[6] In most cases the CCSD(T) approach represents a more reliable method than DFT. While both methods agree quite nicely in the ΔE^{+} values for the open-chain compound **6** larger differences are found for the monocyclic ring systems **5** and **8**. However, while both methods give different absolute values the correct trends are already obtained with DFT.
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Synthetic Inhibitors of Cell Adhesion: A Glycopeptide from E-Selectin Ligand 1 (ESL-1) with the Arabino Sialyl Lewis^x Structure**

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Dedicated to Professor Leopold Horner on the occasion of his 90th birthday

In the course of the inflammatory cascade, carbohydrate-recognizing receptors are expressed on endothelial cells: P-selectin within some minutes; E-selectin, however, with a delay of 4 – 6 hours after the chemotactic stimulus.[1] The sialyl Lewis^x epitope has been identified as the ligand of both selectins.[2, 3]

The carbohydrate-binding domain of E-selectin has been investigated by using transfer-NOE NMR spectroscopic experiments on a complex of sialyl Lewis^x with a recombinant E-selectin – IgG fusion protein, molecular modeling studies,[4] and X-ray crystal structure analysis.[5] These studies give evidence of the decisive role of the fucose moiety of sialyl Lewis^x in the binding to E-selectin which is mediated by the coordination to a calcium ion.[5–7] In the case of the natural selectin ligands, other structural elements are evidently also involved in the specific binding. O-Linked *N*-acetyllactosamine saccharides with sialyl Lewis^x determinants are important for the binding of the P-selectin-selective ligand PSGL-1. However, a peptide sequence that is rich in acidic amino acids and contains O-sulfatyl tyrosines also contributes to the binding.[8, 9] In the case of the endogenous E-selectin adhesion ligand ESL-1, the sialyl Lewis^x ligand is present on an N-glycan.[10, 11] A contribution of peptide epitopes of ESL-1 has not been reported for the binding to E-selectin, which also plays a role in metastasis[2b] and, for example, specifically binds to gastrointestinal tumor cells.[12]

ESL-1 contains five potential N-glycosylation sites.[11] The amino acid sequences in their neighborhood is conserved to a large extent compared to those of other E-selectin-binding sialoglycoproteins. In this sense, the amino acid sequence 672 – 681 of ESL-1 **1** around the sequon NLT is identical to the sequence 676 – 685 of the E-selectin ligand MG160.[13]

-Gly-Asn-Leu-Thr-Glu-Leu-Glu-Ser-Glu-Asp- **1**

In earlier investigations, a modulating influence of the peptide portion on the carbohydrate recognition was found in the binding of synthetic sialyl Lewis^x glycopeptides to P-selectin[14] as well as to E-selectin.[15] As the segment **1** of ESL-1 with its accumulation of acidic amino acids is similar to the binding domain of PSGL-1, we selected this sequence for the construction of a synthetic E-selectin ligand. An additional aim was to find an E-selectin ligand which, like sialyl Lewis^x mimetics,[16] is stabilized against enzymatic degradation. The fucoside bond is a site for the enzymatic attack on sialyl Lewis.[17] The fucose portion, however, is considered essential for the binding of sialyl Lewis^x to E-selectin (see above).[4, 5]

It should now be examined whether the α-L-fucoside can be substituted by a β-D-arabinopyranoside, which exposes its three secondary hydroxy groups in the same spatial arrangement as the fucoside. D-Arabinopyranose, however, is absent in mammals and its glycosides should therefore be biologically more stable.

As in the previous syntheses of glycopeptides,[14, 15] the azido group was used as the protecting group at the anomeric center of the glucosamine unit in the synthesis of the arabino sialyl Lewis^x saccharide.[18] The in situ anomerization method[19] was used to glycosylate 4,6-*O*-benzylidene-*N*-acetylglucosaminyl azide **2**[20] with ethylthio-2,3,4-tri-*O*-benzyl-α,β-D-arabinopyranoside **5** to give β-D-arabinosylglucosamine azide **6** (Scheme 1).

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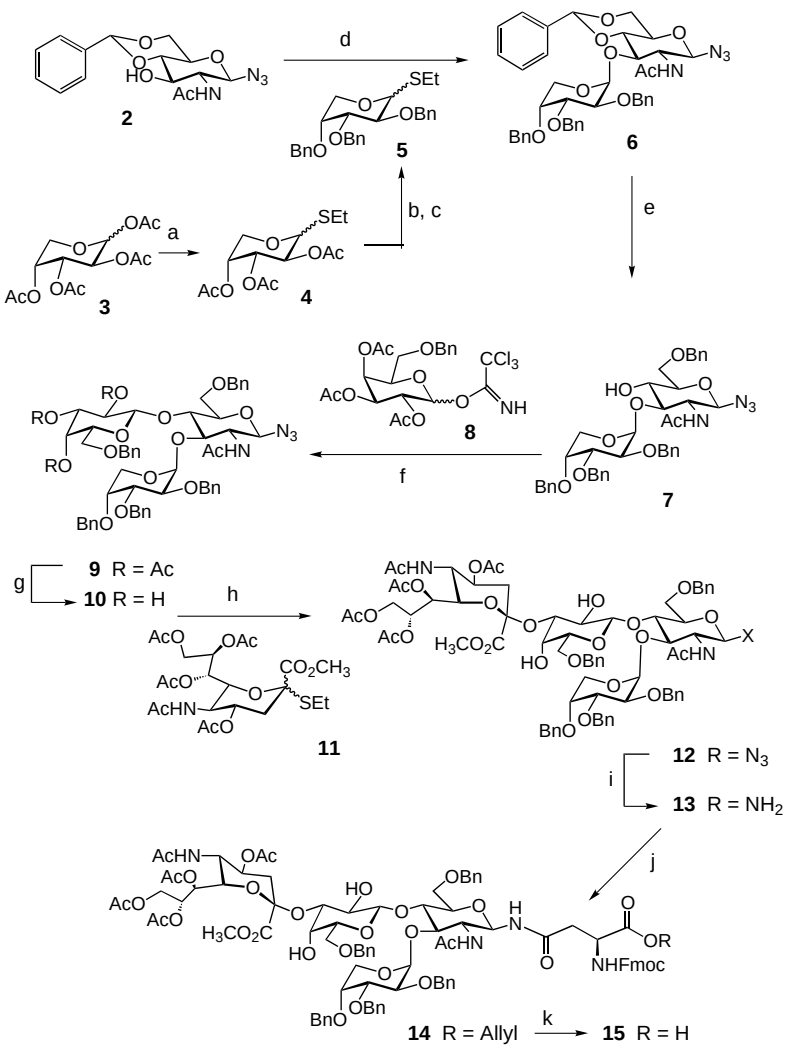


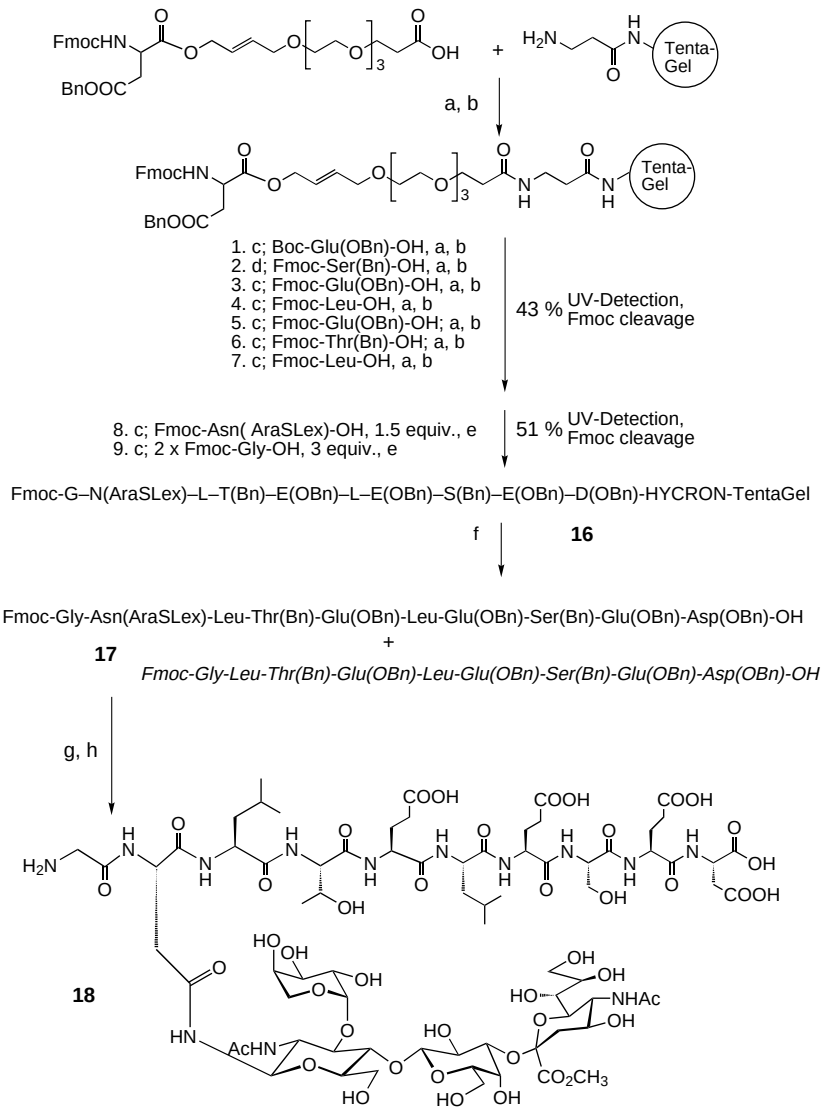
Scheme 1. Reagents and conditions: a) EtSH, $BF_3 \cdot Et_2$, CH_2Cl_2, $-15\,^{\circ}C$, 49%; b) NaOMe, MeOH, $20\,^{\circ}C$, quantitative; c) $C_6H_5CH_2Br$, NaH, DMF, $0\,^{\circ}C$, 88%, d) $CuBr_2$, Bu_4NBr, CH_2Cl_2/DMF, $20\,^{\circ}C$, 57%; e) $NaCNBH_3$, THF, HCl in Et_2O, THF, $0\,^{\circ}C$, 68%; f) TMSOTf, CH_2Cl_2, $-15\,^{\circ}C$, 2 d, 49%; g) MeONa, MeOH, 93%; h) NIS, TfOH, CH_3CH_2CN, $-78 \rightarrow -32\,^{\circ}C$, 24 h, 56%; i) Raney Ni, H_2, *i*PrOH/H_2O (9:1), $20\,^{\circ}C$, 94%, j) Fmoc-Asp-OAll, HATU/HOAT, *N*-methylmorpholine, DMF, 69%; k) $(Ph_3P)_4Pd$, *N*-methylaniline, THF, 86%; (TMSOTf = trimethylsilyl trifluormethanesulfonate, DMF = *N*,*N*-dimethylformamide).

Owing to the high acid sensitivity of arabinopyranose derivatives, tetra-*O*-acetylarabinopyranose **3**[21] was treated with ethanethiol and $BF_3 \cdot Et_2O$ at $-15\,^{\circ}C$, and the reaction mixture was neutralized prior to the isolation of ethylthio-tetra-*O*-acetyl-α,β-D-arabinopyranoside by the addition of triethylamine in amounts equimolar to BF_3. Removal of the *O*-acetyl groups from **4** by using catalytic sodium methanolate in methanol and subsequent benzylation gave the arabinosyl donor **5**. During the regioselective opening of the benzylidene acetal of **6**[22] with sodium cyanoborohydride, hydrogen chloride in dry diethyl ether was added dropwise and monitored by using thin-layer chromatography because of the acid sensitivity of the arabinopyranoside bond. Galactosylation at the rather unreactive 4-OH group of the arabinosyl glucosamine derivative **7** was carried out with the reactive trichloroacetimidate **8**.[23] The O-acetyl groups were then removed from trisaccharide **9** by Zemplén-transesterification.

To achieve a regioselective sialylation at the 3′-OH group of the Lewis^x derivative **10**, the ethylthiosialoside **11** was a more favorable donor than the methylthio analogue. Furthermore, the activation had to be carried out with *N*-iodosuccinimide (NIS) and trifluoromethane sulfonic acid (TfOH)[24] (not with methylsulfonyl triflate) in propionitrile at $-32\,^{\circ}C$ in the presence of molecular sieves (4 Å) without stirring. Only then was the arabino sialyl Lewis^x azide **12**[25] obtained in satisfying yield after two chromatographic purifications. The arabino sialyl Lewis^x amine **13** was obtained by the Raney nickel (neutrally washed) catalyzed hydrogenolysis of the azide.[26] Lewis^x amine **13** was isolated and immediately condensed with Fmoc aspartic acid α-allyl ester[27, 28] by using [2-*O*-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (HATU)[29] and 1-hydroxy-7-azabenzotriazole (HOAT) to give the N^4-[arabino sialyl Lewis^x] asparagine conjugate **14**. Palladium(0)-catalyzed cleavage of the allyl ester by using *N*-methylaniline as the allyl-trapping nucleophile[30] gave the arabino sialyl Lewis^x asparagine building block **15**[31] required for the glycopeptide synthesis.

The solid-phase synthesis of the glycopeptide partial sequence **1** of ESL-1 with the arabino sialyl Lewis^x side chain at Asn^{673} was carried out by using the allylic HYCRON anchor[32] on TentaGel resin[33] (Scheme 2). According to a previously described general procedure,[32, 34] Fmoc aspartic β-benzyl ester was linked to the allylic anchor and coupled to TentaGel resin loaded with β-alanine as the standard amino acid. Except for the first chain-extending step, the solid-phase synthesis was carried out according to Fmoc strategy, with benzylic protection of amino acid side chain functionalities. In this way, final acidolytic removal of the protecting groups, which would affect the β-arabinosyl linkage, is prevented. To form the resin-linked dipeptide, however, the β-benzyl ester of Boc-glutamic acid was used (Boc = *tert*-butoxycarbonyl). The cleavage of the Boc group with trifluoroacetic acid minimizes the undesired release of peptide in the form of diketopiperazine.[35] The first seven coupling reactions were carried out by using four equivalents each of N-protected amino acid, (2-*O*-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium tetrafluoroborate) (TBTU),[36] 1-hydroxy-benzotriazole (HOBt), and *N*-methylmorpholine. Protection with Ac_2O/pyridine followed each coupling step. The Fmoc group was removed with morpholine/DMF and monitored by using UV spectroscopy. The UV analysis of the Fmoc removal showed that the coupling of the *O*-benzylthreonine building block to the glutamic β-benzyl ester remained incomplete, possibly as a result of a back-folding effect.

For the coupling of the arabino sialyl Lewis^x building block **15**, only 1.5 equivalents of this complex component



Scheme 2. Reagents and conditions: a) TBTU, HOBt, *N*-methylmorpholine, DMF; b) Ac_2O, pyridine; c) morpholine/DMF (1:1); d) TFA/CH_2Cl_2 (1:1); e) HATU/HOAT, *N*-methylmorpholine, DMF, $(Ph_3P)_4Pd$, *N*-methylaniline, DMF, DMSO, 3 d, overall yield of mixture 22%; g) $Pd(OH)_2/H_2$, MeOH, dioxane, AcOH, 10 d, h) NaOH, H_2O, pH 10.5, 24 h; (Fmoc = 9-fluorenylmethoxycarbonyl).

(Scheme 2) was available. Therefore, the coupling time was extended from 15 h to 36 h and, as in the subsequent coupling of Fmoc glycine, the reactive coupling reagent HATU/HOAT was used. No capping by acetylation was applied after the last two coupling reactions to prevent incomplete acetylation, which usually occurs at the 2- and 4-OH of the galactose of sialyl Lewis^x saccharides and results in mixtures of products. Moreover, the complete removal of O-acetyl groups from these positions of the carbohydrate is often difficult.[28]

Palladium(0)-catalyzed cleavage of the allylic HYCRON anchor of **16** by using *N*-methylaniline as the allyl scavenger[30] gave the glycopeptide **17** together with the nonapeptide that lacks the glycosyl asparagine unit. The separation of these compounds proved difficult, because of the poor solubility of the mixture in solvents that are suitable for HPLC. Therefore, the solution of the crude products in dichloromethane was extracted with dilute hydrochloric acid and brine, and the benzyl ester, benzyl ether, and the Fmoc protecting groups were hydrogenolyzed in MeOH, 1,4-dioxane, and acetic acid. Subsequently, the O-acetyl groups and the methyl ester of Neu*N*Ac were hydrolyzed by using aqueous NaOH at pH 10.5. Nonpolar impurities were removed from the obtained product mixture (overall yield 22%) by reversed-phase HPLC. The pure arabino sialyl Lewis^x glycopeptide **18** of ESL-1 was isolated by means of two exclusion-chromatography purification steps on Sephadex G15 and monitored by NMR spectroscopy.

The inhibition of adhesion of 32Dc3 cells (a murine neutrophile cell line) to an E-selectin IgG-construct[38] was determined in the presence of sialyl Lewis^x as the standard ligand ($IC_{50} \sim 1$ mM), a divalent sialyl Lewis^x glycocyclooctapeptide[39] ($IC_{50} \sim 0.8$ mM), the completely deprotected arabino sialyl Lewis^x asparagine conjugate **15** ($IC_{50} \sim 2.6$ mM), a RGDA-arabino sialyl Lewis^x glycopeptide[39] ($IC_{50} \sim 2.2$ mM), and the arabino sialyl Lewis^x-ESL-1 glycododecapeptide **18** ($IC_{50} \sim 0.12$ mM). It was revealed in these investigations that **18** is an efficient inhibitor which shows a more than twentyfold affinity to E-selectin than that of the completely deprotected asparagine conjugate (deprotected **15**), and a tenfold higher affinity than that of the sialyl Lewis^x ligand. The influence of the peptide chain becomes clear by the comparison of the RGDA- with the ESL-1-glycopeptide **18**, since the latter exhibits a 19-fold higher inhibition of the adhesion of the neutrophiles to E-selectin. It is concluded from these results that the peptide sequence **1** of ESL-1 may be biologically important for the binding of the ligand to the E-selectin. In addition, these results demonstrate that arabino analogues of sialyl Lewis^x[40] can form efficient, metabolically stabilized inhibitors of the inflammatory cascade and of the invasion of metastatic tumor cells.

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Monolithic Materials: New High-Performance Supports for Permanently Immobilized Metathesis Catalysts

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Olefin metathesis and variations thereof are among the most important tools for C–C bond formation.[1] Polymer chemistry and materials sciences have seen the introduction of new trends by metathesis-based techniques, such as ring-opening metathesis polymerization (ROMP) or acyclic diene polymerization (ADMET). Complementary, cross-metathesis and ring-closing metathesis find ample application in organic chemistry.[2] Molybdenum- and ruthenium alkylidenes (the latter based on N-heterocyclic carbenes, NCH ligands) are used for this purpose but, until recently, only in homogeneous catalysis.[3] The first heterogeneous ruthenium systems have already been described by Grubbs et al. but these in particular turned out to be less suited to polymerization.[4] Meanwhile, a few non-permanently immobilized Grubbs catalysts have been reported,[5–7] although the system described by Blechert et al. basically represents the only recyclable heterogeneous Grubbs catalyst.[8] Despite the good catalytic data that has been reported for RCM, we investigated a new method to reach heterogeneous metathesis catalysts. The final goal was to combine the advantages of homogeneous and heterogeneous catalysis and, simultaneously, eliminate the disadvantages typical for many heterogeneous systems, such as diffusion-controlled reactions and catalyst bleeding, among others. Again, NHC ligands appeared highly attractive for these purposes. On one hand they allow the generation of highly active ruthenium carbenes,[9–12] on the other hand the corresponding NHC/phosphane-based systems are quite sta-

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