Pergamon

Tetrahedron 54 (1998) 3765–3780

TETRAHEDRON

Synthesis of Novel Sialyl-Lewis^X Glycomimetics as Selectin Antagonists

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Received 16 December 1997; accepted 3 February 1998

Abstract: A series of low molecular weight sialyl-Lewis^X analogs based on either rigid or flexible replacements for the carbohydrates were designed as orally available anti-inflammatory drugs, synthesized and tested in cell-based adhesion assays. The flexible glycomimetic **7a** lacking any glycoside or peptide linkage was prepared in 4 steps and 41% overall yield from methyl 3,5-dihydroxybenzoate and the fucose derivative **18** and exhibited about equal binding affinity to E- and P-selectin compared to the parent tetrasaccharide.

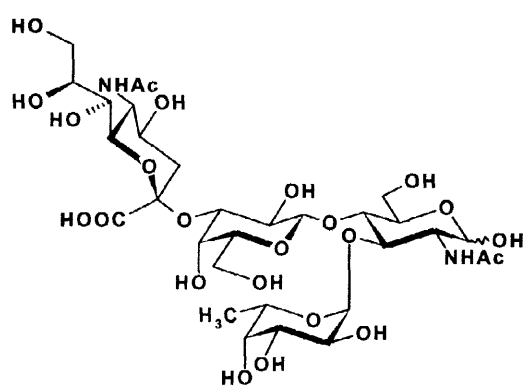


Figure 1: sialyl Lewis^X

Introduction

Oligosaccharide molecules are not regarded as viable drug candidates if they are not designated for delivery per injections or to treat gastrointestinal diseases.[1a] The sialyl Lewis^X tetrasaccharide (Figure 1: sLe^X) structure represents a prominent test case for the development of new drug concepts based on carbohydrates. Sialyl Lewis^X was found on the termini of glycolipids and glycoproteins and is considered to be the minimal recognition motif of the selectins, a group of cell surface lectins with a distinct carbohydrate recognition domain (CRD).[1b-h] This binding event mediates the initial adhesion of several groups of leukocytes to areas of inflammation. Antagonists of this process are therefore potential agents to prevent leukocyte adhesion and their subsequent migration to the affected tissues in several acute and chronic inflammatory diseases. Some

0040-4020/98/$19.00
PII: S0040-4020(98)00105-7

representative examples of selectin antagonists and potential new anti-inflammatory drug leads which were recently published are shown in Figure 2. They were designed as simplified glycomimetics to replace the complex tetrasaccharide sLe^X based on the knowledge about structure-activity relationships which had been obtained by variation of functional groups of sLe^X. For instance, it is well established that the L-fucose or a

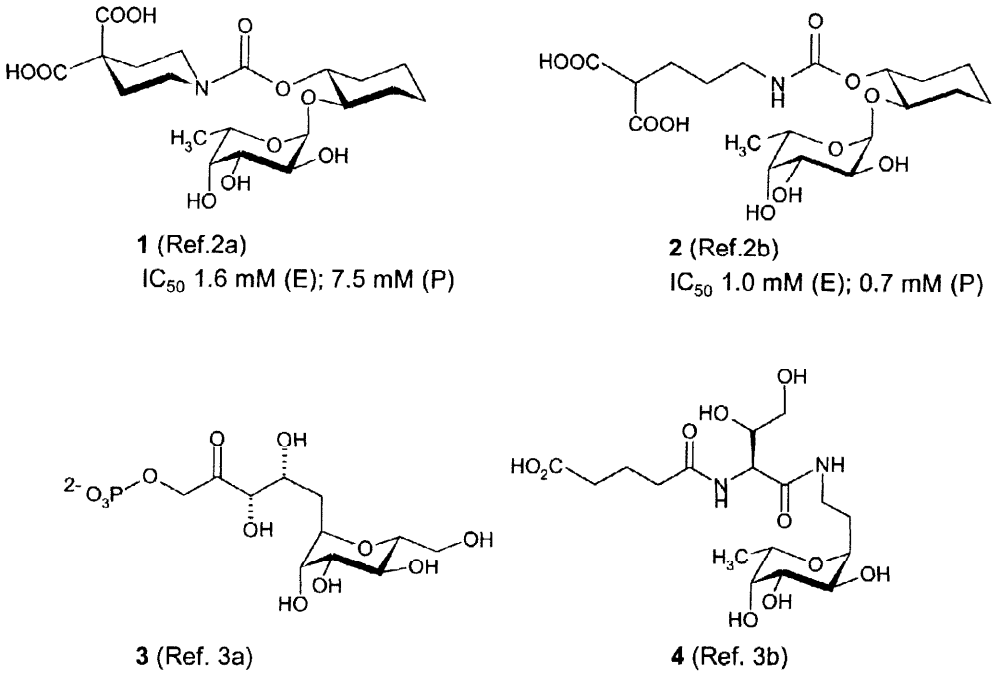


Figure 2: Designated sLe^X mimetics and their IC_{50} [mM] values determined in a cell-based assay. The comparable data for sLe^X are 1.5 mM (E) and 3.0 mM (P). The data published for **3** and **4** are considered to be not comparable with **1** and **2** since they were determined in cell-free assays and from samples which unfortunately had been prepared using ion exchange resins[4,5] (IC_{50} 0.8 mM and 0.005 mM for **3**[3a] with E- and P-selectins, respectively, and IC_{50} 0.3 mM and 0.4 mM for **4**[3b] with E- and P-selectins, respectively.)

related saccharide like D-mannose must be presented in a distinct distance and orientation relative to the acid function being derived from the sialic acid moiety. In cell-based selectin adhesion assays, which are closer related to the *in vivo* binding conditions than cell-free assays, no lower molecular weight sLe^X mimetic lacking any glycoside or peptide moiety, while having receptor affinities equal or even better than the natural tetrasaccharide ligand, thus far has been reported.[4] The more potent compounds were either peptides,[6] quite complex derivates[7] and conjugates[8] of the parent tetrasaccharide and therefore most likely unsuitable for oral drug formulations. Similar arguments apply to other types of potent selectin antagonists including some sugar conjugates carrying lipophilic tails and thus sharing common structural features with detergents,[9] and some very high molecular-weight, charged aggregates[10] which may act in a similar manner dependent on dosage, molecular weight and negative charge distribution/density as was proven for simple polyanions.[4] Those compounds seem to act by virtue of recognition mechanisms differing from sugar-specific binding to the shallow cleft (CRD) presented by the selectin receptors. For example, potent antagonists based on

lipophilic sugar conjugates may act by distortion of the cell membranes *in vivo*.[11] It remains undecided up to now if orally available and much tighter binding small drug candidates which are lacking glycoside, peptide and long-chain lipophilic moieties once can be developed. To achieve this goal, another issue to be addressed here is the requirement for some rigid replacements to be incorporated in the glycomimetic design. Several attempts towards this strategy have been published, especially using the (1R,2R)-1,2-cyclohexanediol system to substitute the N-acetylglucosamine for the proper arrangement of the critical functional groups in selectin binding.[12] If both the O-α-fucose- and the O-β-galactose core structures were retained as the intact carbohydrates, and malonic acid was attached in the 2-position of the galactose *via* a two-carbon spacer to replace the carboxylic acid group of N-acetylneuraminic acid, about equal binding affinities to E- and P-selectins could be obtained.[4a] Similar receptor affinities resulted from properly exchanging the galactose moiety by short flexible spacers,[12a] but further attempts to replace the galactose by aromatic spacers failed,[12b] or they gave puzzling results when an aryl-cyclohexylether was incorporated as a disaccharide scaffold.[12c] In this study, the diastereomeric (1S,2S)-1,2-cyclohexanediol moiety surprisingly exhibited the highest inhibition of soluble E-selectin binding (IC_{50} 0.87 mM), while the IC_{50} of its properly arranged (1R,2R)-diastereomer was reported to be only 3.3 mM (cell-free ELISAs). To achieve a deeper understanding of the structural requirements leading to more efficient sLe^X mimetics, two different synthetic strategies - either targeted at the rigid compounds **6** or at the very flexible mimetics **7** - were investigated (Figure 3).

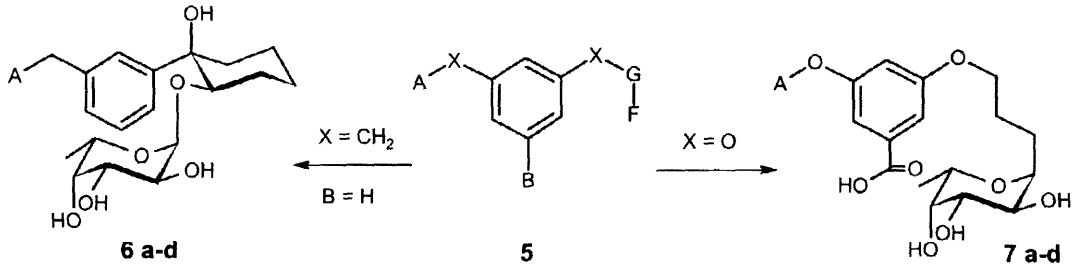
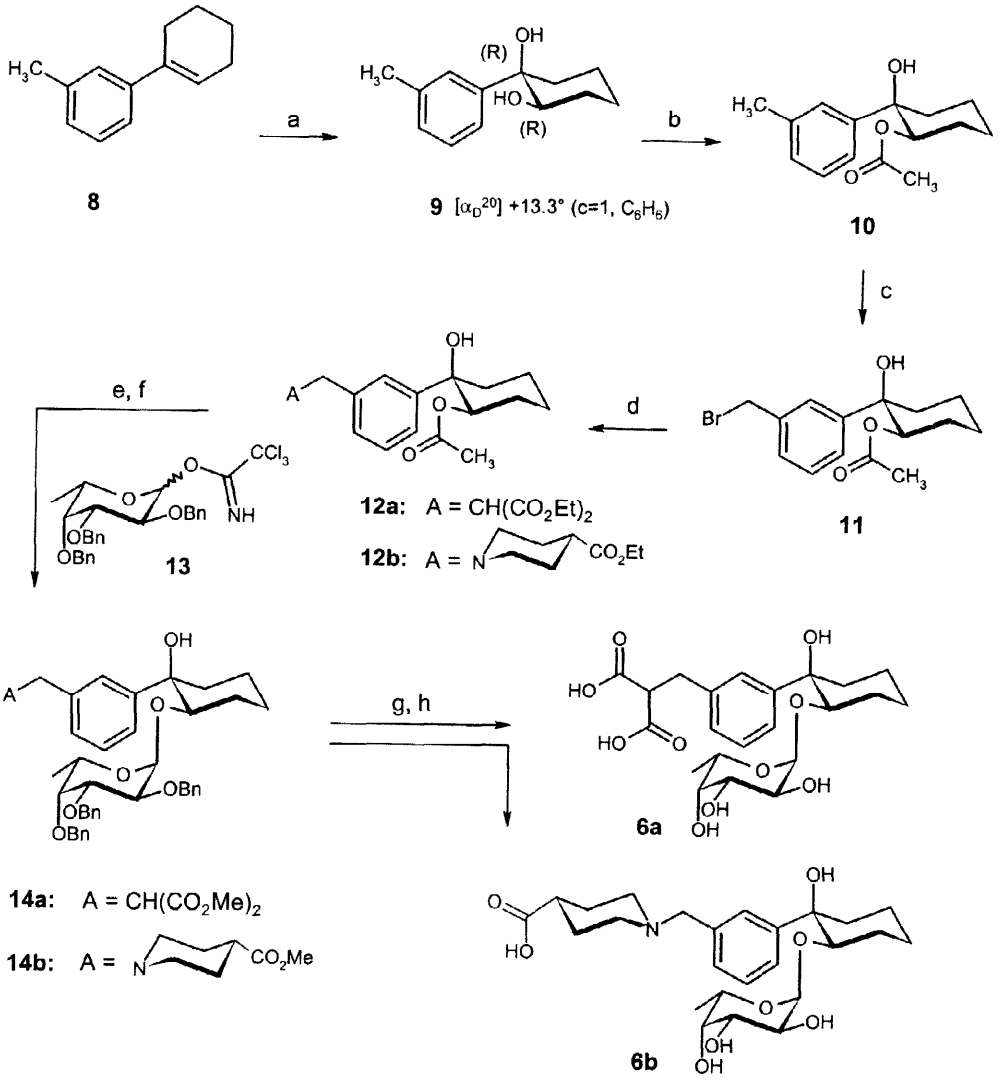


Figure 3: Designed rigid and flexible sLe^X mimetics (**6a-d**) and (**7a-d**), respectively, with replacements A for NAcNeu, G for GlcNAc, F for Fuc, and the substituted benzene derivative for Gal.

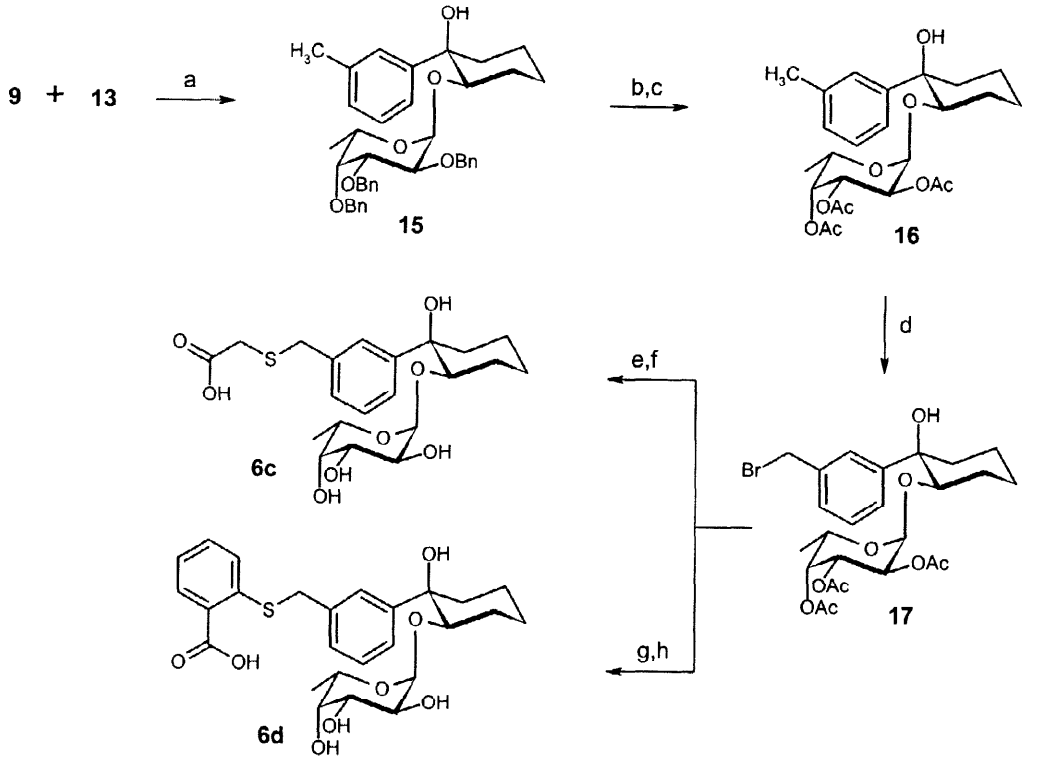
Preparative Results

The first strategy targeted at the rigid glycomimetics **6a-d** incorporates the (1R,2R)-1,2-cyclohexanediol scaffold, directly connected to a substituted phenyl ring as the galactose replacement. The (1R, 2R)-diol **9** was prepared by the *Sharpless* asymmetric dihydroxylation[13] using the ligand 1,4-bis-(9-dihydro-chinidinyl)-phthalazine [$(DHQD)_2$-PHAL] to introduce the 2 stereocenters in one step. The (1R)-hydroxyl group might be removed with *Raney*-Ni with retention of configuration, in an analogous manner as described for the synthesis of (1R, 2S)-*trans*-2-phenylcyclohexanol,[13] but it was decided to retain this functionality to display additional receptor binding options. No additional reaction steps were required to protect this tertiary



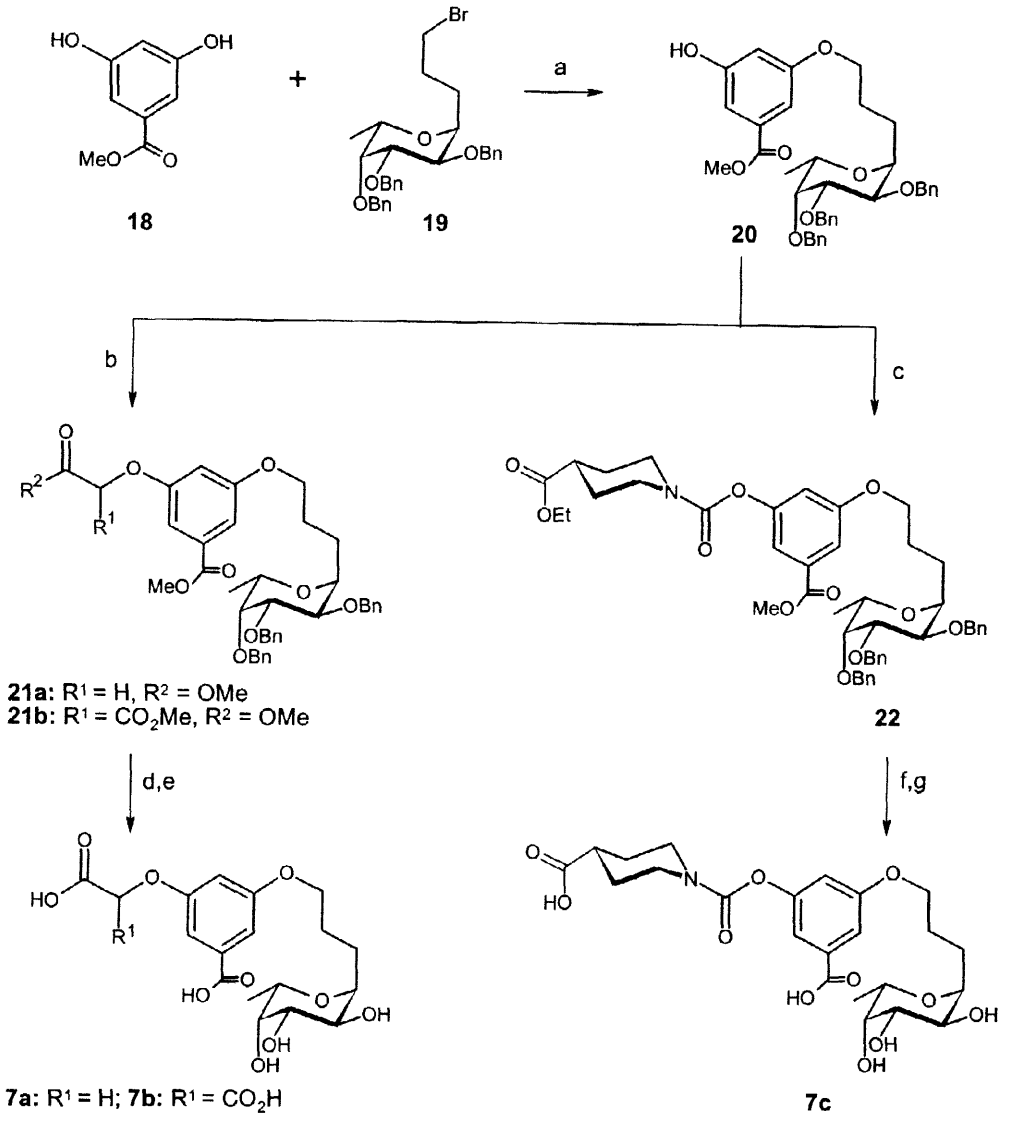
Scheme 1: Synthesis of type **6** mimetics, protocol A: a) *t*-BuOH, H_2O, AD-Mix-β, $CH_3SO_2NH_2$, 0°C, 17h (84%), b) CH_2Cl_2, pyridine, Ac_2O, DMAP (97%); c) CCl_4, NBS, AIBN, rfx, 1 h (86%); d) i) diethyl malonate, CsF, DMF, 24 h, 20°C (71% **12a**), ii) piperidine-4-carboxylic acid-ethylester, K_2CO_3, DMF, 4 h, 60°C (70% **12b**); e) MeOH/NaOMe, 3 h, 20°C f) 1.2 equiv. **13** in Et_2O, mol. sieves 4 Å, cat. TMS-OTf, 20°C (35% **14a** from **12a**; 21% **14b** from **12b**); g) MeOH, H_2, 10%-Pd/C, 20°C; h) 2N NaOH/H_2O, 20°C for 14 h, then HOAc (61% **6a**; 54% **6b**).

hydroxyl group. Subsequently, the other hydroxyl group was protected by selective acetylation and the methyl side chain was brominated with NBS to provide **11**. This reactive building block enables to introduce easily a wide variety of nucleophiles in order to investigate suitable replacements for the N-acetyl-neuraminic acid unit. Alkylations with the C- and N-nucleophiles diethyl malonate and ethyl piperidine-4-carboxylate, respectively, and subsequent deacetylation and fucosylation using the benzyl protected fucosyl-trichloroacetimidate[14] led to the α-fucosides **14a,b** which were then deprotected by standard procedures to the potential sLe^X mimetics **6a,b**. Since the fucosylation of the intermediates **12a,b** was rather low-yielding and S-derivatives were not accessible by this sequence, the alternative procedure shown in Scheme 2 was



Scheme 2: Synthesis of type **6** mimetics, protocol B: a) 0.9 equiv. **13** in Et_2O, mol. sieves 4 Å, cat. TMS-OTf, 20°C (76.2%); b) MeOH, H_2, 10%-Pd/C, 20°C; c) CH_2Cl_2, pyr., Ac_2O, DMAP (88%, 2 steps); d) CCl_4, NBS, AIBN, rfx, 1 h (87%); e) $HSCH_2CO_2Me$ (2.2 equiv.), K_2CO_3, THF, 20°C (55%); f) 2N NaOH/H_2O, 20°C, then HOAc (91%); g) methyl 2-mercaptobenzoate (2.2 equiv.), K_2CO_3, THF, 20°C (55%); h) 2N NaOH/H_2O, 20°C; HOAc (87%).

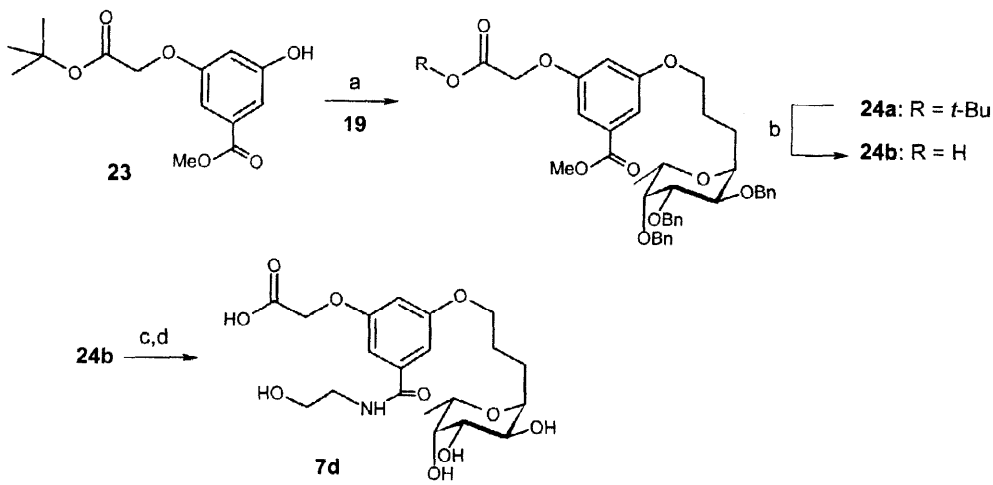
developed. The selective fucosylation proceeded more efficiently with the diol **9** to save one protection step, but then the benzyl groups in the fucoside **15** had to be replaced by acetyl groups. NBS bromination yielded the building block **17** which was coupled to S-nucleophiles, thereby introducing the protected carboxylic acid functions. The fully deprotected test compounds **6c,d** were obtained after hydrolysis of the esters, the acidification steps - very worth mentioning - being performed by acetic acid and *not* by using ion exchange resins.[4] The structures of mimetics **6a-d** were confirmed by H, H- and C, H-COSY-NMR spectra (Table 2) revealing an extremely strong diamagnetic high-field shift of the 5,6-H fucose resonances due to the proximity of the benzene ring current. Compared to the corresponding resonances of the sLe^X system,[8a] the chemical shifts for the 5-Hs in the sugar moiety were moved from 4.83 up to ca. 1.83 ppm, and for the 6-H's from 1.17 up to ca. 0.7-0.8 ppm. To synthesize the flexible mimetics **7a-d** lacking any glycoside linkage, the 3,5-dihydroxybenzoate **18** was chosen as a suitable scaffold to attach the known, protected α-L-fucopyranosyl-1-propyl bromide **19**[3b] to carboxylated building blocks (similar to those already used for the type **6** mimetics) *via* stable ether bonds (Scheme 3). The mimetics **7a-c** were then obtained using standard alkylation/deprotection reactions to introduce the carboxymethyl, malonyl- and 4-carboxypiperidinyl units



Scheme 3: Synthesis of type 7 sLe^X mimetics. a) 3 equiv. **18**, K_2CO_3, DMF, 0°C for 12 h, 20°C for 24 h (61%); b) 2 equiv. $BrCH_2CO_2Me$, K_2CO_3, DMF, 50°C, 5 h (84% **21a**), or 2 equiv. $BrCH(CO_2Et)_2$, $NaHCO_3$, DMF, 0°C, 48 h (50% **21b**); c) 1.1 equiv. 4-nitrophenylchloroformate, NEt_3, cat. DMAP, 0°C, then 2.5 equiv. ethyl piperidine-4-carboxylate (95%); d) MeOH, HOAc, H_2, 10%-Pd/C; e) 2N NaOH, 20°C, then 1N HCl (81% **7a**, 71% **7b**); f) MeOH, HOAc, H_2, 10%-Pd/C, 3 h, 20°C, (65%); 1N NaOH, 12 h, 0°C, then 1N HCl, MPLC on RP (32%).

in good overall yields, e.g. the sLe^X mimetic **7a** could be obtained in 4 steps and 41% overall yield from **19**. The alternative reaction sequence described in Scheme 4 allows to further modify the aromatic carboxyl group before the last deprotection step. For instance, selective cleavage of the *tert.*-butyl ester group in **23** by base treatment and heating the intermediate **24b** together with an excess of ethanolamine, followed by hydrogenolytic cleavage of the benzyl groups afforded the mimetic **7d**.

The compounds **6a-d** and **7a-d** were then examined for their inhibitory potency towards the E- and P-selectin receptors. The bioassays for cell binding to immobilized selectin receptor globulins were carried out as pre-



Scheme 4: a) 1.5 equiv. **23**, K_2CO_3, DMF, 12 h at 20°C, 7 h at 60°C (98%, based on **19**); b) 1N NaOH, 12 h at 0°C, 1N HCl (58%); c) ethanolamine, 1 h at 100°C (99%), then d) 1,4-dioxane, HOAc, H_2, 10%-Pd/C (71%).

viously described.[8a] The concentrations of the inhibitors required to block adhesion of 50% of the HL60 cells are given in Table 1: The simple glycomimetic **7a** showed inhibitory activity equivalent to the parent sLe^X tetrasaccharide with IC_{50}'s of 2.4 mM and 1.6 mM for E- and P-selectin, respectively. Very recently, computational models for the rationalisation and prediction of bioactivity trends towards E-selectin binding were reported.[15] The modelling procedures employed there are predicting that the ligand's ability to preorganise its binding in the right manner is one fundamental requirement for bioactivity, mainly because of entropic factors. Not very surprisingly, this requirement was found to be perfectly fulfilled for a pseudotetrasaccharide very similar to sLe^X itself. It was assumed, that the lack of activity of other compounds may be caused by their higher flexibility and thus lower reorganisation. In contrast, the data presented here for the mimetic **7a** rather suggest that a very tight ligand reorganisation may not necessarily meet the qualification of the selectin receptors to adjust their binding properties to the relatively flexible carbohydrates (and therefore to appropriate glycomimetics). Furthermore, quite drastic structural changes of the complex tetrasaccharide, while retaining its biological activity appear to be possible, especially if suitable hydrophobic and acidic replacements for the lactosamine and neuraminic acid moieties, respectively, can be discovered. Future work will be directed at further improvements of this concept.

	Selectin **IC_{50}** [mM]	
	E	P
reference compound[8a]		
sLe^X-1β–$O(CH_2)_6NH_2$	1.5	3.0
sLe^X glycomimetics		
7a	2.4	1.6
7c	4.0	>10

Table 1: Inhibition of HL60 cell adhesion to recombinant E- and P-selectin-IgG fusion proteins by designed sLe^X glycomimetics. IC_{50} values are concentrations of inhibitors required to block adhesion of 50% of the cells compared with the negative control. Compounds not listed in the table had IC_{50} values >5 mM and were considered to be inactive in this assay system.

EXPERIMENTAL PART

General: Thin layer chromatography (TLC) was carried out on precoated Kieselgel 60 F_{254} plates (0.25 mm thickness, E. Merck) with the specified solvent mixtures. Spots were visualised by spraying the plates with sulphuric acid/anisaldehyde reagent, followed by heating. E.Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. Yields refer to chromatographically (TLC) and spectroscopically (NMR) homogeneous materials. Optical rotations were measured using a Perkin Elmer 241 polarimeter. NMR spectra were recorded on a Bruker WT 300 (300 MHz). NMR chemical shifts are given as δ-values with reference to tetramethylsilane (TMS) as internal standard, if not otherwise noted. The spectra recorded in D_2O as solvent were locked to deuterium. Mass spectra were recorded on a TSQ 700, Finnigan/MAT, electrospray ionisation (ESI), and MS/MS daughter ion scan.

(1R, 2R)-1-(3-Methylphenyl)-cyclohexane-1,2-diol (9) (Protocol A, Scheme 1): 1-(3-Methylphenyl)-cyclohexene (**8**) (25.0 g, 0.145 mol), *tert.*-BuOH (500 ml), H_2O (500 ml), 203 g AD-Mix-β (from *Aldrich*, contains the chiral ligand 1,4-bis-(9-dihydrochinidinyl)-phthalazine $[DHQD]_2$-PHAL) and methanesulfoneamide (13.8 g, 0.145 mol) were stirred at 0°C for 17 h. Na_2SO_3 (220 g) was added at 0°C and stirring continued for another 2 h. After separation of layers, the aqueous phase was extracted with ethyl acetate (3 x 300 ml). Combined organic phase was washed with aqueous 0.1N NaOH and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by filtration over silica gel 60 in *n*-hexane/ethyl acetate (7:1 → 2:1) to give the compound **9** as a white solid (25.2 g, 84%). $[\alpha]_D^{20}$ +13.3° (c = 1.01, C_6H_6). ^1H NMR (300 MHz, $CDCl_3$): 1.30-1.92 (m, 9H, 1-OH, C_4H_8), 2.37 (s, 3H, Me), 2.55 (d, J = 0.8 Hz,1H, 2-OH), 3.98 (ddd, J = 11.0, 3.4, 0.8 Hz, 1H, 2-$H_{cyclohex}$), 7.07 (m, 1H, H-Ar), 7.22-7.34 (m, 3H, H-Ar).

(1R, 2R)-2-Acetoxy-1-hydroxy-1-(3-methylphenyl)-cyclohexane (10):Diol **9** (5.14 g, 0.025 mol), CH_2Cl_2 (80 ml), pyridine (10 ml) and Ac_2O (5 ml) were stirred for 6 h at 20°C. The reaction was washed with H_2O (2 x 50 ml), aqueous 0.1N HCl (3 x 50 ml), $NaHCO_3$ (50 ml) and brine, dried ($MgSO_4$), filtered, evaporated twice with toluene (50 ml) and dried *i.vac.* to give the acetate **10** (6.03 g, 97%). ^1H NMR (300 MHz, $CDCl_3$): 1.35-1.96 (m, 9H, 1-OH, C_4H_8), 1.81 (s, 3H, OAc), 2.34 (s, 3H, 3-Me), 5.26 (dd, J = 10.0, 5.4 Hz, 1H, 2-$H_{cyclohex}$), 7.05 (m, 1H, H-Ar), 7.16-7.29 (m, 3H, H-Ar).

(1R, 2R)-2-Acetoxy-1-hydroxy-1-(3-bromomethylphenyl)-cyclohexane (11):Acetate **10** (2.14 g, 8.61 mmol) CCl_4 (50 ml), N-bromosuccinimide (1.77 g, 9.95 mmol) and α,α′-azoisobutyronitrile (AIBN, 50 mg) were heated under reflux for 1 h. The reaction was filtered, washed with brine, dried ($MgSO_4$), filtered and concentrated *i.vac.*. Flash chromatography on silica gel in *n*-hexane/ethyl acetate (10:1 → 5:1) gave the compound **11** (2.88 g, 102%, incl. some dibromide, corr. yield 86%) ^1H NMR (300 MHz, $CDCl_3$): 1.35-1.97 (m, 9H, 1-OH, C_4H_8), 1.84 (s, 3H, OAc), 4.49 (s, <2H, CH_2Br), 5.26 (dd, J = 10.0, 5.4 Hz, 1H, 2-$H_{cyclohex}$), 7.20-7.40 (m, 4H, H-Ar). The signal at δ = 6.65 ppm was assigned to the dibromide (ca. 16%).

(1R, 2R)-2-Acetoxy-1-hydroxy-1-[3-(2,2-diethoxycarbonyl-1-ethyl)-phenyl]-cyclohexane (12a): Bromide **11** (2.88 g, 7.40 mmol monobromide), diethyl malonate (2 ml, 13.2 mmol), CsF (2.00 g, 13.2 mmol) and DMF

(30 ml) were stirred for 24 h at 20°C. The solvent was evaporated *i.vac.*, the residue taken up in ethyl acetate (100 ml) and washed with brine (3 x 50 ml). The dried organic phase was concentrated *i.vac.*and flash chromatography on silica gel (*n*-hexane/ethyl acetate 8:1 → 3:1) gave **12a** (2.14 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.20, 1.21 (2t, J = 7.0 Hz, 6H, $CH_2\underline{CH_3}$), 1.38-1.95 (m, 8H, C_4H_8), 1.80 (s, 3H, OAc), 2.24 (m, 1H, 1-OH), 3.23 (d, J = 7.7 Hz, 2H, $ArC\underline{H_2}$), 3.62 (t, J = 7.7 Hz, 1H, $CHCO_2$), 4.15 (4q, J = 7.0 Hz, $C\underline{H_2}CH_3$), 5.25 (dd, J = 10.0, 5.4 Hz, 1H, 2-$H_{cyclohex}$), 7.07 (m, 1H, H-Ar), 7.18-7.33 (m, 3H, H-Ar).

(1R, 2R)-1,2-Dihydroxy-2-O-(2,3,4-tri-O-benzyl-a-L-fucopyranosyl)-1-[3-(2,2-dimethoxycarbonyl-1-ethyl)-phenyl]-cyclohexane (14a): A solution of **12a** (2.14 g, 5.26 mmol in dry methanol (20 ml) was treated with a 35% solution of NaOMe/MeOH (1 ml). After 3 h, the reaction was neutralised with HOAc, filtered and concentrated. The residue was taken up in CCl_4 and washed with water, the dried organic phase ($MgSO_4$) was evaporated and concentrated *i.vac.*to obtain 1.74 g (99 %) of the intermediate (1R, 2R)-1,2-dihydroxy-1-[3-(2,2-dimethoxycarbonyl-1-ethyl)-phenyl]-cyclohexane [^{1}H NMR (300 MHz, $CDCl_3$): 3.16 (d, J = 7.8 Hz, 2H, $ArC\underline{H_2}$), 3.60 (t, J = 7.8 Hz, 1H, $CHCO_2$), 3.62, 3.63 (2s, 6H, OMe), 3.88 (dd, J = 10.5, 4.5 Hz, 1H, 2-$H_{cyclohex}$] which was dissolved in dry diethyl ether (30 ml) containing molecular sieves (4 Å) and trimethylsilyltriflate (56 µl, 0.31 mmol), and then fucosylated by dropwise addition of a solution of trichloromethylimidoyl-O-2,3,4-tri-O-benzyl-L-fucopyranoside (**13**) (3.60 g, 6.22 mmol) in dry 1,2-dichloroethane during 20 min at 20°C. After further stirring for 2 h, the reaction was quenched with NEt_3 (100 µl) and filtered. The product was washed with saturated aqueous $NaHCO_3$ solution and brine, the dried organic phase ($MgSO_4$) then concentrated *in vac.*, and the residue chromatographed on silica gel (*n*-hexane/ethyl acetate 4/1 → 2/1) to give the fucoside **14a** (1.40 g, 36%). ^{1}H NMR (300 MHz, $CDCl_3$): 0.68 (d, J 6.5 Hz, 3H, 6-H_{fuc}), 1.35-2.01 (m, 9H, 1-OH, C_4H_8), 2.17 (m, 1H, 5-H_{fuc}), 2.95-3.82 (m, 5H, 3,4-H_{fuc}, $ArCH_2CH$), 3.66, 3.67 (2s, 6H, OMe), 3.90 (m, 2H, 2-$H_{cyclohex}$, 2-H_{fuc}), 4.45-4.95 (m, 6H, OCH_2Ph), 4.95 (d, 1H, J = 3.5 Hz, 1-H_{fuc}),, 6.98 (m, 1H, H-Ar), 7.10-7.40 (m, 18H, H-Ar, 3Ph).

(1R, 2R)-1,2-Dihydroxy-2-O-(a-L-fucopyranosyl)-1-[3-(2,2-dicarboxy-1-ethyl)-phenyl]-cyclohexane (6a): **14a** (1.30 g, 1.72 mmol) was dissolved in dry methanol (50 ml) and hydrogenated in the presence of 10%-Pd/C (0.40 g) for 4 h at 20°C. The reaction was filtered through Celite, washed with methanol and concentrated up to 20 ml under reduced pressure (20 ml). Then 2N aqueous NaOH (4 ml) was added. After stirring at 20°C for 14 h and complete saponification of the intermediate monoester (monitoring by TLC), the pH was adjusted to 4.5 with HOAc and the product was isolated by preparative MPLC (RP, H_2O 100% → H_2O/MeOH 1:1 → MeOH 100%) to give the compound **6a** (0.475 g, 61%). MS: m/e = 454 (100%), 455 (16%) ($C_{22}H_{30}O_{10}$: 454.47), NMR see Table 2.

(1R, 2R)-2-Acetoxy-1-hydroxy-1-[3-(4-ethoxycarbonylpiperidin-1-yl-methyl)-phenyl]-cyclohexane (12b): Bromide **11** (3.96 g, 10.17 mmol monobromide content), piperidine-4-carboxylic acid-ethylester (2.8 ml, 18.2 mmol), K_2CO_3 (3.34 g, 24.2 mmol) and DMF (50 ml) were stirred for 4 h at 60°C. The solvent was evaporated *i.vac.*, the residue taken up in diethyl ether (200 ml) and washed with aqueous NH_4Cl (2 x 50

Table 2: NMR assignments for **6a-d**: (*) D_2O δ [ppm], 4.80 (HDO); (**) D_2O δ [ppm], 0.00 (TMS-sodium-propionate; (a) interchangeable resonances. Sample **6d** contained 5% DMSO-d_6.

	Fucose						*Cycohexane*					
	C-1 H-1	C-2 H-2	C-3 H-3	C-4 H-4	C-5 H-5	C-6 H-6	C-1 H-1	C-2 H-2	C-3 H-3	C-4 H-4	C-5 H-5	C-6 H-6
6a*	96.18 4.98	70.67 3.65	72.10 3.47	74.43 3.35	68.83 2.09	18.25 0.81	79.30	81.00 3.85	27.60	23.38 (a)	26.30 (a)	40.57 1.80/2.05
6b*	96.49 4.92	70.71 3.60	72.26 3.33	74.31 3.21	68.88 1.98	18.22 0.70	79.27	81.36 3.83	27.73 1.60/2.04	23.38 (a)	26.33 (a) 1.46/1.87	40.76 1.80/2.00
6c**	96.29 4.92	70.76 3.59	72.70 3.45	74.46 3.29	68.86 2.02	18.35 0.75	79.28	81.23 3.79	27.68 (a)	23.39	26.33 (a)	40.46 1.78/2.06
6d**	96.44 4.82	70.64 3.51	72.15 3.46	74.64 3.12	68.64 1.83	19.04 0.66	79.21	81.16 3.72	27.92 (a)	23.69	26.57 (a)	40.56

	Aryl						
	C-1 H-1	C-2 H-2	C-3 H-3	C-4 H-4	C-5 H-5	C-6 H-6	*CH_2-A*
6a*	149.86	128.04(a) 7.47	143.12	131.18(a) 7.40 (a)	129.76(a) 7.42 (a)	125.54(a) 7.18	181.06 (C=O), 39.09 (CHA), 3.18 (CHA),
6b*	151.30	130.55 7.63	131.64	132.37 7.40	132.13 7.54	129.74 7.65	184.68 (C=O), 63.26 (CHA), 4.30/4.34 (CHA), 54.55 (C-2), 3.05/3.44 (H-2), 29.04 (C-3), 44.04 (C-4), 2.34 (H-4)
6c**	150.49	128.52 7.54	140.85	126.69 7.42 (a)	131.53 7.42	130.19 7.26 (a)	180.48 (C=O), 39.45 (SCH_2CO), 3.18 (SCH_2CO), 38.96 (CHA), 3.81 (CHA)
6d**	150.99	129.21 7.61	139.48	127.13 7.38 (a)	130.52 7.31	129.02 7.47 (a)	176.77 (C=O), 140.00 (1′-Ar), 138.70 (2′-Ar), 132.27/7.63 (3′-Ar), 127.89/7.22 (4′-Ar), 131.73/7.39 (5′-Ar), 133.50/7.43 (6′-Ar), 39.76 (CHA), 4.18 (CHA)

ml) and brine. The dried organic phase ($MgSO_4$) was evaporated and concentrated *i.vac.*. Flash chromatography on silica gel in *n*-hexane/ethyl acetate (2:1) gave the compound **12b** (2.88 g, 70%). ^1H NMR (300 MHz, $CDCl_3$): 1.17 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.37-2.00 (m, 12H, 3′-CH_{pip}, C_4H_8), 1.72 (s, 3H, OAc), 2.22 (m, 3H, $CHCO_2$, 2′-CH_{pip}), 2.73 (m, 2H, 2′-CH_{pip}), 3.43 (m, 2H, $ArCH_2$), 4.05 (q, J = 7.0 Hz, CH_2CH_3), 5.19 (dd, J = 10.0, 5.4 Hz, 1H, 2-$H_{cyclohex}$), 7.07-7.32 (m, 4H, H-Ar).

(1R, 2R)-1,2-Dihydroxy-2-O-(2,3,4-tri-O-benzyl-a-L-fucopyranosyl)-1-[3-(4-ethoxycarbonylpiperidin-1-yl-methyl)-phenyl]-cyclohexane (14b): The procedure to obtain **14b** (0.454 g, 21% overall from 1.140 g of **12b** was identical to that for **14a**. ^1H NMR (300 MHz, $CDCl_3$: 0.68 (d, J 6.5 Hz, 3H, 6-H_{fuc}), 1.20-2.40 (m, 16H, 2′, 3′-CH_{pip}, $CHCO_2Me$, 5-H_{fuc}, C_4H_8), 2.78 (m, 2H, 2′-CH_{pip}), 2.95-4.00 [m, 9H, 2,3,4-H_{fuc}, $ArCH_2$, OMe (3.65), 2-$H_{cyclohex}$], 4.45-4.90 (m, 6H, OCH_2Ph), 4.95 (d, 1H, J = 3.5 Hz, 1-H_{fuc}), 7.05-7.55 (m, 19H, H-Ar, 3Ph).

*(1R, 2R)-1,2-Dihydroxy-2-O-(a-L-fucopyranosyl)-1-[3-(4-carboxypiperidin-1-yl-methyl)-phenyl]-cyclohexane (**6b**)*: The procedure to obtain **6b** (0.070 g, 54% overall from 0.204 g of **14b**) was identical to that for **6a**. NMR see Table 2.

*(1R, 2R)-1,2-Dihydroxy-2-O-(2,3,4-tri-O-benzyl-a-L-fucopyranosyl)-1-(3-methylphenyl)-cyclohexane (**15**)* (protocol B, Scheme 2): Diol **9** (1.76 g, 8.55 mmol) was dissolved in dry diethyl ether (75 ml) containing molecular sieves (4 Å) and trimethylsilyltriflate (25 µl, 0.19 mmol) and then fucosylated by dropwise addition of a solution of **13** (4.50 g, 7.77 mmol) in dry diethyl ether (40 ml) during 60 min at 20°C, and further stirring for 6 h. The reaction was quenched by addition of triethylamine (100 µl) and filtered. The product was washed with saturated aqueous $NaHCO_3$ solution and brine, the dried organic phase ($MgSO_4$) then concentrated *in vac.*, and the residue chromatographed on silica gel (*n*-hexane/ethyl acetate 6/1 → 4/1) to give the fucoside **15** (3.68 g, 76%). ^1H NMR (300 MHz, $CDCl_3$): 0.69 (d, J 6.5 Hz, 3H, 6-H_{fuc}), 1.35-2.05 (m, 8H, C_4H_8), 2.10 (m, 1H, 5-H_{fuc}), 2.30 (s, 3H, ArCH_3), 3.13 (m, 1H, 4-H_{fuc}), 3.22 (*br* m, 1H, OH), 3.43 (dd, J = 3.0, 10.0 Hz, 1H, 3-H_{fuc}), 3.88 (m, 2H, 2-$H_{cyclohex}$, 2-H_{fuc}), 4.45-4.88, (m, 6H, OCH_2Ph), 4.95 (d, 1H, J = 3.5 Hz, 1-H_{fuc}), 7.00-7.40 (m, 19H, H-Ar, 3Ph).

*(1R, 2R)-1,2-Dihydroxy-2-O-(2,3,4-tri-O-acetyl-a-L-fucopyranosyl)-1-(3-methylphenyl)-cyclohexane (**16**):* **15** (3.65 g, 5.88 mmol) was dissolved in dry MeOH (50 ml) and hydrogenated in the presence of 10%-Pd/C (0.40 g) for 12 h at 20°C. The reaction was filtered (Celite), washed (MeOH) and the solvent removed *i. vac.*. The residue was taken up in CH_2Cl_2 (5 ml), pyridine (2.5 ml), Ac_2O (1 ml) and DMAP (20 mg) and stirred for 12 h at 20°C. The reaction was washed with water (2 x 10 ml), aqueous 0.1N HCl (2 x 10 ml), $NaHCO_3$ (20 ml) and brine, dried ($MgSO_4$), filtered, evaporated twice with toluene (50 ml) and dried *i.vac.* to give compound **16** (2.45 g, ca. 88%). ^1H NMR (300 MHz, $CDCl_3$): 0.65 (d, J 6.5 Hz, 3H, 6-H_{fuc}), 1.87, 2.07, 2.08 (3s, 9H, OAc), 2.35 (m, 1H, 5-H_{fuc}), 2.39 (s, 3H, ArCH_3), 3.88 (dd, J = 4.0, 11.0 Hz, 1H, 2-$H_{cyclohex}$), 4.81 (m, 1H, 4-H_{fuc}), 4.93 (m, 2H, 2,3-H_{fuc}), 5.15 (d, 1H, 1-H_{fuc}), 7.05-7.35 (m, 4H, H-Ar).

*(1R, 2R)-1,2-Dihydroxy-2-O-(2,3,4-tri-O-acetyl-a-L-fucopyranosyl)-1-(3-bromomethyl-phenyl)-cyclohexane (**17**)*: The procedure to obtain the bromide **17** (crude 1.20 g, ca. 97% from 1.06 g of **16**) was identical to that for **11**. ^1H NMR (300 MHz, $CDCl_3$): 0.65 (d, J 6.5 Hz, 3H, 6-H_{fuc}), 4.53 (s, 2H, CH_2Br) The signal at δ = 6.70 ppm (s) was assigned to the dibromide (ca. 12%).

*(1R, 2R)-1,2-Dihydroxy-2-O-(a-L-fucopyranosyl)-1-[3-(carboxymethyl-thiomethyl)-phenyl)]-cyclohexane (**6c**):* The crude bromide **17** (0.417 g, ca. 0.67 mmol), THF (10 ml), $HSCH_2CO_2Me$ (134 µl, 1.49 mmol) and K_2CO_3 (0.310 g, 2.24 mmol) were stirred for 16 h at 20°C. The solvent was exchanged for CH_2Cl_2 and the reaction was washed with aqueous NH_4Cl (2 x 30 ml) and brine, and dried ($MgSO_4$). Flash chromatography on silica (*n*-hexane/ethyl acetate 2:1) gave the intermediate methyl ester [0.211 g, 55%; ^1H NMR ($CDCl_3$): 0.65 (d, J 6.5 Hz, 3H, 6-H_{fuc}), 1.94, 2.07 (3s, 9H, OAc), 2.47 (m, 1H, 5-H_{fuc}), 3.12 (s, 2H, SCH_2), 3.74 (s, 3H, OMe), 3.86 (m, 2H, $ArCH_2S$), 3.90 (m, 1H, 2-$H_{cyclohex}$), 4.84 (m, 1H, 4-H_{fuc}), 4.94 (m, 2H, 2,3-H_{fuc}), 5.15 (d, 1H, 1-H_{fuc}), 7.05-7.35 (m, 4H, H-Ar)] which was saponified as described for **6a**.

The purification was identical to that of **6a** to give **6c** (0.145 g, 91%). MS: m/e = 441 $[M-H]^-$ ($C_{21}H_{30}O_8S$: 442.52), NMR see Table 2.

*(1R, 2R)-1,2-Dihydroxy-2-O-(a-L-fucopyranosyl)-1-[3-(2-carboxyphenyl-thiomethyl)-phenyl)]-cyclohexane (**6d**)*: The procedure to obtain **6d** was identical to that for **6c** [alkylation of 2-mercapto-benzoic acid-methylester with 416 mg (ca. 0.67 mmol) of **17** to give the intermediate sulfide (0.238 mg, 55%), which was then saponified. Yield: 0.162 g (87%)]. MS: m/e = 503 $[M-H]^-$ ($C_{26}H_{32}O_8S$: 504.59), NMR see Table 2.

3-[3-(Tri-O-benzyl-α-L-fucopyranosyl)-1-propyloxy]-5-hydroxybenzoic acid-methylester (**20**): 3-(Tri-O-benzyl-α-L-fucopyranosyl)-1-propyl bromide[3b] (**19**) (1.44 g, 2.66 mmol), 3,5-dihydroxybenzoic acid-methylester (**18**) (1.34 g,7.98 mmol) and K_2CO_3 (0.553 g, 3.99 mmol) in DMF (20 ml) were stirred at 0°C for 12 h and then at 20°C for 24 h. The reaction was taken up in ethyl acetate and saturated NH_4Cl solution (50 ml). The aqueous layer was extracted with ethyl acetate (4 x 25 ml) and the combined organic layers were washed with sat. $NaHCO_3$ solution (50 ml) and brine , followed by drying ($MgSO_4$). After concentration *i. vac.*, the reside was taken up in toluene/ethyl acetate to give 1.03 g (61%) of **20** as a white solid. ^1H NMR (300 MHz, $CDCl_3$): 1.26 (d, J = 6.5 Hz, 3H, 6-H_{fuc}), 1.60-1.90 (m, 4H, FucC$\underline{H_2}$C$\underline{H_2}$), 3.88 (s, 3H, OMe), 3.70-4.07 (m, 7H, 1,2,3,4,5-H_{fuc}, ArOC$\underline{H_2}$), 4.50-4.80 (m, 6H, OC$\underline{H_2}$Ph), 5.33 (s, 1H, OH), 6.56 (t, J = 2.0 Hz, 1H, 4-H_{Ar}), 7.10, 7.13 (2 dd, J = 2.0, 0.7 Hz, 2H, 2-H_{Ar}, 6-H_{Ar}), 7.23-7.37 (m, 15H, Ph).

3-[3-(Tri-O-benzyl-α-L-fucopyranosyl)-1-propyloxy]-5-methoxycarbonyl-phenoxyacetic acid-methylester (**21a**): Compound **20** (0.839 g, 1.34 mmol), bromoacetic acid-methylester (0.247 ml, 2.68 mmol) and K_2CO_3 (0.555 g, 4.02 mmol) in DMF (10 ml) were stirred at 50°C for 5 h. The reaction was taken up in ethyl acetate and 50 ml of saturated NH_4Cl solution. The aqueous layer was further extracted with ethyl acetate (4 x 25 ml) and the combined organic layers were washed with saturated $NaHCO_3$ solution (30 ml) and brine, followed by drying ($MgSO_4$) After evaporation *i. vac.*, the product was purified by silica gel chromatography (*n*-hexane/ethyl acetate 3:1) to give 0.78 g (84%) of **21a**. ^1H NMR (300 MHz, $CDCl_3$): 1.26 (d, J = 6.5 Hz, 3H, 6-H_{fuc}), 1.60-1.92 (m, 4H, FucC$\underline{H_2}$C$\underline{H_2}$), 3.80 (s, 3H, OCH$_2$CO$_2$$\underline{Me}$), 3.88 (s, 3H, OMe), 3.73-4.05 (m, 7H, 1,2,3,4,5-H_{fuc}, ArOC$\underline{H_2}$CH$_2$), 4.50-4.80 (m, 8H, OC$\underline{H_2}$Ph, OC$\underline{H_2}$CO$_2$Me), 6.67 (t, J = 2.0 Hz, 1H, 2-H_{Ar}), 7.14, 7.22 (2 dd, J = 2.0, 0.7 Hz, 2H, 4-H_{Ar}, 6-H_{Ar}), 7.23-7.37 (m, 15H, Ph).

*5-Carboxy-3-[3-(α-L-fucopyranosyl)-1-propyloxy]-phenoxyacetic acid (**7a**)*: Compound **21a** (0.782 g, 1.12 mmol) was dissolved in dry methanol (15 ml) and acetic acid (0.5 ml) and hydrogenated in the presence of 10%-Pd/C (0.10 g) for 2 h at 20°C. The reaction was filtered through Celite, washed with methanol and the solvent removed under reduced pressure to give the hydrogenated intermediate 3-[3-(α-L-fucopyranosyl)-1-propyloxy]-5-methoxycarbonyl-phenoxyacetic acid-methylester {0.40 g, 83%; ^1H NMR (300 MHz, CD_3OD): 1.24 (d, J = 6.0 Hz, 3H, 6-H_{fuc}), 1.60-2.00 (m, 4H, FucC$\underline{H_2}$C$\underline{H_2}$), 3.81 (s, 3H, OCH$_2$CO$_2$$\underline{Me}$), 3.90 (s, 3H, OMe), 3.60-4.10 (m, 7H, 1,2,3,4,5-H_{fuc}, ArOC$\underline{H_2}$CH$_2$), 4.73 (m, 2H, OC$\underline{H_2}$CO$_2$Me), 6.72 (t, J = 2.0 Hz, 1H, 2-H_{Ar}), 7.13, 7.21 (2 dd, J = 2.0, 0.7 Hz, 2H, 4-H_{Ar}, 6-H_{Ar})} which was subsequently stirred in an aqueous 2 N NaOH solution for 0.5 h at 20°C. The reaction was acidified with aqueous 1N HCl,

filtered (0.45μm) and concentrated to dryness. MPLC on RP-18 phase gave the compound **7a** (0.389 g; 98%). ^{1}H NMR (300 MHz, D_2O, δ_{HOD} = 4.78): 1.11 (d, J = 6.0 Hz, 3H, 6-H_{fuc}), 1.65-1.97 (m, 4H, FucC$\underline{H}_2$C$\underline{H}_2$), 3.74-3.86 (m, 3H, 3,4,5-H_{fuc}), 3.93-4.07 (m, 2H, 1,2-H_{fuc}), 4.19 (m, 2H, ArOC$\underline{H}_2$CH$_2$), 4.51 (s, 2H, OC$\underline{H}_2$CO$_2$H), 6.70 (t, J = 2.0 Hz, 1H, 2-H_{Ar}), 7.05, 7.17 (2 dd, J = 2.0, 0.7 Hz, 2H, 4-H_{Ar}, 6-H_{Ar}). ^{13}C NMR (75.4 MHz, APT, δ [ppm], D_2O): 176.48, 174.55 (C=O), 158.90, 158.73 1,3-C_{Ar}), 138.98 (5-C_{Ar}), 108.24, 107.96 (4,6-C_{Ar}), 104.39 (2-C_{Ar}), 75.68, 71.81, 69.77, 67.99, 66.78 (1,2,3,4,5-C_{fuc}), 68.23 (ArO$\underline{C}$H$_2$CH$_2$), 66.91 (O$\underline{C}$H$_2$CO$_2$H), 24.77, 19.74 (Fuc$\underline{C}$H$_2\underline{C}$H$_2$), 15.57 (6-C_{fuc}).

3-[3-(Tri-O-benzyl-α-L-fucopyranosyl)-1-propyloxy]-5-methoxycarbonyl-phenoxymalonic-acid-dimethyl-ester (**21b**): Compound **20** (0.493 g, 0.788 mmol), 0.172 ml (0.87 mmol) bromomalonic acid-diethylester 0.10 g (1.2 mmol) $NaHCO_3$ in 20 ml DMF were stirred at 0°C for 48 h. The reaction was taken up in ethyl acetate and 50 ml of saturated NH_4Cl solution. The aqueous layer was further extracted with ethyl acetate and the combined organic layers were washed with sat. $NaHCO_3$ solution (30 ml) and brine. After evaporation *i. vac.*, the product was purified on silica gel (*n*-hexane/ethyl acetate 3.5:1) to give 0.31 g (50%) of **21b**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (d, J = 6.5 Hz, 3H, 6-H_{fuc}), 1.28, 1.31 (2 t, J = 7.0 Hz, 6H, 2 OCH$_2$C$\underline{H}_3$), 1.58-1.92 (m, 4H, FucC$\underline{H}_2\underline{C}H_2$), 3.88 (s, 3H, OMe), 3.73-4.05 (m, 7H, 1,2,3,4,5-H_{fuc}, ArOC$\underline{H}_2$CH$_2$), 4.31 (q, J = 7.0 Hz, 4H, 2 OC$\underline{H}_2$CH$_3$), 4.45-4.80 (m, 6H, OC$\underline{H}_2$Ph), 5.23 (s, 1H, OC$\underline{H}$CO$_2$Et), 6.75 (t, J = 2.0 Hz, 1H, 2-H_{Ar}), 7.16 (m, 1H, 4-[6]H_{Ar}), 7.23-7.39 (m, 16H, Ph, 6-[4]H_{Ar}).

5-Carboxy-3-[3-(α-L-fucopyranosyl)-1-propyloxy]-phenoxymalonic acid (**7b**): The procedure to obtain **7b** (90 mg, 71% from 0.30 g of **21b**) was identical to that for **7a**. ^{1}H NMR (300 MHz, D_2O, δ_{HOD} = 4.77): 1.11 (d, J = 6.0 Hz, 3H, 6-H_{fuc}), 1.65-2.00 (m, 4H, FucC$\underline{H}_2\underline{C}H_2$), 3.70-3.86 (m, 3H, 3,4,5-H_{fuc}), 3.90-4.05 (m, 2H, 1,2-H_{fuc}), 4.19 (m, 2H, ArOC$\underline{H}_2$CH$_2$), 6.77 (m, 1H, 2-H_{Ar}), 7.07, 7.13 (2 m, 2H, 4,6-H_{Ar}). ^{13}C NMR (75.4 MHz, APT, δ [ppm], D_2O): 158.90, 158.18 (1,3-C_{Ar}), 138.59 (5-C_{Ar}), 108.45, 108.36 (4,6-C_{Ar}), 104.86 (2-C_{Ar}), 75.65, 71.81, 69.74, 67.97, 66.75 (1,2,3,4,5-C_{fuc}), 68.23 (ArO$\underline{C}$H$_2$CH$_2$), 24.74, 19.73 (Fuc$\underline{C}$H$_2\underline{C}$H$_2$), 15.56 (6-C_{fuc}). MS (ESI, NH_4OAc/CH_3CN): $[M-H]^-$= 443.

3-[3-(Tri-O-benzyl-α-L-fucopyranosyl)-1-propyloxy]-5-[(4-ethoxycarbonylpiperidinyl)-1-carbonyloxy]-benzoic acid-methylester (22): Compound **20** (0.690 g, 1.10 mmol), 4-nitrophenylchloroformate (0.245 g, 1.21 mmol), 4-dimethylaminopyridine (DMAP, 15 mg, 0.12 mmol) and NEt_3 (0.17 ml, 1.21 mmol) in CH_2Cl_2 (10 ml) were stirred for h at 0°C. After addition of N,N-diisopropyl-ethylamine (DIPEA, 0.47 ml, 2.76 mmol) and piperidine-4-carboxylic acid-ethylester (0.187 ml, 1.21 mmol), the reaction was stirred at 0°C for 12 h, diluted (CH_2Cl_2), washed mit sat. $NaHCO_3$ solution (3 x 25 ml), dried ($MgSO_4$) and evaporated. The product was purified by flash chromatography (Biotage^{TM}-Flash-40, cartridge 40 M, 90 g silica gel, 32-63 μ, ethyl acetate/*n*-hexane 1:4 → 1:3 →1:2) to give **22** (0.85 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.26 (d, J = 6.5 Hz, 3H, 6-H_{fuc}), 1.28, (t, J = 7.0 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.60-2.04 (m, 8H, 3′-C$\underline{H}_2$pip, FucC$\underline{H}_2\underline{C}H_2$), 2.50 (m, 1H, C$\underline{H}CO_2$Et), 2.96-3.20 (m, 2H, 2′-C$\underline{H}$pip), 3.78-4.05 (m, 7H, 1,2,3,4,5-H_{fuc}, 2′-C$\underline{H}$pip), 3.88 (s, 3H, OMe), 4.17 (q, m, J = 7.0 Hz, 4H, OC$\underline{H}_2$CH$_3$, ArOC$\underline{H}_2$CH$_2$), 4.49-4.80 (m, 6H, OC$\underline{H}_2$Ph), 6.85 (t, J = 2.0 Hz, 1H, 2-H_{Ar}), 7.36, 7.40 (2 m, 2H, 4,6-H_{Ar}), 7.23-7.35 (m, 15H, Ph).

5-[(4-Carboxypiperidinyl)-1-carbonyloxy]-3-[3-(α-L-fucopyranosyl)-1-propyloxy]-benzoic acid (7c): Compound **22** (0.835 g, 1.03 mmol) was dissolved in dry MeOH (30 ml) and HOAc (0.5 ml) and hydrogenated in the presence of 10%-Pd/C (100 mg) for 3 h at 20°C. The reaction was filtered (Celite), washed with MeOH and the solvent removed *i. vac.*. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 17:1) gave the hydrogenated intermediate (0.37 g, 65%) which was subjected to saponification by stirring with 1N NaOH (5 ml) for 12 h at 0°C. The solution was acidified to pH 3 with 1N HCl, filtered (0.45μm) and evaporated *i.vac.*. The product was purified by MPLC on RP phase (MeOH/H_2O 1:1) to yield the compound **7c** (0.110 g, 32%). ^{1}H NMR (300 MHz, D_2O): 1.13 (d, J = 6.5 Hz, 3H, 6-H_{fuc}), 1.52-2.20 (m, 8H, 3′-CH_2pip, FucCH_2CH_2), 2.44 (*pseudo*-tt, J = 11 Hz, J = 3.0 Hz, 1H, $CHCO_2H$), 2.90-3.20 (m, 2H, 2′-CH_{pip}), 3.71-4.35 (m, 7H, 1,2,3,4,5-H_{fuc}, 2′-CH_{pip}), 4.18 (m, 2H, ArOCH_2CH_2), 6.90 (t, J = 2.0 Hz, 1H, 2-H_{Ar}), 7.22, 7.37 (2 dd, J = 2.0, 0.7 Hz, 2H, 4,6-H_{Ar}). ^{13}C NMR (75.4 MHz, APT, D_2O): 183.94 (pipCO_2H), 173.78 (ArC=O), 158.61, 155.18 (3,5-C_{Ar}), 151.59 (NC=O), 139.01 (1-C_{Ar}), 114.96, 112.96, 112.42 (2,4,6-C_{Ar}), 75.63, 71.78, 69.76, 67.96, 66.76 (1,2,3,4,5-C_{fuc}), 68.38 (ArO-CH_2CH_2), 43.97 (2′-C_{pip}), 43.91 (4′-C_{pip}), 28.53 (3′-C_{pip}), 24.74, 19.73 (FucCH_2CH_2), 15.57 (6-C_{fuc}).

3-[3-(Tri-O-benzyl-α-L-fucopyranosyl)-1-propyloxy]-5-methoxycarbonyl-phenoxyacetic acid-tert.-butylester (**24a**): 3-Hydroxy-5-methoxycarbonyl-phenoxyacetic acid-*tert.*-butylester (**23**) was obtained in 78% yield by alkylation of **18** with bromoacetic acid-*tert.*-butylester and K_2CO_3 in DMF {(^{1}H NMR, 300 MHz, $CDCl_3$: 1.50 (s, 9H, *t*-Bu), 3.8 (s, 3H, OMe), 4.54 (s, 2H, OCH_2), 6.30 (s, 1H, OH), 6.67 (t, J = 2.0 Hz, 1H, 2-H_{Ar}), 7.07, 7.17 (dd, J = J = 2.0, 0.7 Hz, 2H, 4,6-H_{Ar})}. Tri-O-benzyl-α-L-fucopyranosyl)-1-propyl bromide[3b] (**19**) (0.885 g, 1.64 mmol), **23** (0.695 g, 2.46 mmol) and K_2CO_3 (0.51 g, 3.69 mmol) in DMF (10 ml) were stirred for 12 h at 20°C and then for 7 h at 60°C. The reaction was taken up in ethyl acetate and 50 ml of saturated NH_4Cl solution. The aqueous layer was further extracted with ethyl acetate (4 x 25 ml) and the combined organic layers were washed with saturated $NaHCO_3$ solution (30 ml) and brine (20 ml) followed by drying ($MgSO_4$). After evaporation *i. vac.* the product was purified by silica gel chromatography (*n*-hexane/ethyl acetate 5:1) to give 1.20 g (98%, based on **19**) of **24a**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (d, J = 6.3 Hz, 3H, 6-H_{fuc}), 1.49 (s, 9H, *t*-Bu), 1.60-1.90 (m, 4H, FucCH_2CH_2), 3.89 (s, 3H, OMe), 3.70-4.10 (m, 7H, 1,2,3,4,5-H_{fuc}, ArOCH_2CH_2), 4.52 (s, 2H, OCH_2CO_2tBu), 4.50-4.80 (m, 6H, OCH_2Ph,). 6.67 (t, J = 2.0 Hz, 1H, 2-H_{Ar}), 7.13, 7.20 (2 dd, J = 2.0, 0.7 Hz, 2H, 4,6-H_{Ar}), 7.24-7.38 (m, 15H, Ph).

3-[3-(Tri-O-benzyl-α-L-fucopyranosyl)-1-propyloxy]-5-methoxycarbonyl-phenoxyacetic acid (**24b**): Compound **24a** (0.901 mg, 1.22 mmol), MeOH (20 ml) and aqueous 1N NaOH (2.5 ml) were stirred for 12 h at 0°C. After acidification (1N HCl, pH 5.3), the reaction was taken up in ethyl acetate (200 ml), washed with aqueous citric acid solution, dried ($MgSO_4$) and evaporated to dryness. The product was purified by flash chromatography (silica gel, ethyl acetate/*n*-hexane (1:1, 1% HOAc) to give **24b** (0.48 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.26 (d, J = 6.4 Hz, 3H, 6-H_{fuc}), 1.60-1.90 (m, 4H, FucCH_2CH_2), 3.89 (s, 3H, OMe), 3.70-4.10 (m, 7H, 1,2,3,4,5-H_{Fuc}, ArOCH_2CH_2), 4.67 (s, 2H, OCH_2CO_2H), 4.50-4.80 (m, 6H, OCH_2Ph,). 6.68 (t, J = 2.0 Hz, 1H, 2-H_{Ar}), 7.15, 7.23 (2 dd, J = 2.0, 0.7 Hz, 2H, 4,6-H_{Ar}), 7.26-7.38 (m, 15H, Ph).

3-[3-(α-L-Fucopyranosyl)-1-propyloxy]-5-(2-hydroxyethyl-1-aminocarbonyl)-phenoxyacetic acid (7d): Compound **24b** (0.462 g, 0.675 mmol) and ethanolamine (7 ml) were heated for 1 h at 100°C. After cooling to 20°C, the mixture was diluted with ethyl acetate (50 ml) and washed with brine (5 x 20 ml). After drying ($MgSO_4$) and concentration *i.vac.*, the residue was filtered over silica gel (CH_2Cl_2/MeOH 10:1, 1% HOAc) to give the 3-[3-(tri-O-benzyl-α-L-fucopyranosyl)-1-propyloxy]-5-(2-hydroxyethyl-1-aminocarbonyl)-phenoxyacetic acid {482 mg, 99%; ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (d, J = 6.2 Hz, 3H, 6-H_{fuc}), 1.60-1.88 (m, 4H, FucCH_2CH_2), 3.47 (m, 2H, NCH_2), 3.69 (m, 2H, NCH_2CH_2O), 3.70-4.10 (m, 7H, 1,2,3,4,5-H_{fuc}, ArOCH_2CH_2), 4.45-4.80 (m, 8H, OCH_2Ph, OCH_2CO_2H). 6.50 (m, 1H, 2-H_{Ar}), 6.83, 6.87 (2 *br* s, 2H, 4,6-H_{Ar}), 7.25-7.36 (m, 15H, Ph)} which was hydrogenated in 1,4-dioxane (6 ml) and acetic acid (0.2 ml) at 20°C in the presence of 10%-Pd/C (0.10 g) for 2 h. The reaction was filtered (Celite), washed with MeOH and the solvent removed under *i. vac.*. The residue was dissolved in water and freeze-dried to give the compound **7d** (0.213 g, 71% based on **24b**). ^{1}H NMR (300 MHz, δ_{HDO} = 4.78, D_2O): 1.12 (d, J = 6.0 Hz, 3H, 6-H_{fuc}), 1.68-1.94 (m, 4H, FucCH_2CH_2), 3.51 (t, J = 5.5 Hz, 2H, NCH_2), 3.69 (m, 2H, NCH_2CH_2O), 3.72-3.83 (m, 5H, CH_2OH, 3,4,5-H_{fuc}), 3.90-4.10 (m, 4H, 1,2-H_{fuc}, ArOCH_2CH_2), 4.58 (s, 3H, OCH_2CO_2H), 6.65 (*pseudo*-t, J = 2.0 Hz, 1H, 2-H_{Ar}), 6.87, 6.93 (2 m, 2H, 4,6-H_{Ar}). ^{13}C NMR (75.4 MHz, APT, D_2O): 174.57, 169.75 (C=O), 159.37, 158.56 (1,3-C_{Ar}), 135.81 (5-C_{Ar}), 106.77, 105.92, 104.83 (2,4,6-C_{Ar}), 75.61, 71.74, 69.80, 67.92, 66.77 (1,2,3,4,5-C_{fuc}), 68.21 (ArOCH_2CH_2), 65.75 (OCH_2CO_2H), 59.93 (CH_2OH), 42.01 (CH_2N), 24.84, 19.76 (FucCH_2CH_2), 15.58 (6-C_{fuc}).

Bioassay for cell binding to immobilized selectin receptor globulins: The bioassays for cell binding to immobilized selectin receptor globulins were performed as previously described.[8a] Briefly, the soluble recombinant E- and P-selectin-IgG fusion proteins which contain the signal sequence, the lectin-like domain, the EGF (epidermal growth factor) repeat domain and six (E-selectin) and two (P-selectin) of the CR-like (complement regulatory) domains obtained from transfected COS cells were adsorbed on anti-human-IgG-antibodies immobilized on ELISA (enzyme-linked immunosorbent assay) plates. Adhesion of labelled HL60 tumour cells was quantitatively measured in a cytofluorometer, and the specific cell binding in the presence of a potential inhibitor, e.g. **7a**, was calculated compared with non-specific binding to the CD4-IgG fusion protein.

ACKNOWLEDGEMENTS

The author wishes to thank *Christoph Hüls* for performing the *in vitro* cell assays, *Manfred Krause* for his technical assistance and *Christian Schumann* for NMR measurements.

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