reaction mixture was stirred for 6 h. After the solid material had been filtered off, the filtrate was condensed to 5 mL, to which excess diethyl ether was added to obtain the solid product. Slow evaporation of the methanol solution gave crystals of **2** in 81.3 % yield. M.p. 147 °C (decomp). ^{1}H NMR (500 MHz, [D$_7$]DMF, TMS): $\delta = 0.95$ (s, 3H), 1.02 (s, 3H), 2.19 (br, 4H), 2.96 (s, 3H), 6.84 – 7.18 (m, 4H), 7.30 (t, 2H, $J = 7.3$ Hz), 7.45 (t, 2H, $J = 7.4$ Hz), 7.91 (d, 2H, $J = 7.5$ Hz), 8.19 (d, 2H, $J = 7.8$ Hz); ^{13}C NMR (125.76 MHz, [D$_7$]DMF, TMS): $\delta = 23.4$, 23.6, 35.7, 50.3, 55.8 (OCH_3), 120.1, 126.2, 127.8, 129.9, 132.8 (C=C), 136.0 (C=C), 137.0, 141.1, 170.9 (C=O); IR (KBr): $\tilde{\nu} = 1666$, 1652, 1634 ($\nu(COO)_{asym}$); 1324 ($\nu(COO)_{sym}$) cm^{-1}; elemental analysis (C, H, N) gave erratic results presumably due to the easy evaporation of solvate methanol molecules.

3: Compound **2** (1.0 mmol) was dissolved in acetic anhydride (20 mL), and the resulting solution was then stirred for 3 h. After the solid residue had been filtered off, the filtrate was evaporated to dryness. Slow evaporation of the DMF solution gave crystals of **3** in 80.3 % yield. M.p. 168 °C (decomp). ^{1}H NMR (500 MHz, [D$_7$]DMF, TMS): $\delta = 0.84$ (s, 3H), 0.92 (s, 3H), 0.99 (s, 3H), 1.77 – 1.93 (m, 2H), 2.39 – 2.52 (m, 2H), 2.58 (s, 3H, $^3J_{Pt,H} = 27.10$ Hz), 7.16 – 7.38 (br, 2H), 7.25 (t, 2H, $J = 7.6$ Hz), 7.39 (t, 2H, $J = 7.6$ Hz), 7.84 (d, 2H, $J = 7.5$ Hz), 7.98 – 8.22 (br, 2H), 8.15 (d, 2H, $J = 7.8$ Hz); ^{13}C NMR (125.76 MHz, [D$_7$]DMF, TMS): $\delta = 22.2$, 23.0, 24.8 (OOC*CH$_3$*), 35.8, 50.2, 57.3 (OCH_3), 120.0, 126.5, 127.7, 129.9, 133.9 (C=C), 134.6 (C=C), 137.2, 141.2, 170.6 (C=O), 180.2 (C=O); IR (KBr): $\tilde{\nu} = 1666$, 1601 ($\nu(COO)_{asym}$); 1302 ($\nu(COO)_{sym}$) cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{28}N_2O_7Pt \cdot C_3H_7NO$: C 44.75, H 4.87, N 5.80; found: C 44.60, H 4.85, N 5.88.

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Design, Synthesis, and Biological Evaluation of $\alpha_4\beta_1$ Integrin Antagonists Based on β-D-Mannose as Rigid Scaffold

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The tuning of protein – protein interactions by small non-peptidic molecules remains one of the great challenges in medicinal chemistry. Although already proposed in 1980 by Farmer,[1] only a few successful examples on the synthesis of peptidomimetics based on rigid scaffolds such as cyclohexane and pyranose sugars have been reported so far.[2] Starting from the β-D-mannose scaffold we developed peptidomimetics in a rational combinatorial approach focusing on the interaction of the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins with their ligands. The basis of this research were cyclic hexapeptides as potent and selective $\alpha_4\beta_7$ integrin antagonists recently developed by our group using the "spatial screening" procedure.[3]

$\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins play an important role in numerous inflammatory and autoimmune disorders.[4] The most important biological ligands for these α_4 integrins are fibronectin

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(Fn), vascular cell adhesion molecule-1 (VCAM-1), and mucosal addressin cell adhesion molecule-1 (MAdCAM-1), the latter being an exclusive ligand for $\alpha_4\beta_7$ integrin under physiological conditions.[4, 5]

The cyclic hexapeptide *cyclo*(-Leu-Asp-Thr-Ala-D-Pro-Ala-) **P1** and several related peptides with the general formula *cyclo*(-Leu-Asp-Thr-Xaa-D-Pro-Xbb-), which include the bioactive Leu-Asp-Thr (LDT) motif of the MAdCAM-1 ligand,[6] were recently developed in our group as potent and selective inhibitors of the MAdCAM-1/$\alpha_4\beta_7$ ligand/integrin interaction.[3] The bioactive conformation of these constrained cyclic peptides consists of two β-turns with the D-proline in the $i+1$ position of a βII′-turn and aspartic acid in the $i+1$ position of a βI- and/or βII-turn.[7]

The elucidation of the bioactive conformation of these peptides led us to the replacement of the whole peptidic backbone by a sugar scaffold which should present the pharmacophoric LDT side chain mimetics in similar spatial orientation. A successful implementation of Farmer's approach[1] would then imply that the amide backbone is not necessarily involved in receptor binding while all essential functional groups are maintained in their active conformation by the scaffold.

The orientation of the LDT side chain mimetics attached to a β-D-mannose core at positions 6, 1, and 2 (all facing upwards) resembles the configuration of the pharmacophoric side chains in our lead peptides (Figure 1).[3] The free hydroxyl groups at positions 3 and 4 of the carbohydrate scaffold were modified to methyl ethers in order to introduce further hydrophobicity.

Molecular modeling studies (InsightII, DISCOVER, CVFF) confirmed that β-D-mannopyranose is indeed a proper scaffold as the LDT-mimetic sequence is presented in the bioactive arrangement. The superposition of the 2-methyl-propylene, carboxylmethylene, and (2*R*)-hydroxypropylene groups of the mannose derivative **11c** with the LDT side chains of the potent and selective *cyclo*(-Leu-Asp-Thr-Ala-D-Pro-Phe-) **P2** revealed a good match of these key pharmacophoric groups (Figure 2). An energy minimized conformation of compound **11c** was used for the superposition representing one of the accessible structures in solution.

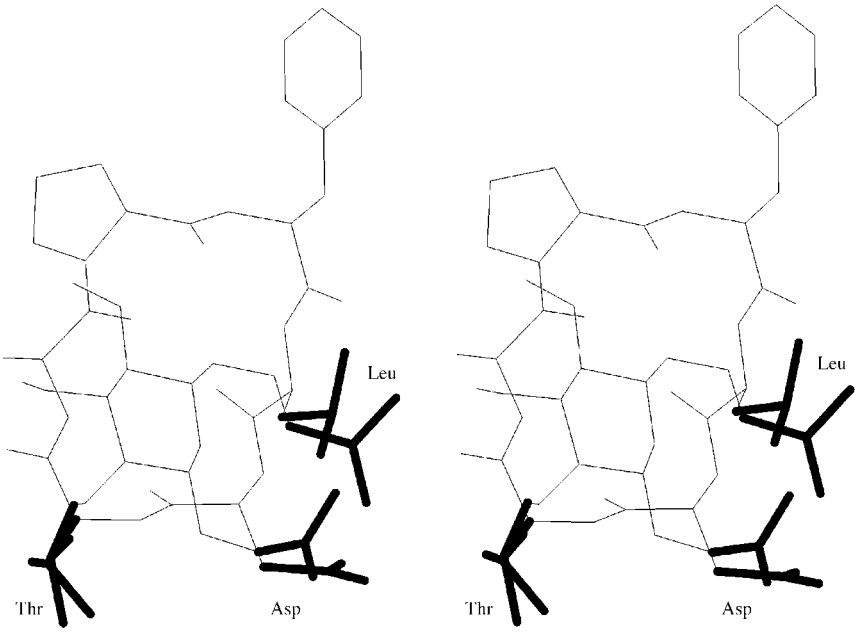
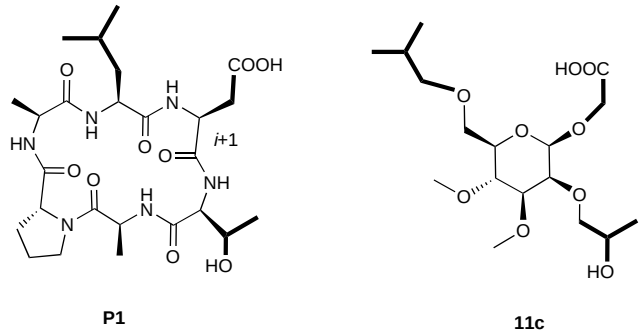


Figure 2. Stereoview of the superposition between an energy minimized structure of **11c** and the structure of **P2** as determined by NMR spectroscopy.

In Figure 2, the leucine, aspartic acid, and threonine side chains and the respective mimetics attached to the mannose core are highlighted using the stick model. The peptidic and sugar backbone are given as thin lines. The relative distance between the aspartic acid and threonine pharmacophores in **P2** (C^β–$C^\beta = 4.60$ Å), which is controlled by the positioning of these two amino acids in the $i+1$ and $i+2$ position of the β-turn, is being maintained in the mannose derivative (4.56 Å). The leucine side chain mimetic at the primary hydroxyl group of the mannose core exhibits high flexibility as in its peptidic precursor and it is therefore likely to mediate the binding to the receptor by an induced fit mechanism.

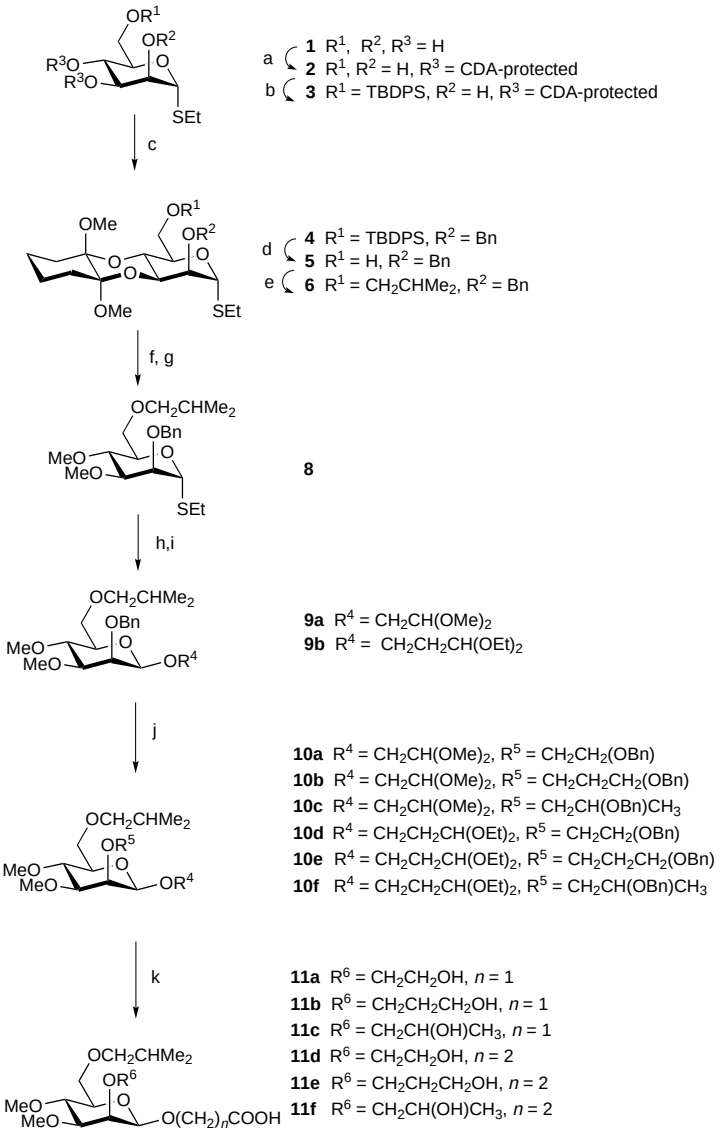
Based upon our model a small biased library of peptidomimetics with β-D-mannose as the rigid core was synthesized. The anchoring of aspartic as well as glutamic acid-type side chains at the hydroxyl group in position 1 and the attachment of the serine-type side chain and its homologue together with the use of a racemic threonine mimetic at position 2 led to eight different mannose derivatives.

The synthetic protocol is shown in Scheme 1. The desired products **11a–f** were synthesized in eleven steps starting from ethyl thio-α-D-mannopyranoside (**1**). The key compound in our synthetic strategy was the fully protected mannose derivative **4**.[8] The orthogonal protecting groups of compound **4** were successively cleaved and replaced by the pharmacophoric side chains. Starting with desilylation of the primary



P1 **11c**

Figure 1. Cyclic peptide **P1** and carbohydrate-based peptidomimetic **11c** (see also Scheme 1). In the peptide, the pharmacophoric LDT motif is localized within a β-turn with the aspartic acid in the $i+1$ position. The carbohydrate scaffold presents the essential pharmacophoric groups in the same relative orientation as the lead peptide.



Scheme 1. a) 1,1,2,2-Tetramethoxycyclohexane[8] (1.5 equiv), CSA, TMOF, MeOH (43%); b) TBDPSCl (1.5 equiv), imidazole, DMF (85%); c) $KN(SiMe_3)_2$, BnBr (96%); d) TBAF, THF (96%); e) $KN(SiMe_3)_2$, $BrCH_2CHMe_2$ (89%); f) 90% TFA (73%); g) $KN(SiMe_3)_2$, MeI (87%); h) NBS, cat. HCl, CH_3CN/H_2O (91%); i) $SOCl_2$, CH_2Cl_2 then Ag_2CO_3, CH_2Cl_2, RT, **9a**: $HOCH_2CH(OMe)_2$ (72%), **9b**: $HOCH_2CH_2CH(OEt)_2$ (62%); j) 10% Pd/C, H_2 then $KN(SiMe_3)_2$, THF, **10a**: $BrCH_2CH_2OBn$ (60%), **10b**: $BrCH_2CH_2CH_2OBn$ (58%), **10c**: $BrCH_2CH_2(OBn)CH_3$ (60%), **10d**: $BrCH_2CH_2OBn$ (60%), **10e**: $BrCH_2CH_2CH_2OBn$ (58%), **10f**: $BrCH_2CH_2(OBn)CH_3$ (60%); k) 1) 3N HCl, THF, RT; 2) *t*BuOH, 2-methyl-2-butene, $NaClO_2$ (1 equiv), NaH_2PO_4, H_2O, RT; 3) 10% Pd/C, H_2, MeOH, products **11a** (62%), **11b** (92%), **11c** (60%), **11d** (65%), **11a** (71%), **11f1** (35%), **11f2** (21%). Bn = Benzyl, CSA = camphorsulfonic acid, NBS = *N*-bromosuccinimide, TBAF = tetra-*n*-butylammonium fluoride, TBDPSCl = tert-butyldiisopropylsilyl chloride, TFA = trifluoroacetic acid, TMOF = trimethyl orthoformate.

alcohol function with tetra-*n*-butylammonium fluoride (TBAF), the leucine side chain mimetic was introduced by ether formation using 1-bromo-2-methylpropane and potassium bistrimethylsilylamide as base. The resulting compound **6** was isolated in 89% yield. Subsequently, cleavage of the cyclohexane-1,2-diacetal (CDA) protecting group and conversion of the free *trans* vicinal diol into methyl ethers afforded the mannose derivative **8** in 87% yield. Compound **8** was hydrolyzed after activation with *N*-bromosuccinimide/H^+ and subsequently dissolved in thionyl chloride leading to the corresponding mannosyl chloride. Coupling of the activated mannose derivative with glycolaldehyde dimethyl acetal and 3-hydroxypropionaldehyde diethyl acetal in CH_2Cl_2 using solid silver carbonate as the halogenophil led to compounds **9a** and **9b** as the required β-D-mannoglycosides in 72% and 62% yields, respectively.[9] After cleavage of the remaining benzyl ether protecting group at position 2, 2-benzyl-3-bromopropyl ether, and 2-benzyl tosylpropyl ether were introduced by ether formation using potassium bistrimethylsilylamide as base. The products **10a–f** were isolated in yields between 58% and 60%. The reaction of the mannose derivative **9a** and **9b** with racemic 2-benzyl tosylpropyl ether resulted in two pairs of diastereomeric products **10c** and **10f** as a 1/1 mixtures. The acetal protected aldehyde functions at the anomeric position of compounds **10a–f** serve as precursors of carboxylic acid groups. This strategy was chosen to avoid by-products during the ether formation as a result of the C^{α} acidity of the carboxylic acid derivatives. After cleavage of the acetals the free aldehydes were immediately oxidized to the corresponding carboxylic acids using sodium chlorite and 2-methyl-2-butene as the scavenger.[10] The remaining benzyl protecting groups of the side chains of position 2 were removed by hydrogenation with Pd/C under neutral conditions. The final products **11a–f** were purified by HPLC. Thereby, the two diastereomeric compounds **11f** could be separated yielding products **11f1** and **11f2**. However, compounds **11c1** and **11c2** were not resolved (see Table 1).

To evaluate the biological activity of the carbohydrate-based peptidomimetics **11a–f**, we tested whether these compounds interfered with the binding of integrin $\alpha_4\beta_1$ to its VCAM-1 ligand or with the binding of integrin $\alpha_4\beta_7$ to the VCAM-1 and MAdCAM-1 ligand. The integrin ligands VCAM-1 and MAdCAM-1 were immobilized on tissue culture plates and adhesion of the lymphoid cell lines 38-β7 ($\alpha_4\beta_7^{pos}$, $\alpha_4\beta_1^{neg}$) and Jurkat ($\alpha_4\beta_1^{pos}$, $\alpha_4\beta_7^{neg}$) was analyzed in the presence or absence of compounds **11a–f** at 5 mM concentration as described.[11] The results are summarized in Table 1. The inhibitory activity of the $\alpha_4\beta_1$ integrin antagonist *cyclo*[1,7](C-Q-I-D-S-P-C) was measured at 1 mM as a control.[12]

Although our approach started with potent and selective $\alpha_4\beta_7$ antagonists, no activity was found for this integrin. However, variation of the pharmacophoric groups led to an enhanced activity towards the cognate $\alpha_4\beta_1$ integrin. Compound **11a** inhibited integrin $\alpha_4\beta_1$-mediated binding of Jurkat cell to VCAM-1 by 70% (Table 1) at 5 mM concentration. This compound was also tested at the concentration of 2.5 mM. In this case the cell adhesion was inhibited by 34%. In contrast, $\alpha_4\beta_7$ integrin-dependent adhesion of 38-β7 cells to MAdCAM-1 or VCAM-1 was not affected by compound **11a**; this indicates selective antagonist activity for the $\alpha_4\beta_1$ integrin (Table 1). Compounds **11b–e**, **11f1**, and **11f2** did not exhibit significant biological activity in any of the assays investigated.

The side chains at positions 6, 1 and 2 of the active mannose derivative **11a** mimic the LDS peptide sequence. The inhibitory activity reported in Table 1 can therefore be

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Table 1. Effect of mannose-based peptidomimetics at 5 mM concentration on Jurkat and 38-β7 lymphoma cell binding to immobilized VCAM-1 and MAdCAM-Ig.

	Jurkat ($\alpha_4\beta_1$) VCAM-1		38-β7 ($\alpha_4\beta_7$) VCAM-1		38-β7 ($\alpha_4\beta_7$) MAdCAM-Ig	
	[%][a]	n[b]	[%]	n	[%]	n
11a	30 ± 15	7	78 ± 9	8	104 ± 26	4
11a[c]	66 ± 3	3	n.t.[d]		n.t.	
11b	75 ± 9	9	89 ± 5	6	108 ± 18	5
11c1,2[e]	79 ± 23	8	85 ± 3	6	122 ± 15	3
11d	93 ± 10	3	79 ± 1	2	130 ± 10	5
11e	81 ± 19	10	85 ± 8	6	132 ± 19	4
11f1	68 ± 8	5	88 ± 4	3	104 ± 11	4
11f2	n.t.		94 ± 10	3	126 ± 26	4
Ref.[f]	9 ± 6	5	n.t.		n.t.	

[a] Cell adhesion is presented as % of medium control. The data represent the mean values ± the standard deviation; [b] number of experiments; [c] adhesion at 2.5 mM concentration of the inhibitor; [d] n.t.: not tested; [e] racemic mixture not resolved; [f] Ref.: reference peptide at 1 mM concentration.

explained by the similarity with the IDS(P) sequence which represents the key motif in VCAM-1 necessary for binding to $\alpha_4\beta_1$ integrin.[13] These data demonstrate that inhibition of the VCAM-1/$\alpha_4\beta_1$ integrin interaction does not necessarily require amide bonds. Based upon this result physiologically more stable and bioavailable drugs might be accessible, which overcome the well known restriction of conventional peptide or peptide-related compounds. Further investigations are currently in progress in our group.

In summary, we have reported on the design and synthesis of a biological active sugar derivative which can be considered as a new lead structure for rational combinatorial development of anti-inflammatory drugs. Starting from large proteins the cell adhesion molecules VCAM-1 and MAdCAM-1 highly potent cyclic peptides were designed[3] which served as a basis for the sugar derivatives presented here. This class of peptidomimetics have all requirements necessary for orally available drugs. Furthermore, active compound **11a** fulfills Lipinski's rules[14] for bioavailability ($MG = 366.4$; $\log P = -0.60$;[15] number of hydrogen donors: 2; number of hydrogen acceptors: 9). Therefore, it represents a promising starting platform for lead optimization.

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[11] Cell adhesion assay: 96-well plates were coated with donkey anti-human IgG (0.5 µg in 100 µL PBS per well) over night at 4 °C. The plates were washed with adhesion assay buffer (Click's RPMI, 1% BSA, 1.0 mM Ca^{2+}, 1.0 mM Mg^{2+}) and incubated with 100 ng per well MAdCAM-Ig for 30 min at room temperature. After washing with adhesion assay buffer, the plates were blocked with adhesion assay buffer for 1 h at 37 °C. Alternatively, the plates were coated over night at 4 °C with 400 ng per well VCAM-1 in 50 mM carbonate buffer (pH 9.4). 38-β7 lymphoma cells or Jurkat lymphoma cells were labelled for 30 min at 37 °C with 12 µg mL^{-1} H33342 dye (Calbiochem, LA Jolla, CA) in cell adhesion buffer and washed with PBS containing 1 mM EDTA and with PBS. The cells (8×10^5 cells mL^{-1}) were resuspended in cell adhesion buffer containing 1.0 mM Ca^{2+} and 1.0 mM Mg^{2+}. The mannose derivatives were preincubated with the cells at the final concentration of 2 mg mL^{-1} for 10 min at 37 °C. Subsequently, cells were allowed to adhere for 30 min at 37 °C and non-adherent cells were removed by inverse centrifugation for 10 min at 50 g. Adhesion assays were quantified by fluorimetry using a Cytofluor 2300 (Millipore, Bedford, MA). BSA = bovine serum albumin, PBS = phosphate buffered saline (solution).

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