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- [13] Reaction with the diastereomeric isomer (*R*),(*S*),(*S*)-**2e**, either pre-formed or formed in situ, gave the *S* alcohol in 15 ± 2%.
- [14] Various alkaline bases, such as KOH, (CH₃)₂CHOK, (CH₃)₂CHONa, (CH₃)₃COK, and K₂CO₃ can be used as cocatalysts. For reactions with a high S/C, acidic impurities should be carefully removed from substrates and solvents.
- [15] Reaction of [RuCl₂](*S*)-TolBINAP(dmf)_n and (*S*),(*S*)-DPEN in DMF at 50 °C (method B) gave a mixture of (*S*),(*S*),(*S*)-**2d** and its *cis* isomer (³¹P NMR, δ = 50.2 (d, *J* = 38.0 Hz), 57.0 (d, *J* = 38.0 Hz)). Hydrogenation of **5g** with the *cis* isomer showed comparable reactivity to (*S*),(*S*),(*S*)-**2d**, to give (*R*)-**6g** with 97% *ee*.
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Parallel Synthesis of Sialyl Lewis X Mimetics on a Solid Phase: Access to a Library of Fucopeptides**

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In response to injury or inflammation the damaged tissue releases cytokines, which trigger the expression of P-selectin followed by E-selectin on the endothelium. The initial recognition of the tetrasaccharide sialyl Lewis X (sLe^x) of the terminal unit of surface glycoconjugates by the selectins leads to leukocyte “rolling” followed by protein–protein interactions (integrins CD11/18, ICAM-1 ligand) and extravasation of leukocytes into the endothelium.^[1] Thus, blocking the sLe^x/selectin interactions at an early stage of the inflammatory cascade, especially the P-selectin/ligand interactions, has been considered to be an effective way of treating acute and perhaps chronic inflammatory diseases.^[2]

Although sLe^x is being clinically evaluated for the treatment of reperfusion injury, it must be administered by injection at high doses, as it binds the selectins weakly and is orally inactive and unstable in the blood. However, the structure of sLe^x has served as a useful guide for designing simpler and better low molecular weight compounds as

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selectin antagonists.^[3] On the basis of the crystal structure of E-selectin, NMR studies of the conformations of sLe^x in solution and bound to E-, P-, and L-selectin,^[5] and structure/activity studies on sLe^x derivatives and mimetics,^[6] the essential functional groups and their spatial arrangement required for binding of the sLe^x epitope to the selectins have been elucidated. By using this recognition model, numerous structurally diverse low molecular weight sLe^x mimetics have been prepared (Figure 1).^[3, 7] Some of them exhibit an affinity towards the selectins equal to or higher than that of sLe^x.

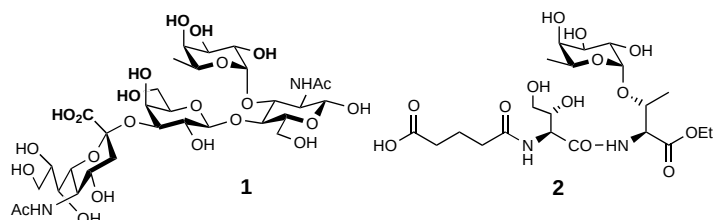
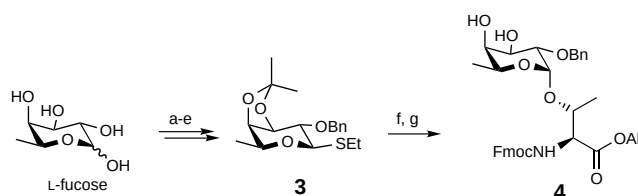


Figure 1. The tetrasaccharide sialyl Lewis X (**1**) and the fucosepeptide **2** as an oligosaccharide mimic.

Recently, interest in solid-phase syntheses has increased dramatically, since they allow combinatorial chemistry to be performed for the discovery of biologically active compounds and for optimization of lead structures.^[8] In particular, the parallel synthesis of individual compounds on solid phases is considered to be a promising approach to rapid optimization of previously identified lead structures. Here we report on our efforts to develop new strategies for the parallel and/or combinatorial synthesis of a substance library of *O*- and *C*-fucosylpeptides structurally related to **2**, which is nearly as active as sLe^x towards E-selectin.^[7a]

Fucose, which contains the three hydroxyl groups required for recognition of sLe^x by E-selectin, was retained as the only carbohydrate moiety in the mimic, while GlcNAc was replaced by L-threonine and its derivatives. Anchoring the fucose–GlcNAc surrogate through its 3,4-*cis*-diol unit^[9] enables the bidirectional elongation of the glycosylated amino acid while bound to the solid support. *N*-terminal elongation allows the elaboration of optimal substitutions for the galactose and sialic acid residues. *C*-terminal modifications^[10] can be used to install additional functionalities that interact with new groups in selectins.^[7b, 11] The use of Fmoc–peptide chemistry and the application of an orthogonal protective-group strategy ($R^1 = \text{All}$, $R^2 = \text{Fmoc}$, $R^3 = \text{Bn}$; for abbreviations, see legends to schemes), as well as the reversible immobilization of the 3,4-*cis*-diol moiety of fucose by a highly acid labile linker group, enable the rapid and bidirectional assembly of fucosylpeptides.

The synthesis of orthogonally protected α -fucoside **4** is depicted in Scheme 1. L-Fucose was converted into ethylthiofucoside

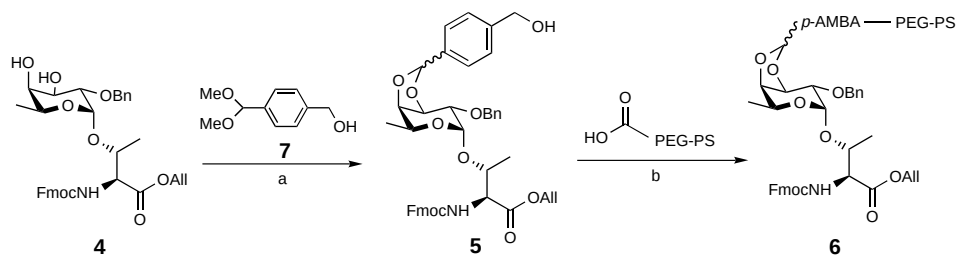


Scheme 1. a) Ac_2O , 4-DMAP, pyridine, $0 \rightarrow 20^\circ\text{C}$; b) EtSH , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, $0 \rightarrow 20^\circ\text{C}$ (60%, two steps); c) NaOMe (cat.) in MeOH , 20°C ; d) 2,2-dimethoxypropane, cat. $p\text{-TsOH} \cdot \text{H}_2\text{O}$, CH_2Cl_2 , 20°C (94%, two steps, $\alpha/\beta = 1:7$); e) NaH , BnBr , TBAI (cat.), THF (84%, 100% β); f) Fmoc-Thr-OAll, $\text{CuBr}_2/\text{TBAI}$, CH_2Cl_2 , DMF; g) aqueous AcOH , (80%, 1% TFA). All = allyl, Bn = benzyl, 4-dmap = 4-(dimethylamino)pyridine, Fmoc = 9-fluorenylmethyloxycarbonyl, TBAI = tetrabutylammonium iodide, TFA = trifluoroacetic acid, Thr = threonine, Ts = toluenesulfonate.

3 (five steps, 47% overall yield) by standard methods. By using $\text{CuI}_2/[\text{Bu}_4\text{N}]\text{I}$,^[12] Fmoc-protected L-threonine allyl ester was glycosylated with **3** to give selectively the α anomer ($\alpha/\beta \approx 9/1$). Cleavage of the acetone with 80% aqueous acetic acid containing 1% TFA followed by column chromatography gave fucoside **4** as the pure α anomer (64% yield, two steps).

Treatment of the diol **4** with the dimethyl acetal **7** and a catalytic amount of $p\text{-TsOH} \cdot \text{H}_2\text{O}$ gave a diastereomeric mixture of benzylidene acetals **5** (Scheme 2). The bifunctional linker **7** was easily derived from commercially available 4-formylbenzoic acid by formation of the dimethyl acetal and reduction of the acid group (62%, two steps). By using a moderate excess (2.1 equiv) of the alcohol **5** and DIC/4-DMAP activation, **5** was immobilized nearly quantitatively (0.24 mmol g^{-1}) on a carboxyl-functionalized poly(ethylene glycol) graft copolymer resin (PEG-PS) to give **6**.^[13] The loading was determined by photometric analysis of the cleaved Fmoc groups and gravimetrically by means of the product released from the resin with aqueous acetic acid (80% + 2% TFA). The diol **4** was liberated quantitatively without any detectable cleavage of the acid-sensitive α -fucosidic bond. Thus, the combination of the *para*-acyloxymethylbenzylidene acetal (*p*-AMBA) anchor group and PEG-PS solid support achieved maximal loading, recovery of excess reagent, appropriate swelling of the solid support, desirable stability of the acetal linkage during synthesis, and selective cleavage by a weak acid.

Starting with 0.8 mmol resin-bound **6**, we conducted a parallel synthesis of sLe^x mimetics **8** on a preparative scale (Scheme 3). At branching points of the synthesis, the material



Scheme 2. Immobilization of fucosepeptide **4** on a carboxyl-functionalized PEG-PS resin by anchor group **7**. a) **7**, $p\text{-TsOH}$ (cat.), CH_2Cl_2 , 20°C ; b) DIC, 4-DMAP (cat.), CH_2Cl_2 , 20°C , 18 h, 100% (0.24 mmol g^{-1}). *p*-AMBA = *p*-(acyloxymethyl)benzylidene acetal anchor group, DIC = diisopropylcarbodiimide, PEG-PS = poly(ethylene glycol) graft copolymer; for other abbreviations, see legend to Scheme 1.

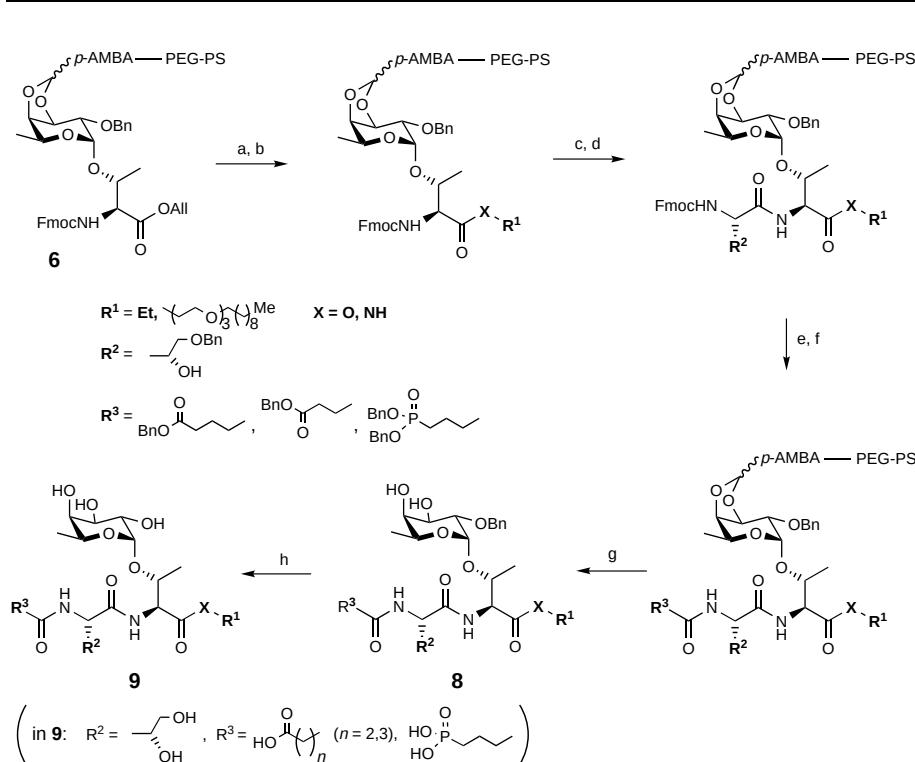


Table 1. Structures, yields, and biological activities of the sLe^x mimics **8** and **9**.

8 or 9 ^[a]	Yield of 8 ^[b]	Yield of 9 ^[c]	XR ¹	R ³ ^[d]	E-selectin IC ₅₀ [mM] ^[e]	P-selectin IC ₅₀ [mM] ^[e]
a	62	88	OE _{Et}		0.8	3.0
b	65	97	OE _{Et}		4.0	0.66
c	47	76			3.2	0.057
d	58	67			4.1	0.030
e	49	81			1.8	0.059
f	51	95			3.2	0.256
g	65	94	OE _{Et}		0.7	> 1.0
h	55	90			4.1	0.017

[a] In this series R² remains constant, and Fmoc-protected γ -benzyloxy-L-*allo*-threonine^[17] was used as amino acid building block. [b] Yields based on purified fucoseptides **8**. [c] Yields based on purified **9** after fractional precipitation of crude hydrogenation products from MeOH/Et₂O (**9a–f**), ion-exchange chromatography (**9g** and **9h**) and lyophilization from H₂O. [d] The substituents shown refer to **9**; compounds **8** contain the corresponding benzylated substituents. [e] The activities were measured according to the procedure described previously with sLe^x-polyacrylamide conjugate. The values are an average of three measurements, $\pm 10\%$; IC₅₀ for sLe^x = 0.8 mM towards E-selectin and > 3 mM towards P-selectin).^[16a]

DMF (6 $\times$, 1 mL per 100 mg dry resin), a pre-stirred (5–10 min) solution of the acids used for coupling (3 equiv for step d and 6 equiv for step f, Scheme 4), HOBT, NMM, and HBTU (1.6 equiv, 2.2 equiv and 1.05 equiv, based on the amount of acid) in dry DMF (0.2–0.25 M in acid) was added to the resin. After shaking for 4–4.5 h at room temperature, the coupling reaction was terminated by filtration, and the resin was washed with DMF and CH₂Cl₂ (6 $\times$ each).

Cleavage from the resin: A suspension of resin in aqueous AcOH (80%, 0.9 mL per 100 mg dry resin) containing 2% TFA was shaken for 18–22 h at room temperature. After filtration and washing three times with AcOH (80%), the cleavage procedure was repeated. The filtrate was concentrated in vacuo, and residual AcOH and H₂O were removed by coevaporating twice with dry toluene. The colorless to slightly yellow oil or solid was purified by column chromatography on silica gel to afford material that was homogeneous according to HR-MS, ¹H, and ¹³C NMR spectroscopy.

9b: colorless hygroscopic solid; ¹H NMR (500 MHz, D₂O): δ = 4.95 (d, *J* = 3.5 Hz, 1H), 4.68 (brs, 1H), 4.54 (d, *J* = 7.2 Hz, 1H), 4.44 (q, *J* $\approx$ 6.1 Hz, 1H), 4.22 (dq, *J* = 10.6, 7.2 Hz, 1H), 4.12 (dq, *J* = 10.6, 7.2 Hz, 1H), 3.97 (m, 1H), 3.74–3.69 (m, 5H), 3.60 (dd, *J* = 12.1, 6.4 Hz, 1H), 2.62–2.52 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.15 (br d, *J* $\approx$ 6.4 Hz, 6H); HR-MS: *m/z* calcd for C₂₀H₃₄O₁₃N₂CS: 643.1115 [*M*+CS]⁺, found: 643.1139. **9d**: colorless hygroscopic solid; ¹H NMR (500 MHz, D₂O): δ = 4.94 (d, *J* = 3.7 Hz, 1H), 4.53 (d, *J* = 9.0 Hz, 1H), 4.44 (brs, 1H), 4.41 (d, *J* = 6.3 Hz, 1H), 3.89–3.87 (m, 1H), 3.75–3.52 (m, 16H), 3.43 (t, *J* = 6.7 Hz, 2H), 3.31–3.36 (m, 2H), 2.29 (t, *J* $\approx$ 7.1 Hz, 2H), 2.24 (t, *J* = 7.4 Hz, 2H), 1.81 (t, *J* $\approx$ 7.3 Hz, 2H), 1.55–1.50 (m, 2H), 1.28–1.21 (m, 14H), 1.18 (d, *J* = 6.1 Hz, 3H), 1.14 (d, *J* = 6.4 Hz, 3H), 0.83 (brt, *J* $\approx$ 6.6 Hz, 3H); HR-MS: *m/z* calcd for C₃₅H₆₅O₁₅N₃CS: 900.3470 [*M*+CS]⁺, found: 900.3498. **9e**: colorless hygroscopic solid; ¹H NMR (500 MHz, D₂O): δ = 4.94 (d, *J* = 3.5 Hz, 1H), 4.70 (brs, 1H), 4.58 (d, *J* = 7.2 Hz, 1H), 4.42–4.35 (m, 2H), 4.18–4.16 (m, 1H), 3.97–3.96 (m, 1H), 3.74–3.55 (m, 16H), 3.42 (t, *J* = 6.5 Hz, 2H), 2.64–2.53 (m, 4H), 1.53 (brs, 2H), 1.30–1.23 (m, 14H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.85 (brt, *J* $\approx$ 6.5 Hz, 3H); HR-MS: *m/z* calcd for C₃₄H₆₂O₁₆N₂CS: 887.3154 [*M*+CS]⁺, found: 887.3184.

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Complex Fluids Based on the Flexible One-Dimensional Mineral Polymers [K(MPS₄)]_∞ (M = Ni, Pd): Autofragmentation to Concave, Cyclic (PPh₄)₃[(NiPS₄)₃]**

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In memory of Jean Rouxel

The discovery of the lyotropic nematic phase of LiMo₃Se₃ in *N*-methylformamide,^[1] a rare example of a liquid crystal based on a mineral core, was achieved 70 years after the pioneering work of the German physicist H. Zocher.^[2] This event, soon followed by the study of the nematic behavior of V₂O₅ ribbons^[3] and smectic clays^[4] in water, has aroused acute interest in the development of solution-phase chemistry of charged, all-inorganic molecules. The motivation for such investigations is the prospect of unraveling the organic/inorganic interfacial chemistry and physics of unprecedented anisotropic fluids based on one- and two-dimensional, charged, extended mineral polymers.^[5, 6]

The solid-state chemistry of transition metal chalcogenides^[7] is abound with low-dimensional motifs, such as ¹[Mo₃Se₃][−]. Their dimensionality arises from the balance between the strong covalent character of the transition metal–chalcogen bonds within the negatively charged chains or slabs and their effective ionic screening by alkali metal cations.^[8, 9] A recent example is the series of transition metal chalcogenide phosphates KMPS₄ (M = Ni, Pd) with infinite anionic chains ¹[MPS₄][−].^[10] Here we demonstrate 1) that KMPS₄ compounds are soluble in polar organic solvents such as dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), and form complex fluids made up of flexible inorganic polymers; 2) that [(NiPS₄)₃]^{3−}—an unprecedented, concave trimetallic thiophosphate molecular trianion adopting pseudo-C_{3v} symmetry—is formed in DMF at room temperature from the autofragmentation and rearrangement of ¹[NiPS₄][−]; and 3) that it is possible to follow the dissolution and fragmentation processes with mass spectrometry, solution-state ³¹P NMR spectroscopy, and transmission electron microscopy (TEM). Thus, the contrasting behavior and stability of the Ni and Pd phases can be revealed.

In accordance with their highly anisotropic bonding, KNiPS₄ and KPdPS₄ are soluble in polar organic solvents

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