **9b**, but some starting material was still present along with a similar ratio of products **10a** and **10b** after 4 h (entry 4). The C9-axial **9a** benzoate was significantly more reactive and led to an excellent yield at this temperature (entry 5). The optimal alignment of the endocyclic oxygen lone pair (O8) with the $\sigma^*_{C\text{-}O}$ of the benzoate leaving group may explain why this anomer can ionize and react more rapidly.[24] The change of solvent to MeCN had a remarkable effect on the selectivity, giving >20:1 axial selectivity at 0 °C (entry 6). The isolated yields were significantly improved at −35 °C for both **9b** and **9a**, although the latter resulted in a slightly lower 17:1 ratio (entries 7 and 8). The unseparated mixture **9a**:**9b** (1:3) obtained after benzoylation of lactols **14a** and **14b** resulted in a 20:1 ratio favoring the axial cyano group, which is consistent considering the ratios obtained when each isomer reacted independently (entry 9 versus entries 7 and 8). Performing the reaction in $MeNO_2$ also provided an improved 15:1 selectivity of **10a**:**10b** and a shorter reaction time relative to DCM, but the yield was lower than that obtained in MeCN (entry 10).

The stereoselective formation of axial cyano **10a** is noteworthy since TMSCN tends to react unselectively with oxocarbenium ions.[25] Pentacoordinate anionic siliconate ion intermediates have been shown to serve as the nucleophile reacting at, or near, diffusion control rates on both faces of oxocarbenium ions.[25] The restricted conformation of the *trans*-bicyclo[4,4,0] galactopyranoside system likely contributes to the axial attack preference. A top face attack on the oxocarbenium intermediate after activation would lead to a 4,9-*cis* twist boat transition state with higher ring strain energy accompanied by steric clash with the silyl group (Scheme 3). The α:β ratio would reflect the free energy difference between these two reaction pathways. A certain level of erosion of selectivity, as previously proposed for similar additions to cyclic oxocarbenium ions, could occur due to the high degree of reactivity of TMSCN toward oxocarbenium ions in DCM.[25] In MeCN, the enhanced charge stabilization reduces the high reactivity of the anionic nucleophile TMSCNBz, resulting in decreased erosion of selectivity and a higher ratio that favors axial attack.[25] This solvent should also facilitate ionization to the reacting oxocarbenium intermediate and explain the shorter reaction time in MeCN for the equatorial benzoate, which does not fully convert to the product in DCM, even after 4 h at −40 °C (entry 4 versus 7, Table 1).[25]

An alternative pathway that has been proposed to rationalize the selectivity for axial cyanation in similar bicyclic systems

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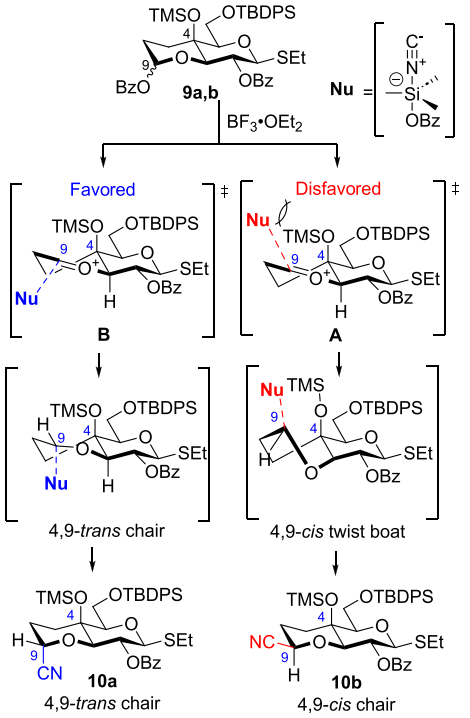
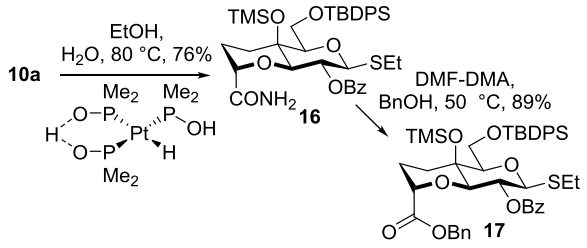
Scheme 3. Mechanistic Rationale for the Stereoselective C-Glycosidation of 9a and 9b



involves the addition of MeCN at the anomeric position to form α,β-acetonitrilium reaction intermediates.[26] These intermediates could equilibrate to the preferred equatorial orientation and undergo S_N2-like displacement, leading to the axial selectivity.[26] The equatorial preference for acetonitrilium has been rationalized by invoking the debated reverse anomeric effect,[27,28] where a positively charged anomeric substituent could be electrostatically better stabilized by having two gauche interactions with the two lone pairs of the ring oxygen.[29] However, the selectivity (15:1 dr) obtained in $MeNO_2$ (entry 10, Table 1), a solvent that is not likely to form these stabilized intermediates, leads us to attribute the observed stereocontrol in MeCN to a difference in the proposed transition states **A** and **B** (Scheme 3).

After successfully optimizing the *C*-glycosidation for the desired axial C9-nitrile **10a**, the next step in the synthesis involved the use of the Ghaffar–Parkins platinum phosphine complex to catalyze the hydration and produce the corresponding amide **16** in 76% yield (Scheme 4).[30] The amide can be converted to the carbonyl ester **17** in good yield employing 3 equiv of DMF-DMA in a benzylic alcohol solution at 50 °C.[31] This represents an improvement (overall

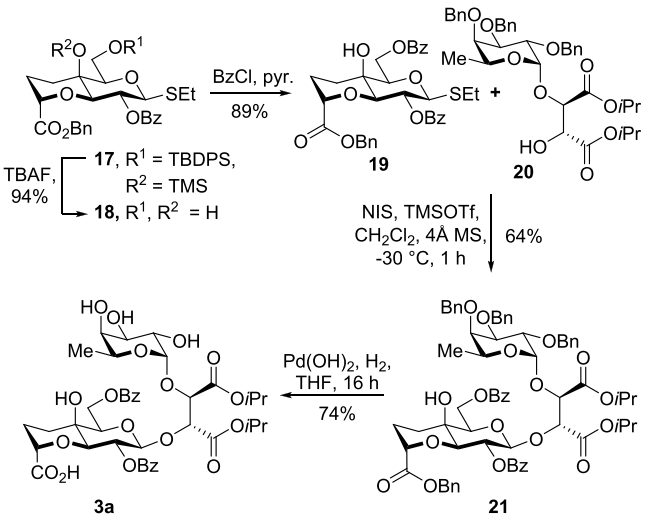
Scheme 4. Synthesis of Bicyclic Galactoside Donor 17 by Derivatization toward Axial C9-ester



33% yield and 10 steps from alcohol **11**) as compared to bicyclic glycosyl donor **5** (Figure 1) previously reported by our group (overall 12% and 12 steps from alcohol **11**).[17]

Removal of the silyl ethers with TBAF followed by benzoylation of the primary hydroxyl group afforded the desired galactopyranoside **19** (Scheme 5). This product was

Scheme 5. Completion of the Synthesis of 3a



coupled to the fucosylated tartrate tether **20**[14] to provide exclusively the β-anomer **21**, the diastereoselectivity of the *O*-glycosidation being induced by anchimeric participation of the proximal benzoate at C2. The benzyl ethers and ester were removed by hydrogenation under palladium catalysis to give the lead compound **3a**.

The nitrile moiety at C9 can be easily converted to a carboxyl substituent or bioisostere functionalities, such as tetrazoles or amides. This feature allows for the late-stage introduction of various functional groups at C9, enabling the synthesis of a range of derivatives with potentially interesting activity.[32−34] For example, after glycosidation of **10a** with tartrate derivative **20**[14] and removal of the silyl groups with TBAF (Scheme 6), benzoate protection of the primary alcohol followed by hydrolysis of the nitrile with the Ghaffar–Parkins catalyst generated amide **24**.[30] Alternatively, a 1,3-dipolar cycloaddition of nitrile **23** in the presence of NaN_3 and triethylamine-HCl salt afforded tetrazole **25**.[34,35]

Peritonitis Model. To study the *in vivo* effect of **3a** and **3b**[17] against acute inflammation, we adapted the well-characterized thioglycolate (TG)-induced murine peritonitis model. Similar studies are planned for the analogues bearing carboxyl bioisosteres at C9. Leukocyte influx into the peritoneal cavity is a hallmark of abdominal inflammation, and interestingly, the nature and timing of cell migration in a thioglycolate-induced peritoneal exudate has been reported. In this model, leukocyte infiltration was significantly delayed using homozygous PSGL-1-deficient mice,[36] suggesting that selectins are involved. To study the effect of the selectin antagonists, C57BL/6 wild-type mice were first injected intraperitoneally (IP) with a 3% solution of TG. After 10 min, sLe^X, analogues **3a** and **3b**, or vehicle were administered intravenously (IV). Two hours later, mice were sacrificed, and the peritoneal cavity was lavaged. A block of 1 million cells was then stained with antibodies for subsequent flow cytometric analysis. *In vivo* cell migration assays showed that **3a**

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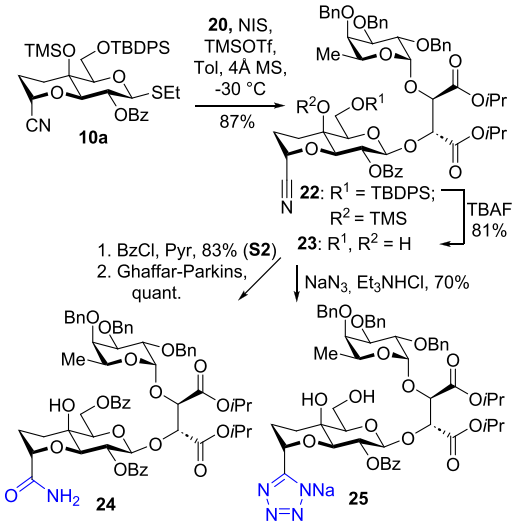
Scheme 6. Synthesis of Amide or Tetrazole Carboxyl Bioisosteres



significantly reduced the neutrophil population even at the lowest 0.25 μmol/kg dose (Figure 2). Consistent with their low *in vitro* activities,[17] the equatorial isomer **3b** as well as sLe^X did not reduce inflammation with observable statistical significance.

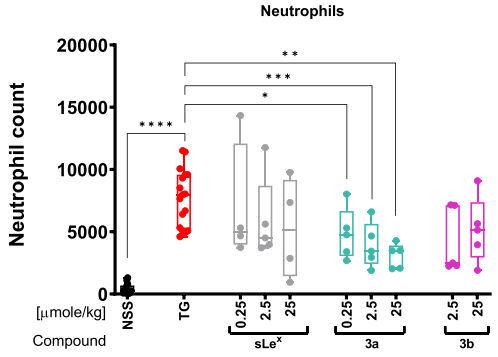


Figure 2. *In vivo* cell migration assay. C57BL/6 wild-type mice were injected with 1 mL of 3% thioglycolate (TG) in the peritoneal cavity to stimulate cell recruitment. Mice were then treated with compounds at indicated doses through single IV injection. Cells were collected after 2 h from the cavity and identified using flow cytometry. Total neutrophil population was identified as CD11b$^+$, CD11c$^-$, Ly-6C$^+$, and Ly-6G$^+$. Significance was determined in comparison to thioglycolate-stimulated mice using one-way ANOVA. *p < 0.05, **p < 0.001, ***p < 0.0001, and ****p < 0.00001. Natural saline solution (NSS) served as the vehicle.

CONCLUSIONS

The discovery that L-tartaric esters could be used as an acyclic tether to replace the GlcNAc unit present in sLe^X was a key finding that led to the development of our first generation of glycomimetics. The pre-organized gauche conformation of the tether, along with its potential for flexibility during binding, likely accounts for the P- and E-selectin antagonist activity of this family of glycomimetics, distinguishing them from the majority of sialyl Lewis^X derivatives that primarily exhibit selectivity for E-selectin. The new synthetic strategies reported in this study enable the replacement of the freely rotating C3-lactic acid derivative in the galactopyranoside with a bicyclic system that immobilizes the carboxyl moiety in an axial conformation. Two important transformations in this route are the diastereoselective equatorial addition of three-carbon nucleophiles to cyclic ketones and the axial introduction of a cyano group onto the bicyclic system. The latter allows late-stage derivatizations at the carboxyl position, the analogues of which are currently being evaluated for E- and P-selectin binding. Promising *in vivo* evidence suggests that the intravenous administration of **3a**, which bears an axial carboxylate functionality, reduces selectin-dependent neutrophil recruitment to sites of inflammation in a peritonitis-elicited animal model, demonstrating the potential effectiveness of these compounds. Further studies are currently underway to determine the immunoregulatory potential of these compounds under various conditions and disease models.

EXPERIMENTAL SECTION

General Comments. All experiments that required anhydrous conditions were performed under a nitrogen or argon atmosphere in flame-dried glassware using standard syringe techniques. Prior to use, all anhydrous solvents were dried with 4 Å molecular sieves. The 4 Å molecular sieves, which were 1−2 mm beads, were activated by heating them at 180 °C for 48 h under vacuum before being added to new bottles of solvent that had been purged with nitrogen. Commercially available reagents were used as received.

Flash chromatography was conducted using silica gel 60 (0.040−0.063 mm) with either a forced flow of the indicated solvent system or using an automated flash purification system. Analytical thin-layer chromatography (TLC) was performed on precoated (0.25 mm) silica gel aluminum plates, and visualization was achieved using UV short wavelength or by revealing with potassium permanganate solutions.

^{1}H NMR spectra were obtained at room temperature on a 500 MHz NMR spectrometer, and they are reported as follows: chemical shift in parts per million (ppm), referenced to residual solvent ($CDCl_3$ δ 7.26 ppm, D_2O δ 4.79 ppm; CD_3OD δ 3.31 ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, td = triplet of doublets, q = quartet, hept = heptet, m = multiplet, app = apparent), coupling constants (in hertz), and integration. The ^{13}C NMR spectra were recorded at room temperature using 126 MHz, and they are reported as follows: chemical shift in parts per million, referenced to residual solvent ($CDCl_3$ δ 77.16 ppm; CD_3OD δ 49.00 ppm). Structural assignments were made with additional information from gNOESY and gHSQC experiments.

Infrared spectra were measured using a Fourier transform infrared spectrophotometer with a single reflection diamond ATR module, and signals are reported in cm^{-1}. The mass spectra were obtained through electrospray ionization positive ion mode. A Hybrid Quadrupole-Orbitrap mass analyzer was used for high-resolution mass spectrometry (HRMS) measurements. Optical rotations were measured at room temperature from the sodium D line (589 nm) using $CHCl_3$ as the solvent, unless otherwise noted. They were calculated using the formula $[\alpha]_D = (100)\alpha_{obs}/(l \cdot c)$, where c = (g of substrate/100 mL of solvent) and l = 1 dm. Compound purity of greater than 95% was confirmed for all compounds tested *in vitro* and *in vivo* by HPLC/MS/UV (254 and 700 nM).

*(+)-Ethyl 4-C-Allyl-6-O-(tert-butyldiphenylsilyl)-2,3-di-O-(p-methoxybenzyl)-1-thio-β-D-galactopyranoside (**7a**) and (+)-Ethyl 4-C-Allyl-6-O-(tert-butyldiphenylsilyl)-2,3-di-O-(p-methoxybenzyl)-1-thio-β-D-glucopyranoside (**7b**).* To a solution of alcohol **11**[17] (3.07 g, 4.37 mmol, 1.00 equiv) in DMSO (5.1 mL, 0.85 M), acetic anhydride (3.55 mL, 37.6 mmol, 8.60 equiv) was added. The solution was stirred at 65 °C in an oil bath for 2 h. The reaction mixture was cooled to room temperature before water (20 mL) was added, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic

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layers were washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was co-evaporated with toluene (2 × 50 mL) to ensure dryness. The resulting ketone **6** can be purified by flash chromatography (see ref 17), but here, the viscous oil was directly dissolved in anhydrous THF (2.4 mL, 0.10 M) and 3 Å molecular sieves (4.0 g) were added. The reaction mixture was cooled to −40 °C, and a solution of allylmagnesium chloride (2.0 M in THF, 5.4 mL, 2.5 equiv) was added dropwise. The reaction mixture was stirred for 2 h at −40 °C, after which the solution was filtered with EtOAc, and a saturated solution of NH_4Cl (50 mL) was added. The reaction mixture was stirred at room temperature for 15 min, and the aqueous layer was subsequently extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 9:1 mixture of C4 diastereomers **7a**:**7b**. Purification by flash chromatography (hexanes/Et_2O, 60:40) allowed for the major products **7a** (2.5 g, 63%) and **7b** (0.27 g, 7%) to be isolated as pale-yellow oils.

7a (major diastereoisomer): R_f = 0.32 (hexanes/Et_2O, 60:40); $[\alpha]_D^{25}$ +7.4 (*c* 3.8, $CHCl_3$); formula: $C_{43}H_{54}O_7SSi$; MW = 743.0430 g mol^{-1}; IR (neat) ν_{max} 3485, 3071, 2931, 1613, 1514, 1248 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (m, 4H), 7.46−7.32 (m, 8H), 7.27 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 4H), 5.41 (m, 1H), 4.97−4.84 (m, 4H), 4.70−4.61 (m, 2H), 4.42 (d, *J* = 9.8 Hz, 1H), 3.99 (dd, *J* = 3.8, 1.4 Hz, 2H), 3.86 (dd, *J* = 9.8, 8.6 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.46 (s, 1H), 3.42 (d, *J* = 8.8 Hz, 1H), 3.31 (dd, *J* = 4.3, 3.2 Hz, 1H), 2.88 (dq, *J* = 12.6, 7.5 Hz, 1H), 2.76 (dq, *J* = 12.0, 7.2 Hz, 1H), 2.70 (ddt, *J* = 14.4, 7.3, 1.6 Hz, 1H), 2.26 (ddt, *J* = 14.2, 7.7, 1.0 Hz, 1H), 1.35 (t, *J* = 7.4 Hz, 3H), 1.05 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.5, 159.4, 135.9, 135.8, 132.9, 132.8, 132.6, 130.6, 130.5, 130.1, 130.0, 129.9, 129.8, 127.9, 127.8, 118.9, 114.0, 113.9, 84.7, 81.6, 80.4, 79.4, 76.0, 75.2, 75.0, 63.7, 55.5, 55.4, 39.8, 26.8, 24.4, 19.2, 15.3 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{43}H_{54}O_7SSiNa$ [M + Na^+], 765.3257; found, 765.3244 (−1.7 ppm).

7b (minor diastereoisomer): R_f = 0.40 (hexanes/Et_2O, 60:40); $[\alpha]_D^{25}$ +2.8 (*c* 0.43, $CHCl_3$); formula: $C_{43}H_{54}O_7SSi$; MW = 743.0430 g mol^{-1}; IR (neat) ν_{max} 3546, 3068, 2994, 1512, 1247 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72−7.64 (m, 4H), 7.47−7.33 (m, 6H), 7.32−7.25 (m, 4H), 6.91−6.81 (m, 4H), 5.94 (dddd, *J* = 16.8, 10.1, 8.4, 6.5 Hz, 1H), 5.09−5.00 (m, 2H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.77 (d, *J* = 11.1 Hz, 1H), 4.73 (d, *J* = 9.8 Hz, 1H), 4.63 (d, *J* = 9.9 Hz, 1H), 4.45 (d, *J* = 9.8 Hz, 1H), 3.91 (dd, *J* = 10.7, 5.6 Hz, 1H), 3.81 (s, 3H), 3.82−3.77 (m, 1H), 3.80 (s, 3H), 3.53 (d, *J* = 9.3 Hz, 1H), 3.49 (dd, *J* = 6.6, 5.8 Hz, 1H), 3.34 (appt, *J* = 9.5 Hz, 1H), 2.88 (s, 1H), 2.79−2.61 (m, 3H), 2.36 (dd, *J* = 14.5, 8.4 Hz, 1H), 1.28 (d, *J* = 14.9 Hz, 3H), 1.04 (s, *J* = 2.9 Hz, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.4, 159.2, 135.8, 135.7, 134.6, 133.0, 132.95, 131.4, 130.5, 130.1, 130.0, 129.9, 129.4, 127.91, 127.88, 118.4, 113.91, 113.87, 110.1, 89.0, 85.7, 82.2, 79.8, 75.5, 75.4, 75.3, 63.5, 55.4, 35.0, 29.9, 26.9, 24.9, 19.2, 15.1 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{43}H_{54}O_7SSiNa$ [M + Na^+], 765.3257; found, 765.3246 (−0.7 ppm).

*(+)-Ethyl 4-C-Allyl-6-O-(tert-butyldiphenylsilyl)-2,3-di-O-(p-methoxybenzyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**12**).* To a vigorously stirred solution of alcohol **7a** (4.5 g, 6.1 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (61 mL, 0.10 M) at −40 °C, 2,6-lutidine (1.4 mL, 12 mmol, 2.0 equiv) and TMSOTf (1.3 mL, 7.3 mmol, 1.2 equiv) were added. The reaction vessel was sealed with a Teflon cap and kept at −20 °C for 16 h. Water (60 mL) was then slowly added, and the solution was warmed to room temperature. The organic layer was collected and washed with an HCl solution (1 M, 60 mL) and a saturated solution of $NaHCO_3$ (60 mL), followed by brine (60 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc, 60:40) provided galactopyranoside **12** (3.6 g, 72%) as a pale-yellow oil. R_f = 0.29 (hexanes/Et_2O, 80:20); $[\alpha]_D^{25}$ +36 (*c* 1.2, $CHCl_3$); formula: $C_{46}H_{62}O_7SSi_2$; MW = 815.2250 g mol^{-1}; IR (neat) ν_{max} 2954, 1613, 1513, 1246 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72−7.64 (m, 4H), 7.46−7.29 (m, 8H), 7.27−7.24 (m, 2H), 6.89−6.82 (m, 4H), 5.50−5.40 (m, 1H), 4.98−4.88 (m, 3H), 4.84 (d, *J* = 9.8 Hz, 1H), 4.62 (d, *J* = 9.9 Hz, 1H), 4.57 (d, *J* = 10.6 Hz, 1H), 4.38 (d, *J* = 9.8 Hz, 1H), 3.92 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.82 (dd, *J* = 11.1, 6.7 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.64 (dd, *J* = 9.8, 9.0 Hz, 1H), 3.43 (dd, *J* = 6.7, 3.8 Hz, 1H), 3.40 (d, *J* = 9.0 Hz, 1H), 2.84 (dq, *J* = 12.6, 7.4 Hz, 1H), 2.80−2.68 (m, 2H), 2.07 (dd, *J* = 13.6, 6.5 Hz, 1H), 1.33 (t, *J* = 7.4 Hz, 3H), 1.05 (s, 9H), −0.01 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.5, 159.3, 135.84, 135.80, 133.9, 133.6, 133.1, 130.8, 130.6, 130.11, 130.10, 129.9, 129.8, 129.7, 127.8, 119.0, 114.0, 113.8, 84.8, 82.1, 81.4, 80.2, 79.5, 75.4, 74.9, 63.0, 55.42, 55.40, 39.6, 27.0, 24.7, 19.3, 15.2, 2.9 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{46}H_{62}O_7SSi_2Na$ [M + Na^+], 837.3652; found, 837.3639 (−1.0 ppm).

*(+)-Ethyl 4-C-(3-Hydroxypropyl)-6-O-(tert-butyldiphenylsilyl)-2,3-di-O-(p-methoxybenzyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**13**).* To a solution of alkene **12** (1.0 g, 1.2 mmol, 1.0 equiv) in anhydrous THF (6.1 mL, 0.20 M) at 0 °C, a solution of 9-borabicyclo[3.3.1]nonane (0.50 M in THF, 7.4 mL, 3.0 equiv) was added. The reaction mixture was warmed to room temperature and stirred for 4 h. The mixture was subsequently cooled to 0 °C, and EtOH (1.4 mL, 25 mmol, 20 equiv), an aqueous solution of NaOH (3.9 mL, 2.5 M), and hydrogen peroxide 30% (w/w) in H_2O (0.98 mL, 9.6 mmol, 7.8 equiv) were added. The solution was warmed to room temperature and stirred for 2 h before a saturated solution of $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/Et_2O, 45:55) provided alcohol **13** (0.75 g, 74%) as a clear oil. R_f = 0.31 (hexanes/Et_2O, 40:60); $[\alpha]_D^{25}$ +19 (*c* 2.2, $CHCl_3$); formula: $C_{46}H_{64}O_8SSi_2$; MW = 833.2400 g mol^{-1}; IR (neat) ν_{max} 3498, 3071, 2932, 1613, 1514, 1248 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.45−7.31 (m, 8H), 7.25−7.22 (m, 2H), 6.89−6.83 (m, 4H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.84 (d, *J* = 9.8 Hz, 1H), 4.65 (d, *J* = 9.8 Hz, 1H), 4.58 (d, *J* = 10.9 Hz, 1H), 4.39 (d, *J* = 9.8 Hz, 1H), 3.86 (dd, *J* = 11.2, 6.7 Hz, 1H), 3.83−3.79 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.65 (dd, *J* = 9.8, 8.9 Hz, 1H), 3.38−3.31 (m, 2H), 3.18 (ddt, *J* = 20.8, 9.7, 5.1 Hz, 2H), 2.85 (dq, *J* = 12.7, 7.4 Hz, 1H), 2.76 (dq, *J* = 12.7, 7.5 Hz, 1H), 1.87 (td, *J* = 13.3, 3.8 Hz, 1H), 1.35 (t, *J* = 7.4 Hz, 3H), 1.16 (td, *J* = 13.2, 4.6 Hz, 1H), 1.05 (s, 9H), 1.03−0.99 (m, 1H), 0.94 (ddd, *J* = 13.4, 6.7, 4.1 Hz, 1H), 0.76 (s, 1H), 0.00 (s, 9H) ppm. Labile proton was not observed due to exchange in deuterated solvent. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.5, 159.4, 135.8, 134.1, 133.6, 130.7, 130.6, 130.5, 130.3, 130.2, 129.8, 129.7, 127.8, 127.7, 114.0, 113.8, 84.9, 81.5, 81.4, 81.3, 80.2, 79.2, 75.2, 75.0, 63.0, 62.9, 55.4, 30.8, 27.8, 27.0, 24.8, 19.3, 15.2, 3.0 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{46}H_{64}O_8SSi_2Na$ [M + Na^+], 855.3758; found, 855.3756 (+0.4 ppm).

*Ethyl 3-O,4-C-(1R-Hydroxyprop-1,3-diyl)-6-O-(tert-butyldiphenylsilyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**14a**) and Ethyl 3-O,4-C-(1S-Hydroxyprop-1,3-diyl)-6-O-(tert-butyldiphenylsilyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**14b**).* To a stirring solution of alcohol **13** (720 mg, 864 μmol, 1.00 equiv) in CH_2Cl_2 (8.6 mL, 0.10 M), solid $NaHCO_3$ (145 mg, 1.73 mmol, 2.00 equiv) and Dess−Martin periodinane (403 mg, 951 μmol, 1.10 equiv) were added. The reaction mixture was stirred vigorously for 1 h before a saturated solution of $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was dissolved in a 20:1 solution of CH_2Cl_2 and H_2O (18 mL), and DDQ (392 mg, 1.73 μmol, 2.00 equiv) was added. The reaction mixture was stirred for 30 min before being refluxed for 30 min. After cooling to room temperature, a saturated solution of $NaHCO_3$ (20 mL) was added, and the aqueous layer was extracted with EtOAc (2 × 20 mL), washed with brine (60 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of an inseparable 2:1 mixture of diastereomers. Purification by flash chromatography (hexanes/EtOAc, 45:55) provided lactols **14a** and **14b** (0.36 g, 71% over two steps) as a clear oil. This mixture corresponded to the

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^{1}H NMR analysis of the two anomers formed from **15**, for which characterizations are provided below.

*(+)-Ethyl 4-C-(Methyloxycarbonylethynyl)-6-O-(tert-butyldiphenylsilyl)-2,3-di-O-(p-methoxybenzyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**8**).* To a solution of previously reported alcohol **11**[17] (2.00 g, 2.87 mmol, 1.00 equiv) in DMSO (8.5 mL, 0.85 M), acetic anhydride (2.34 mL, 24.8 mmol, 8.70 equiv) was added. The reaction mixture was warmed to 65 °C in an oil bath and stirred for 2 h. The reaction mixture was cooled to room temperature before water (15 mL) was added, and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was co-evaporated with toluene (2 × 30 mL) to ensure dryness. Ketone **6** can be purified by flash chromatography (see ref 17 for characterizations), but here, the crude residue was dissolved directly in anhydrous THF (15 mL, 0.20 M) and cannulated dropwise (slow addition) into a freshly prepared solution of methyl lithiopropiolate (0.10 M in THF, 28.7 mL, 1.05 equiv) at −78 °C. After 30 min, TMSCl (1.1 mL, 8.6 mmol, 3.0 equiv) was added and the reaction was warmed to room temperature and stirred for 2 h. A saturated solution of NH_4Cl (50 mL) was added and the aqueous layer was extracted with Et_2O (2 × 50 mL), and the combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a > 20:1 ratio of C4 diastereomers. Purification by flash chromatography (hexanes/Et_2O, 60:40) provided alkyne **8** (2.1 g, 85% over two steps) as a pale-yellow oil. R_f = 0.20 (hexanes/Et_2O, 70:30); $[\alpha]_D^{25}$ +1.3 (*c* 0.8, $CHCl_3$); formula: $C_{47}H_{60}O_9SSi_2$; MW = 857.2180 g mol^{-1}; IR (neat) ν_{max} 3071, 2955, 2856, 2234, 1718, 1613, 1514, 1249 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71−7.64 (m, 4H), 7.43−7.23 (m, 10H), 6.84 (dd, *J* = 14.3, 8.6 Hz, 4H), 4.85−4.76 (m, 2H), 4.76 (d, *J* = 10.0 Hz, 1H), 4.64 (d, *J* = 10.0 Hz, 1H), 4.47 (d, *J* = 8.3 Hz, 1H), 4.00 (dd, *J* = 11.3, 2.5 Hz, 1H), 3.84 (dd, *J* = 11.3, 7.6 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.57−3.47 (m, 3H), 2.82 (dq, *J* = 13.3, 7.4 Hz, 1H), 2.73 (dq, *J* = 12.9, 7.4 Hz, 1H), 1.33 (t, *J* = 7.4 Hz, 3H), 1.05 (s, 9H), 0.04 (s, 9H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.5, 159.4, 153.2, 135.8, 135.7, 133.8, 133.5, 130.4, 130.3, 130.2, 130.1, 129.7, 129.6, 127.8, 127.7, 113.9, 113.7, 86.3, 86.1, 85.2, 83.6, 78.5, 78.1, 76.2, 75.4, 72.8, 64.0, 55.4, 55.3, 52.9, 26.9, 24.9, 19.3, 15.2, 1.9 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{47}H_{60}O_9SSi_2Na$ [M + Na$^+$], 879.3389; found, 879.3400 (+1.3 ppm).

*(−)-Ethyl 4-C-(2Z-Methyloxycarbonylethenyl)-6-O-(tert-butyldiphenylsilyl)-2,3-di-O-(p-methoxybenzyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**S1**).* To a solution of alkyne **8** (3.5 g, 4.1 mmol, 1.0 equiv) in THF (70 mL, 0.058 M), palladium (10 wt %) on activated carbon (1.1 g, 1.0 mmol, 0.30 equiv) and $Pd(OH)_2$ (20 wt %) on activated carbon (0.72 g, 1.0 mmol, 0.30 equiv) were added. The reaction mixture was degassed under reduced pressure and backfilled with hydrogen (3×). After stirring at room temperature under a standard hydrogen atmosphere for 16 h, the reaction mixture was filtered through Celite with Et_2O and concentrated *in vacuo*. Purification by flash chromatography (hexanes/Et_2O, 70:30) provided alkene **S1** (3.2 g, 92%) as a clear oil. R_f = 0.41 (hexanes/Et_2O, 70:30); $[\alpha]_D^{25}$ −19 (*c* 1.1, $CHCl_3$); formula: $C_{47}H_{62}O_9SSi_2$; MW = 859.2340 g mol^{-1}; IR (neat) ν_{max} 2953, 2241, 1721, 1613, 1513, 1247 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 6.5 Hz, 2H), 7.62 (d, *J* = 6.6 Hz, 2H), 7.44−7.32 (m, 8H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.03 (d, *J* = 13.7 Hz, 1H), 5.55 (d, *J* = 13.7 Hz, 1H), 4.85 (d, *J* = 9.9 Hz, 1H), 4.79 (d, *J* = 10.8 Hz, 1H), 4.78 (d, *J* = 9.9 Hz, 1H), 4.66 (d, *J* = 9.9 Hz, 1H), 4.65 (d, *J* = 9.0 Hz, 1H), 4.52 (d, *J* = 10.8 Hz, 1H), 4.48 (dd, *J* = 6.7, 4.0 Hz, 1H), 3.85 (dd, *J* = 11.0, 6.7 Hz, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.73−3.70 (m, 1H), 3.69 (s, 3H), 3.62 (dd, *J* = 9.8, 9.0 Hz, 1H), 2.94−2.76 (m, 2H), 1.39 (t, *J* = 7.5 Hz, 3H), 1.03 (s, 9H), 0.10 (s, 9H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.5, 159.4, 159.2, 153.8, 135.7, 135.6, 133.9, 133.7, 130.7, 130.44, 130.40, 130.0, 129.6, 129.5, 127.6, 127.5, 118.8, 113.8, 113.4, 84.8, 81.8, 81.5, 81.3, 80.1, 77.4, 75.3, 74.9, 64.1, 55.4, 55.3, 51.6, 26.8, 25.1, 19.2, 15.3, 2.7 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{47}H_{62}O_9SSi_2Na$ [M + Na$^+$], 881.3551; found, 881.3538 (−0.9 ppm).

*(−)-Ethyl 3-O,4-C-(Oxoprop-2-en-1,3-diyl)-6-O-(tert-butyldiphenylsilyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**15**).* To a solution of alkene **S1** (3.5 g, 4.1 mmol, 1.0 equiv) in a 20:1 mixture of CH_2Cl_2 and H_2O (73 mL, 55 mM), DDQ (2.0 g, 9.0 mmol, 2.2 equiv) was added. The reaction mixture was stirred for 3 h before a saturated solution of $NaHCO_3$ (70 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (130 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was co-evaporated with toluene (2 × 30 mL) to ensure dryness. The crude residue was dissolved in anhydrous toluene (81 mL, 50 mM), and camphorsulfonic acid (95 mg, 0.41 mmol, 0.10 equiv) was added. The reaction mixture was warmed to 65 °C and stirred for 90 min. The solution was cooled to room temperature, and a saturated solution of $NaHCO_3$ (80 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine (140 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/Et_2O, 50:50) provided lactone **15** (2.2 g, 92%) as a clear oil. R_f = 0.23 (hexanes/Et_2O, 50:50); $[\alpha]_D^{25}$ −61 (*c* 0.6, $CHCl_3$); formula: $C_{30}H_{42}O_6SSi_2$; MW = 586.8900 g mol^{-1}; IR (neat) ν_{max} 3373, 2071, 2931, 1732, 1428, 1253 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.61 (m, 4H), 7.47−7.38 (m, 6H), 7.29 (d, *J* = 9.9 Hz, 1H), 6.15 (d, *J* = 9.9 Hz, 1H), 4.29 (d, *J* = 9.2 Hz, 1H), 4.10 (d, *J* = 9.7 Hz, 1H), 4.02−3.92 (m, 2H), 3.77 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.45 (dd, *J* = 6.9, 4.5 Hz, 1H), 2.74−2.57 (m, 3H), 1.26 (t, *J* = 7.5 Hz, 3H), 1.08 (s, 9H), 0.03 (s, 9H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.3, 144.7, 135.7, 132.9, 132.8, 130.2, 130.1, 128.0, 125.0, 85.7, 84.6, 80.1, 69.5, 66.8, 62.8, 27.0, 23.8, 19.2, 15.3, 2.2 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{30}H_{42}O_6SSi_2Na$ [M + Na$^+$], 609.2138; found, 609.2152 (+3.2 ppm).

*Ethyl 3-O,4-C-(1R-Hydroxyprop-1,3-diyl)-6-O-(tert-butyldiphenylsilyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**14a**) and Ethyl 3-O,4-C-(1S-Hydroxyprop-1,3-diyl)-6-O-(tert-butyldiphenylsilyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**14b**).* To a stirring solution of lactone **15** (0.47 g, 0.80 mmol, 1.0 equiv) in MeOH (4.7 mL, 0.10 M) cooled to −50 °C, sodium borohydride (0.30 g, 8.0 mmol, 10 equiv) was added. The reaction mixture was stirred vigorously for 15 min before copper(I) chloride (40 mg, 0.40 mmol, 0.50 equiv) was added. The solution was warmed to −20 °C and stirred for 30 min (until gas evolution ceased). The reaction mixture was diluted with EtOAc (5 mL), and a saturated solution of NH_4Cl (10 mL) was added. After stirring for 30 min at room temperature, the layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of an inseparable 1:5 mixture of diastereomers. Purification by flash chromatography (hexanes/EtOAc, 45:55) provided lactols **14a** and **14b** (0.45 g, 94%) as a clear oil. R_f = 0.23 (hexanes/EtOAc, 50:50); formula: $C_{30}H_{46}O_6SSi_2$; MW = 590.9220 g mol^{-1}; IR (neat) ν_{max} 3419, 3071, 2957, 1428, 1252 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73−7.64 (m, 8H, a and b), 7.46−7.34 (m, 12H, a and b), 5.34 (d, *J* = 3.6 Hz, 1H, b), 4.83 (d, *J* = 9.0 Hz, 1H, a), 4.31 (d, *J* = 9.4 Hz, 1H, b), 4.27 (d, *J* = 9.5 Hz, 1H, a), 3.87−3.78 (m, 3H, a and b), 3.79−3.64 (m, 4H, a and b), 3.41 (dd, *J* = 6.2, 4.6 Hz, 1H, b), 3.30 (dd, *J* = 6.1, 4.7 Hz, 1H, a), 3.24 (d, *J* = 5.3 Hz, 1H, a), 3.18 (d, *J* = 9.3 Hz, 1H, a), 3.00 (s, 1H, b), 2.77−2.63 (m, 4H, a and b), 2.49 (s, 1H, a), 2.42 (s, 1H, b), 1.96 (m, 1H, b), 1.87−1.80 (m, 2H, a), 1.80−1.69 (m, 2H, a and b), 1.65−1.59 (m, 2H, b), 1.46−1.34 (m, 1H, a), 1.29 (t, *J* = 7.5 Hz, 3H, b), 1.28 (t, *J* = 7.5 Hz, 3H, a), 1.06 (s, 9H, a), 1.05 (s, 9H, b), 0.06 (s, 9H, a) 0.03 (s, 9H, b) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.89 (a), 135.86 (b), 135.77 (a), 135.75 (b), 133.7 (b), 133.6 (a), 133.4 (b), 133.3 (a), 129.94 (a), 129.93 (b), 129.87 (a), 129.82 (b), 127.89 (a), 127.86 (b), 127.84 (a), 127.82 (b), 96.5 (a), 91.3 (b), 86.5 (b), 86.0 (a), 83.55 (a), 83.48 (b), 82.5 (a), 74.7 (b), 73.2 (b), 72.3 (a), 67.9 (b), 67.8 (a), 63.1 (a), 62.9 (b), 30.1 (a), 28.3

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(a), 27.00 (b), 26.98 (a), 25.5 (b), 25.1 (b), 23.9 (b), 23.7 (a), 19.30 (b), 19.29 (a), 15.5 (b), 15.4 (a), 2.9 (a) 2.8 (b) ppm; HRMS (ESI) m/z: calcd for $C_{30}H_{46}O_6SSi_2Na$ [M + Na^+], 613.2451; found, 613.2444 (−0.4 ppm).

*(+)-Ethyl 3-O,4-C-(1R-Benzoyloxyprop-1,3-diyl)-2-O-benzoyl-6-O-(tert-butyldiphenylsilyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**9a**) and (+)-Ethyl 3-O,4-C-(1S-benzoyloxyprop-1,3-diyl)-2-O-benzoyl-6-O-(tert-butyldiphenylsilyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**9b**).* To a 1:5 mixture of lactols **14a** and **14b** (1.54 g, 2.61 mmol, 1.0 equiv) in CH_2Cl_2 (26 mL, 0.10 M), triethylamine (1.1 mL, 7.8 mmol, 3.0 equiv), benzoyl chloride (0.76 mL, 1.6 mmol, 2.5 equiv), and 4-dimethylaminopyridine (64 mg, 0.52 mmol, 0.20 equiv) were added. After stirring for 16 h at room temperature, a saturated solution of $NaHCO_3$ (30 mL) was added. The aqueous layer was extracted with Et_2O (2 × 30 mL), and the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a 1:2.5 mixture of diastereomers **9a**:**9b**. Purification by flash chromatography (toluene) provided dibenzoates **9a** (0.32 g, 15%) and **9b** (1.3 g, 62%) as white foams.

9a (C9-axial): R_f = 0.20 (toluene); $[\alpha]_D^{25}$ +2.7 (c 1.0, DCM); formula: $C_{44}H_{54}O_8SSi_2$; MW = 799.1380 g mol^{-1}; IR (neat) ν_{max} 2957, 1727, 1265, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07−8.00 (m, 2H), 7.91−7.83 (m, 2H), 7.78−7.69 (m, 4H), 7.68−7.61 (m, 1H), 7.58−7.37 (m, 9H), 7.35−7.24 (m, 2H), 6.32 (d, J = 3.4 ,1.2 Hz, 1H), 5.39 (t, J = 9.8 Hz, 1H), 4.56 (d, J = 9.8 Hz, 1H), 4.03 (d, J = 9.9 Hz, 1H), 3.92 (dd, J = 11.0, 4.5 Hz, 1H), 3.81 (dd, J = 11.0, 6.2 Hz, 1H), 3.51 (dd, J = 6.2, 4.5 Hz, 1H), 2.80−2.60 (m, 2H), 2.31−2.13 (m, 1H), 1.89−1.68 (m, 3H), 1.22 (t, J = 9.5 Hz, 3H), 1.09 (s, 9H), 0.14 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 165.7, 164.6, 135.9, 135.8, 133.6, 133.4, 133.3, 132.9, 130.4, 130.3, 129.93, 129.90, 129.87, 129.8, 128.6, 128.2, 127.91, 127.87, 110.1, 92.2, 83.7, 83.6, 77.2, 76.1, 73.1, 68.7, 62.8, 27.0, 26.7, 24.4, 23.6, 19.3, 14.9, 2.8. HRMS (ESI) m/z: calcd for $C_{44}H_{54}O_8SSi_2Na$ [M + Na^+], 821.2976; found, 821.2989 (2.3 ppm).

9b (C9-equatorial): R_f = 0.39 (toluene); $[\alpha]_D^{25}$ +43 (c 1.0, DCM); formula: $C_{44}H_{54}O_8SSi_2$; MW = 799.1380 g mol^{-1}; IR (neat) ν_{max} 2958, 1731, 1269, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03−7.93 (m, 4H), 7.74−7.66 (m, 4H), 7.55−7.48 (m, 2H), 7.48−7.35 (m, 10H), 5.92 (dd, J = 9.8, 2.6 Hz, 1H), 5.47 (appt, J = 9.7 Hz, 1H), 4.51 (d, J = 9.7 Hz, 1H), 3.91 (dd, J = 10.8, 4.7 Hz, 1H), 3.81 (dd, J = 10.7, 5.6 Hz, 1H), 3.64 (d, J = 9.7 Hz, 1H), 3.43 (t, J = 5.0 Hz, 1H), 2.80−2.65 (m, 2H), 2.10−1.96 (m, 2H), 1.90−1.82 (m, J = 11.0 Hz, 1H), 1.59 (td, J = 13.3, 3.6 Hz, 1H), 1.21 (t, J = 7.4 Hz, 3H), 1.08 (s, 9H), 0.20 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 165.8, 164.6, 135.8, 135.7, 133.6, 133.4, 133.2, 132.9, 130.4, 130.00, 129.95, 129.92, 129.90, 129.7, 128.4, 128.3, 127.89, 127.86, 94.9, 83.7, 83.3, 81.4, 77.2, 72.6, 68.5, 62.9, 30.4, 27.0, 25.8, 23.5, 19.3, 14.9, 2.9. HRMS (ESI) m/z: calcd for $C_{44}H_{54}O_8SSi_2Na$ [M + Na^+], 821.2976; found, 821.2985 (1.8 ppm).

*(+)-Ethyl 3-O,4-C-(1S-Cyanoprop-1,3-diyl)-2-O-benzoyl-6-O-(tert-butyldiphenylsilyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside and (**10a**) and (+)-Ethyl 3-O,4-C-(1R-cyanoprop-1,3-diyl)-2-O-benzoyl-6-O-(tert-butyldiphenylsilyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**10b**).* To protected galactopyranosides **9a** (0.075 g, 0.94 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1.0 mL, 0.10 M), trimethylsilyl cyanide (0.035 mL, 0.28 mmol, 3.0 equiv) and boron trifluoride diethyl etherate (23 μL, 0.188 mmol, 2 equiv) were added at −40 °C. The reaction mixture was stirred for 4 h at this temperature before a cooled mixture of Et_3N:MeOH:DCM (1:1:1) (1 mL) was added. Next, a solution of $NaHCO_3$ (1 mL) was added, and the layers were separated. The aqueous layer was then extracted with AcOEt (2 × 2 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a 5:1 (**10a**:**10b**) mixture of nitrile diastereomers. Purification by flash chromatography (hexanes/Et_2O, 60:40) provided **10a** (0.057 g, 85%) and **10b** (8 mg, 12%) as clear oils.

10a (major diastereoisomer): R_f = 0.53 (hexanes/Et_2O, 50:50); $[\alpha]_D^{25}$ +6 (c 0.7, $CHCl_3$); formula: $C_{38}H_{49}NO_6SSi_2$; MW = 704.0410 g mol^{-1}; IR (neat) ν_{max} 2957, 1729, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06−8.01 (m, 2H), 7.72−7.67 (m, 4H), 7.59−7.53 (m, 1H), 7.48−7.39 (m, 8H), 5.41 (t, J = 9.7 Hz, 1H), 4.84 (dd, J = 5.8, 0.8 Hz, 1H), 4.58 (d, J = 9.8 Hz, 1H), 3.86 (dd, J = 11.0, 5.1 Hz, 1H), 3.82 (d, J = 9.6 Hz, 1H), 3.76 (dd, J = 11.0, 5.8 Hz, 1H), 3.50 (dd, J = 5.8, 5.1 Hz, 1H), 2.78−2.62 (m, 2H), 2.32−2.22 (m, 1H), 1.95−1.87 (m, 1H), 1.76−1.65 (m, 2H), 1.21 (t, J = 7.5 Hz, 3H), 1.07 (s, 9H), 0.12 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 165.8, 135.9, 135.8, 133.4, 133.2, 133.1, 130.0, 129.9, 128.5, 128.0, 127.9, 117.3, 83.7, 83.0, 79.7, 73.0, 68.3, 64.5, 62.6, 27.7, 27.0, 24.1, 23.8, 19.3, 14.9, 2.8 ppm (due to overlapping carbon signals in the aromatic region, 2 peaks are hidden); HRMS (ESI) m/z: calcd for $C_{38}H_{49}NO_6SSi_2Na$ [M + Na^+], 726.2717; found, 726.2700 (−1.5 ppm).

10b (minor diastereoisomer): R_f = 0.44 (hexanes/Et_2O, 50:50); $[\alpha]_D^{25}$ +30 (c 1.2, $CHCl_3$); formula: $C_{38}H_{49}NO_6SSi_2$; MW = 704.0410 g mol^{-1}; IR (neat) ν_{max} 2958, 1727, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.05−7.99 (m, 2H), 7.71−7.65 (m, 4H), 7.59−7.54 (m, 1H), 7.48−7.38 (m, 8H), 5.43 (t, J = 9.7 Hz, 1H), 4.49 (d, J = 9.8 Hz, 1H), 4.26 (dd, J = 12.4, 2.8 Hz, 1H), 3.87 (dd, J = 11.0, 5.2 Hz, 1H), 3.76 (dd, J = 11.0, 5.7 Hz, 1H), 3.41−3.35 (m, 2H), 2.77−2.61 (m, 2H), 2.24 (m, 1H), 1.99 (ddd, J = 14.3, 4.5, 2.5 Hz, 1H), 1.86 (ddt, J = 13.8, 4.9, 2.5 Hz, 1H), 1.45 (td, J = 13.9, 4.6 Hz, 1H), 1.20 (t, J = 7.4 Hz, 3H), 1.06 (s, 9H), 0.17 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 165.4, 135.8, 135.7, 133.4, 133.2, 133.1, 130.1, 130.0, 129.9, 128.5, 128.0, 127.9, 117.4, 83.6, 83.4, 83.0, 72.5, 68.3, 65.7, 62.6, 30.4, 27.0, 25.7, 23.5, 19.3, 14.9, 2.9 ppm (due to overlapping carbon signals in the aromatic region, 1 peak is hidden); HRMS (ESI) m/z: calcd for $C_{38}H_{49}NO_6SSi_2Na$ [M + Na^+], 726.2717; found, 726.2687 (−3.4 ppm).

*(+)-Ethyl 3-O,4-C-(1S-Carbamoylprop-1,3-diyl)-2-O-benzoyl-6-O-(tert-butyldiphenylsilyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**16**).* To a reaction vessel containing nitrile **10a** (0.30 g, 0.43 mmol, 1.0 equiv) in a 2:1 mixture of EtOH and H_2O (6.4 mL, 67 mM), a Ghaffar−Parkins catalyst (9.1 mg, 21 μmol, 0.050 equiv) was added. The reaction vessel was sealed, and the solution was warmed to 80 °C. The reaction mixture was stirred vigorously for 3 h before being cooled to room temperature and concentrated *in vacuo*. The crude residue was dissolved in EtOAc, filtered through a pad of silica, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc, 60:40) provided amide **16** (0.24 g, 76%) as a white foam. R_f = 0.35 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ +17 (c 1.0, $CHCl_3$); formula: $C_{38}H_{51}NO_7SSi_2$; MW = 722.0560 g mol^{-1}; IR (neat) ν_{max} 3471, 3337, 2957, 1731, 1690, 1262 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06−8.01 (m, 2H), 7.73−7.65 (m, 4H), 7.62−7.56 (m, 1H), 7.49−7.37 (m, 8H), 6.32 (d, J = 4.0 Hz, 1H), 5.67 (d, J = 3.9 Hz, 1H), 5.46 (t, J = 9.7 Hz, 1H), 4.53 (d, J = 9.8 Hz, 1H), 4.35 (d, J = 6.5 Hz, 1H), 3.86 (dd, J = 11.0, 4.4 Hz, 1H), 3.75 (dd, J = 11.0, 6.2 Hz, 1H), 3.51 (d, J = 9.7 Hz, 1H), 3.42 (dd, J = 6.2, 4.4 Hz, 1H), 2.79−2.63 (m, 2H), 2.31−2.23 (m, 1H), 2.05−1.97 (m, 1H), 1.74 (ddd, J = 14.1, 5.0, 2.5 Hz, 1H), 1.43 (td, J = 13.8, 4.9 Hz, 1H), 1.22 (t, J = 7.5 Hz, 3H), 1.06 (s, 9H), 0.13 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.6, 165.3, 135.9, 135.7, 133.6, 133.5, 133.2, 129.90, 129.86, 129.80, 129.7, 128.8, 127.9, 127.8, 83.7, 83.5, 78.9, 73.9, 73.0, 69.3, 62.7, 28.0, 27.0, 23.6, 19.3, 18.8, 14.9, 2.8 ppm; HRMS (ESI) m/z: calcd for $C_{38}H_{51}NO_7SSi_2Na$ [M + Na^+], 744.2822; found, 744.2816 (−1.4 ppm).

*(+)-Ethyl 3-O,4-C-(1S-Benzyloxycarbonylprop-1,3-diyl)-2-O-benzoyl-6-O-(tert-butyldiphenylsilyl)-4-O-trimethylsilyl-1-thio-β-D-galactopyranoside (**17**).* To a stirring solution of amide **16** (0.13 g, 0.18 mmol, 1.0 equiv) in dry BnOH (3.6 mL, 0.050 M), DMF-DMA (72 μL, 0.54 mmol, 3.0 equiv) was added. The reaction mixture was warmed to 50 °C and stirred for 16 h. The solution was cooled to room temperature, and a saturated solution of NH_4Cl (10 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/Et_2O, 90:10) provided benzylester **17** (0.13 g, 89%) as a white foam. R_f = 0.22 (hexanes/Et_2O, 80:20); $[\alpha]_D^{25}$ +8 (c 0.9, $CHCl_3$); formula:

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$C_{45}H_{56}O_8SSi_2$; MW = 813.1650 g mol^{-1}; IR (neat) ν_{max} 2929, 1730, 1452, 1270 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dt, J = 8.4, 1.3 Hz, 2H), 7.69 (tq, J = 6.6, 1.4 Hz, 4H), 7.54 (td, J = 7.5, 1.3 Hz, 1H), 7.47−7.34 (m, 8H), 7.37−7.23 (m, 5H), 5.43−5.35 (m, 1H), 5.21 (d, J = 12.3 Hz, 1H), 5.15 (d, J = 12.2 Hz, 1H), 4.53−4.46 (m, 2H), 3.89−3.81 (m, 2H), 3.74 (dd, J = 11.0, 6.1 Hz, 1H), 3.35 (t, J = 5.4 Hz, 1H), 2.78−2.63 (m, 2H), 2.19 (tdd, J = 13.3, 6.7, 4.4 Hz, 1H), 1.98 (dt, J = 12.3, 3.1 Hz, 1H), 1.74 (dt, J = 14.2, 3.6 Hz, 1H), 1.39−1.30 (m, 1H), 1.21 (t, J = 7.5 Hz, 3H), 1.06 (s, 9H), 0.13 (s, 9H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.7, 166.0, 135.9, 135.7, 133.6, 133.3, 132.9, 130.6, 130.1, 129.9, 129.8, 128.7, 128.5, 128.4, 128.3, 127.9, 127.8, 83.6, 83.4, 78.3, 73.2, 72.4, 69.2, 66.7, 62.8, 28.0, 27.0, 23.5, 21.6, 19.3, 14.9, 2.8 ppm (due to overlapping carbon signals in the aromatic region, 1 peak is hidden); HRMS (ESI) m/z: calcd for $C_{45}H_{56}O_8SSi_2Na$ [M + Na$^+$], 835.3132; found, 835.3126 (−0.4 ppm).

*(−)-Ethyl 3-O,4-C-(1S-Benzyloxycarbonylprop-1,3-diyl)-2-O-benzoyl-1-thio-β-D-galactopyranoside (**18**).* To a solution of glycoside **17** (0.056 g, 0.069 mmol, 1.0 equiv) in anhydrous THF (1.4 mL) at 0 °C, TBAF (0.15 mL, 1.0 M in THF, 2.2 equiv) was added dropwise. The reaction mixture was stirred for 2 h before being diluted with EtOAc (2 mL), and a saturated solution of NH_4Cl (2 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 2 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc, 30:80) provided diol **18** (0.033 g, 94%) as a white foam. R_f = 0.27 (hexanes:EtOAc, 30:70); $[\alpha]_D^{25}$ −6.8 (c 0.85, DCM); formula: $C_{26}H_{30}O_8S$; MW = 502.5780 g mol^{-1}; IR (neat) ν_{max} 3570, 3513, 2976, 1712, 1272 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11−8.04 (m, 2H), 7.59−7.52 (m, 1H), 7.47−7.39 (m, 2H), 7.35−7.26 (m, 5H), 5.45 (appt, J = 9.7 Hz, 1H), 5.18 (d, J = 12.2 Hz, 1H), 5.14 (d, J = 12.2 Hz, 1H), 4.62 (d, J = 9.9 Hz, 1H), 4.57 (d, J = 6.6 Hz, 1H), 4.03 (d, J = 9.5 Hz, 1H), 3.95 (dd, J = 12.1, 5.6 Hz, 1H), 3.86 (bd, J = 12.0 Hz, 1H), 3.34 (dd, J = 5.6, 2.9 Hz, 1H), 3.03 (bs, 1H), 2.83−2.70 (m, 2H), 2.40 (tdd, J = 14.0, 6.7, 4.6 Hz, 1H), 2.23 (bs, 1H), 2.07 (bd, J = 14.2 Hz, 1H), 1.75 (ddd, J = 13.0, 3.8, 2.4 Hz, 1H), 1.44 (td, J = 13.6, 4.5 Hz, 1H), 1.26 (t, J = 7.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.4, 165.8, 135.5, 133.1, 130.3, 130.1, 128.8, 128.6, 128.5, 128.4, 84.2, 81.1, 77.7, 72.6, 69.5, 69.1, 66.9, 60.9, 27.7, 24.2, 21.5, 15.1 ppm; HRMS (ESI) m/z: calcd for $C_{26}H_{30}O_8SNa$ [M + Na$^+$], 525.1559; found, 525.1546 (−1.4 ppm).

*(+)-Ethyl-3-O,4-C-(1S-benzyloxycarbonylprop-1,3-diyl)-2,6-di-O-benzoyl-1-thio-β-D-galactopyranoside (**19**).* To a solution of diol **18** (0.040 g, 0.069 mmol, 1.0 equiv) in CH_2Cl_2 (1.8 mL, 0.1 M), pyridine (43 μL, 0.53 mmol, 3.0 equiv) and benzoyl chloride (41 μL, 0.35 mmol, 2.0 equiv) were added. The reaction mixture was stirred for 16 h before a saturated solution of $NaHCO_3$ (3 mL) was added. The aqueous layer was extracted with Et_2O (2 × 5 mL), and the organic layers were combined, washed with brine (1 × 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc, 75:25) provided dibenzoate **19** (96 mg, 89%) as a white solid. R_f = 0.17 (hexanes/Et_2O, 40:60); $[\alpha]_D^{25}$ +12 (c 1.6, $CHCl_3$); formula: $C_{33}H_{34}O_9S$; MW = 606.6860 gmol^{-1}; IR (neat) ν_{max} 3503, 2963, 1719, 1451, 1268 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (m, 4H), 7.61−7.53 (m, 2H), 7.44 (m, 4H), 7.31−7.27 (m, 5H), 5.36 (t, J = 9.8 Hz, 1H), 5.19 (d, J = 12.2 Hz, 1H), 5.13 (d, J = 12.2 Hz, 1H), 4.72−4.64 (m, 2H), 4.57 (appd, J = 6.7 Hz, 1H), 4.45 (dd, J = 12.0, 7.1 Hz, 1H), 4.13 (d, J = 9.6 Hz, 1H), 3.70 (dd, J = 7.1, 3.7 Hz, 1H), 2.79−2.62 (m, 2H), 2.61 (s, 1H), 2.42−2.32 (m, 1H), 2.12−2.06 (m, 1H), 1.93−1.85 (m, 1H), 1.53 (m, 1H), 1.23 (t, J = 7.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.3, 166.5, 165.8, 135.5, 133.8, 133.4, 133.1, 130.3, 130.1, 129.8, 128.8, 128.7, 128.6, 128.5, 128.4, 84.2, 79.8, 77.6, 72.6, 69.4, 69.3, 66.9, 62.6, 27.4, 24.7, 21.5, 15.1 ppm; HRMS (ESI) m/z: calcd for $C_{33}H_{34}O_9SNa$ [M + Na$^+$], 629.1821; found, 629.1821 (+0.9 ppm).

*(−)-(2R,3R)-2-O-(3-O,4-C-(1S-Benzyloxycarbonylprop-1,3-diyl)-2,6-di-O-benzoyl-β-D-galactopyranosyl)-3-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-tartaric Acid Diisopropyl Ester (**21**).* To a solution of **19** (30 mg, 49 μmol, 1.0 equiv) and **20**[14] (64 mg, 99 μmol, 2.0 equiv) in anhydrous CH_2Cl_2 (1.0 mL, 0.050 M), activated 4 Å molecular sieves (1.0 equiv) were added. The solution was stirred at room temperature for 30 min before being cooled to −35 °C, and *N*-iodosuccinimide (33 mg, 0.15 mmol, 3.0 equiv) and TMSOTf (2.0 μL, 10 μmol, 0.20 equiv) were added sequentially. The reaction mixture was stirred for 2 h at −35 °C or until the starting material was completely consumed, as verified by TLC. Upon completion, the reaction mixture was filtered using Et_2O, and a saturated solution of $Na_2S_2O_3$ was added dropwise to the dark brown solution until it became clear. After warming to room temperature, a saturated solution of $NaHCO_3$ was added. The aqueous layer was extracted with Et_2O (3×), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **21** (38 mg, 64%) as a colorless oil. R_f = 0.35 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ −17 (c 1.0, $CHCl_3$); formula: $C_{68}H_{74}O_{19}$; MW = 1195.3210 g mol^{-1}; IR (neat) ν_{max} 3501, 2981, 1727, 1453, 1271 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, J = 6.9, 1.5 Hz, 4H), 7.61−7.54 (m, 1H), 7.50−7.43 (m, 3H), 7.41−7.32 (m, 5H), 7.31−7.20 (m, 17H), 5.39 (dd, J = 10.0, 7.4 Hz, 1H), 5.17 (d, J = 12.3 Hz, 1H), 5.01 (d, J = 12.2 Hz, 1H), 4.97 (d, J = 7.4 Hz, 1H), 4.94−4.79 (m, 4H), 4.79−4.70 (m, 3H), 4.67 (dd, J = 12.0, 3.8 Hz, 1H), 4.64−4.60 (m, 2H), 4.57−4.51 (m, 2H), 4.41 (d, J = 5.4 Hz, 1H), 4.32 (dd, J = 11.9, 6.9 Hz, 1H), 4.01 (q, J = 6.3 Hz, 1H), 3.98 (d, J = 10.0 Hz, 1H), 3.93−3.89 (m, 2H), 3.46 (m, J = 7.3 Hz, 2H), 2.37 (tt, J = 13.5, 7.3 Hz, 1H), 2.06−1.99 (m, 1H), 1.88−1.83 (m, 2H), 1.38 (td, J = 13.6, 4.4 Hz, 1H), 1.19−1.10 (m, 9H), 1.08 (d, J = 6.3 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.3, 168.2, 168.0, 166.5, 165.8, 139.1, 139.0, 138.9, 135.5, 133.3, 132.9, 130.5, 130.1, 130.0, 129.9, 128.74, 128.7, 128.6, 128.5, 128.44, 128.4, 128.38, 128.3, 128.27, 128.2, 127.8, 127.6, 127.5, 127.4, 100.7, 99.9, 79.6, 78.4, 77.9, 77.7, 76.7, 76.3, 75.5, 74.8, 73.0, 72.8, 72.5, 71.2, 69.4, 69.1, 69.0, 67.5, 66.7, 62.3, 27.4, 21.8, 21.72, 21.7, 21.6, 21.4, 16.6 ppm; HRMS (ESI) m/z: calcd for $C_{68}H_{78}O_{19}N$ [M + NH_4^+], 1212.5163; found, 1212.5200 (+3.1 ppm).

*(−)-(2R,3R)-2-O-(3-O,4-C-(1S-Carboxyprop-1,3-diyl)-β-D-galactopyranosyl)-3-O-(α-L-fucopyranosyl)-tartaric Acid Diisopropyl Ester (**3a**).* To a solution of glycoside **21** (31 mg, 26 μmol, 1.0 equiv) in THF (2.1 mL, 0.012 M), palladium hydroxide (20 wt %) on carbon (27 mg, 39 μmol, 1.5 equiv) was added with stirring under the standard hydrogen atmosphere at room temperature for 20 h. The reaction mixture was filtered through Celite (pre-washed with MeOH) with MeOH and concentrated *in vacuo*. Purification by reverse-phase C18 (H_2O/MeOH) provided the previously reported selectin antagonist **3a**[17] (16 mg, 74%) as a clear film.

*(−)-(2R,3R)-2-O-(3-O,4-C-(1S-Cyanoprop-1,3-diyl)-2-O-benzoyl-6-O-(tert-butyldiphenylsilyl)-4-O-trimethylsilyl-β-D-galactopyranosyl)-3-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-tartaric Acid Diisopropyl Ester (**22**).* To a solution of nitrile **10a** (0.18 g, 0.26 mmol, 1.0 equiv) and previously reported tartrate-fucoside unit **20**[14] (0.33 g, 0.51 mmol, 2.0 equiv) in anhydrous toluene (5.1 mL, 50 mM), activated 4 Å molecular sieves were added. The solution was stirred at room temperature for 30 min. The solution was cooled to −30 °C, and *N*-iodosuccinimide (0.17 g, 0.77 mmol, 3.0 equiv) and TMSOTf (9.3 μL, 51 μmol, 0.20 equiv) were added. The reaction mixture was stirred for 1 h at −30 °C. The reaction mixture was filtered, and a saturated solution of $Na_2S_2O_3$ was added dropwise to the dark brown solution until it became clear. After warming to room temperature, a saturated solution of $NaHCO_3$ was added. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/Et_2O, 55:45) provided glycoside **22** (0.29 g, 87%) as a pale-yellow oil. R_f = 0.58 (hexanes/Et_2O, 50:50); $[\alpha]_D^{25}$ −25 (c 0.3, $CHCl_3$); formula: $C_{73}H_{89}NO_{16}Si_2$; MW = 1292.6760 g mol^{-1}; IR (neat) ν_{max} 2934, 1735, 1453, 1269 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06−8.00 (m, 2H), 7.66 (ddd, J = 8.0, 6.3, 1.6 Hz, 4H), 7.47−7.26 (m, 24H), 5.41 (dd, J = 10.2, 7.8 Hz, 1H), 4.93−4.79 (m, 6H), 4.78−4.66 (m, 3H), 4.61−4.51 (m, 3H), 4.38 (d, J = 5.0 Hz, 1H), 4.00 (appq, J = 6.5

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Hz, 1H), 3.91−3.80 (m, 3H), 3.67 (dd, J = 10.8, 5.4 Hz, 1H), 3.64 (d, J = 10.2 Hz, 1H), 3.43 (d, J = 2.4 Hz, 1H), 3.31 (t, J = 5.4 Hz, 1H), 2.30−2.20 (m, 1H), 1.85 (d, J = 13.7 Hz, 1H), 1.67 (d, J = 14.3 Hz, 1H), 1.58 (dd, J = 13.7, 4.2 Hz, 1H), 1.18 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H), 1.08 (s, 9H), 1.07 (d, J = 6.4 Hz, 3H), 1.03 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.14 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 168.4, 167.9, 165.6, 139.2, 139.1, 138.9, 135.8, 135.6, 133.4, 133.0, 132.9, 130.3, 130.10, 130.05, 130.00, 128.5, 128.42, 128.40, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.4, 127.3, 117.4, 100.9, 100.1, 79.6, 79.2, 78.6, 78.4, 77.7, 76.7, 75.6, 74.7, 73.2, 72.9, 72.6, 70.1, 69.1, 68.9, 67.4, 64.5, 62.2, 28.3, 27.0, 24.1, 21.9, 21.74, 21.70, 21.6, 19.3, 16.6, 2.9 ppm; HRMS (ESI) m/z: calcd for $C_{73}H_{89}NO_{16}Si_2Na$ [M + Na^+], 1314.5618; found, 1314.5590 (−1.7 ppm).

*(−)-(2R,3R)-2-O-(3-O,4-C-(1S-Cyanoprop-1,3-diyl)-2-O-benzoyl-β-D-galactopyranosyl)-3-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-tartaric Acid Diisopropyl Ester (**23**).* To a solution of glycoside **22** (0.26 g, 0.20 mmol, 1.0 equiv) in anhydrous THF (4.0 mL, 50 mM) at −10 °C, TBAF (0.42 mL, 1.0 M in THF, 2.1 equiv) was added dropwise. The reaction mixture was stirred for 30 min before being diluted with EtOAc (5 mL), and a saturated solution of NH_4Cl (10 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc, 20:80) provided diol **23** (0.16 g, 81%) as a clear oil. R_f = 0.21 (hexanes/EtOAc, 30:70); $[\alpha]_D^{25}$ −31 (c 0.7, $CHCl_3$); formula: $C_{54}H_{63}NO_{16}$; MW = 982.0890 g mol^{-1}; IR (neat) ν_{max} 3474, 2936, 1731, 1453, 1271 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (dd, J = 8.3, 1.4 Hz, 2H), 7.57−7.50 (m, 3H), 7.47−7.39 (m, 6H), 7.36−7.25 (m, 9H), 5.56 (d, J = 7.9 Hz, 1H), 5.31 (dd, J = 9.9, 7.9 Hz, 1H), 5.07 (hept, J = 6.2 Hz, 1H), 4.99 (d, J = 4.0 Hz, 1H), 4.95 (d, J = 11.6 Hz, 1H), 4.88 (d, J = 5.5 Hz, 1H), 4.88−4.73 (m, 7H), 4.64 (d, J = 11.6 Hz, 1H), 4.52 (dd, J = 10.3, 2.8 Hz, 1H), 4.22 (appq, J = 6.5 Hz, 1H), 4.12 (dd, J = 11.0, 2.7 Hz, 1H), 4.04 (dd, J = 10.3, 3.9 Hz, 1H), 3.77−3.70 (m, 2H), 3.69 (d, J = 9.9 Hz, 1H), 3.49 (td, J = 12.3, 11.6, 2.7 Hz, 1H), 3.41 (dd, J = 8.5, 2.7 Hz, 1H), 2.67 (s, 1H), 2.46−2.35 (m, 1H), 1.69 (dd, J = 14.2, 3.7 Hz, 1H), 1.64−1.57 (m, 1H), 1.47 (td, J = 13.7, 4.4 Hz, 1H), 1.27 (d, J = 6.3 Hz, 3H), 1.25 (d, J = 6.3 Hz, 3H), 1.15 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 6.5 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.7, 167.3, 166.2, 139.3, 138.7, 138.5, 133.0, 130.4, 130.2, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 127.6, 127.3, 117.1, 99.1, 98.8, 79.1, 77.9, 77.8, 77.4, 76.3, 75.9, 75.7, 75.0, 73.9, 72.5, 70.7, 70.5, 69.8, 68.7, 67.8, 64.4, 59.5, 26.5, 23.8, 21.9, 21.8, 21.7, 21.6, 16.7 ppm (due to overlapping carbon signals in the aromatic region, 1 peak is hidden); HRMS (ESI) m/z: calcd for $C_{54}H_{63}NO_{16}Na$ [M + Na^+], 1004.4045; found, 1004.4027 (−1.2 ppm).

*(−)-(2R,3R)-2-O-(3-O,4-C-(1S-Cyanoprop-1,3-diyl)-2,6-di-O-benzoyl-β-D-galactopyranosyl)-3-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-tartaric Acid Diisopropyl Ester (**S2**).* To a solution of diol **23** (150 mg, 153 μmol, 1.00 equiv) in CH_2Cl_2 (3.05 mL, 50.0 mM), pyridine (37.1 μL, 458 μmol, 3.00 equiv) and benzoyl chloride (35.5 μL, 305 μmol, 2.00 equiv) were added. After stirring for 16 h at room temperature, a saturated solution of $NaHCO_3$ (4 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided dibenzoate **S2** (0.14 g, 83%) as a white foam. R_f = 0.31 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ −24 (c 1.1, $CHCl_3$); formula: $C_{61}H_{67}NO_{17}$; MW = 1086.1970 g mol^{-1}; IR (neat) ν_{max} 3456, 2981, 2245, 1724, 1452, 1268 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08−7.99 (m, 4H), 7.61−7.56 (m, 1H), 7.51−7.35 (m, 7H), 7.32−7.21 (m, 13H), 5.41 (dd, J = 9.9, 7.4 Hz, 1H), 5.02 (d, J = 7.4 Hz, 1H), 4.94−4.80 (m, 6H), 4.75−4.67 (m, 2H), 4.67−4.60 (m, 3H), 4.55 (d, J = 11.5 Hz, 1H), 4.42 (d, J = 5.2 Hz, 1H), 4.36 (dd, J = 11.9, 6.3 Hz, 1H), 4.04 (dd, J = 6.5, 1.2 Hz, 1H), 3.94−3.88 (m, 2H), 3.74 (d, J = 9.9 Hz, 1H), 3.52−3.46 (m, 2H), 2.53−2.42 (m, 1H), 1.99−1.93 (m, 1H), 1.80−1.73 (m, 1H), 1.73−1.65 (m, 1H), 1.17 (d, J = 6.2 Hz, 3H), 1.14 (d, J = 6.3 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.3 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H) ppm (labile proton was not observed because of exchange in deuterated solvent); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 168.2, 167.9, 166.3, 165.6, 139.1, 138.9, 138.8, 133.5, 133.3, 130.3, 130.0, 129.9, 129.8, 129.7, 128.8, 128.53, 128.50, 128.47, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 117.1, 100.6, 99.9, 79.7, 78.1, 77.9, 77.6, 76.2, 75.6, 74.8, 73.0, 72.98, 72.90, 70.5, 69.5, 69.2, 68.8, 67.5, 64.6, 62.0, 26.8, 23.7, 21.8, 21.74, 21.70, 21.6, 16.6 ppm; HRMS (ESI) m/z: calcd for $C_{61}H_{67}NO_{17}Na$ [M + Na^+], 1108.4307; found, 1108.4322 (+1.9 ppm).

*(−)-(2R,3R)-2-O-(3-O,4-C-(1S-Carbamoylprop-1,3-diyl)-2,6-di-O-benzoyl-β-D-galactopyranosyl)-3-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-tartaric Acid Diisopropyl Ester (**24**).* To a reaction vessel containing nitrile **S2** (12 mg, 11 μmol, 1.0 equiv) in a 2:1 mixture of EtOH and H_2O (0.17 mL, 65 mM), a Ghaffar−Parkins catalyst (0.50 mg, 1.2 μmol, 0.11 equiv) was added. The reaction vessel was sealed, and the solution was warmed to 80 °C. The reaction mixture was stirred vigorously for 3 h before being cooled to room temperature and concentrated *in vacuo*. The crude residue was dissolved in EtOAc, filtered through a pad of silica, and concentrated *in vacuo* to provide amide **24** (12 mg, >99%) as a white foam. R_f = 0.53 (EtOAc 100%); $[\alpha]_D^{25}$ −10 (c 1.0, CH_2Cl_2); formula: $C_{61}H_{69}NO_{18}$; MW = 1104.2120 g mol^{-1}; IR (neat) ν_{max} 3489, 3351, 2981, 1723, 1689, 1452, 1269 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11−7.98 (m, 4H), 7.63−7.50 (m, 2H), 7.51−7.37 (m, 6H), 7.32−7.21 (m, 13H), 6.13 (d, J = 3.9 Hz, 1H), 5.43 (dd, J = 9.9, 7.6 Hz, 1H), 5.39 (d, J = 3.8 Hz, 1H), 5.09 (d, J = 7.6 Hz, 1H), 4.95−4.84 (m, 4H), 4.84 (d, J = 12.3 Hz, 1H), 4.74 (d, J = 12.3 Hz, 1H), 4.66 (d, J = 5.4 Hz, 1H), 4.65 (d, J = 11.4 Hz, 1H), 4.63 (dd, J = 11.9, 4.8 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.42 (d, J = 5.4 Hz, 1H), 4.40 (dd, J = 11.7, 6.4 Hz, 1H), 4.40 (d, J = 5.6 Hz, 1H), 4.03 (appq, J = 6.2 Hz, 1H), 3.94 (dd, J = 10.2, 3.4 Hz, 1H), 3.90 (dd, J = 10.2, 2.5 Hz, 1H), 3.51−3.45 (m, 2H), 3.40 (d, J = 10.0 Hz, 1H), 2.32−2.26 (m, 1H), 2.14 (ddd, J = 19.5, 13.2, 5.7 Hz, 1H), 1.86−1.79 (m, 1H), 1.40 (td, J = 13.4, 4.9 Hz, 1H), 1.18 (d, J = 6.2 Hz, 3H), 1.15 (d, J = 6.3 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H) ppm (labile proton was not observed because of exchange in deuterated solvent); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.0, 168.2, 167.9, 166.3, 165.1, 139.1, 138.8, 138.7, 133.5, 133.4, 130.2, 129.9, 129.8, 129.7, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 127.7, 127.6, 127.5, 100.1, 99.8, 79.8, 78.2, 77.4, 77.2, 77.0, 76.4, 75.7, 74.8, 74.2, 73.0, 72.9, 71.2, 69.5, 69.2, 69.1, 67.5, 62.1, 27.4, 21.8, 21.73, 21.70, 21.6, 18.5, 16.6 ppm (due to overlapping carbon signals in the aromatic region, 2 peaks are hidden); HRMS (ESI) m/z: calcd for $C_{61}H_{69}NO_{18}Na$ [M + Na^+], 1126.4412; found, 1126.4415 (+0.7 ppm).

*(−)-(2R,3R)-2-O-(3-O,4-C-(1S-5-Tetrazolylprop-1,3-diyl)-2-O-benzoyl-β-D-galactopyranosyl)-3-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-tartaric Acid Diisopropyl Ester (**25**).* To a reaction vessel containing nitrile **23** (0.12 g, 0.13 mmol, 1.0 equiv) in anhydrous DMF (2.5 mL, 50 mM), trimethylamine hydrochloride (69 mg, 0.50 mmol, 4.0 equiv) and sodium azide (33 mg, 0.5 mmol, 4.0 equiv) were added. The reaction vessel was sealed, and the reaction mixture was warmed to 130 °C and stirred for 2 h. After cooling to room temperature, trimethylamine hydrochloride (69 mg, 0.50 mmol, 4.0 equiv) and sodium azide (33 mg, 0.5 mmol, 4.0 equiv) were added. The reaction mixture was warmed to 130 °C and stirred for another 2 h. The reaction mixture was cooled to room temperature, filtered over silica, and concentrated *in vacuo*. Purification by reverse-phase C18 (H_2O/MeOH, 20:80) provided tetrazole **25** (90 mg, 70%) as a clear oil. R_f = 0.37 (MeOH/CH_2Cl_2, 20:80); $[\alpha]_D^{25}$ −69 (c 1.5, MeOH); formula: $C_{54}H_{64}N_4O_{16}$; MW = 1025.1180 g mol^{-1}; IR (neat) ν_{max} 3386, 2933, 1726, 1657, 1453, 1274 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.95 (d, J = 6.9 Hz, 2H), 7.57−7.50 (m, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.38−7.35 (m, 2H), 7.33−7.23 (m, 13H), 5.43 (dd, J = 10.0, 7.8 Hz, 1H), 5.33 (d, J = 6.3 Hz, 1H), 4.84−4.76 (m, 5H), 4.71−4.64 (m, 4H), 4.59 (d, J = 11.9 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.43 (d, J = 3.9 Hz, 1H), 4.10−4.02 (m, 2H), 3.80 (dd, J = 10.3, 3.8 Hz, 1H), 3.76−3.68 (m, 3H), 3.38−3.34 (m, 1H), 3.34−3.32 (m, 1H), 2.56 (m, 1H), 2.17−2.10 (m, 1H), 1.98 (m, 1H), 1.79 (m, 1H),

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1.18 (d, J = 6.3 Hz, 3H), 1.15−1.09 (m, 9H), 0.95 (d, J = 6.5 Hz, 3H) ppm (labile protons were not observed because of exchange with deuterated solvent); $^{13}C\{^{1}H\}$ NMR (126 MHz, CD_3OD) δ 169.9, 169.8, 167.3, 164.4, 140.20, 140.14, 140.10, 134.1, 131.8, 131.0, 129.40, 129.37, 129.30, 129.27, 129.20, 128.84, 128.80, 128.7, 128.6, 128.5, 102.0, 101.0, 80.2, 80.1, 79.1, 78.8, 78.7, 76.8, 76.7, 76.1, 74.1, 73.6, 72.0, 70.9, 70.7, 70.2, 68.9, 67.1, 60.8, 28.0, 22.2, 22.0, 21.90, 21.84, 21.80, 16.8 ppm; HRMS (ESI) m/z: calcd for $C_{54}H_{64}N_4O_{16}Na$ [M + Na^+], 1047.4215; found, 1047.4231 (+2.1 ppm).

***In Vivo* Cell Migration Assay.** The cell migration assay was carried out as described by Ray and Dittel.[37] Briefly, C57BL/6 mice were injected according to the experimental timeline.[37] One milliliter of 3% thioglycolate (Sigma-Aldrich, 70157) was added in the peritoneal cavity to stimulate leukocyte recruitment. Mice were sacrificed, the skin of the peritoneal cavity was removed, the cavity was washed with 5 mL of 2% heat-inactivated FBS 1× PBS (Gibco, 70013-032), PBS was collected, and red blood cells were lysed with Red Blood Cell Lysing Buffer Hybri-Max (Sigma-Aldrich, R7767). One million cells were used for identification by flow cytometry. Neutrophils were identified using a live/dead marker, and several surface proteins, PSGL1+, CD11b+, CD11c−, Ly-6C+, Ly-6G+, were used to identify cell populations.

Animals. All experiments performed on mice were approved by the institutional animal care and use committee (IACUC) of the University of Ottawa under the reference 3533. Biological studies were performed with C57BL/6 mice.

Flow Cytometry. Flow cytometry experiments were performed on Cytek Aurora or LSR Fortessa (BD Pharmigen) instruments. PSGL-1 antibody was obtained from BD Pharmigen (562806). CD11b antibody was obtained from BD Pharmigen (563402). CD11c antibody was obtained from BD Pharmigen (563735). Ly-6C antibody was obtained from BD Pharmigen (560592). Viability dye was obtained from BD Pharmigen (565388). Results were analyzed using FlowJo V10.8.1.

Statistical Analysis. Data are reported as the mean ± SEM or in quartiles. Statistics were obtained using unpaired Student's t-test for two-group comparison. For multiple groups, one-way ANOVA with Tukey's correction test was used. A P-value of <0.05 was considered significant.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c00956.

^{1}H NMR and ^{13}C NMR spectra for all new compounds along with proofs of structure; HPLC-UV chromatogram of **3a** (PDF)

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Notes

The authors declare no competing financial interest.

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