Novel Synthetic Inhibitors of Selectin-Mediated Cell Adhesion: Synthesis of 1,6-Bis[3-(3-carboxymethylphenyl)-4-(2-α-D-mannopyranosyloxy)phenyl]hexane (TBC1269)

Timothy P. Kogan,* Brian Dupré, Huong Bui, Kathy L. McAbee, Jamal M. Kassir, Ian L. Scott, Xin Hu,† Peter Vanderslice,† Pamela J. Beck,†,‡ and Richard A. F. Dixon

Departments of Chemistry & Biophysics and Immunology, Texas Biotechnology Corporation, 7000 Fannin, Suite 1920, Houston, Texas 77030

Received July 29, 1997

Reports of a high-affinity ligand for E-selectin, sialyl di-Lewis^x (sLe^{x}Le^x, **1**), motivated us to incorporate modifications to previously reported biphenyl-based inhibitors that would provide additional interactions with the protein. These compounds were assayed for the ability to inhibit the binding of sialyl Lewis^x (sLe^x, **2**) bearing HL-60 cells to E-, P-, and L-selectin fusion proteins. We report that dimeric or trimeric compounds containing multiple components of simple nonoligosaccharide selectin antagonists inhibit sLe^x-dependent binding with significantly enhanced potency over the monomeric compound. The enhanced potency is consistent with additional binding interactions within a single selectin lectin domain; however, multivalent interaction with multiple lectin domains as a possible alternative cannot be ruled out. Compound **15e** (TBC1269) showed optimal in vitro activity from this class of antagonists and is currently under development for use in the treatment of asthma.

Introduction

The selectins participate in the adhesion of leukocytes to endothelial cells by mediating the initial rolling of leukocytes on the lumen wall of blood vessels. They are a family of three structurally related calcium-dependent cell adhesion molecules which are expressed on the surface of activated vascular endothelial cells (E- and P-selectin), activated platelets (P-selectin), and leukocytes (L-selectin).[1] These proteins function by binding sialyl Lewis^x (sLe^x, **2**, Figure 1)[2,3] and related oligosaccharides which are present on the surface of neutrophils, monocytes, a subset of T lymphocytes, eosinophils, basophils, and endothelial cells. One of the initial events following injury is the recruitment of leukocytes to activated endothelium in the vicinity of the injury and is mediated by the interaction between sLe^x on the leukocyte and E- and P-selectin expressed on activated endothelial cells. Amplification of adherance is achieved by L-selectin-mediated interactions between circulating leukocytes and adhered leukocytes. However, the accumulation of excess leukocytes, or inappropriate leukocyte recruitment, may contribute to the development of several disease states. Thus, the ability to regulate the interactions between the selectins and sLe^x or other ligands could have potential utility in a number of clinical conditions such as asthma, reperfusion injury, psoriasis, cancer, lupus, ARDS, septic shock, rheumatoid arthritis, and other cell adhesion-mediated diseases.[4]

The key functional groups of sLe^x necessary for interaction with the selectins have been identified,[5] and a number of antagonists have been reported, which are mainly represented by oligosaccharides[6] and glycosylated peptides.[7] Both classes of compounds may suffer from a number of problems regarding development as pharmaceutical agents, particularly regarding cost of goods, stability, and pharmacokinetic half-life. Our efforts in this area resulted in the identification of a novel class of low molecular weight, non-oligosaccharide biphenyl-based compounds exemplified by **3** (Figure 1), which possess significant advantages over oligosaccharide-based inhibitors.[8] Benefits include fewer chiral centers, providing easier synthetic access and the potential for lower cost of materials, as well as increased thermal and chemical stability, and the potential for oral bioavailability. These compounds were designed to utilize mannose and carboxylic acid functionalities as replacements for the critical fucose and sialic acid groups of sLe^x, respectively, and a biphenyl unit to replace the lactosamine core. No direct evidence exists regarding the specific set of interactions made between E-selectin and sLe^x; however several pieces of circumstantial evidence[9] support our earlier hypothesis in which the fucose is coordinated to calcium, and the sialic acid is oriented toward Arg-97 and Lys-99.[10,11] Regardless of the actual mode of binding used by sLe^x, **3** can be considered a good functional mimetic, since it is a competitive inhibitor of sLe^x binding to E-, P-, and L-selectin.[8] By comparison, compounds lacking either the acid group or the mannose group in this series were found to be essentially devoid of activity against each of the three selectins.

As part of our ongoing research in this area, we sought to investigate rational approaches to the generation of selectin inhibitors with increased potency. Recently there have been reports of more complex oligosaccharides that may represent relevant in vivo E-selectin

* To whom correspondence should be addressed; e-mail: tkogan@tbc.com. Tel: (713) 796-8822. Fax: (713) 796-8232.
† Department of Immunology.
‡ Current address: Institute of Molecular Medicine for the Prevention of Human Disease, The University of Texas, Houston Health Science Center, 2121 W. Holcombe, Houston, TX 77030.

S0022-2623(97)00491-3 CCC: $15.00
Published on Web 02/28/1998

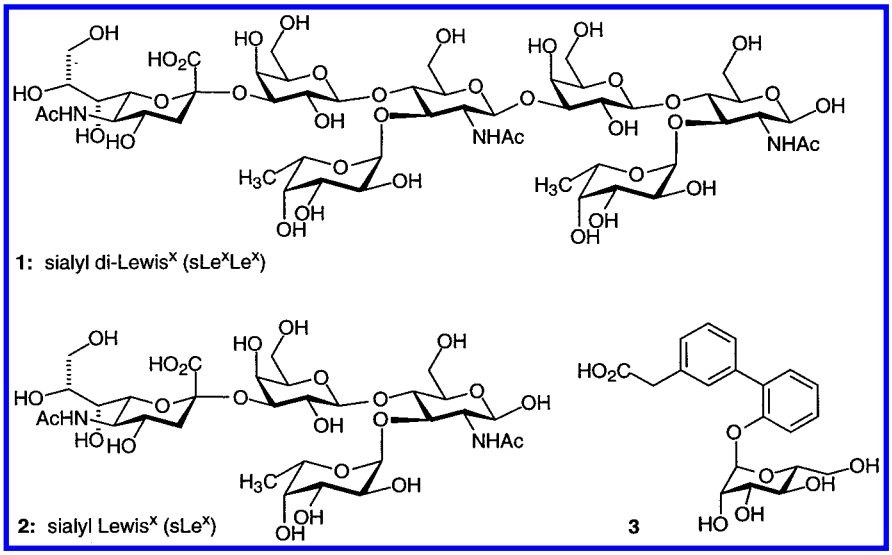
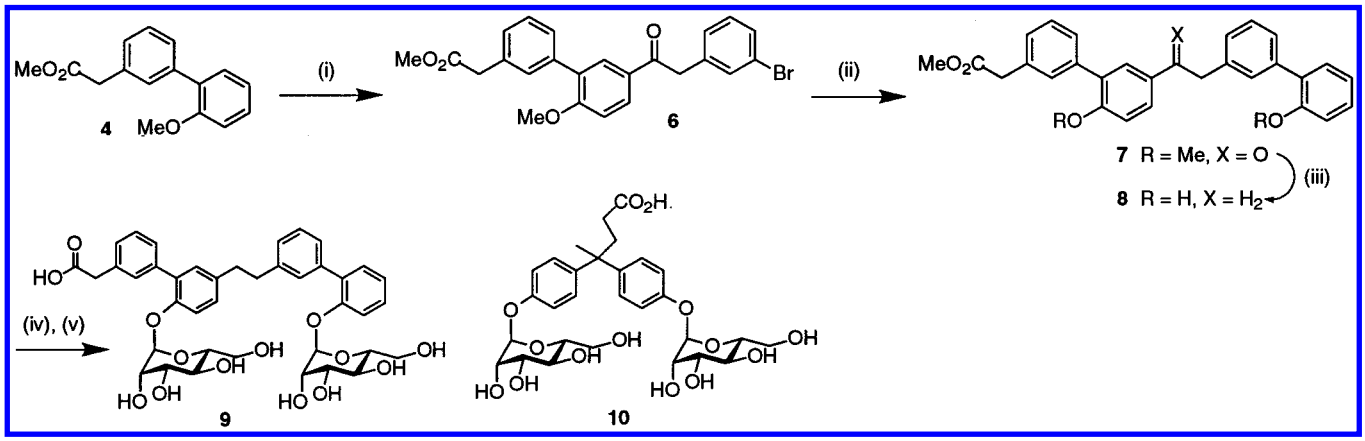


Figure 1. Characterized E-selectin ligands sLe^{x}Le^{x}1 and sLe^{x}2, and the biphenyl-based glycomimetic **3**.

Scheme 1[a]



[a] Reagents: (i) 3-bromophenylacetyl chloride, $AlCl_3$; (ii) 2-methoxyphenylboronic acid, Pd(0), aqueous Na_2CO_3; (iii) (a) aqueous KOH; (b) N_2H_4; (c) BBr_3; (d) MeOH, H^+; (iv) α-D-mannose pentaacetate, $BF_3{\cdot}Et_2O$; (v) aqueous LiOH.

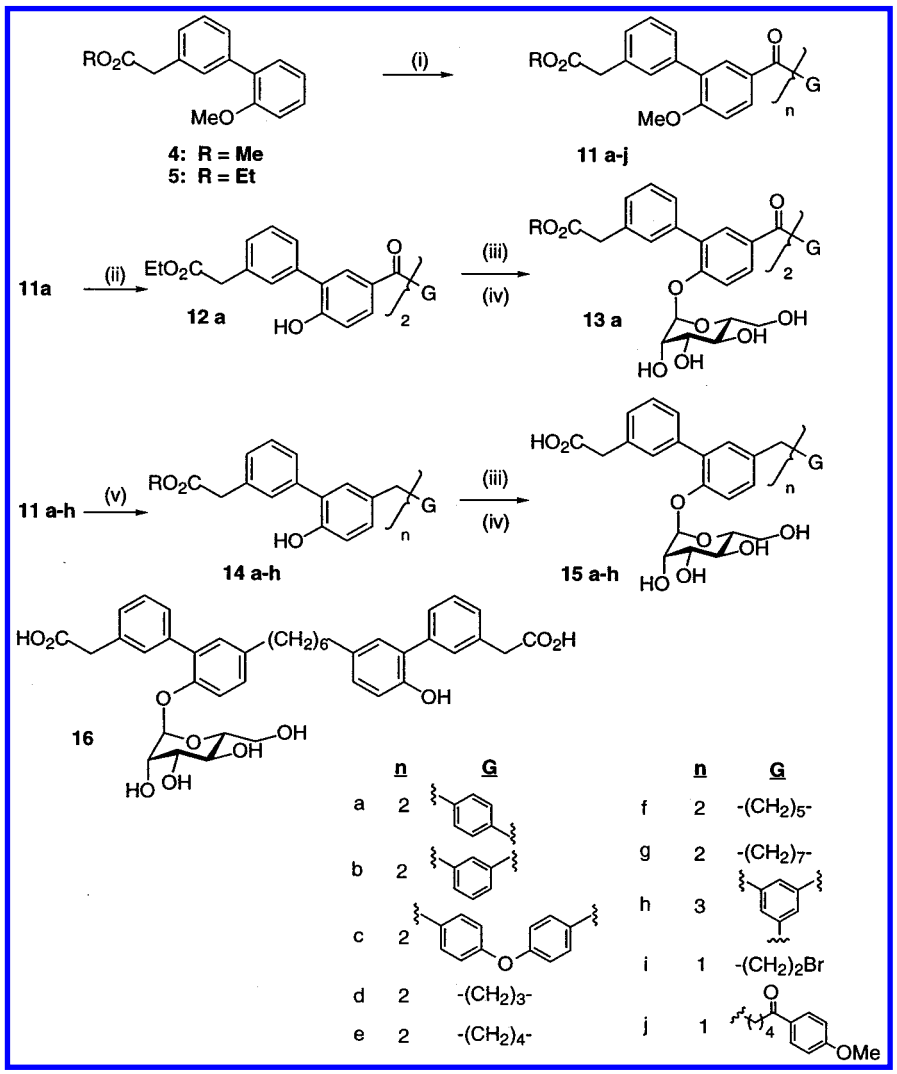
ligands of high potency, as well as reports that multivalent sLe^x presentation may be important in obtaining high-affinity interactions.[12] We report here the results of investigations into the design of mimetics of higher affinity selectin ligands which possess increased structural complexity, as well as preliminary investigations of potential multivalent analogues of compound **3**, which have led to the development of a class of inhibitors with increased potency.

Design and Synthesis

While some knowledge has recently been gained regarding the nature of selectin ligands, a clear understanding of the structure of all relevant in vivo ligands for each of the selectins remains elusive.[3b,13] For example, the glycoprotein PSGL-1 has been reported as a native ligand of both L- and P-selectin and bears the sLe^x carbohydrate motif. Further known ligands include ESL-1 for E-selectin and GlyCAM-1, MAdCAM-1, and CD34 for L-selectin. The sLe^x motif was identified as a natural oligosaccharide capable of selectin recognition some time ago. However, doubts have remained about the relevance of a ligand with millimolar potency in in vitro assays to the in vivo adhesion of leukocytes. Several hypotheses have been offered to explain this discrepancy, including the conformational biasing of the mobile sialic acid residue in the proximity of other complex glycoproteins on the cell surface.[14] Clearly, an alternative explanation is the presence of other ligands of higher affinity which remain to be identified. Along these lines, Parekh has reported the identification of several tetra-antennary oligosaccharide structures isolated from U937 cells and human neutrophils.[12] Upon characterization, these oligosaccharides were each shown to contain one branch bearing the extended sialyl di-Lewis^x (sLe^{x}Le^x, **1**, Figure 1) motif. These oligosaccharides were reported to bind E-selectin with much greater affinity than either sLe^x or sLe^a (K_I's of approximately 1 μM) yet are expressed on less than 3% of cell surface glycoproteins.

We considered that incorporation of an additional mannose unit via an appropriate spacer may result in derivatives of **3** that would be mimetics of the more potent sLe^{x}Le^x oligosaccharide. Preliminary modeling studies suggested that a biphenylethyl unit would function suitably, and that the biphenyl ether **4** (Scheme 1) would permit synthetic access, since it would undergo Friedel–Crafts chemistry selectively at the desired 4-position (para to the methoxy substituent). Thus **4** was treated with 3-bromophenylacetyl chloride and

Scheme 2[a]



[a] Reagents: (i) acid chloride, $AlCl_3$; (ii) BBr_3; (iii) α-D-mannose pentaacetate, $BF_3 \cdot Et_2O$; (iv) aqueous NaOH or aqueous LiOH; (v) (a) aqueous LiOH, then N_2H_4; or Et_3SiH, TFA, $BF_3 \cdot Et_2O$; or $Pd(OH)_2/H_2$; then (b) BBr_3; (c) MeOH, H^+.

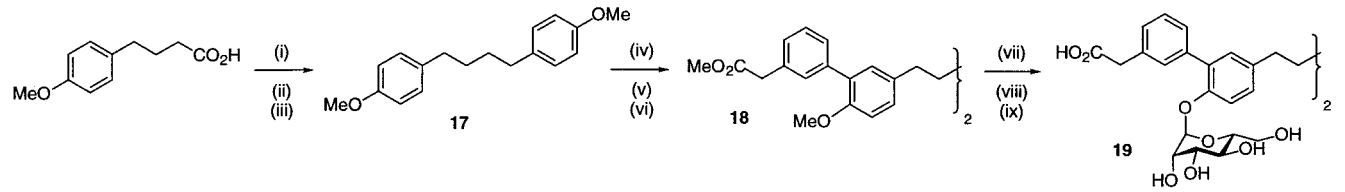
aluminum chloride to afford ketone **6**. A Suzuki coupling with 2-methoxyphenylboronic acid,[15] followed by Wolff–Kishner reduction of the ketone, demethylation of the two methyl ethers and re-esterification of the acid gave the bis-phenol **8**. Glycosylation using α-D-mannose pentaacetate, followed by hydrolysis of the esters, gave **9**. For comparison, a control compound with alternate spacing of the two mannose groups and carboxylic acid, the bis[(mannosyloxy)phenyl]valeric acid **10** was prepared by treatment of 4,4′-bis(4-hydroxyphenyl)valeric acid with α-D-mannose pentaacetate, followed by deprotection.

Having established that Friedel–Crafts acylation provided a facile route to functionalization of the biphenyl unit, we recognized that the use of a multivalent acid chloride would allow an alternative and concise route to compounds bearing multiple mannose units through a dimerization or trimerization process. Thus, Friedel–Crafts acylation of **4** or **5** using a variety of acid chlorides was used as a convenient route to access these structures (Scheme 2). Ether cleavage, followed by glycosylation and hydrolysis, produced **13a**. Phenols **14a–h** were obtained from **11a–h** by one of three different methods: (a) Wolff–Kishner reduction of the ketone followed by ether cleavage and re-esterification, (b) reduction of the ketone using triethylsilane in the presence of boron trifluoride etherate and trifluoroacetic acid followed by ether cleavage, or (c) catalytic reduction followed by ether cleavage with boron tribromide. Use of the ethyl rather than methyl ester (starting from **5** rather than **4**) suppressed ester cleavage which was occasionally observed during demethylation of the phenol. Finally, compounds **15a–h** were obtained by standard glycosylation, followed by hydrolysis. During the preparation of **15e**, a sample of the monoglycoside **16** was also isolated and characterized.

An alternative method was used to prepare derivative **19** (Scheme 3). Commercially available 4-(4-methoxyphenyl)butyric acid was converted to the acid chloride with thionyl chloride, and subjected to Friedel–Crafts acylation with anisole followed by reduction of the ketone to the symmetrical bis-ether **17**. Bis-ortholithiation, boronation, and hydrolysis gave the intermediate bis-boronic acid, which was subjected to Suzuki coupling with methyl 3-bromophenylacetate to give bis-biphenyl **18**. Demethylation using boron tribromide, followed by glycosylation and then hydrolysis, gave **19**.

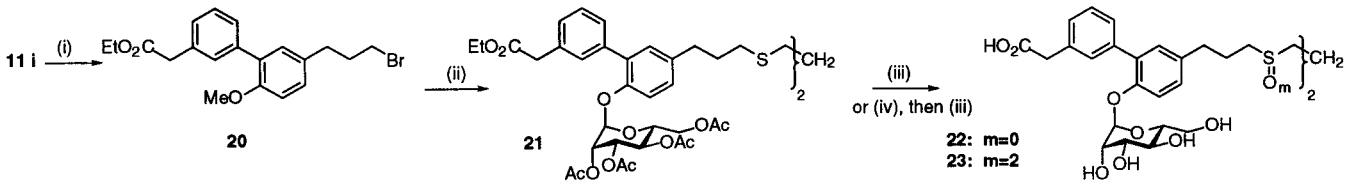
The sulfide and sulfone spaced compounds **22** and **23**, respectively, were obtained from the propanoyl bromide **11i** (Scheme 4). Reduction of the ketone followed by

Scheme 3[a]



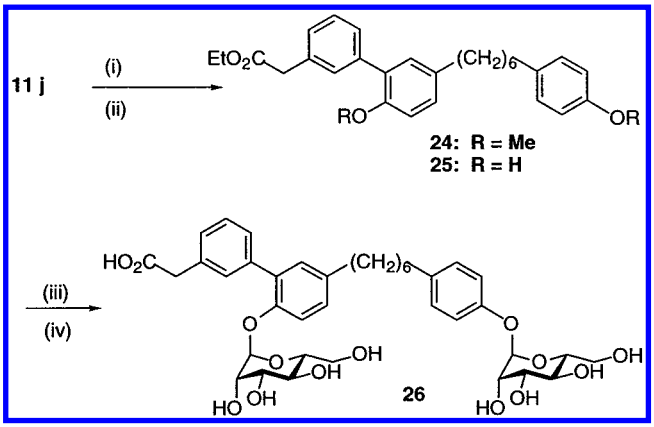
[a] Reagents: (i) $SOCl_2$; (ii) anisole, $AlCl_3$; (iii) Et_3SiH, TFA, $BF_3{\cdot}Et_2O$; (iv) *n*-BuLi, THF, TMEDA; (v) (a) $B(OMe)_3$; (b) H_3O^+; (vi) methyl 3-bromophenyl acetate, Pd(0), K_3PO_4; (vii) BBr_3; (viii) α-D-mannose pentaacetate, $BF_3{\cdot}Et_2O$; (ix) aqueous LiOH.

Scheme 4[a]



[a] Reagents: (I) Et_3SiH, TFA, $BF_3{\cdot}Et_2O$; (ii) (a) NaH, 1,3-propanedithiol, (b) BBr_3, (c) α-D-mannose pentaacetate, $BF_3{\cdot}Et_2O$; (iii) aqueous NaOH or aqueous LiOH; (iv) *m*-CPBA.

Scheme 5[a]



[a] Reagents: (i) Et_3SiH, TFA, $BF_3{\cdot}Et_2O$; (ii) BBr_3; (iii) α-D-mannose pentaacetate, $BF_3{\cdot}Et_2O$; (iv) aqueous NaOH.

reaction of the bromide **20** with propane dithiol and then demethylation and glycosylation gave **21**. Hydrolysis of the esters gave the sulfide **22**, while prior oxidation of the bis-sulfide followed by hydrolysis gave the bis-sulfone **23**.

The bis-glycoside with only a single carboxylate **26** (Scheme 5) was prepared from **11j** by reduction of the ketone groups with triethylsilane, followed by demethylation which gave **25**. Glycosylation of the phenols and then deprotection gave **26**.

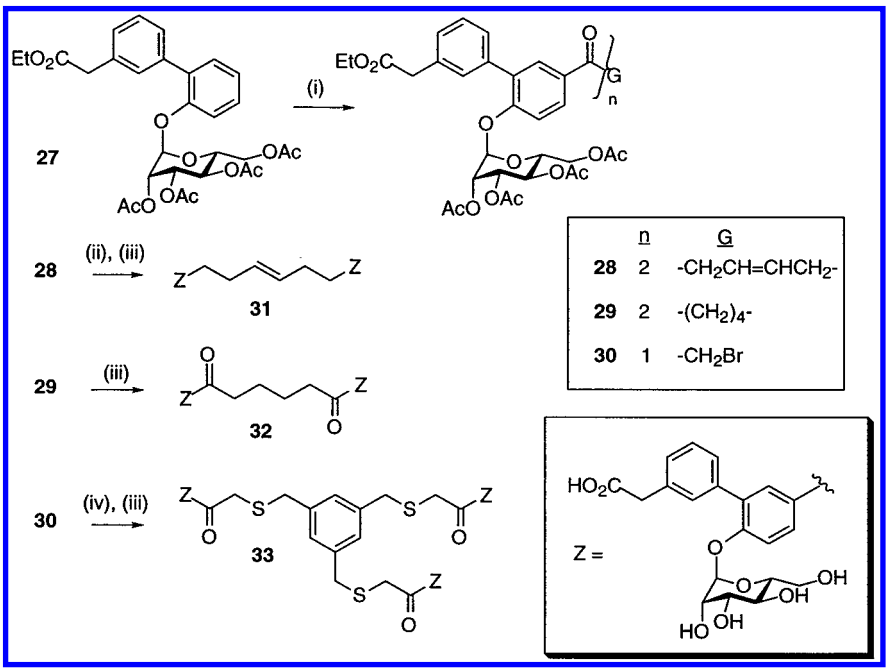
An alternative approach permitted the use of the glycosylated ester **27** (prepared from **5** by ether cleavage and glycosylation) as an advanced intermediate (Scheme 6). Friedel–Crafts acylation with either *trans*-3-hexenedioic acid chloride, adipoyl chloride, or bromoacetyl bromide gave the ketones **28**–**30**, respectively. Reduction of the ketone **28** with triethylsilane, followed by hydrolysis of the protecting groups, gave **31**, while **29** was hydrolyzed directly to provide the diketone **32**. A trimer was prepared by reaction of **30** with 1,3,5-tris(mercaptomethyl)benzene and sodium hydride, followed by hydrolysis of the protecting groups which gave **33**.

We sought to further investigate a variety of linking groups which included amides and amines due to their potential to address variations of both distance and relative conformation of the terminal units. Toward this end, a series of derivatives were prepared as outlined in Scheme 7. For the amine series of compounds, the more stable pivalate protecting group was used for the mannose hydroxyls to prevent acyl migration onto the basic nitrogen.[16] The pivotal intermediate for these, **35**, was prepared by Friedel–Crafts acylation of **34** with succinic anhydride. Reduction of the ketone, generation of the acid chloride, and condensation with a number of amines gave **36a**–**e**. Hydrolysis of the esters then gave the target amides **37a**–**e**. Alternatively, amide **36a** was reduced with borane in THF, and then hydrolyzed to provide the target amine **38a**. Compound **39** was obtained by reduction of the ketone and acid functional groups of **35** with borane in THF, followed by reaction of the resulting alcohol with cyanuric chloride and then hydrolysis of the protecting groups with aqueous base.

The methods used to prepare the previous biphenyl derivatives were unsuitable for access to **42**. Due to the additional oxygen substitution on the biphenyl system, a single position was no longer preferred in the Friedel–Crafts acylation; therefore an alternate route was devised as outlined in Scheme 8. Thus, 1,6-bis(4-methoxyphenyl)hexane **40** was prepared by Friedel–Crafts acylation of anisole with adipoyl chloride, followed by Wolff–Kishner reduction of the ketones. Bromination ortho to the methoxy groups with bromine/ferric chloride followed by cleavage of the methyl ethers with boron tribromide and glycosylation using α-D-mannose pentaacetate gave **41**. Suzuki coupling of the bromide **41** with 3-hydroxybenzene boronic acid followed by alkylation of the phenol with ethyl bromoacetate and then hydrolysis gave the target compound **42**.

In Vitro Assay Data. The compounds described above were evaluated for their ability to inhibit the binding of sLe^x expressing HL-60 cells to recombinant fusion proteins bearing the lectin domain of human E-, P-, or L-selectin, the EGF-like domain, and two complement repeats fused to the hinge, CH_2, and CH_3 domains of mouse IgG, and the results are reported in Table 1.[17] Compound **9**, which was designed to mimic the sLe^xLe^x motif, displayed improved affinity for E- and L-selectin, compared with **3**. As anticipated, the relative spatial arrangement of the two mannose units and carboxylic

Scheme 6[a]



[a] Reagents: (i) acid chloride, $AlCl_3$; (ii) Et_3SiH, TFA, $BF_3{\cdot}Et_2O$; (iii) aqueous NaOH; (iv) NaH, 1,3,5-tris(mercaptomethyl)benzene.

acid were shown to be important, as the control compound **10** was essentially inactive at the concentration tested.

The binding data obtained for the series of dimer and trimer compounds provided additional insight into structure/activity relationships. Although diketone **13a** could not be tested due to insolubility under the assay conditions, the diketone **32** displayed improved activity compared to the parent compound **3**. In the series of compounds **15a**,**b**,**d**−**h**, **19**, and **31** the optimum spacing and orientation appears to be present in **15d** for E- and L-selectin (a pentane linker), and **15e** for P-selectin (a hexane linker). Of note in this series of compounds was the complete lack of activity of **31** at 3 mM compared with **15e**. These compounds differ only in that **31** has an (*E*)-3-hexenyl linkage rather than the hexyl linker in **15e**.

The monoglycoside **16** was inactive against E- and L-selectin at the concentration tested; however, activity in the P-selectin assay was comparable to that of **3**, yet significantly less potent than **15e**. Conversely, the bis-glycoside monocarboxylate **26** was about as active as **15e** in the E- and L-selectin assays and had diminished activity against P-selectin.

In the series of sulfur-containing compounds **22**, **23**, and **33**, only **22** showed activity at the concentrations tested and was P-selectin selective. All of the nitrogen-containing compounds, **37a**−**e**, **38a**, and **39**, were inactive at the concentrations tested, except for **37b** which showed a slight improvement for E- and P-selectin compared to the parent monomeric compound. The oxygen-containing derivative **15c** was selective for P-selectin, as was the compound with ether linkages between the biphenyl and carboxylic acid moieties, **42**. None of the trimeric compounds prepared, **15h**, **33**, **37d**, or **39**, showed improved properties over the preferred dimeric compounds such as **15e**.

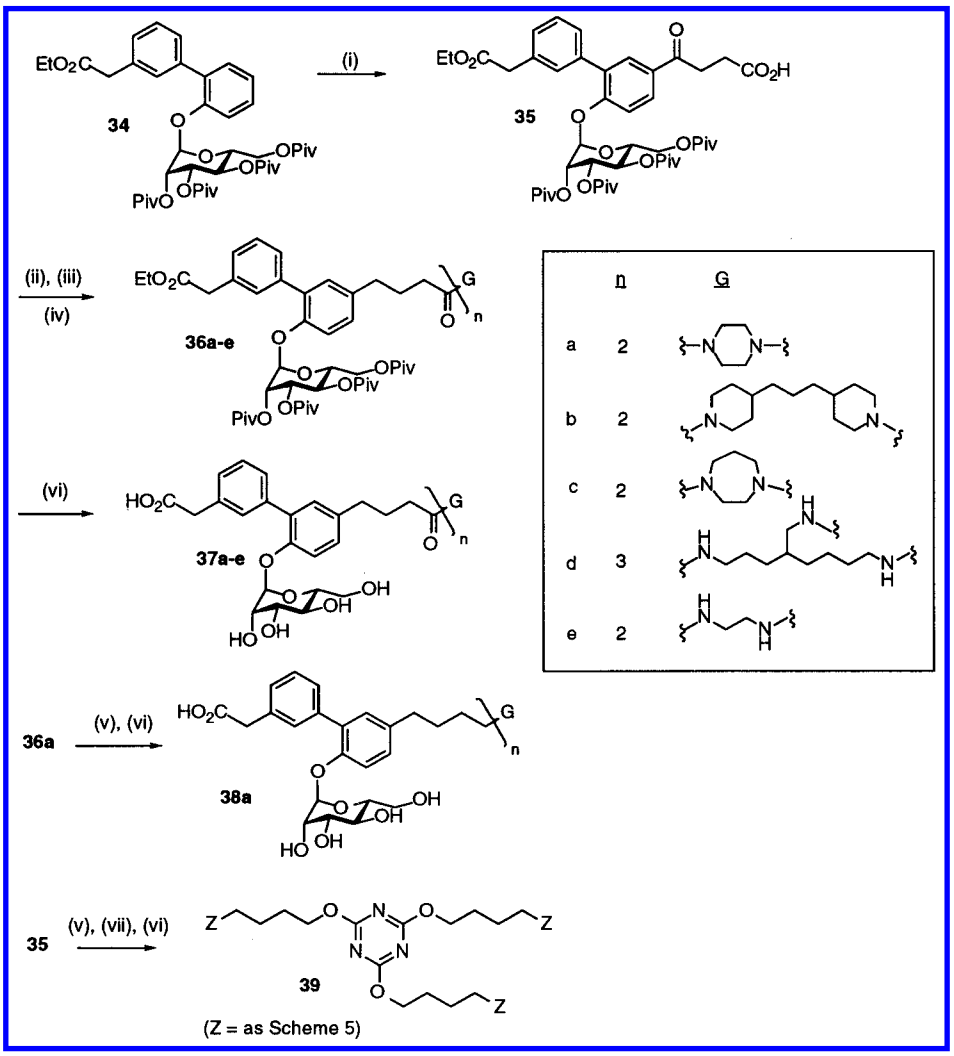
Discussion

While the binding of carbohydrates such as sLe^x and related oligosaccharides to proteins is typically weak in nature, more complex oligosaccharide structures such as sialyl di-Lewis^x show higher affinity. The results presented here demonstrate that the design of non-oligosaccharide mimetics of complex oligosaccharides can result in high-affinity antagonists. From the data reported it is of interest to consider whether these compounds are likely to work as functional mimetics of sialyl di-Lewis^x, or if other mechanisms/modes of action are responsible for their enhanced potency. Although a definitive answer to this question is not currently possible, evaluation of the available SAR data provides for speculation.

One alternative hypothesis due consideration is that of multivalent interaction between these compounds and two independent selectin molecules. Indeed, several groups have shown significantly enhanced potency achieved through multiple presentation of selectin recognizing oligosaccharides on either protein,[18] liposomal,[19] or polymeric templates.[20] The published data suggests that more than bivalent presentation of ligands is required to observe significant enhancements in potency,[18] although dimers of sLe^x have been reported with 4−6-fold greater activity than the monomer, perhaps functioning as mimetics of sLe^xLe^x.[21]

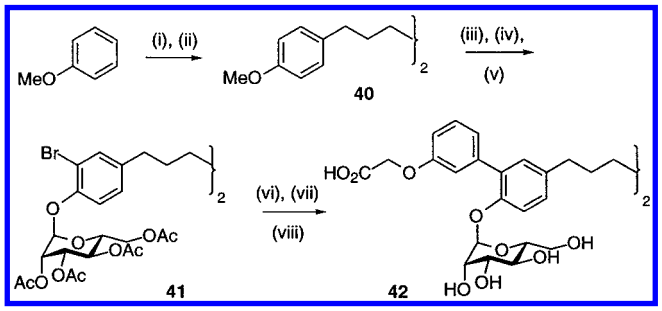
The most compelling data to support the action of these compounds as sialyl di-Lewis^x mimetics comes from the set of compounds that contain varying numbers of either carboxylates or mannose units present. These include **9** (two mannose, one carboxylate), **26** (two mannose, one carboxylate), **16** (one mannose, two carboxylates), and **15e** (two mannose, two carboxylates). It was observed that a second carboxylate was not required for enhanced acivity against each of the selec-

Scheme 7[a]



[a] Note: Piv is used as an abbreviation for trimethylacetyl. Reagents: (i) succinic anhydride, $AlCl_3$; (ii) Et_3SiH, TFA, $BF_3{\cdot}Et_2O$; (iii) $SOCl_2$; (iv) amines a−e, NEt_3; (v) $BH_3{\cdot}THF$; (vi) NaOMe, then aqueous NaOH; (vii) NaH, cyanuric chloride.

Scheme 8[a]



[a] Reagents: (i) adipoyl chloride, $AlCl_3$; (ii) N_2H_4, KO-*t*-Bu, DMSO; (iii) Br_2, $FeCl_3$; (iv) BBr_3; (v) α-D-mannose pentaacetate, $BF_3{\cdot}Et_2O$; (vi) 3-hydroxyphenyl boronic acid, Pd(0), K_3PO_4; (vii) ethyl bromoacetate, Cs_2CO_3; (viii) aqueous NaOH.

tins (compounds **9** and **26**), whereas the monomannosylated compound, **16**, had significantly reduced activity.

Additional implications with regard to the mode of lectin binding adopted by the dimeric compounds are derived from evaluating the nature of the linking group. Dimers linked by five, six, or seven saturated carbon atoms (**15d**,**e**,**f**) displayed significant improvements in inhibiting all three selectin proteins compared to the monomeric compound **3**. Surprisingly the more rigid analogue, **31**, which contained a six carbon spacer with a trans olefin, was inactive. These data suggest that conformations of the alkyl spacer that are required for enhanced activity are not available to the more rigid compound **31**. Specifically, those conformations in which the hexyl linker is folded back are required to enable both mannose units to interact with the same protein surface. Other variations in length or atom type in the linker did not lead to improved activity. In fact, many of those with longer, nitrogen-containing linkers (**37a**−**e** and **38a**) had reduced or no observable activity. In the series of trimeric compounds investigated (**15h**, **33**, **37d**, or **39**), only **15h** proved to be effective, while the others in the series were inactive at the concentrations tested.

The results presented in this paper, particularly with regard to the potency of divalent structures, suggest that both units of compounds such as **15e** likely bind to the same lectin domain. This hypothesis is consistent with a number of results published from groups working with other systems in which enhanced potency was obtained through establishing an additional set of interactions.[22] Preliminary modeling suggests that compounds of this type may adopt conformations in which the mannose units occupy positions similar to

Table 1. In Vitro Inhibition of sLe^X Bearing HL-60 Cells to Selectin-IgG Fusion Proteins[24]

	IC_{50}(mM) or % inhib at mM		
compd	E-selectin	P-selectin	L-selectin
sLe^X	3.3	3.4	3.5
3	3.1	2.6	4.1
9	1.0	2.0	0.75
10	12 at 3	0 at 3	20 at 3
13a	*a*	*a*	*a*
15a	2.0	2.0	3.0
15b	0 at 1	0.225	3.0
15c	2.5	0.7	0 at 2
15d	0.4	0.3	0.3
15e	0.5	0.07	0.56
15f	0.5	0.4	0.75
15g	40 at 1	40 at 1	1.0
15h	45 at 0.65	0.2	0.5
16	0 at 3	2.0	10 at 3
19	5.0	2.5	12 at 2
22	29 at 2	0.5	5.0
23	0 at 3	0 at 3	0 at 3
26	0.3	1.0	0.6
31	0 at 3	0 at 3	0 at 3
32	1.0	1.0	3.0
33	4.0	0 at 3	2.0
37a	0 at 3	0 at 3	0 at 3
37b	1.5	1.0	0 at 3
37c	40 at 3	0 at 3	0 at 3
37d	15 at 3	0 at 3	0 at 3
37e	0 at 3	0 at 3	0 at 3
38a	0 at 3	0 at 3	0 at 3
39	0 at 3	0 at 3	25 at 3
42	3.2	0.54	1.4

[a] Compound not soluble at concentration tested

each of the fucose units of sialyl di-Lewis^x, as indicated by a comparison of selected low energy confomations (Figure 2). A more extensive molecular modeling approach has been initiated to investigate which modes of binding of **15e** are likely to be preferred, and how such interactions differ for the three selectin proteins. Initial studies reveal that **15e** can adopt a low-energy conformation wherein the two mannose groups can be overlaid with the two fucose residues of **1**, while one of the carboxylates of **15e** is positioned in similar proximity to the sialyl carboxylate (Figure 2). More detailed studies correlating the conformational flexibility and relative energies of possible bound conformations are ongoing and will be published elsewhere.

While the data presented support the notion that the second carboxylate of **15e** is functionally redundant, this is more than compensated for by simplification of the synthetic chemistry which results in a symmetrical molecule. Due to the interesting in vitro data gathered on **15e**, this compound has been evaluated in animal models of inflammation, and the results from these studies will be reported elsewhere.[23] Current efforts are directed toward further enhancements of activity in the monovalent series of compounds, as well as approaches to a series of compounds with considerably extended in vivo half-life. Results from these studies, as well as the clinical development of **15e**, will be reported in due course.

Experimental Section

Reagents and solvents were used as received unless otherwise specified. All reactions involving organometallic compounds or other air or moisture sensitive materials were conducted under a nitrogen atmosphere, in oven-dried glassware. Preparative reverse-phase HPLC was conducted on a

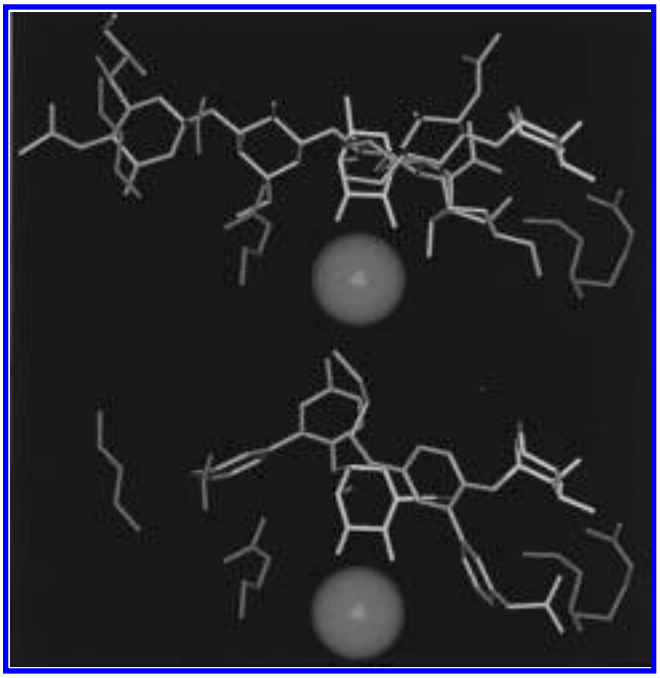


Figure 2. Views of a low-energy conformation of **1** (top) and **15e** (bottom) bound to the E-selectin calcium site. The compounds are color coded to indicate the similar relative positioning possible for the carboxylic acids (magenta) and the mannose and fucose residues (yellow). The E-selectin calcium is shown as a blue sphere, while the residues Lys-99, Arg-97, Lys-111, and Arg-108 (blue) are positioned sequentially from left to right. The distances from the carboxylate carbon to a centoid between the calcium coordinating hydroxyl groups are 12.07 Å for **1** and 11.24 Å for **15e**.

Rainin Dynamax 300 Å 5 μm (21 mm i.d. × 25 cm) C-18 column using a gradient of water and acetonitrile (with 0.1% TFA) for elution, with UV monitoring at 254 nm. Pure fractions were lyophilized and analyzed for purity. Proton NMR spectra were recorded on a JEOL 400 MHz spectrometer using an internal reference. Infrared spectra were recorded on a Bruker IFS-25 instrument as thin films on sodium chloride plates, or as KBr pellets. Melting points were determined using a Fisher-Johns hot stage apparatus and are uncorrected.

3-(2-α-D-Mannopyranosyloxy-5-(2-(3-(2-α-D-mannopyranosyloxyphenyl)phenyl)ethyl)phenyl)phenylacetic Acid (9). Step 1. Methyl 3-(2-methoxyphenyl)phenylacetate (**4**, 0.82 g, 3.2 mmol) and 3-bromophenylacetyl chloride (0.77 g, 3.3 mmol) were dissolved in 1,2-dichloroethane (11 mL) and chilled in an ice bath. Aluminum chloride (0.88 g, 6.6 mmol) was added in one portion and the mixture was warmed at 50 °C for 15 min then mixed with ice water. The organic materials were separated, dried ($MgSO_4$), then concentrated under reduced pressure which gave 1.68 g of methyl 3-(2-methoxy-5-(1-oxo-2-(3-bromophenyl)ethyl)phenyl)phenylacetate (**6**) as a yellow oil which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 7.95−8.20 (m, 2H), 7.35−7.45 (m, 6H), 7.29 (br d, J = 6.9 Hz, 1H), 7.18−7.22 (m, 1H), 7.01 (d, J = 8.4 Hz, 1H), 4.22 (s, 2H), 3.87 (s, 3H), 3.70 (s, 3H), 3.69 (s, 2H) ppm. IR (NaCl): 1730, 1686, 1262 cm^{-1}.

Step 2. The crude halide **6** was mixed with (2-methoxyphenyl)boronic acid (0.54 g, 3.55 mmol) in toluene (20 mL), then tetrakis(triphenylphosphine)palladium(0) (120 mg, 3 mol %) and 2 N sodium carbonate (6 mL) were added, and the mixture was degassed. The mixture was heated at reflux for 14 h, then mixed with water, and extracted with ethyl acetate. The organic materials were combined, washed with saturated sodium chloride, dried ($MgSO_4$), and then concentrated under reduced pressure. Purification by flash chromatography (SiO_2, gradient elution, hexane to 3:1 hexane/ethyl acetate) gave 1.57 g (77%) of methyl 3-(2-methoxy-5-(1-oxo-2-(3-(2-methoxyphe-

nyl)phenyl)ethyl)phenyl)phenylacetate (**7**) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): 8.00−8.05 (m, 2H), 7.23−7.46 (m, 10H), 6.93−7.03 (m, 3H), 4.29 (s, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 3.69 (s, 3H), 3.65 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 196.3, 172.1, 160.3, 156.3, 138.7, 136.8, 134.2, 133.9, 132.0, 131.0, 130.7, 130.5, 130.4 (3), 129.7, 128.7, 128.4 (4), 128.1, 128.0, 120.9, 111.2, 110.7, 55.9, 55.6, 52.2, 45.6, 41.3 ppm. IR (NaCl): 1739, 1674, 1269, 1244 cm^{-1}.

Step 3. The ketone (**7**, 2.25 g, 4.68 mmol) was dissolved in DMSO (15 mL), and the solution was treated with 2 N potassium hydroxide (2.5 mL) and then stirred at 60 °C under nitrogen for an hour. The mixture was cooled to room temperature, treated with hydrazine hydrate (0.4 mL, 11.7 mmol), and then heated at 60 °C for an additional hour. Potassium *tert*-butoxide (1.31 g, 11.7 mmol) was added, and the temperature was increased to 100 °C. After 18 h the mixture was cooled, mixed with water, and acidified to pH 4 with 2 N HCl. The mixture was saturated with sodium chloride and extracted with THF/ethyl acetate (1:1), and the extracts were combined, dried ($MgSO_4$), and then concentrated under reduced pressure which gave 2.29 g of a dark oil. IR (NaCl): 1709 cm^{-1}. The crude product was dissolved in dichloromethane (25 mL) and cooled in a dry ice/2-propanol bath. Boron tribromide (2.4 mL, 25 mmol) was added dropwise, and the mixture was stirred at −78 °C for 2 h, warmed to 0 °C for 2 h, then re-cooled to −78 °C, and quenched with methanol. The mixture was concentrated under reduced pressure, and the residue was partitioned between THF and saturated sodium chloride. The organic material was separated, dried ($MgSO_4$), and then concentrated. The residue (2.63 g) was dissolved in methanol (30 mL), and 5 drops of concentrated sulfuric acid was added. The mixture was refluxed overnight, filtered through a pad of sodium carbonate, and then concentrated. Purification by flash chromatography (SiO_2, gradient elution, hexane to 3:1 hexane/ethyl acetate) gave 0.89 g (43%) of methyl 3-(2-hydroxy-5-(1-oxo-2-(3-(2-hydroxyphenyl)phenyl)ethyl)phenyl)phenylacetate **8** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.15−7.50 (m, 10H), 6.80−7.10 (m, 5H), 5.26 (s, 1H), 5.17 (s, 1H), 3.71 (s, 3H), 3.68 (s, 2H), 2.90−3.00 (m, 4H) ppm. IR (NaCl): 3417, 1718 cm^{-1}.

Step 4. The bis-phenol (**8**, 0.69 g, 1.57 mmol) was dissolved in 1,2-dichloroethane (10 mL), and α-D-mannose pentaacetate (1.8 g, 4.5 mmol) was added in one portion, and then boron trifluoride etherate (2.3 mL, 18.8 mmol) was added slowly. The mixture was stirred overnight at room temperature and then mixed with water. The organic material was separated, and the aqueous portion was extracted with dichloromethane. The extracts were combined with the original organic fraction, dried ($MgSO_4$) then concentrated under reduced pressure. Purification by flash chromatography (SiO_2, gradient elution, hexane to 3:1 hexane/ethyl acetate) provided 1.38 g (66%) of the protected bis-glycoside as a foam, which was used in the next step without further purification.

The product was dissolved in acetonitrile (5 mL), treated with a solution of lithium hydroxide (0.24 g, 5.6 mmol in 5 mL water), stirred at room temperature overnight, then acidified to pH 3 with concentrated HCl, and concentrated under reduced pressure. The residue was purified by reverse-phase HPLC (0−50% acetonitrile in water) which gave 3-(2-α-D-mannopyranosyloxy-5-(2-(3-(2-α-D-mannopyranosyloxyphenyl)phenyl)ethyl)phenyl)phenylacetic acid (**9**) (142 mg, 18%) as a white solid, mp 129−134 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.10−7.40 (m, 15H), 5.33 (d, J = 1.7 Hz, 1H), 5.27 (d, J = 1.7 Hz, 1H), 3.30−3.70 (m, 14H, plus H_2O), 2.92 (2, 4H). IR (KBr): 3410, 1710. MS (CI): *m/e* 425 [M − (mannose)$_2$]$^+$. Anal. ($C_{40}H_{44}O_{14}$·2.2H_2O) C, H.

4,4′-Bis(4-α-D-mannopyranosyloxyphenyl)valeric acid (10). The compound was prepared from 4,4′-bis(4-hydroxyphenyl)valeric acid by glycosylation followed by base hydrolysis as described in the other examples: mp 130−132 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.08 (d, J = 8.0 Hz, 4H), 6.98 (d, J = 8.0 Hz, 4H), 5.30 (s, 2H), 4.40 (br s, 8H), 3.79 (m, 2H), 3.65 (dd, J = 3.3, 9.2 Hz, 2H), 3.59 (d, J = 9.8 Hz, 2H), 3.38−3.51 (m, 6H), 2.28 (m, 2H), 1.94 (m, 2H), 1.52 (s, 3H) ppm. IR (KBr): 3405, 1710 cm^{-1}. Anal. ($C_{29}H_{38}O_{14}$·0.7TFA) C, H.

1,4-Bis[3-(3-carboxymethylphenyl)-4-α-D-mannopyranosyloxy]benzoylbenzene (13a). Step 1. Ethyl 3-(2-methoxyphenyl)phenylacetate (**5**, 1.7 g, 6.33 mmol) in 1,2-dichloroethane (5 mL) was added to a suspension of terephthaloyl chloride (0.61 g, 3.0 mmol) and aluminum chloride (2.54 g, 19.1 mmol) in 1,2-dichloroethane (15 mL). The mixture was stirred at room temperature under nitrogen for 30 min, then mixed with ice water, and extracted with dichloromethane. The organic materials were combined, washed with saturated sodium chloride, dried ($MgSO_4$), and then concentrated under reduced pressure. Purification by flash chromatography (SiO_2, gradient elution, 3:1 hexane/ethyl acetate to ethyl acetate) gave 1.0 g (50%) of **11a** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (m, 10 H), 7.43 (m, 2H), 7.37 (t, J = 8.0 Hz, 2H), 7.28 (m, 2H), 7.05 (d, J = 8.0 Hz, 2H), 4.14 (q, J = 7.0 Hz, 4H), 3.90 (s, 6H), 3.65 (s, 4H), 1.24 (t, J = 7.0 Hz, 6H) ppm. IR (NaCl): 1737, 1650 cm^{-1}.

Step 2. 1,4-Bis[3-(3-carbethoxymethylphenyl)-4-methoxybenzoyl]benzene (**11a**, 0.86 g, 1.28 mmol) was dissolved in 1,2-dichloroethane (10 mL) under nitrogen, and chilled in an ice bath. Boron tribromide (0.85 mL, 9.0 mmol) was added slowly, then the cooling bath was removed, and the mixture was stirred for 15 min. The reaction was cooled to 0 °C in an ice bath, quenched with ethanol, and then mixed with ice water. The mixture was extracted with dichloromethane, and the extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure which provided 0.66 g (80%) of 1,4-bis[3-(3-carboethoxymethylphenyl)-4-hydroxybenzoyl]benzene (**12a**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.70−7.82 (m, 10H), 7.30−7.50 (m, 6H), 7.02−7.08 (m, 2H), 7.02 (s, 2H), 4.15 (q, J = 7.6 Hz, 4H), 3.68 (s, 4H), 1.25 (t, J = 7.6 Hz, 6H) ppm. IR (NaCl): 3352, 1732 cm^{-1}.

Step 3. 1,4-Bis[3-(3-carbethoxymethylphenyl)-4-hydroxybenzoyl]benzene (**12a**, 0.30 g, 0.46 mmol) and α-D-mannose pentaacetate (0.54 g, 1.37 mmol) were dissolved in 1,2-dichloroethane (5 mL), and then boron trifluoride etherate (0.68 mL, 5.5 mmol) was added slowly. The mixture was stirred under nitrogen for 16 h at room temperature and then mixed with water. The organic material was separated, and the aqueous portion was extracted with dichloromethane. The combined organic fractions were dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was dissolved in acetonitrile (7 mL), treated with 2 N sodium hydroxide (9.8 mL), stirred at room temperature overnight, and then acidified to pH 2 with concentrated HCl. The volatiles were removed under reduced pressure, and a portion of the residue was purified by reverse-phase HPLC (0−50% acetonitrile in water) which gave 1,4-bis[3-(3-carboxymethylphenyl)-4-(α-D-mannopyranosyloxy)benzoyl]benzene (**13a**) as a white solid, mp 127−130 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.65−7.92 (m, 8H), 7.20−7.51 (m, 8H), 7.11 (d, J = 8 Hz, 2H), 5.28 (s, 2H), 5.07 (br, 2H), 4.86 (br, 2H), 4.72 (br, 2H), 4.50 (br, 2H), 3.89 (s, 2H), 3.69−3.78 (m, 4H), 3.55−3.67 (m, 8H) ppm. IR (KBr): 3424, 1716, 1642, 1594 cm^{-1}. Anal. ($C_{48}H_{44}O_{16}$·0.6TFA) C, H.

1,6-Bis[3-(3-carboxymethylphenyl)-4-(α-D-mannopyranosyloxy)phenyl]hexane (15e): Step 1. Adipoyl chloride (2.0 g, 10.9 mmol) was dissolved in 1,2-dichloroethane (55 mL) and cooled in an ice bath. Aluminum chloride (5.8 g, 43.5 mmol) was added followed by methyl 3-(2-methoxyphenyl)-phenylacetate (**4**, 11.2 g, 43.5 mmol), and the mixture was stirred at room temperature overnight. The mixture was cooled in an ice bath, and ice water was added slowly while stirring. The organic materials were isolated, and the aqueous portion was extracted with dichloromethane. The combined organic materials were dried ($MgSO_4$) and then concentrated under reduced pressure. Purification by flash chromatography (SiO_2, gradient elution, hexane to 3:1 hexane/ethyl acetate) provided 2.23 g (33%) of **11e**. ^{1}H NMR (400 MHz, $CDCl_3$): 7.96 (dd, J = 6.6, 1.9 Hz, 2H), 7.92 (d, J = 1.9 Hz, 2H), 7.42 (m, 2H), 7.34 (t, J = 6 Hz, 2H), 7.18−7.28 (m, 4H), 7.00 (d, J =

6.3 Hz, 2H), 3.87 (s, 6H), 3.69 (s, 6H), 3.68 (s, 4H), 3.01 (m, 4H), 1.84 (m, 4H) ppm. IR (NaCl): 1741, 1677 cm^{-1}.

Step 2. The product from step 1 (2.23 g, 3.6 mmol) was dissolved in acetonitrile, treated with a solution of lithium hydroxide (0.76 g, 18 mmol in 8 mL water), stirred at room temperature overnight, acidified to pH 4 with 2 N HCl, and extracted with ethyl acetate. The extracts were combined, dried ($MgSO_4$), and then concentrated under reduced pressure. The keto acid (1.86 g, 3.1 mmol) was dissolved in dimethyl sulfoxide (15 mL), hydrazine (1.0 mL, 31 mmol) was added and the mixture was heated at 80 °C under nitrogen for 2.5 h. After cooling, potassium *tert*-butoxide (3.5 g, 31 mmol) was added, and the mixture was again heated at 80 °C overnight, mixed with water, acidified with 2 N HCl, and extracted with ethyl acetate. The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure which gave 1.6 g (91%) of the diacid.

The diacid (1.6 g, 2.8 mmol) was dissolved in dichloromethane (14 mL) under nitrogen and chilled to −78 °C. Boron tribromide (1.4 mL, 14 mmol) was added slowly, and the mixture was then stirred at room temperature for 2 h and subsequently quenched with ice water. The organic material was separated, washed with saturated sodium chloride, then dried ($MgSO_4$), and concentrated under reduced pressure which gave 2.38 g of the crude phenol.

The residue from the previous step was mixed with methanol (50 mL), and sulfuric acid (5 drops) was added. The mixture was heated at reflux overnight and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL), treated with sodium carbonate, and then filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (SiO_2, gradient elution, hexane to 3:1 hexane/ethyl acetate) which provided 0.9 g (38%) of 1,6-bis-[3-(3-carbomethoxymethylphenyl)-4-hydroxyphenyl]hexane (**14e**). ^{1}H NMR (400 MHz, $CDCl_3$): 6.80−7.50 (m, 14H), 3.70 (s, 6H), 3.68 (s, 4H), 2.55 (dd, J = 5.5, 5.5 Hz, 4H), 1.59 (m, 4H), 1.36 (m, 4H) ppm. IR (NaCl): 3430, 1731 cm^{-1}.

Step 3. The bisphenol (**14e**, 0.9 g, 1.6 mmol) was dissolved in 1,2-dichloroethane (8 mL) and glycosylated with α-D-mannose pentaacetate (1.9 g, 4.8 mmol) as before, which provided 1.5 g (77%) of 1,6-bis[3-(3-carbomethoxymethylphenyl)-4-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)phenyl]-hexane contaminated with a small amount of unreacted α-D-mannose pentaacetate which coeluted with the product. ^{1}H NMR (400 MHz, $CDCl_3$): 7.31−7.37 (m, 6H), 7.19−7.24 (m, 4H), 7.09−7.13 (m, 4H), 5.25 (d, J = 0.6 Hz, 2H), 3.57−3.66 (m, 6H), 3.3−3.50 (m, 10H), 2.54 (m, 4H), 1.58 (m, 4H), 1.34 (m, 4H) ppm. IR (NaCl): 1752 cm^{-1}.

1,6-Bis[3-(3-carbomethoxymethylphenyl)-4-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)phenyl]hexane (1.5 g, 1.2 mmol) hydrolyzed with lithium hydroxide solution as before. Purification by reverse-phase HPLC (5−50% acetonitrile in water) gave 0.35 g (33%) of 1,6-bis[3-(3-carboxymethylphenyl)-4-(2-α-D-mannopyranosyloxy)phenyl] hexane (**15e**) as a white solid, mp 115−117 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.31−7.37 (m, 6H), 7.19−7.24 (m, 4H), 7.09−7.13 (m, 4H), 5.25 (d, J = 0.6 Hz, 2H), 3.57−3.66 (m, 6H), 3.3−3.50 (m, 10H), 2.54 (m, 4H), 1.58 (m, 4H), 1.34 (m, 4H) ppm. IR (KBr): 3420, 1711 cm^{-1}. MS (CI): *m/e* 864 $(M + H)^+$, 683 $(M -$ mannose$)^+$. Anal. ($C_{46}H_{54}O_{16}$·0.75TFA) C, H.

1,4-Bis[3-(3-carboxymethylphenyl)-4-(2-α-D-mannopyranosyloxy)phenyl] butane (19): Step 1. 4-(4-Methoxyphenyl)butyric acid (2.0 g, 10.3 mmol) was treated with thionyl chloride (20 mL), stirred at room temperature for 3 h, then heated at 65 °C overnight, and concentrated under reduced pressure which gave 2.3 g of 4-(4-methoxyphenyl)-butyryl chloride as a yellow oil which was used without further purification. IR (NaCl): 1795 cm^{-1}.

The crude acid chloride (2.07 g, 9.7 mmol) and anisole (1.26 g, 11.6 mmol) were dissolved in 1,2-dichloroethane (32 mL) and chilled in an ice bath. Aluminum chloride (3.9 g, 29.1 mmol) was added in portions, stirred for 5 min, and then mixed with ice water. The mixture was extracted with dichloromethane, and the combined extracts were washed with saturated sodium chloride, dried ($MgSO_4$), and then concentrated under reduced pressure. Purification through silica gel with 10:1 hexane/ethyl acetate gave 2.49 g (82%) of 4-(4-methoxyphenyl)butyryl-4-methoxybenzene. ^{1}H NMR (400 MHz, $CDCl_3$): 7.90 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6,91 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 2.90 (t, J = 7.3 Hz, 2H), 2.65 (t, J = 7.7 Hz, 2H), 2.02 (m, 2H) ppm. IR (NaCl): 1674, 1602, 1244 cm^{-1}.

Step 2. The ketone (2.49 g, 8.8 mmol) was dissolved in dichloromethane (30 mL) and treated with trifluoroacetic acid (2.7 mL, 35.2 mmol), triethylsilane (2.8 mL, 17.6 mmol), and then boron trifluoride etherate (4.4 mL, 35.2 mmol). The mixture was stirred at room temperature for 2 h, then cooled in an ice bath, and mixed with water. The mixture was extracted with dichloromethane, and the combined extracts were washed with saturated sodium chloride, dried ($MgSO_4$), and then concentrated under reduced pressure. The residue was flushed through silica gel with 10:1 hexane/ethyl acetate and concentrated which provided 2.0 g (85%) of **17** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.07 (d, J = 8.4 Hz, 4H), 6.81 (d, J = 8.4 Hz, 4H), 3.78 (s, 6H), 2.56 (m, 4H), 1.61 (m, 4H) ppm. IR (NaCl): 1605, 1248 cm^{-1}.

Step 3. The bis-ether **17** (1.78 g, 6.6 mmol) and TMEDA (4.0 mL, 26.5 mmol) were mixed with anhydrous ether (30 mL) and chilled in an ice bath. *n*-Butyllithium (10.5 mL of a 2.5 M solution, 26.5 mmol) was added, and the mixture was warmed to room temperature and stirred for an hour. The reaction mixture was cooled to 0 °C and treated with trimethyl borate (3.0 mL, 26.5 mmol). The mixture was stirred at room temperature overnight, then quenched with 2 N HCl (to pH 2), and stirred for 1 h. The organic phase was separated, the aqueous portion was extracted with ethyl acetate, and the extracts were combined with the original organic fraction, dried ($MgSO_4$), and then concentrated under reduced pressure, which gave 3.0 g of the boronic acid which was used without further purification. IR (NaCl): 1328 cm^{-1}.

A solution of the crude boronic acid and methyl 3-bromophenylacetate (3.8 g, 16.8 mmol) in dimethoxyethane (30 mL) was degassed under nitrogen. The mixture was treated with tribasic potassium phosphate (10.7 g, 50.5 mmol) and bis-(triphenylphosphine)palladium(II) chloride (100 mg, 0.17 mmol). The mixture was degassed again, then heated at reflux for 2 h, cooled to room temperature, and mixed with water. The mixture was extracted with dichloromethane, and the combined extracts were washed with water and saturated sodium chloride, dried ($MgSO_4$), and then concentrated under reduced pressure. Purification by flash chromatography (SiO_2, gradient elution, 8:1 hexane/ethyl acetate to 4:1 hexane/ethyl acetate) gave 1.14 g (24%) of **18** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.41−7.44 (m, 4H), 7.34 (t, J = 7.7 Hz, 2H), 7.21−7.60 (m, 2H), 7.08−7.13 (m, 4H), 6.87 (d, J = 8.0 Hz, 2H), 3.77 (s, 6H), 3.68 (s, 6H), 3.66 (s, 4H), 2.61 (m, 4H), 1.67 (m, 4H) ppm. IR (NaCl): 1737, 1606, 1239 cm^{-1}.

Step 4. 1,4-Bis[3-(3-carbomethoxymethylphenyl)-4-methoxyphenyl]butane (**18**, 0.9 g, 1.6 mmol) was dissolved in dichloromethane (3.0 mL), cooled to −78 °C, and treated with boron tribromide (1.2 mL, 12.8 mmol) as before which gave 0.4 g (47%) of 1,4-bis[3-(3-carbomethoxymethylphenyl)-4-hydroxyphenyl]butane. ^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (d, J = 7.4 Hz, 2H), 7.35−7.38 (m, 4H), 7.27−7.32 (m, 2H), 7.02−7.05 (m, 4H), 6.87 (d, J = 8.0 Hz, 2H), 5.12 (s, 2H), 3.70 (s, 6H), 3.68 (s, 4H), 2.59 (m, 4H), 1.65 (m, 4H) ppm. IR (NaCl): 3439, 1732 cm^{-1}.

Step 5. Glycosylation of 1,4-bis[3-(3-carbomethoxymethylphenyl)-4-hydroxyphenyl]butane (0.4 g, 0.74 mmol) with α-D-mannose pentaacetate (0.72 g, 1.85 mmol) in 1,2-dichloroethane (4 mL) as before gave 0.88 g (99%) of 1,4-bis[3-(3-carbomethoxymethylphenyl)-4-(tetra-*O*-acetyl-α-D-mannopyranosyloxy)phenyl]butane as a foam. ^{1}H NMR (400 MHz, $CDCl_3$): 7.38−7.44 (m, 6H), 7.25−7.29 (m, 2H), 7.17 (br s, 2H), 7.07−7.11 (m, 4H), 5.40 (s, 2H), 5.20−5.30 (m, 6H), 4.15 (dd, J = 12.3, 4.8 Hz, 2H), 3.93 (dd, J = 12.4, 2.2 Hz, 2H), 3.76−3.82 (m, 2H), 3.72 (s, 4H), 3.68 (s, 6H), 2.63 (m, 4H), 2.13 (s,

6H), 2.01 (s, 6H), 2.00 (s, 6H), 1.97 (s, 6H), 1.67 (m, 4H) ppm. IR (NaCl): 1748, 1219 cm^{-1}.

Step 6. 1,4-Bis[3-(3-carbomethoxymethylphenyl)-4-(tetra-*O*-acetyl-α-D-mannopyranosyloxy)phenyl]butane (0.87 g, 0.73 mmol) was dissolved in acetonitrile (3 mL) and hydrolyzed with a solution of lithium hydroxide as before which gave 230 mg of **19** as a white solid, mp 195−197 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.31−7.39 (m, 6H), 7.20−7.25 (m, 4H), 7.10−7.15 (m, 4H), 5.25 (s, 2H), 4.88 (br d, J = 4.0 Hz, 2H), 4.76 (br s, 2H), 4.60 (br s, 2H), 4.45 (br t, J = 5.9 Hz, 2H), 3.55−3.68 (m, 5H), 3.62 (s, 4H), 3.40−3.50 (m, 7H), 2.60 (m, 4H), 1.62 (m, 4H) ppm. IR (KBr): 3333, 3229, 1729, 1224 cm^{-1}. Anal. ($C_{44}H_{50}O_{16}$·0.4TFA) C, H.

1,3-Bis[3-(3-(3-carboxymethylphenyl)-4-(α-D-mannopyranosyloxy)phenyl)prop-1-ylthio]propane (22). Step 1. Ethyl 3-(2-methoxyphenyl)phenyl acetate (**5**, 5.04 g, 18.66 mmol) and 3-bromopropionyl chloride (1.88 mL, 18.66 mmol) were mixed with 1,2-dichloroethane (30 mL), and the mixture was cooled to 0 °C and then treated with aluminum chloride (7.6 g, 57 mmol). After 15 min the reaction was mixed with ice water, and the organic materials were separated. The aqueous portion was extracted with dichloromethane, and the organic materials were combined, dried ($MgSO_4$), and then concentrated under reduced pressure, which gave **11i**.

Step 2. The bromo ketone **11i** (8.5 g, 19 mmol) was dissolved in dichloromethane (40 mL) and cooled in an ice water bath. Trifluoroacetic acid (5.9 mL, 76 mmol), triethylsilane (6.1 mL, 38 mmol), and then boron trifluoride etherate (9.4 mL, 76 mmol) were added, and the cooling bath was removed. The mixture was stirred at room temperature overnight, then cooled in an ice bath, and quenched with cold water. The organic materials were separated, the aqueous portion was extracted with dichloromethane, and the organic materials were combined, washed with saturated sodium chloride solution, dried ($MgSO_4$), and then concentrated under reduced pressure, which provided 6.53 g (90%) of ethyl 3-(2-methoxy-5-(3-bromopropyl)phenyl)phenylacetate **20**. ^{1}H NMR (400 MHz, $CDCl_3$): 7.41−7.45 (m, 2H), 7.36 (t, J = 8 Hz, 1H), 7.25−7.28 (m, 1H), 7.12−7.16 (m, 2H), 6.90 (d, J = 8.6 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 3.78 (s, 3H), 3.67 (s, 2H), 3.41 (t, J = 6.6 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H), 2.15 (m, 2H), 1.26 (t, J = 7.3 Hz, 3H). IR (NaCl): 1736 cm^{-1}.

Step 3. A solution of 1,3-propanedithiol (0.109 g, 0.94 mmol) in THF (4.5 mL) was degassed and then cooled to 0 °C. Sodium hydride (86.5 mg, 2.1 mmol) was added, and the mixture was stirred at room temperature for 2 h. A solution of the bromide **20** (0.83 g, 2.12 mmol) in THF (1.0 mL) was added, and the mixture was heated under reflux overnight. The reaction was partitioned between water and ethyl acetate, and the organic materials were separated, washed with saturated sodium chloride, dried ($MgSO_4$), and then concentrated under reduced pressure. Purification by flash chromatography (SiO_2, gradient elution, hexane to 3:1 hexane/ethyl acetate) gave 166.2 mg (24%) of 1,3-bis[3-(3-(3-carbethoxymethylphenyl)-4-methoxyphenyl)prop-1-ylthio]propane. ^{1}H NMR (400 MHz, $CDCl_3$): 7.39−7.45 (m, 4H), 7.32−7.38 (m, 2H), 7.21−7.28 (m, 2H), 7.08−7.15 (m, 4H), 6.85−6.92 (m, 2H), 4.14 (q, J = 7.0 Hz, 4H), 3.77 (s, 6H), 3.65 (s, 4H), 2.80−2.95 (m, 2H), 2.77 (t, J = 7.3 Hz, 2H), 2.68 (t, J = 8.0 Hz, 4H), 2.60 (t, J = 7.0 Hz, 2H), 2.52 (t, J = 7.0 Hz, 2H), 2.04−2.16 (m, 2H), 1.81−1.93 (m, 4H), 1.25 (t, J = 7.0 Hz, 6H). IR (NaCl): 1731 cm^{-1}.

A solution of the bis-sulfide (70.7 mg, 0.1 mmol) in dichloromethane (2 mL) was treated with boron tribromide (0.8 mL of 1 M in dichloromethane, 0.8 mmol) as before, which gave 68 mg (100%) of 1,3-bis[3-(3-(3-carbethoxymethylphenyl)-4-hydroxyphenyl)prop-1-ylthio]propane. ^{1}H NMR (400 MHz, $CDCl_3$): 7.43 (t, J = 7.7 Hz, 2H), 7.34−7.39 (m, 4H), 7.30 (br d, J = 7.3 Hz, 2H), 7.03−7.08 (m, 4H), 6.87 (br d, J = 8.8 Hz, 2H), 4.96−5.30 (br s, 2H), 4.15 (q, J = 7.0 Hz, 4H), 3.66 (s, 4H), 2.66 (t, J = 7.3 Hz, 4H), 2.60 (t, J = 7.0 Hz, 2H), 2.52 (t, J = 7.0 Hz, 4H), 1.80−1.92 (m, 6H), 1.26 (t, J = 7.3 Hz, 6H), 1.21−1.27 (m, 2H). IR (NaCl): 3420, 1726 cm^{-1}.

1,3-Bis[3-(3-(3-carbethoxymethylphenyl)-4-hydroxyphenyl)-prop-1-ylthio]propane (0.47 g, 0.68 mmol) was glycosylated with α-D-mannose pentaacetate (0.8 g, 2.0 mmol) as before, which gave 0.331 g (36%) of 1,3-bis[3-(3-(3-carbethoxymethylphenyl)-4-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)-phenyl)prop-1-ylthio]propane **21** contaminated with a small amount of unreacted α-D-mannose pentaacetate which coeluted with the product. IR (NaCl): 1752 cm^{-1}.

Step 4. The tetraacetate **21** (0.64 g, 0.47 mmol) dissolved in acetonitrile (5 mL) was treated with 2 N sodium hydroxide (5.0 mL) and stirred overnight at room temperature. The mixture was acidified with concentrated hydrochloric acid to pH 2, and the volatiles were removed under reduced pressure. A portion of the aqueous residue was purified by reverse-phase HPLC (10−50% acetonitrile in water) which provided **22** as a white solid, mp 96−100 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.31−7.39 (m, 6H), 7.20−7.27 (m, 4H), 7.11−7.15 (m, 4H), 5.26 (s, 2H), 3.30−3.75 (m, 28H), 2.64 (t, J = 7.7 Hz, 4H), 2.57 (t, J = 7.0 Hz, 4H), 2.45−2.52 (m, 4H), 1.75−1.84 (m, 4H), 1.66−1.74 (m, 2H). IR (KBr): 3430, 1711 cm^{-1}. Anal. ($C_{49}H_{60}S_2O_{16}$·0.5TFA) C, H.

1-(3-(3-Carboxymethylphenyl)-4-α-D-mannopyranosyloxyphenyl)-6-(4-α-D-mannopyranosyloxyphenyl)hexane (26). Step 1. Adipic acid monomethyl ester (2.0 g, 12.5 mM) was treated with thionyl chloride (1.1 mL, 15 mM), and the mixture was heated to 80 °C for 30 min and then concentrated under reduced pressure. The residue was mixed with dichloromethane (20 mL) and cooled to 0 °C. Anisole (1.36 mL, 12.5 mM) was added and then aluminum chloride (4.25 g, 37.5 mM). After 30 min, the reaction was mixed with ice water and extracted with dichloromethane. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure. ^{1}H NMR (400 MHz, $CDCl_3$): 7.92 (d, J = 12 Hz, 2H), 6.92 (d, J = 12 Hz, 2H), 3.86 (s, 3H), 3.66 (s, 3H), 2.93 (t, J = 6.8 Hz, 2H), 2.36 (t, J = 6.8 Hz, 2H), 1.62−1.79 (m, 4H) ppm. IR (NaCl): 3433, 1731, 1675 cm^{-1}. A portion of the keto ester (1.0 g, 4.0 mM) was dissolved in THF (6 mL) and treated with 2 N sodium hydroxide (2.25 mL), and the mixture was stirred at room temperature overnight and then neutralized with concentrated hydrochloric acid (pH 5.5). The solids were collected and dried under vacuum which gave 0.78 g (87%) of 5-(4-methoxybenzoyl)valeric acid. ^{1}H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 12 Hz, 2H), 7.03 (d, J = 12 Hz, 2H), 3.84 (s, 3H), 2.96 (t, J = 6.8 Hz, 2H), 2.24 (t, J = 6.8 Hz, 2H), 1.50−1.70 (m, 4H) ppm. IR (NaCl): 3472, 1702, 1668 cm^{-1}.

Step 2. 5-(4-Methoxybenzoyl)valeric acid (0.7 g, 2.96 mM) was mixed with thionyl chloride (0.43 mL, 5.9 mM), heated at 80 °C for 10 min, and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (10 mL), and ethyl 3-(2-methoxyphenyl)phenylacetate (**5**, 0.81 g, 3.0 mM) and then aluminum chloride (2.0 g, 15 mM) were added. The mixture was stirred at room temperature overnight, then quenched with ice water, and extracted with dichloromethane. The extracts were dried ($MgSO_4$), filtered through a pad of silica gel, and concentrated under reduced pressure, which gave 1.1 g (79%) of **11j** as a clear oil, which was used without further purification. IR (NaCl): 1730, 1666, 1598 cm^{-1}. The diketone was dissolved in dichloromethane (12 mL) and treated with TFA (1.8 mL, 23.1 mM), boron trifluoride etherate (2.9 mL, 23.1 mM), and then triethylsilane (1.8 mL, 11.5 mM). The mixture was stirred at room temperature for 10 h and then mixed with water. The mixture was extracted with dichloromethane, and the extracts were dried ($MgSO_4$) and then concentrated under reduced pressure which gave 0.61 g (59%) of the bis-ether **24**. IR (NaCl): 1732, 1172 cm^{-1}.

Step 3. The bis-ether **24** was dissolved in dichloromethane (6 mL), cooled to −78 °C, and treated with boron tribromide (1.1 mL, 12 mM). The reaction mixture then was stirred for 3 h at 0 °C and quenched with ethanol. Water was added, and the mixture was extracted with dichloromethane. The extracts were dried ($MgSO_4$) and then concentrasted under reduced pressure. Purification by flash chromatography (SiO_2, gradient elution, hexane to 3:1 hexane/ethyl acetate) gave 100 mg (17%) of the di-phenol **25**. ^{1}H NMR (400 MHz, DMSO-d_6):

7.28−7.45 (m, 4H), 6.97−7.52 (m, 4H), 6.87 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 8 Hz, 2H), 4.16 (q, J = 8.2 Hz, 2H), 3.67 (s, 3H), 2.51 (m, 4H), 1.58 (m, 4H), 1.35 (m, 4H) ppm.

Step 4. The di-phenol (100 mg, 0.23 mM) was dissolved in dichloromethane (2 mL) and treated with α-D-mannnose pentaacetate (0.25 g, 0.65 mM) and then boron trifluoride etherate (0.26 mL, 2.1 mM). After 16 h, the reaction was quenched with water, and the organic material was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dissolved in acetonitrile (2 mL), and 2 N sodium hydroxide (1.2 mL) was added. After 18 h, the mixture was acidified with concentrated HCl (pH 3). Purification of a portion by reverse-phase HPLC (10−100% acetonitrile in water) provided 22 mg of **26** as a white solid, mp 106−108 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.34−7.40 (m, 3H), 7.21−7.25 (m, 2H), 7.06−7.13 (m, 4H), 6.96 (d, J = 8 Hz, 2H), 5.28 (d, J = 1.5 Hz, 1H), 5.25 (d, J = 1.5 Hz, 1H), 3.30−3.81 (m, 14H), 2.55 (m, 4H), 1.55 (m, 4H), 1.33 (m, 4H) ppm. IR (NaCl): 3400, 1734 cm^{-1}. Anal. ($C_{38}H_{48}O_{14}$·0.5TFA) C, H.

1,3,5-Tris[(3-(3-carboxymethylphenyl)-4-(α-D-mannopyranosyloxy)phenyl)-2-oxoethylthiomethyl]benzene (33). Step 1. Ethyl 3-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxyphenyl)phenylacetate **27** (0.32 g, 0.547 mmol) and bromoacetyl bromide (0.06 mL, 0.689 mmol) were dissolved in 1,2-dichloroethane (3 mL) and cooled to −78 °C. The mixture was treated with aluminum chloride (1.45 g, 10.9 mmol), and the bath was replaced with an ice water bath. After 15 min, the reaction was quenched with ice water and stirred for 15 min. The organic materials were isolated, and the aqueous portion was extracted with dichloromethane. The organic materials were combined, dried ($MgSO_4$), and then concentrated under reduced pressure, which gave 0.387 g of **30**, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 8.03 (d, J = 2.5 Hz, 1H), 7.95 (dd, J = 8.8, 2.5 Hz, 1H), 7.41−7.47 (m, 3H), 7.35 (m, 1H), 7.31 (d, J = 8.8 Hz, 1H), 5.62 (d, J = 1.8 Hz, 1H), 5.21−5.34 (m, 3H), 4.42 (s, 2H), 4.10−4.25 (m, 5H), 3.99 (dd, J = 12.1, 2.2 Hz, 1H), 3.80−3.85 (m, 1H), 3.74 (s, 2H), 2.18 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.26 (t, J = 8.0 Hz, 3H). IR (NaCl): 1746 1220 cm^{-1}.

Step 2. 1,3,5-Tris(mercaptomethyl)benzene (102 mg, 0.47 mmol) in THF (1 mL) was treated with sodium hydride (59.8 mg, 1.49 mmol), and the mixture was stirred at room temperature for 30 min. A solution of bromo ketone **30** (1.02 g, 1.44 mmol) in THF (2.0 mL) was added, and the mixture was stirred at room temperature overnight. The reaction was mixed with water and extracted with ethyl acetate. The organic materials were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, gradient elution, 3:1 hexane/ethyl acetate to 1:1 hexane/ethyl acetate) gave 0.59 g (60%) of the corresponding trisulfide. ^{1}H NMR (400 MHz, $CDCl_3$): 7.98 (d, J = 2.5 Hz, 3H), 7.89 (dd, J = 8.8, 2.5 Hz, 3H), 7.40−7.46 (m, 6H), 7.25−7.35 (m, 12H), 5.61 (s, 3H), 5.22−5.33 (m, 9H), 4.10−4.25 (m, 10H), 3.97 (dd, J = 12.1, 2.2 Hz, 3H), 3.78−3.84 (m, 3H), 3.72 (s, 6H), 3.69 (s, 3H), 3.64 (s, 3H), 2.16 (s, 9H), 2.02 (s, 9H), 2.01 (s, 9H), 1.97 (s, 9H), 1.25 (t, J = 8.0 Hz, 9H). IR (NaCl): 1747, 1219 cm^{-1}.

Step 3. The trisulfide from step 2 (0.59 g, 0.28 mmol) in THF (3 mL) was treated with a solution of freshly prepared sodium methoxide (93 mg, 4.04 mmol in 3 mL methanol), and the mixture was stirred at room temperature overnight. The precipitate which had formed was collected by vacuum filtration, washed several times with cold THF/methanol (2:1), and dried under vacuum which gave 0.38 g of a white solid. The solid was dissolved in water (12 mL), 2 N sodium hydroxide was added to pH 14, and the mixture was stirred at room temperature for 4 h. The reaction was acidified with Dowex 50W acidic ion-exchange resin and filtered, and the volatiles were removed under reduced pressure. Purification of a portion by reverse-phase HPLC (20−80% acetonitrile in water) gave 135 mg of **33** as a white solid, mp 140−143 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.95 (dd, J = 8.8, 2.5 Hz, 3H), 7.89 (d, J = 2.2 Hz, 3H), 7.32−7.45 (m, 12H), 7.26 (d, J = 7.3 Hz, 3H), 7.16−7.20 (m, 3H), 5.54 (s, 3H), 5.05 (br s, 3H), 4.85 (br s, 3H), 4.70 (br s, 3H), 4.50 (br s, 3H), 3.88−3.92 (m, 6H), 3.58−3.73 (m, 18H), 3.40−3.49 (m, 6H), 3.30−3.40 (m, 6H plus H_2O). IR (KBr): 3429, 1708, 1669 cm^{-1}.

1,3-Bis[*N*-(4-(3-(3-carboxymethylphenyl)-4-(α-D-mannopyranosyloxy)phenyl)butanoyl)piperidin-4-yl]propane (37b). Step 1. Succinic anhydride (2.0 g, 19.9 mmol) and aluminum chloride (17.7 g, 132 mmol) in 1,2-dichloroethane (45 mL) were cooled to 0 °C. The mixture was treated with a solution of ethyl 3-(2,3,4,6-tetra-*O*-pivaloyl-α-D-mannopyranosyloxyphenyl)phenylacetate[16] **34** (10.0 g, 13.2 mmol) in 1,2-dichloroethane (10 mL), and the mixture was stirred overnight while the bath gradually came to room temperature. The reaction was quenched with ice water and stirred for 15 min. The organic materials were isolated, and the aqueous portion was extracted with dichloromethane. The organic materials were combined, dried ($MgSO_4$), and then concentrated under reduced pressure, which gave 13.5 g of **35** which was used without further purification. IR (NaCl): 1738, 1685 cm^{-1}.

Step 2. To a solution of **35** (13.5 g, 19.7 mmol) in dichloromethane (65 mL) was added boron trifluoride etherate (15.3 mL, 122 mmol), trifluoroacetic acid (9.4 mL, 122 mmol), and then triethylsilane (9.4 mL, 59.1 mmol), and the mixture was stirred at room temperature overnight. The reaction was quenched with water (200 mL), and the organic materials were separated. The aqueous portion was extracted with dichloromethane, and the extracts were combined with the original organic portion, dried ($MgSO_4$), and then concentrated under reduced pressure which provided 1.49 g (97%) of 4-(3-(3-carbethoxymethylphenyl)-4-(2,3,4,6-tetra-*O*-pivaloyl-α-D-mannopyranosyloxy)phenyl)butanoic acid as a clear oil. IR (NaCl): 1737 cm^{-1}.

Step 3. The acid prepared in step 2 (16.0 g, 23.8 mmol) was stirred with thionyl chloride (50 mL), and the mixture was stirred at room temperature for 36 h and then concentrated under reduced pressure, which gave 16.3 g (99%) of the acid chloride, which was used without further purification. IR (NaCl): 1797, 1740 cm^{-1}. 1,3-Bis(piperidin-4-yl)propane (0.4 g, 1.9 mmol) in dichloromethane (5 mL) was added to a solution of the acid chloride (2.8 g, 3.26 mmol) in dichloromethane (5 mL) at 0 °C. Triethylamine (0.61 mL, 4.4 mmol) and 4-(dimethylamino)pyridine (35 mg, 10 mol %) were added, and the reaction was stirred at room temperature for 1 h and then quenched with water. The organic materials were washed with saturated sodium chloride, then dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, gradient elution, hexane to 3:1 hexane/ethyl acetate) gave 1.1 g (18%) of the bis-amide **36b**. ^{1}H NMR (400 MHz, $CDCl_3$): 7.40−7.45 (m, 4H), 6.98−7.30 (m, 10 H), 5.25−5.42 (m, 6H), 4.09−4.19 (m, 4H), 3.50−3.96 (m, 8H), 2.62−2.69 (m, 4H), 2.28−2.36 (m, 4H), 1.90−2.02 (m, 4H), 1.60−1.74 (m, 6H), 1.35−1.50 (m, 2H), 1.08−1.28 (98H). IR (NaCl): 1739 cm^{-1}.

Step 4. Bisamide **36b** (1.0 g, 0.54 mmol) was dissolved in THF (3 mL), 0.33 N sodium hydroxide (3 mL) was added, and the mixture was stirred at room temperature overnight. The THF was removed under reduced pressure, and the residue was acidified to pH 2 with concentrated hydrochloric acid. Purification by reverse-phase HPLC (20−80% acetonitrile in water) gave 30 mg (5%) of 1,3-bis[*N*-(4-(3-(3-carboxymethylphenyl)-4-(α-D-mannopyranosyloxy)phenyl)butanoyl)piperidin-4-yl]propane (**37b**) as a white solid, mp 119−121 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.32−7.40 (m, 6H), 7.20−7.27 (m, 4H), 7.10−7.14 (m, 4H), 5.26 (br s, 2H), 4.36 (br d, J = 11.0 Hz, 2H), 4.05 (br s, 8H), 3.77 (br d, J = 11.0 Hz, 2H), 3.50−3.70 (m, 8H), 3.40−3.52 (m, 5H), 3.31−3.40 (m, 2H), 2.92 (br t, J = 14.0 Hz, 2H), 2.55−2.62 (m, 4H), 2.42−2.53 (m, 3H), 2.27−2.34 (m, 4H), 1.73−1.82 (m, 4H), 1.57−1.67 (m, 4H), 1.36−1.47 (m, 2H), 1.22−1.33 (m, 2H), 1.11−1.20 (m, 4H), 0.80−1.02 (m, 4H). IR (KBr): 3415, 1713, 1609 cm^{-1}. MS (FAB): 1150 (M + Na)$^+$. Anal. ($C_{61}H_{78}O_{18}$·1.4TFA) C,H.

1,6-Bis(3-(3-carboxymethoxyphenyl)-4-(α-D-mannopyranosyloxy)phenyl) hexane (42). Step 1. Anisole (1.0 g, 9.25 mmol) was dissolved in dichloromethane (20 mL) and

cooled to 0 °C. Adipoyl chloride (0.7 mL, 4.62 mmol)and then aluminum chloride (6.2 g, 46 mmol) were added in portions. After 4 h, the reaction was quenched with ice water and extracted with dichloromethane. The organic materials were combined, dried ($MgSO_4$), and then concentrated under reduced pressure, which gave 1.57 g of a solid, which was recrystallized from ethanol and gave 1.4 g (93%) 1,4-bis(4-methoxybenzoyl)butane as a white solid, mp 137−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.93 (d, J = 7.0 Hz, 4H), 6.92 (d, J = 7.0 Hz, 4H), 3.86 (s, 6H), 2.97 (m, 4H), 1.82 (m, 4H) ppm. IR (KBr): 1675 cm^{-1}.

The diketone (1.4 g, 4.29 mmol) in DMSO (10 mL) was treated with hydrazine hydrate (0.3 mL, 9.44 mmol) and warmed at 60 °C for 1 h, potassium *tert*-butoxide (1.44 g, 12.9 mmol) was added, and the reaction was heated at reflux. After 3 h, the reaction was cooled, mixed with water, and extracted with ethyl acetate. The organic materials were combined, dried ($MgSO_4$), and concentrated under reduced pressure, which gave 1.07 g (84%) of **40** as a clear oil which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 7.07 (d, J = 7.0 Hz, 4H), 6.81 (d, J = 7.0 Hz, 4H), 3.79 (s, 6H), 2.53 (m, 4H), 1.57 (m, 4H), 1.34 (m, 4H) ppm. IR (NaCl): 1612 cm^{-1}.

Step 2. The bis-ether **40** (6.25 g, 20.9 mmol) was dissolved in dichloromethane (100 mL) and cooled to 0 °C. Ferric chloride (0.7 g, 1 mol %) was added, and then bromine (2.18 mL, 42.3 mmol) was added dropwise. The reaction was stirred for 3 h and then mixed with water. The organic materials were separated, dried ($MgSO_4$), and then concentrated under reduced pressure, which gave 9.27 g (98%) of a pale yellow oil which solidified on standing, mp 84−85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.34 (d, J = 1.8 Hz, 2H), 7.04 (dd, J = 1.8, 8.0 Hz, 2H), 6.80 (d, J = 8.0 Hz, 2H), 3.86 (s, 6H), 2.50 (t, J = 8.0 Hz, 4H), 1.55 (m, 4H), 1.31 (m, 4H) ppm.

Step 3. 1,6-Bis(3-bromo-4-methoxyphenyl)hexane (6.0 g, 13.15 mmol) was dissolved in dichloromethane (100 mL), and cooled to 0 °C, and then treated dropwise with boron tribromide (3.1 mL, 32.9 mmol). After 3 h, the reaction was quenched with ice water, and the organic material was separated, dried ($MgSO_4$), and then concentrated under reduced pressure, which gave 5.0 g of an off-white solid which was recrystallized from dichloromethane and gave 4.55 g (81%) of a white solid, mp 63−65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.24 (d, J = 1.8 Hz, 2H), 6.99 (dd, J = 1.8, 8.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 5.33 (s, 2H), 2.49 (t, J = 7.7 Hz, 4H), 1.55 (m, 4H), 1.32 (m, 4H) ppm. IR (KBr): 3419 cm^{-1}.

Step 4. 1,6-Bis(3-bromo-4-hydroxyphenyl)hexane (1.0 g, 2.34 mmol) was dissolved in 1,2-dichloroethane (10 mL) and glycosylated with α-D-mannose pentaacetate (2.3 g, 5.84 mmol) as before, which gave 1.15 g (46%) of **41** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.35 (s, 2H), 7.01 (s, 4H), 5.61 (dd, J = 3.3, 10.1 Hz, 2H), 5.51 (m, 4H), 5.38 (t, J = 10.3 Hz, 2H), 4.27 (dd, J = 5.1, 12.1 Hz, 2H), 4.17 (m, 2H), 4.06 (dd, J = 2.2, 12.1 Hz, 2H), 2.51 (t, J = 8.0 Hz, 4H), 2.19 (s, 6H), 2.05 (s, 6H), 2.03 (s, 6H), 2.02 (s, 6H), 1.54 (m, 4H), 1.30 (m, 4H) ppm.

Step 5. The bis-glycoside **41** (446 mg, 0.41 mmol) was dissolved in dimethoxyethane (3.0 mL) and treated with 3-hydroxyphenylboronic acid (124 mg, 0.9 mmol), bis(triphenylphosphine)palladium(II) chloride (10 mg), and potassium phosphate tribasic (348 mg, 1.64 mmol), and the mixture was degassed and then heated at reflux for 2 h. The reaction was mixed with 2N HCl (5 mL), then extracted with ethyl acetate. The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, gradient elution, hexane to ethyl acetate), gave 320 mg (71%) of a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.30 (t, J = 8.0 Hz, 2H), 7.25 (m, 4H), 7.07 (m, 4H), 7.01 (d, J = 8.3 Hz, 2H), 6.88 (dd, J = 2.6, 8.4 Hz, 2H), 6.64 (s, 2H), 5.51 (s, 2H), 5.42 (m, 2H), 5.40 (m, 2H), 5.33 (t, J = 9.6 Hz, 2H), 4.18 (dd, J = 5.1, 12.4 Hz, 2H), 4.10 (q, J = 7.0 Hz, 2H), 3.99 (dd, J = 2.2, 12.5 Hz, 2H), 3.88 (m, 2H), 2.57 (t, J = 7.3 Hz, 4H), 2.15 (s, 6H), 2.04 (s, 6H), 2.03 (s, 6H), 2.01 (s, 6H), 1.60 (m, 4H), 1.35 (m, 4H), 1.24 (t, J = 7.0 Hz, 4H) ppm. IR (NaCl): 3470, 1749 cm^{-1}.

Step 6. 1,6-Bis(3-(3-hydroxyphenyl)-4-(2,3,4,6-tetra-*O*-acetyl-α-D-mannnopyranosyloxyphenyl))hexane (342 mg, 0.307 mmol) was dissolved in THF (2 mL), and cesium carbonate (0.2 g, 0.62 mmol) was added. The mixture was stirred for 10 min at room temperature, and then ethyl bromoacetate (0.07 mL, 0.63 mmol) was added. The mixture was stirred at room temperature overnight, and then water was added. The mixture was extracted with ethyl acetate, and the extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure, which gave 0.4 g (100%) of the ester, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 7.36 (t, J = 7.7 Hz, 2H), 7.16 (m, 4H), 7.08 (d, J = 1.2 Hz, 4H), 7.01 (m, 2H), 6.90 (m, 2H), 5.40 (s, 2H), 5.26 (m, 6H), 4.68 (d, J = 2.6 Hz, 4H), 4.22 (m, 2H), 4.12 (m, 4H), 3.93 (J = 2.2, 12.0 Hz, 2H), 3.77 (m, 2H), 2.58 (t, J = 7.2 Hz, 4H), 2.13 (s, 6H), 2.02 (s, 6H), 2.00 (s, 6H), 1.96 (s, 6H), 1.61 (m, 4H), 1.37 (m, 4H), 1.30 (m, 6H) ppm. IR (KBr): 1752 cm^{-1}.

Step 7. The product from step 6 was dissolved in THF (5 mL) and then treated with 2 N sodium hydroxide (2.0 mL). After 3 h, the mixture was acidified with 2 N HCl, and the solvent was removed under reduced pressure. A portion was purified by reverse-phase HPLC (10−100% acetonitrile in water) which provided 56 mg of **42** as a white solid, mp 114−118 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.30 (t, J = 7.7 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.11 (m, 4H), 7.07 (d, J = 7.7 Hz, 2H), 6.95 (m, 2H), 6.87 (m, 2H), 5.24 (s, 2H), 4.68 (s, 4H), 3.67 (m, 2H), 3.58 (d, J = 10.2 Hz, 2H), 3.31−3.49 (m, 8H), 2.55 (t, J = 7.0 Hz, 4H), 1.58 (m, 4H), 1.34 (m, 4H) ppm. IR (KBr): 3414, 1735 cm^{-1}. MS (CI methane): *m/e* 571 [M − (mannose)$_2$]$^+$. Anal. ($C_{46}H_{54}O_{18}$·0.8TFA) C, H.

Acknowledgment. One of the authors (B.D.) acknowledges insightful discussions with Larry Denner and Jon O. Nagy. We thank Tony J. You and David S. Maxwell for providing assistance with generating Figure 2, and Karin M. Keller for intellectual contributions to methodology development and assistance with proofreading the manuscript. A sample of 4-(aminomethyl)-1,8-octanediamine (triaminononane) was supplied by Monsanto and is gratefully acknolwedged. We thank one of the reviewers for bringing to our attention additional relevant references regarding enhanced multivalent binding.

Supporting Information Available: Analytical data on final compounds not contained in the Experimental Section (4 pages). Ordering information is given on any current masthead page.

References

(1) (a) Bertozzi, C. R. Cracking the Carbohydrate Code for Selectin Recognition. *Chem. Biol.* **1995**, *2*, 703−708. (b) Kansas, G. S. Selectins and Their Ligands: Current Concepts and Controversies. *Blood* **1996**, *88*, 3259−3287. (c) Sharon, N.; Lis, H. Lectins as Cell Recognition Molecules. *Science* **1989**, *246*, 227−246.

(2) Phillips, M. L.; Nudelman, E.; Gaeta, F. C. A.; Perez, M.; Singhal, A. K.; Hakomori, S.-I.; Paulson, J. C. ELAM-1 Mediates Cell Adhesion by Recognition of a Carbohydrate Ligand, Sialyl-Le^x. *Science* **1990**, *250*, 1130−1132.

(3) (a) Walz, G.; Aruffo, A.; Kolanus, W.; Bevilacqua, M.; Seed, B. Recognition by ELAM-1 of the Sialyl-Le^x Determinant on Myeloid and Tumor Cells. *Science* **1990**, *250*, 1132−1135. (b) Handa, K.; Stroud, M. R.; Hakomori, S. Sialosyl-Fucosyl Poly-LacNac without Sialosyl-Le^x Epitope as the Physiological Myeloid Cell Ligand in E-Selectin-Dependent Adhesion: Studies under Static and Dynamic Flow Conditions. *Biochemistry* **1997**, *36*, 12412−12420.

(4) (a) Paulson, J. C. In *Adhesion: its role in inflammatory disease*; Harlan, J., Liu, D., Ed.; H. W. Freeman: New York, 1992; Chapter 2, p 19. (b) Murohara, T.; Margiotta, J.; Phillips, L. M.; Paulson, J. C.; DeFrees, S.; Zalipsky, S.; Guo, L. S. S.; Lefer, A. M. Cardioprotection by Liposome-Conjugated Sialyl Lewis^x-Oligosaccharide in Myocardial Ischemia and Reperfusion Injury. *Cardiovasc. Res.* **1995,** *30*, 965−974. (c) Bevilacqua, M. P.; Nelson, R. M. Selectins. *J. Clin. Invest.* **1993**, *91*, 379−387.

(5) (a) DeFrees, S. A.; Gaeta, F. C. A.; Lin, Y.-C.; Ichikawa, Y.; Wong, C.-H. Ligand Recognition by E.-Selectin: Analysis of Conformation and Activity of Synthetic Monomeric and Bivalent Sialyl Lewis X Analog. *J. Am. Chem. Soc.* **1993**, *115*, 7549−7550. (b) Ramphal, J. Y.; Zheng, Z.-L.; Perez, C.; Walker, L. E.; DeFrees, S. A.; Gaeta, F. C. A. Structure−Activity Relationships of Sialyl Lewis X-Containing Oligosaccharides. 1. Effect of Modifications of the Fucose Moiety. *J. Med. Chem.* **1994**, *37*, 3459−3463. (c) Brandley, B. K.; Tiemeyer, M.; Swiedler, S. J.; Moreland, M.; Schweingruber, H. New Carbohydrate-Based Anti-inflammatory Agents. Patent WO92/02527, February 20, 1992. (d) Rosen, S. D.; Bertozzi, C. R. The Selectins and Their Ligands. *Curr. Opin. Cell Biol.* **1994**, *6*, 663−673. (e) Stahl, W.; Spengard, U.; Krezschmar, G.; Kunz, H. Synthesis of Deoxy Sialyl Lewis^x Analogues, Potential Selectin Antagonists. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2096−2098.

(6) References to oligosaccharides as selectin antagonists include the following: (a) Hirumi, K.; Kajimoto, T.; Weitz-Schmidt, G.; Ollmann, I.; Wong, C.-H. Rational Design and Synthesis of a 1,1-Linked Disaccharide that is 5 Times as Active as Sialyl Lewis X in Binding to E-Selectin. *J. Am. Chem. Soc.* **1996**, *118*, 9265−9270. (b) Manning, D. D.; Bertozzi, C. R.; Rosen, S. D.; Kiessling, L. L. Tin-Mediated Phosphorylation: Synthesis and Selectin Binding of a Phospho Lewis a Analog. *Tetrahedron Lett.* **1996**, *1996*, 1953−1956. (c) Ohmoto, H.; Nakamura, K.; Inoue, T.; Kondo, N.; Inoue, Y.; Yoshino, K.; Kondo, H. Studies on Selectin Blocker 1. Structure−Activity Relationships of Sialyl Lewis X Analogs. *J. Med. Chem.* **1996**, *39*, 1339−1343. (d) Ragan, J. A.; Cooper, K. Synthesis of a Galactose-Fucose Disaccharide Mimic of Sialyl Lewis^x. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2563−2566. (e) Ramphal, J. Y.; Hiroshige, M.; Lou, B.; Gaudino, J. J.; Hayashi, M.; Chen, S. M.; Chiang, L. C.; Gaeta, F. C. A.; DeFrees, S. A. Ligand Interactions with E-Selectin. Identification of a New Binding Site for Recognition of N-Acyl Aromatic Glucosamine Substituents of Sialyl Lewis X. *J. Med. Chem.* **1996**, *39*, 1357−1360. (f) Stahl, W.; Spengard, U.; Krezschmar, G.; Kunz, H. Synthesis of Deoxy Sialyl Lewis x Analogues, Potential Selectin Antagonists. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2096−2098. (g) Wada, Y.; Saito, T.; Matsuda, N.; Ohmoto, H.; Yoshino, K.; Ohashi, M.; Kondo, H. Studies on Selectin Blocker 2. Novel Selectin Blocker as Potential Therapeutics for Inflammatory Disorders. *J. Med. Chem.* **1996**, *39*, 2055−2059. (h) Yoshino, K.; Ohmoto, H.; Kondo, N.; Tsujishita, H.; Hiramatsu, Y.; Inoue, Y.; Kondo, H.; Ishida, H.; Kiso, M.; Hasegawa, A. Studies on Selectin Blockers. 4. Structure-Function Relationships of Sulfated Sialyl Lewis X Hexasaccharide Ceramides Toward E-, P-, and L−Selectin Binding. *J. Med. Chem.* **1997**, *40*, 455−462. (i) Hayashi, M.; Tanaka, M.; Itoh, M.; Miyauchi, H. A Convenient and Efficient Synthesis of SLe^x Analogs. *J. Org. Chem.* **1996**, *61*, 2938−2945. (j) Dekany, G.; Wright, K.; Ward, P.; Toth, I. Synthesis of sialyl Lewis X analogues 2. *J. Carbohydr. Chem.* **1997**, *16*, 11−24. (k) Koenig, A.; Jain, R.; Vig, R.; Norgard-Sumnicht, K. E.; Matta, K. L.; Varki, A. Selectin inhibition: Synthesis and evaluation of novel sialylated, sulfated and fucosylated oligosaccharides, including the major capping group of GlyCAM-1. *Glycobiology* **1997** *7*, 79−93.

(7) (a) Wu, H. S.; Shimazaki, M.; Lin, L. Q.; Moree, W. J.; Weitz-Schmidt, G.; Wong, C.-H. Synthesis of Fucopeptides as Sialyl Lewis^x Mimetics. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 88−89. (b) Sprengard, U.; Schudok, M.; Schmidt, W.; Kretzschmar, G.; Kunz, H. Multiple Sialyl Lewis x N-Glycopeptides: Effective Ligands for E-Selectin. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 321−324. (c) Cappi, M. W.; Moree, W. J.; Quiao, L.; Marron, T. G.; Weitz-Schmidt, G.; Wong, C.-H. The Synthesis of Novel 6-Amido-6-Deoxy-L-Galactose Derivatives as Potent Sialyl Lewis x Mimetics. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2346−2348.

(8) (a) Kogan, T. P.; Dupré, B.; Keller, K. M.; Scott, I. L.; Bui, H.; Market, R. V.; Beck, P. J.; Voytus, J. A.; Revelle, B. M.; Scott, D. Rational Design and Synthesis of Small Molecule, Non-oligosaccharide Selectin Inhibitors: (α-D-Mannopyranosyloxy)-biphenyl-Substituted Carboxylic Acids. *J. Med. Chem.* **1995**, *38*, 4976−4984. (b) Dupré, B.; Bui, H.; Scott, I. L.; Market, R. V.; Keller, K. M.; Beck, P. J.; Kogan, T. P. Glycomimetic Selectin Inhibitors: (α-D-Mannopyranosyloxy)methylbiphenyls. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 569−572.

(9) (a) Sanders, W. J.; Katsumoto, T. R.; Bertozzi, C. R.; Rosen, S. D.; Kiessling, L. L. L-Selectin-Carbohydrate Interactions: Relevant Modifications of the Lewis x Trisaccharide. *Biochemistry* **1996**, *35*, 14862−14867. (b) Tsujishita, H.; Hiramatsu, Y.; Kondo, N.; Ohmoto, H.; Kondo, H.; Kiso, M.; Hasegawa, A. Selectin-Ligand Interactions Revealed by Molecular Dynamics Simulation in Solution. *J. Med. Chem.* **1997**, *40*, 362−369.

(10) Kogan, T. P.; Revelle, B. M.; Tapp, S.; Scott, D.; Beck, P. J. A Single Amino Acid Residue can Determine the Ligand Specificity of E-Selectin. *J. Biol. Chem.* **1995**, *270*, 14047−14055.

(11) The recent report (below) of a mannose binding protein mutant that will recognize sLe^x and bears the K111, K113 motif in E-selectin is ambiguous with regard to implications for selectin binding, since the 96-101 insertion loop present in the selectins is missing in this mutant, while the sialic acid (required for selectin binding) has no direct contact with the protein. Ng, K. K.-S.; Weis, W. I. Structure of a Selectin-like Mutant of Mannose-Binding Protein Complexed with Sialylated and Sulfated Lewis^x Oligosaccharides. *Biochemistry* **1997**, *36*, 979−988.

(12) (a) Patel, T. P.; Goelz, S. E.; Lobb, R. R.; Parekh, R. B. Isolation and Characterization of Natural Protein-Associated Carbohydrate Ligands for E-Selectin. *Biochemistry* **1994**, *33*, 14815−14824. (b) Patel, T. P.; Edge, C. J.; Parekh, R. B.; Goelz, S. E.; Lobb, R. In *Cell Adhesion and Human Disease*; Wiley: Chichester, 1995; (Ciba Foundation Symposium 189); pp 212−226.

(13) Varki, A. Selectin Ligands. Will the Real Ones Please Stand Up? *J. Clin. Invest.* **1997**, *99*, 158−162.

(14) Varki, A. Selectin Ligands. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 7390−7397.

(15) Miyaura, N.; Yanagi, T.; Suzuki, A. The Palladium-Catalyzed Cross-Coupling of Phenylboronic Acid with Haloarenes in the Presence of Bases. *Synth. Commun.* **1981**, *11*, 513−519.

(16) Scott, I. L.; Market, R. V.; Deorazio, R.; Meckler, H.; Kogan, T. P. Manuscript in preparation.

(17) For further information regarding assay format, see ref 8a.

(18) Welply, J. K.; Abbas, S. Z.; Scudder, P.; Keene, J. L.; Broschat, K.; Casnocha, S.; Gorka, C.; Steininger, C.; Howard, S. C.; Schmuke, J. J.; Graneto, M.; Rotsaert, J. M.; Manger, I. D.; Jacob, G. S. Multivalent Sialyl-Le^x: Potent Inhibitors of E-Selectin-Mediated Cell Adhesion; Reagent for Staining Activated Endothelial Cells. *Glycobiology* **1994**, *4*, 259−265.

(19) (a) DeFrees, S. A.; Phillips, L.; Guo, L.; Zalipski, S. Sialyl Lewis x Liposomes as a Multivalent Ligand and Inhibitor of E-Selectin Mediated Cellular Adhesion. *J. Am. Chem. Soc.* **1996**, *118*, 6101−6104. (b) Spevak, W.; Foxall, C.; Charych, D. H.; Dasgupta, F.; Nagy, J. O. Carbohydrates in an Acidic Multivalent Assembly: Nanomolar P-Selectin Inhibitors. *J. Med. Chem.* **1996**, *39*, 1018−1020. (c) Kiessling, L. L.; Pohl, N. L. Stength in Numbers: Non-Natural Polyvalent Carbohydrate Derivatives. *Chem. Biol.* **1996**, *3*, 71−77.

(20) (a) Kiessling, L. L.; Pohl, N. L. Stength in Numbers: Non-Natural Polyvalent Carbohydrate Derivatives. *Chem. Biol.* **1996**, *3*, 71−77. (b) Manning, D. D.; Hu, X.; Beck, P.; Kiessling, L. L. Synthesis of Sulfated Neoglycopolymers: Selective P-Selectin Inhibitors. *J. Am. Chem. Soc.* **1997**, *1997*, 3161−3162. (c) Miyauchi, H.; Tanaka, M.; Koike, H.; Kawamura, N.; Hayashi, M. Synthesis and Inhibitory Effect of a Sialyl Lewis X-acrylamide Homopolymer at Preventing Cell Adhesion. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 985−988.

(21) Miyauchi, H.; Tanaka, M.; Koike, H.; Kawamura, N.; Hayashi, M. Synthesis and Inhibitory Effect of Bivalent Sialyl Lewis X Analogs at Preventing Cell Adhesion. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 989−992.

(22) (a) Pang, Y.-P.; Quiram, P.; Jalacic, T.; Hong, F.; Brimijoin, S. Highly Potent, Selective, and Low Cost Bistetahydroaminacrine Inhibitors of Acetylcholinesterase. *J. Biol. Chem.* **1996**, *271*, 23646−23649. (b) Halazy, S.; Perez, M.; Fourrier, C.; Pallard, I.; Pauwels, P. J.; Palmier, C.; John, G. W.; Valentin, J.-P.; Bonnafous, R.; Martinez, J. Serotonin Dimers: Application of the Bivalent Ligand Approach to the Design of New Potent and Selective 5-HT1B/1D Agonists. *J. Med. Chem.* **1996**, *39*, 4920−4927. (c) Gazit, A.; Osherov, N.; Gilon, C.; Levitzki, A. Tyrphostins. 6. Dimeric Benzylidinemalononitrile Tyrphostins: Potent Inhibitors of EGF Receptor Tyrosine Kinase *in Vitro*. *J. Med. Chem.* **1996**, *39*, 4905−4911. (d) Hajduk, P. J.; Sheppard, G.; Nettesheim, D. G.; Olejniczak, E. T.; Shuker, S. B.; Meadows, R. P.; Steinman, D. H.; Carrera, G. M., Jr.; Marcotte, P. A.; Severin, J.; Walter, K.; Smith, H.; Gubbins, E.; Simmer, R.; Holzman, T. F.; Morgan, D. W.; Davidsen, S. K.; Summers, J. B.; Fesik, S. W. Discovery of Potent Nonpeptide Inhibitors of Stromelysin using SAR by NMR. *J. Am. Chem. Soc.* **1997**, *119*, 5818-5827. (e) Shuker, S. B.; Hajduk, P. J.; Meadows, R. P.; Fesik, S. W. Discovering high−affinity ligands for proteins: SAR by NMR. *Science* **1996**, *274*, 1531−1534.

(23) (a) Palma-Vargas, J. M.; Toledo-Pereyra, L. H.; Dean, R. E.; Dixon, R. A. F.; Kogan, T. P. Small-Molecule Selectin Inhibitor Protects Against Liver Inflammatory Response After Ischemia and Reperfusion *J. Am. Coll. Surgeons* **1997**, *185*, 365−372. (b) Abraham, W. M.; Ahmed, A.; Cortes, A.; Bjercke, R.; Hu, X.; Revelle, B. M.; Kogan, T. P.; Dupré B., Scott I. L.; Dixon, R. A. F.; Yeh, E. T. H.; Beck, P. J. Selectin Blockade Prevents Antigen-Induced Late Broncial Responses and Airway Hyperresponsiveness in Allergic Sheep. Manuscript in preparation.

(24) Differences in IC_{50} values for sLe^x and **3** from those previously reported[8a] are due to minor changes in the assay format. All data presented in this table are from multiple assays, and the values reported are consistent within this table.

JM9704917