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Is adamantane a suitable substituent to pre-organize the acid orientation in E-selectin antagonists?

Alexander Titz,[a] John Patton,[b] André M. Alker,[c] Michele Porro,[a] Oliver Schwardt,[a] Michael Hennig,[c] Eric Francotte,[d] John Magnani[b] and Beat Ernst[a,*]

[a]*Institute of Molecular Pharmacy, University of Basel, CH-4056 Basel, Switzerland*
[b]*GlycoMimetics Inc., Gaithersburg, MD 20878, USA*
[c]*F. Hoffmann-La Roche Ltd, X-ray Crystallography 65/310, CH-4070 Basel, Switzerland*
[d]*Novartis Institutes for BioMedical Research, CH-4002 Basel, Switzerland*

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Abstract—The selectins play a key role in the inflammatory process, that is, the recruitment of leukocytes from blood vessels into inflamed tissue. Because excessive infiltration of leukocytes can induce acute or chronic reactions, the control of leukocyte extravasation is of great pharmaceutical interest. All physiological ligands of the selectins contain the tetrasaccharide epitope sialyl Lewis^x, which therefore became the lead structure in selectin antagonist research. Previous studies indicated that an important factor for the affinity of sLe^x is the fact that in solution its pharmacophores are already conformationally pre-organized in the bioactive orientation. In mimics where the Glc*N*Ac- and the Neu*N*Ac-moieties of sLe^x were replaced by (*R*,*R*)-cyclohexane-1,2-diol and (*S*)-cyclohexyllactic acid, respectively, an optimized pre-organization of the pharmacophores could be realized, leading to antagonists with improved affinities. To further optimize the pre-organization of the carboxylic acid, a pharmacophore essential for binding, the replacement of Neu*N*Ac by bulky (*R*)- and (*S*)-adamantyl-lactic acid was studied. Although antagonist (***S*)-7** showed a slightly reduced affinity, the expected beneficial effect of the (*S*)-configuration at C-2 of the lactate could be confirmed.

1. Introduction

The selectins play a key role in the body's defense mechanism against inflammation.[1] They form a class of three cell adhesion molecules (E-, P-, and L-selectin), which, in case of an inflammatory stimulus, are responsible for the initial steps of the inflammatory response, that is, the tethering and rolling of leukocytes on endothelial cells. As shown with anti-selectin antibodies[2–4] and E-, P-, and L-selectin k.o. mice,[5,6] these early steps are a prerequisite for the inflammatory cascade to take place. The following steps, that is, firm adhesion and finally extravasation of leukocytes into the adjacent inflamed tissue, do not take place when the initial rolling is prevented. On the other hand, excessive infiltration of leukocytes into the adjacent tissue can lead to acute or chronic reactions, as observed in reperfusion injuries, stroke or rheumatoid arthritis.[7] Therefore, the antagonism of selectins is regarded as a valuable pharmaceutical goal.

Since all physiological ligands of the selectins contain the sialyl Lewis^x motif (sLe^x, **1**, Fig. 1),[8] this tetrasaccharide, although it exhibits only a moderate affinity (IC_{50} = 1 mM), was chosen as lead structure in the search for E-selectin antagonists. The solution[9] and the bioactive[10,11] conformation of sLe^x are known, and its pharmacophores have been identified.[12–15]

We have shown that the pre-organization of the pharmacophores in the bioactive conformation contributes substantially to the affinity of E-selectin antagonists.[16,17] To describe the degree of pre-organization of E-selectin antagonists, two internal dihedral angles have been defined (Fig. 2): (i) the core conformation depicting the relative orientation of L-fucose and D-galactose and (ii) the acid orientation indicating the tilting angle of the carboxylic acid toward the D-Gal(β1–4)[L-Fuc(α1–3)]D-Glc*N*Ac core. By a Monte-Carlo (jumping between

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* Corresponding author. Tel.: +41 61 267 1550; fax: +41 61 267 1552; e-mail: beat.ernst@unibas.ch

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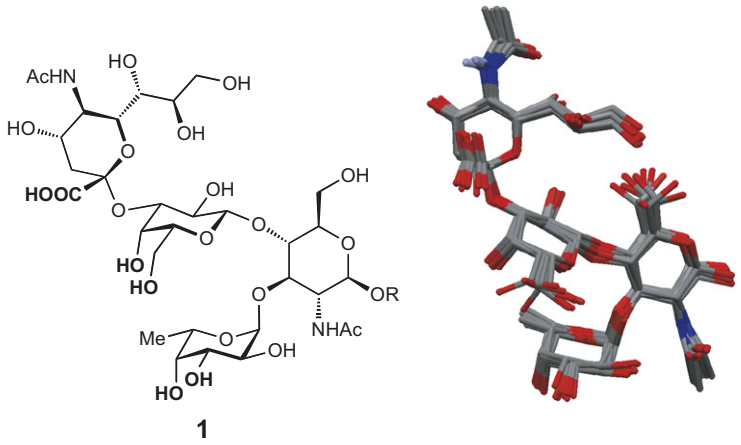
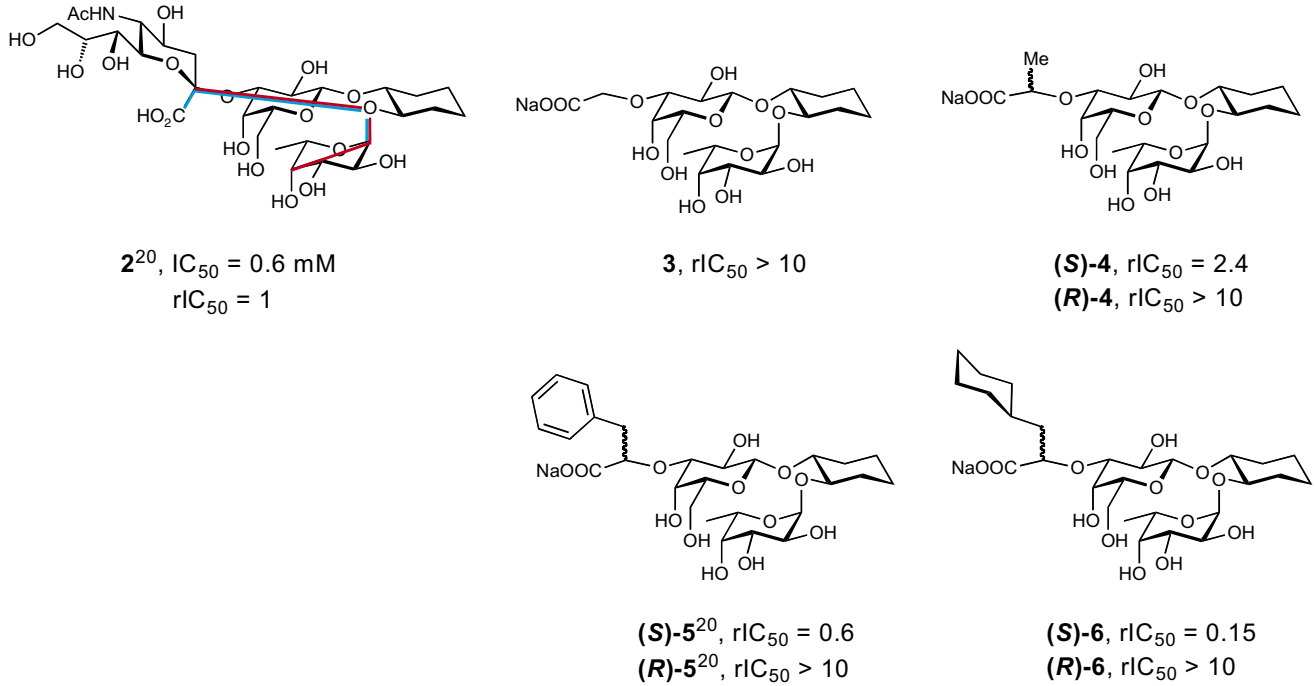


Figure 1. The natural tetrasaccharide epitope sialyl Lewis^x (**1**, sLe^x, essential pharmacophores for binding to E-selectin are highlighted in boldface) and its bioactive conformation as determined by trNOE NMR.[10,11]



2^{20}, IC_{50} = 0.6 mM, rIC_{50} = 1

3, rIC_{50} > 10

(***S***)-**4**, rIC_{50} = 2.4

(***R***)-**4**, rIC_{50} > 10

(***S***)-**5**^{20}, rIC_{50} = 0.6

(***R***)-**5**^{20}, rIC_{50} > 10

(***S***)-**6**, rIC_{50} = 0.15

(***R***)-**6**, rIC_{50} > 10

Figure 2. Mimics **3**–**6** of the sLe^x derivative **2** indicate the influence of the acid orientation for affinity.[16] The affinities are given as rel. affinities, that is, relative to mimic **2** which has an IC_{50} of 0.6 mM and rIC_{50} = 1. Core conformation (=relative orientation of L-fucose and D-galactose, indicated in red) and acid orientation (=tilting angle of the carboxylic acid relative to the core, indicated in blue) are shown in **2**.

wells)/stochastic dynamics (MC(JBW)/SD) protocol, affinities of selectin antagonists could be predicted as a function of their pre-organization with respect to core/acid orientation.[16]

From the crystal structure of all three selectins co-crystallized with sLe^x (**1**),[18] it is known that the D-Glc*N*Ac residue solely serves as a linker to orient the D-Gal- and the L-Fuc-moiety in the correct spatial orientation and does not contribute to the binding enthalpy. This is in agreement with the observation that the replacement of the D-Glc*N*Ac moiety by flexible 1,2-diols[16–19] leads to a tremendous loss in affinity as a consequence of the loss in pre-organization. On the other hand, D-Glc*N*Ac replacements by rigid linkers, for example, (*R*,*R*)-cyclohexane-1,2-diol (→**2**,[20] Fig. 2), resulted in equal or even improved affinities.[16,19–21]

Although the importance of the pre-organization of the acid orientation for the affinity of selectin antagonists has been demonstrated,[16] only a few studies to further stabilize the acid orientation in the bioactive conformation have been reported. Since only the carboxylic acid of D-Neu*N*Ac acts as a pharmacophore, the sugar moiety was replaced by non-carbohydrate acids. The first attempt using glycolic acid showed a substantial reduction in affinity due to reduced pre-organization of the carboxylic acid function (**3**, Fig. 2).[16] However, when D-Neu*N*Ac was replaced by (*S*)-lactic acid (→(***S***)-**4**) and lactic acid derivatives (→(***S***)-**5**^{20} or (***S***)-**6**), affinity was

regained. The corresponding diastereomers (***R***)-**4** to (***R***)-**6**, however, showed no affinity. A careful analysis of *R*- and *S*-isomers by MC(JBW)/SD simulations clearly indicated that the *S*-isomers are pre-organized in the bioactive conformation, whereas the *R*-isomers are not. For binding to E-selectin, the *R*-isomers have therefore to undergo a conformational change accompanied by substantial entropy costs.[16] In addition to the observed configurational prerequisite, the affinity also depends on the lipophilicity or the bulkiness of the lactic acid substituent, that is, going from glycolate, to lactate, 2-phenyl lactate, and 2-cyclohexyl lactate an increase in affinity could be observed.

From the docking studies[22] of the lowest energy conformation of a Monte-Carlo search of (***S***)-**6** to E-selectin using the *Yeti* program,[23] it becomes evident that the cyclohexyl group is not establishing an additional lipophilic contact with the binding site of the lectin. Therefore, it was assumed that the increase in activity originates predominantly from an increased degree of pre-organization. To further verify the influence of the lipophilicity/bulkiness of the lactic acid substituent, the corresponding adamantyl derivatives (***R***)-**7** and (***S***)-**7** were analyzed by molecular modeling, synthesized, and biologically evaluated.

2. Results and discussion

The analysis of the two diastereomeric adamantyl derivatives (***R***)-**7** and (***S***)-**7** (Fig. 3) was conducted according to the MC(JBW)/SD protocol.[16] The *S*-isomer shows a high degree of pre-organization in the area of the bioactive window (indicated in the core conformation/acid orientation plot by a red square, Fig. 3b). The *R*-isomer of **7**, however, shows a conformational focus point outside the bioactive area (Fig. 3a). Since (***S***)-**7** shows a higher degree of pre-organization than (***S***)-**6**, the most active compound in Figure 2, an improved affinity was expected.

The retrosynthetic analysis for the two diasteromeric adamantyl derivatives (***R***)/(***S***)-**7** (Scheme 1) generated the adamantyl-lactic acid derivatives (***R***)/(***S***)-**8** and the known building blocks **9**[24] and **10**.[19]

Racemic adamantyl-lactic acid (**rac-12**, Scheme 2) was obtained by a Giese-type radical addition of the adamantyl radical generated from 1-adamantyl bromide to the acrylate **11**, followed by hydrolysis of the ethyl ester.[25] Subsequent formation of the benzyl ester (→**rac-13**) followed by preparative chiral resolution on a Chiralpak AD-H column yielded the two enantiomers (***S***)-**13** (ee 99.5%) and (***R***)-**13** (ee 99.6%). The chiral resolution with the corresponding methyl and *p*-nitrobenzyl derivatives was less efficient, because the differences in retention time for the two enantiomers were smaller than in case of the benzyl ester **rac-13**. By transforming the enantiomers (***S***)-**13** and (***R***)-**13** into the corresponding triflates (***S***)-**14** and (***R***)-**14**, the electrophiles needed for the alkylation of the 3-position of the galactose moiety were obtained.

For the assignment of the absolute configuration of the adamantyl building blocks, racemic adamantyl-lactic acid (**rac-12**) was treated with the chiral auxiliary (*S*)-α methylbenzylamine (**15**)[26] to yield the two corresponding diastereomeric amides **16** and **17** (Scheme 3). Since the two diastereomers exhibit significantly different R_f values, they could be separated by standard column chromatography on silica gel. Because diastereomer **16**

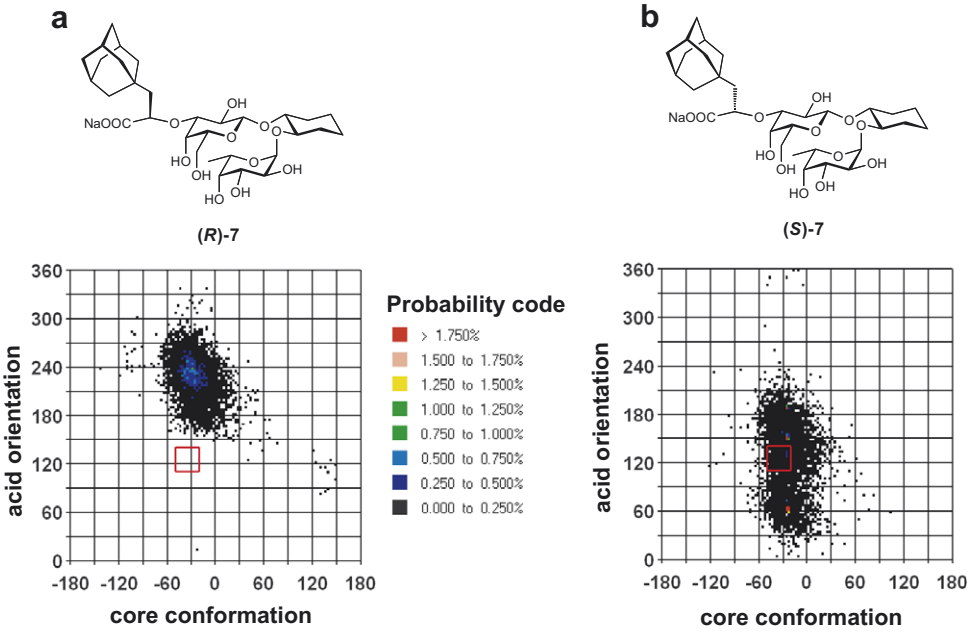
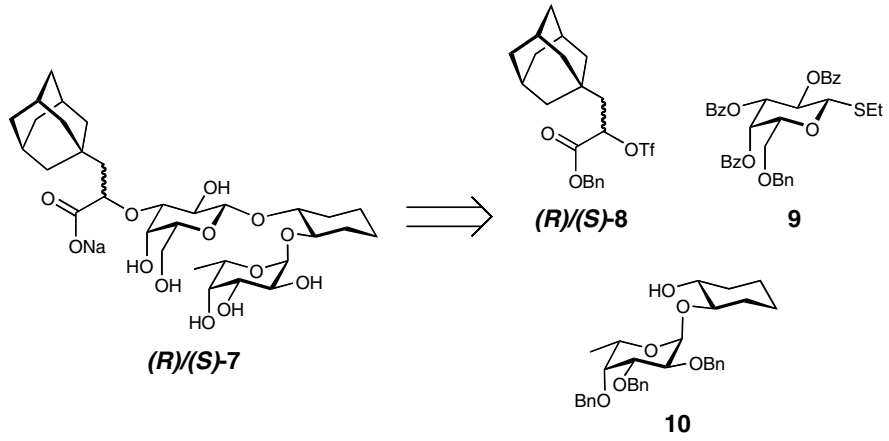
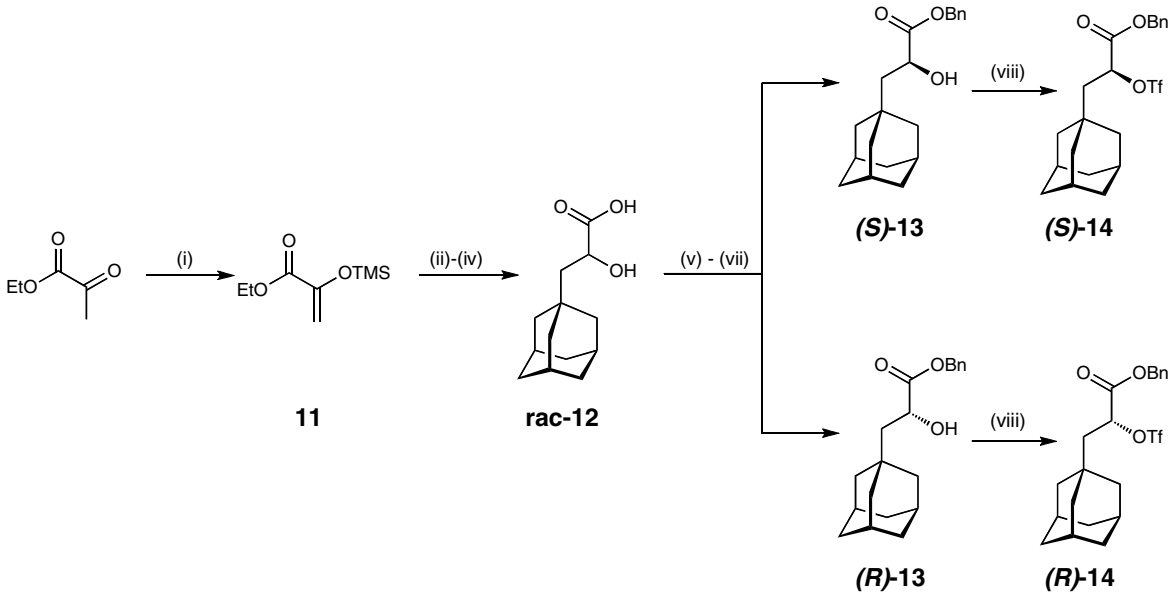


Figure 3. Core conformation/acid orientation plot of both adamantyl bearing E-selectin antagonist (***R***)-**7** and (***S***)-**7**. The bioactive window is indicated with a red square.



Scheme 1. Retrosynthetic analysis for the target compounds.

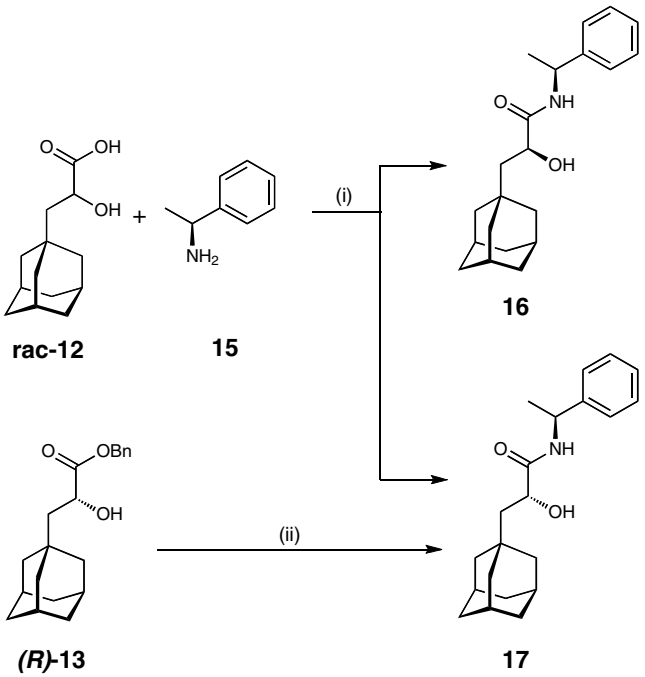


Scheme 2. Reagents and conditions: synthesis of the adamantyl-lactic acids. (i) TMSCl, TEA, Et_2O, 0 °C–rt, 3.5 h (85%); (ii) Bu_3SnH, AIBN, 1-adamantyl bromide, PhMe, reflux, 14 h; (iii) KF, H_2O, rt, overnight; (iv) NaOH, H_2O, 50 °C, 12 h; HCl (54% for three steps); (v) Cs_2CO_3, MeOH, H_2O; (vi) BnBr, DMF, rt, 20 h (73% for two steps); (vii) chiral resolution, HPLC Chiralpak AD-H ((***S***)-**13**: ee 99.5%; (***R***)-**13**: ee 99.6%); (viii) Tf_2O, DCM, 2,6-^{t}Bu$_2$–py, 0–20 °C, 3 h ((***S***)-**14**: 96%; (***R***)-**14** 79%).

could be crystallized, the determination of its absolute configuration by X-ray crystallography was possible (Table 1 and Fig. 4). It is noteworthy that the asymmetric unit contains three molecules of which two have a stretched and one a collapsed conformation (Fig. 4). Because (***R***)-**13** could be transformed into **17**, the allocation of the absolute configuration of the adamantyl derivatives (***S***)-**13** and (***R***)-**13** was achieved.

The synthesis of the selectin antagonists **7** started from (*R*, *R*)-cyclohexane-1,2-diol (**19**) which was α-fucosylated with the thiofucoside donor **18**[17] according to the in situ anomerization procedure developed by Lemieux[27] (Scheme 4). In a second glycosylation step, **10** was galactosylated with thiogalactoside donor **9** using DMTST[28] as promotor. Finally, removal of the benzoate protective groups by transesterification yielded the core molecule **21**.[21]

For the desired antagonist (***S***)-**7**, the regioselective alkylation of the 3-position of the galactose moiety was achieved using the alkylating agent (***R***)-**14** and the mild tin-acetal coupling procedure.[29] Due to the increased steric bulk of the adamantyl substituent, the yield (21%) was rather low. In addition, a significant amount of a side product, benzyl (*S*)-3-(1-adamantyl)-2-fluoro-propionate (**23**, see experimental part for details), was isolated. The formation of **23** is a consequence of the bulkiness of the adamantyl substituent, allowing the stannophilic fluoride ion, which is used to open the stannylene acetal regioselectively, to act also as nucleophile. The sodium salt of the acid (***S***)-**7** was obtained after hydrogenolysis and ion exchange chromatography. Finally, possible traces of the polyanionic ion exchange resin, which would lead to false positive results,[30] were removed by size exclusion chromatography.



Scheme 3. Reagents and conditions: determination of the absolute configuration of the adamantyl derivatives (***S***)-**13** and (***R***)-**13**: (i) dioxane, μW, 180 °C, 15 min (85%); (ii) **15**, dioxane, 80 °C, 48 h (quant.).

Table 1. Crystallographic data of amide **16**

Compound	**16**
CCDC number	626224
Empirical formula	$C_{21}H_{29}NO_2$
Formula weight	327.45
Temperature (K)	100
Wavelength (Å)	1.54184
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Cell dimensions	
a (Å)	10.386(2)
b (Å)	18.795(4)
c (Å)	28.311(6)
α (°)	90
β (°)	90
γ (°)	90
Volume (Å^3)	5526.1(19)
Z	12
Density calculated (kg/dm^3)	1.181
F_{000}	2136
θ range for data collection (°)	3.12–64.44
Reflections collected	31059
Independent reflections	9154
Data/restraints/parameters	9154/0/667
Goodness of fit on F^2	0.810
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0323$, $wR2 = 0.0564$
R indices (all data)	$R1 = 0.0512$, $wR2 = 0.0611$
Largest diff. peak and hole (e Å^3)	0.136 and −0.150

In the synthesis of the second diastereomer (***R***)-**7**, the alkylation of the 3-position of galactose with (***S***)-**14** was accompanied by the formation of lactone **24**. In this case, the lactone is particularly easily formed, because the bulky adamantyl-methyl substituent adopts an equatorial position in the δ-lactone ring (vs an axial position in case of (***R***)-**14**). After hydrogenolysis, the crude product was treated with aqueous sodium hydroxide to open the δ-lactone. Diastereomer (***R***)-**7** was finally obtained after size exclusion chromatography.

The results obtained in a competitive binding assay[31] confirmed our prediction that the *S*-configurated lactic acid substituent leads to active antagonists, whereas the *R*-configuration produces inactive compounds. However, contrary to the predicted properties, (***S***)-**7** ($rIC_{50} = 0.32$) is slightly less active than (***S***)-**6** ($rIC_{50} = 0.15$).

3. Conclusion

Docking studies using the crystal structure of E-selectin and a bioactive conformation of (***S***)-**7**, which was extrapolated from the one of **1**,[11] clearly demonstrated that no interaction of the adamantyl substituent with the protein occurs. Thus, the bulky adamantyl substituent solely contributes to the stabilization of the acid orientation. Since the predicted acid orientation in (***S***)-**7** (Fig. 3) is superior to the one in (***S***)-**6**,[16] lower entropy costs upon binding, and therefore an improved affinity to E-selectin was expected. One possible explanation for the discrepancy between our prediction based on molecular modeling and the test results may be related to the lipophilicity of the adamantyl substituent, which could lead to aggregate formation or unfavorable solvation properties.

4. Experimental

4.1. General methods

Analyses of the conformational preferences of the E-selectin antagonists were performed in aqueous solution by applying the systematic pseudo-Monte-Carlo (MC) (SUMM, systematic multiple minimum search) simulation technique[32] and the 'Jumping Between Wells/Stochastic Dynamics' ((JBW)/SD) protocol[16] implemented in MacroModel 5.0.[33] First, the locations of the most relevant energy minima (conformations) of a compound were determined in an internal coordinate systematic pseudo-Monte-Carlo SUMM simulation.[32] 2000 steps were performed for each free-rotatable bond excluding terminal CH_3 groups. All structures within 20 kJ/mol from the energy of the global minimum were retained. The shape of the potential energy surface was then probed in a subsequent JBW/SD simulation, which used the information obtained in the SUMM analysis. Thus, a Boltzmann-weighted ensemble of states was generated in a 10 ns MC(JBW)/SD simulation by jumping between different energy wells, that is, the energetically best 100 conformations found in the preceeding SUMM analysis, and performing stochastic dynamics simulations within each well. All calculations were performed using the AMBER[34] force field augmented by parameters for carbohydrates[16,35] and in conjunction with the GB/SA continuum water model for implicit solvation.[36] This led to a realistic sampling of the conformational space of the structure of interest.

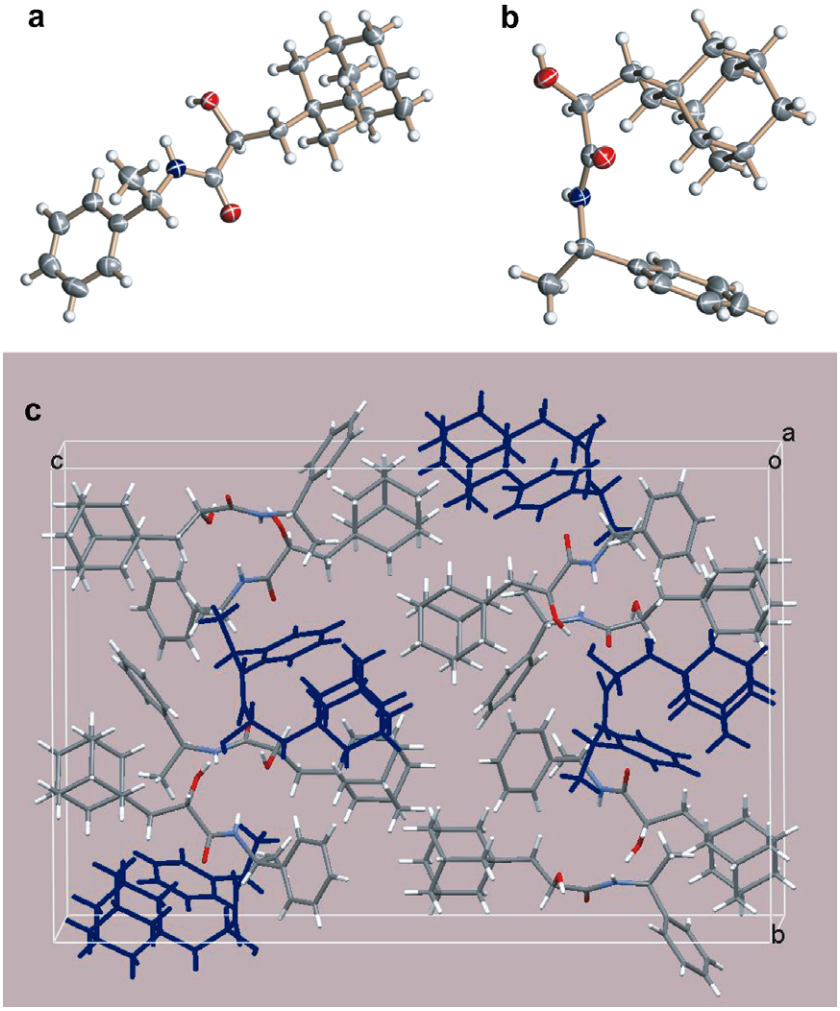


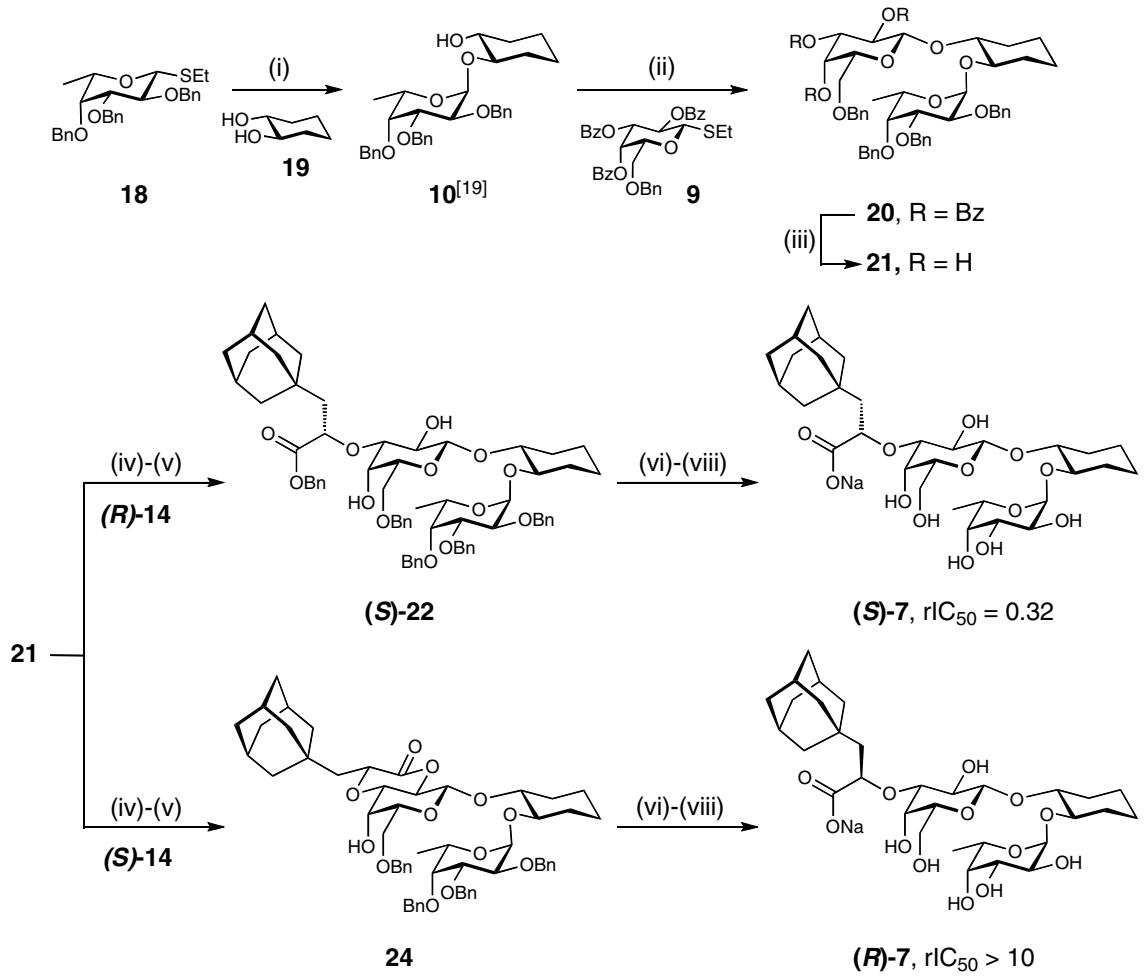
Figure 4. X-ray crystal structure of **16**: The asymmetric unit (c) contains stretched molecules (a) and conformationally collapsed conformers (b).

Nuclear magnetic resonance spectroscopy was performed on a Bruker Avance 500 UltraShield spectrometer at 500.13 MHz (^{1}H) or 125.76 MHz (^{13}C). Chemical shifts are given in ppm and were calibrated on residual solvent peaks[37] or to tetramethyl silane as internal standard. Multiplicities were specified as s (singlet), d (doublet), dd (doublet of a doublet), t (triplet), q (quartet), dq (doublet of a quartet), quint. (quintublet) or m (multiplet). Interpretation of the spectra was performed according to first order[38] and higher order where possible.

The signals were assigned with the help of DEPT-135, ^{1}H,^{1}H-COSY/TOCSY and ^{1}H,^{13}C-HSQC/HMBC experiments. Assignments are indicated according to IUPAC nomenclature. For complex molecules, the following prefixes for substructures are used: Ad (adamantyl), Cy (cyclohexyl), Fuc (fucose), Gal (galactose), and Lac (lactate). C^i indicates the *ipso* substituted carbons of aromatic systems.

Optical rotations were measured on a Perkin Elmer 341 polarimeter in the indicated solvents in p.a. quality. Microanalyses were performed at the Department of Chemistry, University of Basel, Switzerland. ESI mass spectra were recorded on a Waters micromass ZQ instrument. High resolution mass spectra were obtained on an ESI Bruker Daltonics micrOTOF spectrometer equipped with a TOF hexapole detector.

TLC was performed using silica gel 60 coated glass plates containing fluorescence indicator (Merck KGaA, Darmstadt, Germany) using either UV light (254 nm) and by charring in aqueous $KMnO_4$ solution or in a molybdate solution (a 0.02 M solution of ammonium cerium sulfate dihydrate and ammonium molybdate tetrahydrate in aqueous 10% H_2SO_4) with heating to 140 °C for 5 min. Column chromatography was performed using silica gel 60 (0.040–0.063 mm) from Fluka. Microwave reactions were performed in a CEM Discover microwave apparatus. Hydrogenation reactions were performed in a shaking apparatus (Parr Instruments Company, Moline, Illinois, USA) in 250 mL or 500 mL bottles with 4 bar H_2 pressure. Solvents were purchased from Fluka and dried prior to use. DCM was dried by filtration through basic aluminum oxide (Fluka). Dioxane, DME, Et_2O, and PhMe were dried by distillation from sodium/benzophenone. DMF was dried by distillation from calcium hydride and MeOH by distillation from sodium methoxide.



Scheme 4. Reagents and conditions: synthesis of selectin antagonists containing adamantyl-lactic acid. (i) Br_2, Bu_4NBr, DCM, DMF, mol. sieves 4 Å, −20 °C–rt, 12 h (58%); (ii) DMTST, DCM, mol. sieves 4 Å, rt, 5 days; (iii) NaOMe, MeOH, rt, overnight (85% for two steps); (iv) Bu_2SnO, MeOH, mol. sieves 3 Å, reflux, 18 h; (v) CsF, DME, rt, 3 d (**22**: 21%; **24**: 25%); (vi) H_2, $Pd(OH)_2/C$, dioxane–H_2O, 4 bar, rt, 4 d; (vii) Na^+–ion exchange; (viii) NaOH, H_2O; (ix) Sephadex-G15 ((***S***)-**7**: 92%; (***R***)-**7**: 31%).

rac-13 was separated using a Gilson preparative HPLC apparatus equipped with a 5 × 50 cm Chiralpak AD column and a UV detector (210 nm). For elution, an isocratic solvent system ethanol/hexanes 5/95 was used (50 mL/min). Analytical chiral HPLC was performed on a Chiralpak AD-H column (250 × 4.6 mm, 1 mL/min, 210 nm). Enantiomeric excess was determined from the peak areas after integration of the analytical chromatograms.

The X-ray crystal structure of **16** was solved at Hoffmann-La Roche, Pharmaceutical Division, Pharma Research 65/308, Basel, Switzerland. The diffraction pattern was measured on a Gemini Ruby diffractometer from Oxford Diffraction, Abingdon, UK, using Cu–K_α-radiation with a wavelength of 1.54184 Å. Structure solution and refinement was performed using the ShelX software[39,40] (G. Sheldrick, Göttingen, Germany).

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary Publication No. CCDC 626224. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Biological data were obtained using the published ELISA procedure with (***S***)-**6** as reference compound.[31]

4.2. Ethyl 2-trimethylsilyloxy-acrylate (11)

To a solution of ethyl pyruvate (4.78 mL, 43.1 mmol) and chlorotrimethylsilane (6.33 mL, 49.5 mmol) in anhydrous diethylether (50 mL) was added triethylamine (7.19 mL, 51.7 mmol) dropwise over a period of 10 min at 0 °C. After stirring for 1 h at 0 °C, the solution was allowed to warm to rt and stirred for additional 3 h. The reaction mixture was diluted with petrol ether (250 mL), cooled to 0 °C, and washed with cold brine (3 × 50 mL). Drying over Na_2SO_4 and evaporation of the solvent in vacuo gave the volatile crude product **11** as clear yellow oil (8.46 g), which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 5.45, 4.82 (A, B of AB, ^2J = 1.0 Hz, 2H, H3), 4.16 (q, ^3J = 7.14 Hz, 2H, CH_3CH_2–), 1.25 (t, ^3J = 7.15 Hz, 3H, CH_3CH_2–), 0.17 (s, 9H, $(CH_3)_3Si$–); ^{13}C NMR

($CDCl_3$): δ 164.4 (C1), 147.2 (C2), 103.9 (C3), 61.2 (–*C*H_2CH$_3$), 14.1 (–CH$_2$*C*H_3), −0.1 ((CH$_3$)$_3$Si–).

4.3. rac-3-(1-Adamantyl)-lactic acid (rac-12)

To a solution of 1-bromo-adamantane (7.90 g, 36.7 mmol), **11** (13.8 g, 73.4 mmol), and AIBN (1.50 g, 9.18 mmol) in toluene (100 mL), tributyltinhydride (11.7 mL, 44.0 mmol) was added. The reaction mixture was refluxed for 25 h. After cooling to rt, a solution of KF (5.11 g, 88.0 mmol) in water (150 mL) was added and the heterogeneous mixture stirred vigorously overnight. Ethyl acetate (1.5 L) was added, the phases were separated, and the organic layer was washed with water (300 mL) and brine (300 mL). After drying over Na_2SO_4, the solvent was removed in vacuo to give the crude ethyl ester. The residue was dissolved in a mixture of aqueous 1 N NaOH (250 mL) and EtOH (100 mL). After stirring overnight at 50 °C, the ethanol was removed in vacuo and the aqueous phase was diluted with water (1 L), washed with DCM (2 × 350 mL), acidified to pH 0 with aqueous 6 N HCl, and then extracted with DCM (3 × 400 mL). Washing of the combined organic layers with brine (200 mL), drying over Na_2SO_4, and evaporation of the solvent gave **rac-12** as a spectroscopically pure, off-white solid (4.43 g, 54%) which was used without further purification. ^{1}H NMR ($CDCl_3$): δ 4.40 (d, ^3J = 9.4 Hz, 1H, H2), 1.98 (br s, 3H, H6), 1.77–1.58 (m, 13H, Ad-CH_2, H3b), 1.41 (A of ABM, ^3J = 9.5, ^2J = 14.5 Hz, 1H, H3a); ^{13}C NMR ($CDCl_3$): δ 181.0 (C1), 67.5 (C2), 48.9 (C3), 42.6 (C5), 36.9 (C7), 32.5 (C4), 28.6 (C6); ESI-MS Calcd for $C_{13}H_{21}O_3$ $[M+H]^+$: 225.1; Found: 225.0.

4.4. rac-Benzyl 3-(1-adamantyl)-lactate (rac-13)

To a suspension of **rac-12** (679 mg, 3.03 mmol) in MeOH/water (3:1) was added Cs_2CO_3 (591 mg, 1.82 mmol) under stirring to give a clear solution. The solvents were removed in vacuo. After drying the residue in high vacuum overnight, it was resuspended in anhydrous DMF (2.5 mL). Then benzyl bromide (2.15 mL, 18.2 mmol) was added and the suspension was stirred for 20 h at rt. Removal of the solvent and purification of the crude product by column chromatography on silica (PE/EE 100:0 > 85:15) gave pure **rac-13** as a colorless oil (690 mg, 73%). R_f (PE/EE 4/1) 0.67; ^{1}H NMR ($CDCl_3$): δ 7.40–7.35 (m, 5H, Ar–H), 5.22, 5.18 (A, B of AB, ^2J = 12.3 Hz, 2H, Ph*C*H_2), 4.36–4.33 (m, 1H, H2), 1.96 (br s, 3H, H6), 1.71–1.56 (m, 13H, H3b, 12× Ad-CH_2), 1.37 (A of ABM, ^3J = 9.3, ^2J = 14.0 Hz, 1H, H3a); ^{13}C NMR ($CDCl_3$): δ 176.2 (C1), 135.3 (Ar–C^i), 128.6 (Ar–C), 128.5 (Ar–C), 128.2 (Ar–C), 67.8 (C2), 67.3 (Ph*C*H$_2$), 49.0 (C3), 42.7–42.6 (3C, C5), 37.0–36.9 (3C, C7), 32.4 (C4), 28.7–28.5 (3C, C6); ESI-MS calcd for $C_{20}H_{26}NaO_3$ $[M+Na]^+$: 337.1; Found: 337.1; Anal. calcd. for $C_{20}H_{26}O_3$ + 1/4 H_2O: C 75.32, H 8.38; Found: C 75.32, H 8.26.

With preparative HPLC on a 5 × 50 cm Chiralpak AD column the two enantiomers (***R***)-**13** and (***S***)-**13** were separated: **Benzyl (*R*)-3-(1-adamantyl)-lactate ((*R*)-13)**. Analytical chiral HPLC: t_R = 10.57 min, optical purity: ee > 99.6%, $[\alpha]_D^{20}$ +3.1 (*c* 2.35, $CHCl_3$); **Benzyl (*S*)-3-(1-adamantyl)-lactate ((*S*)-13)**. Analytical chiral HPLC: t_R = 12.01 min, optical purity: ee > 99.5%, $[\alpha]_D^{20}$ = −4.2 (*c* 1.67, $CHCl_3$).

4.5. Benzyl (*R*)-3-(1-adamantyl)-2-(trifluoromethyl)sulfonyloxy-propionate ((*R*)-14)

Ester (***R***)-**13** (162 mg, 0.52 mmol) was dissolved in dry DCM (3 mL) under argon and cooled to −20 °C. 2,6-Di-*tert*-butyl pyridine (197 μL, 0.88 mmol) was added, followed by dropwise addition of triflic anhydride (147 μL, 0.88 mmol). After 2 h at −20 °C, the mixture was diluted with DCM (30 mL) and washed with aqueous 1 M KH_2PO_4 solution (25 mL). The aqueous phase was then extracted with DCM (3 × 40 mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent in vacuo gave the crude product as a colorless oil. Purification by column chromatography on silica (PE/EE 20/1) gave pure (***R***)-**14** as a colorless oil (186 mg, 78%), which was used immediately for the next reaction. R_f (PE/EE 20/1) 0.40; ^{1}H NMR ($CDCl_3$): δ 7.38–7.35 (m, 5H, Ar–H), 5.27–5.21 (m, 3H, Ph*C*H_2, H2), 1.96 (br s, 3H, H6), 1.83 (A of ABM, ^2J = 15.4, ^3J = 7.7 Hz, 1H, H3a), 1.74–1.53 (m, 13H, H3b, 12× Ad-CH_2); ^{13}C NMR ($CDCl_3$): δ 168.1 (C1), 134.3 (Ar–C^i), 128.8, 128.7, 128.6 (3Ar–C), 81.0 (C2), 68.2 (Ph*C*H$_2$), 45.8 (C3), 42.0 (3C, C5), 36.5 (3C, C7), 32.3 (C4), 28.3 (3C, C6).

4.6. (*S*)-Benzyl 3-(1-adamantyl)-2-(trifluoromethyl)sulfonyloxy-propionate ((*S*)-14)

Two hundred and sixty milligrams (96%) of the title compound was obtained using the same procedure as described for (***R***)-**14**. R_f and ^{1}H/^{13}C NMR see (***R***)-**14**.

4.7. (*S*)-1-Phenylethyl (*S*)-3-(1-adamantyl)-lactamide (16) and (*S*)-1-phenylethyl (*R*)-3-(1-adamantyl)-lactamide (17)

A microwave vial was charged with a magnetic stirring bar, **rac-12** (224 mg, 1.00 mmol), and (*S*)-α-methylbenzylamine (**15**) (140 μL, 1.10 mmol). Dioxane (2 mL) was added and the vial was sealed under argon. The mixture was heated under microwave irradiation to 180 °C for 70 min. After cooling to rt, the solvent was evaporated, the residue was taken up in ethyl acetate (100 mL) and washed with saturated aqueous K_2CO_3 (2 × 10 mL) and aqueous 0.5 N HCl (2 × 20 mL). The organic layer was dried over Na_2SO_4. Evaporation of the solvent gave the crude mixture of **16** and **17** as a light yellow oil (279 mg, 85%). The diastereomers could be separated by column chromatography on silica (PE/EE 3/1). ESI-MS Calcd for $C_{21}H_{29}NNaO_2$ $[M+Na]^+$: 350.2; Found: 350.2.

(*S*)-1-phenylethyl (*S*)-3-(1-adamantyl)-lactamide (16). R_f (PE/EE 4/1) 0.55; $[\alpha]_D^{20}$ −59.7 (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.32–7.23 (m, 5H, Ar–H), 6.962 (d, ^3J = 7.15 Hz, 1H, N*H*), 5.069 (m, 1H, MeC*H*–), 4.188 (M of ABM, ^3J = 9.32 Hz, 1H, Lac-H2), 3.050 (br s, 1H, O*H*), 1.95 (br s, 3H, Ad-H3), 1.700 (m, 4H, 3× Ad-CH_2, Lac-H3b), 1.623 (A′ of A′B′, ^2J = 11.83 Hz,

3H, 3× Ad-CH_2), 1.576 (s, 6H, Ad-CH_2), 1.464 (d, ^3J = 6.93 Hz, 3H, –CH_3), 1.332 (A of ABM, ^2J = 14.57, ^3J = 9.45 Hz, 1H, Lac-H3a); ^{13}C NMR ($CDCl_3$): δ 174.15 (C1), 143.09 (Ar–C^i), 128.57 (2Ar–C), 127.25 (*p*Ar–C), 126.08 (2 Ar–C), 69.27 (C2), 49.34 (C3), 48.40 (Ph*C*H–), 42.72 (3C, Ad-CH_2), 36.88 (3C, Ad-CH_2), 32.29 (Ad-C1), 28.57 (3C, Ad-C3), 21.83 (–*C*H_3).

(*S*)-1-phenylethyl (*R*)-3-(1-adamantyl)-lactamide (17). R_f (PE/EE 4/1) 0.45; $[\alpha]_D^{20}$ −49.2 (*c* 0.035, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.35–7.24 (m, 5H, Ar–H), 6.881 (br s, 1H, N*H*), 5.097 (m, 1H, MeC*H*–), 4.241 (M of ABM, ^3J = 9.50 Hz, 1H, Lac-H2), 1.96 (br s, 3H, Ad-H3), 1.713–1.665 (m, 4H, 3× Ad-CH_2, Lac-H3a), 1.624 (A′ of A′B′, ^2J = 11.64 Hz, 3H, Ad-CH_2), 1.574 (s, 6H, Ad-CH_2), 1.492 (d, ^3J = 6.92 Hz, 3H, –CH_3), 1.297 (B of ABM, ^2J = 14.56, ^3J = 9.68 Hz, 1H, Lac-H3b); ^{13}C NMR ($CDCl_3$): δ 174.11 (C1), 142.97 (Ar–C^i), 128.62 (2Ar–C), 127.29 (*p*Ar–C), 126.03 (2Ar–C), 69.40 (C2), 49.41 (C3), 48.38 (Ph*C*H–), 42.73 (3C, Ad-CH_2), 36.87 (3C, Ad-CH_2), 32.32 (Ad-C1), 28.57 (3C, Ad-C3), 21.86 (–*C*H_3).

4.8. (*1R*,*2R*)-2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-cyclohexyl 2,3,4-tri-*O*-benzoyl-6-*O*-benzyl-β-D-galactopyranoside (20)

Fucoside **10** (4.54 g, 8.52 mmol) and galactose donor **9** (5.88 g, 9.37 mmol) were dissolved in dry DCM (140 mL). Powdered activated molecular sieves (4 Å, 15.0 g) were added and the mixture was stirred for 3.5 h under argon at rt. DMTST (25.6 mmol, 6.60 g) was dissolved in dry DCM (40 mL) and powdered activated molecular sieves (4 Å, 3.75 g) were added and this suspension was stirred for 2 h under argon at rt as well. Then the two suspensions were combined and stirred for 5 days at rt under argon. The mixture was filtered over Celite. After washing of the organic layer with 8% aqueous $NaHCO_3$ (30 mL), the aqueous layer was extracted with DCM (2× 40 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product **20** was obtained as white foam (9.95 g). It was used without further purification. A small sample was purified by column chromatography on silica (PE/EE 5/1) for analyses. R_f (PE/EE 4/1) 0.11; ^{1}H NMR ($CDCl_3$): δ 7.91 (m, 2H, Bz-H2/5), 7.86 (m, 2H, Bz′-H2/5), 7.71 (m, 2H, Bz″-H2/5), 7.48–7.02 (m, 29 H, Ar–H), 5.86 (br s, 1H, Gal-H4), 5.60 (dd, ^3J = 8.1, ^3J = 10.2 Hz, 1H, Gal-H2), 5.43 (dd, ^3J = 3.2, ^3J = 10.4 Hz, 1H, Gal-H3), 4.89 (A of AB, ^2J = 11.5 Hz, 1H, $PhCH_2$), 4.86 (br s, 1H, Fuc-H1), 4.77 (d, ^3J = 7.9 Hz, 1H, Gal-H1), 4.73 (A′ of A′B′, ^2J = 11.7 Hz, 1H, $PhCH_2$), 4.68 (A″ of A″B″, ^2J = 11.0 Hz, 1H, $PhCH_2$), 4.59 (B″ of A″B″, ^2J = 12.0 Hz, 1H, $PhCH_2$), 4.54 (B of AB, B′ of A′B′, ^2J = 11.6 Hz, 2H, $PhCH_2$), 4.89 (q, ^3J = 6.1 Hz, 1H, Fuc-H5), 4.38, 4.25 (A‴,B‴ of A‴B‴, ^2J = 11.9, 2H, $PhCH_2$), 3.99–3.94 (m, 2H, Fuc-H2, Gal-H5), 3.70 (m, 1H, Cy-CH), 3.64 (s, 1H, Fuc-H4), 3.59–3.48 (m, 4H, Fuc-H3, Gal-H6, Cy-CH), 1.86 (br s, 2H, Cy-CH_2), 1.55–1.02 (m, 6H, Cy-CH_2), 1.22 (d, ^3J = 6.8 Hz, 3H, Fuc-H6); ^{13}C NMR ($CDCl_3$): δ 165.5, 165.4, 165.0 (3C, Ph-*C*O_2–), 139.03, 139.01, 138.7, 137.4 (4C, Bn-C^i), 133.4, 133.1 (3C, Bz-C^i), 129.7–127.1 (Ar–C), 99.5 (Gal-C1), 94.1 (Fuc-C1), 79.8 (CH), 79.1, 79.0, 76.4, 74.9 (CH), 74.8 (CH_2), 73.6 (CH_2), 73.0 (CH_2), 72.5 (CH), 72.0 (CH), 70.0 (Gal-C2), 68.5 (Gal-C4), 67.7 (Gal-C6), 66.3 (Fuc-C5), 29.5 (Cy-CH_2), 28.5 Cy-(CH_2), 22.94 (Cy-CH_2), 22.87 (Cy-CH_2), 16.7 (Fuc-C6); ESI-MS Calcd for $C_{67}H_{68}NaO_{14}$ $[M+Na]^+$: 1119.5; Found: 1119.6.

4.9. (*1R*,*2R*)-2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-cyclohexyl 6-*O*-benzyl-β-D-galactopyranoside (21)

The protected pseudotrisaccharide **20** (9.70 g crude material) was dissolved in dry MeOH (100 mL). When 3 M NaOMe in MeOH (3.5 mL) was added to the solution, a white precipitate appeared which dissolved after a few minutes. The solution was stirred at rt for 16 h and then neutralized with Dowex 50 × 8 ion exchange resin. The mixture was filtered and the solvent evaporated to give the crude product as a colorless oil. Purification by column chromatography on silica (DCM/MeOH, gradient 25/1 to 10/1) yielded pure **21** as a white foam (5.53 g, 85% over two steps from **10**). R_f (DCM/MeOH 8/1) = 0.50; ^{1}H NMR ($CDCl_3$): δ 7.38–7.24 (m, 20 H, Ar–H), 4.97 (d, ^3J = 3.6 Hz, 1H, Fuc-H1), 4.94 (A of AB, ^2J = 11.6 Hz, 1H, $PhCH_2$), 4.81 (A′ of A′B′, ^2J = 11.6 Hz, 1H, $PhCH_2$), 4.75 (A″ of A″B″, ^2J = 11.8 Hz, 1H, $PhCH_2$), 4.68 (B′ of A′B′, ^2J = 11.5 Hz, 1H, $PhCH_2$), 4.67 (B″ of A″B″, ^2J = 11.8 Hz, 1H, $PhCH_2$), 4.59 (B of AB, ^2J = 11.6 Hz, 1H, $PhCH_2$), 4.52 (s, 2H, $PhCH_2$), 4.33 (q, ^3J = 6.3 Hz, 1H, Fuc-H5), 4.32 (d, ^3J = 7.4 Hz, 1H, Gal-H1), 4.02 (dd, ^3J = 3.6, ^3J = 9.4 Hz, 1H, Fuc-H2), 3.97 (s, 1H, Gal-H5), 3.96–3.95 (m, 1H, Fuc-H3), 3.79–3.73 (m, 2H, 1× Cy-CH), 3.69 (dd, 1H, *J* = 5.3, *J* = 9.8 Hz), 3.63 (br s, 1H, Fuc-H4), 3.60–3.53 (m, 4H, 1× Cy-CH, Gal-H2), 2.72 (br s, 3H, OH), 2.07–1.98 (m, 2H, Cy-CH_2), 1.70–1.65 (m, 2H, Cy-CH_2), 1.42–1.18 (m, 4H, Cy-CH_2), 1.09 (d, ^3J = 6.4 Hz, 3H, Fuc-H6); ^{13}C NMR ($CDCl_3$): δ 139.1, 138.8, 138.6, 137.8 (4C, 4 Bn-C^i), 128.5–127.3 (Ar–C), 100.3 (Gal-C1), 94.5 (Fuc-C1), 79.5 (CH), 78.0 (CH), 77.1 (CH), 76.34 (CH), 76.29 (CH), 74.8 (Ph*C*H_2), 73.6 (Ph*C*H_2), 73.4 (CH), 73.2 (CH), 73.1 (Ph*C*H_2), 73.0 (Ph*C*H_2), 71.1 (CH), 69.2 (Gal-C6), 68.6 (CH), 66.3 (CH), 30.3, 29.2, 23.3 (4C, 4 Cy-CH_2), 16.6 (Fuc-C6); Anal. calcd. for $C_{46}H_{56}O_{11}$ + 2/3 H_2O: C 69.33, H 7.25; Found: C 69.39, H 7.22; ESI-MS Calcd for $C_{46}H_{56}NaO_{11}$ $[M+Na]^+$: 807.4; Found: 807.4.

4.10. Benzyl (*2S*)-3-(1-adamantyl)-2-*O*-{1-*O*-[(*1R*,*2R*)-2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-cyclohexyl] 6-*O*-benzyl-β-D-galactopyranos-3-yl}-propionate (22)

Compound **21** (199 mg, 253 μmol) and dibutyltinoxide (69.3 mg, 278 μmol) were dissolved in dry MeOH (15 mL). Activated molecular sieves 3 Å (400 mg) were added to the solution, which was then refluxed under argon for 17 h. Filtration of the suspension over Celite, evaporation of the solvent, and drying for 27 h in high vacuum gave a yellow oily substance (258 mg). This residue was suspended in dry DME (6 mL) under argon.

Extensively dried CsF (50 mg, 0.33 mmol) was added and the reaction mixture was stirred for 25 min at rt. Then, a solution of dry (***R***)-**14** (134 mg, 300 μmol) in dry DME (6 mL) was added to the reaction, which turned turbid upon addition, but cleared again after 2.5 h. After stirring for 4 d at rt, the reaction mixture was concentrated and the residue was purified by two consecutive column chromatographies on silica (1: PE/EE 10/1 to 2/1, 2: DCM/MeOH 50/1) to yield **22** as a white solid (58 mg, 21%) and, as a byproduct, (*S*)-benzyl 3-(1-adamantyl)-2-fluoro-propionate (**23**, 48 mg, 51%). **22**: R_f (PE/EE 2/1) 0.50; $[\alpha]_D^{20}$ −48.3 (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.37–7.20 (m, 25 H, Ar–H), 5.18, 5.11 (A, B of AB, ^2J = 12.2 Hz, 2H, PhCH_2), 4.94 (A′ of A′B′, ^2J = 11.6 Hz, 1H, $PhCH_2$), 4.91 (d, ^3J = 2.5 Hz, 1H, Fuc-H1), 4.80 (A″ of A″B″, ^2J = 11.6 Hz, 1H, $PhCH_2$), 4.75 (A‴ of A‴B‴, ^2J = 12.0 Hz, 1H, $PhCH_2$), 4.68 (m, 2H, $PhCH_2$), 4.60 (B′ of A′B′, ^2J = 11.6 Hz, 1H, $PhCH_2$), 4.54–4.46 (m, 3H, 2H of $PhCH_2$, Lac-H2), 4.43–4.40 (m, 1H, Fuc-H5), 4.28 (d, ^3J = 7.7 Hz, 1H, Gal-H1), 4.04–3.94 (m, 2H, Fuc-H2), 3.85 (d, ^3J = 2.8 Hz, 1H, Gal-H4), 3.79–3.63 (m, 6H, 1H of Cy-CH, Fuc-H3/4, Gal-H2/6a,b), 3.59–3.53 (m, 1H, Cy-CH), 3.48 (t, ^3J = 6.0 Hz, 1H, Gal-H5), 3.27 (dd, ^3J = 3.2, ^3J = 9.2 Hz, 1H, Gal-H3), 2.89 (br s, 1H, OH), 2.48 (br s, 1H, OH), 1.97 (br s, 2H, Cy-CH_2), 1.91 (br s, 3H, Ad-H3), 1.72–1.40 (m, 16H, 1H of Cy-CH_2, 12H of Ad-CH_2, Lac-H3a,b), 1.38–1.09 (m, 4H, 4H of Cy-CH_2), 1.06 (d, ^3J = 6.5 Hz, 3H, Fuc-H6); ^{13}C NMR ($CDCl_3$): δ 174.9 (Lac-C1), 139.2, 138.9, 138.8, 138.2, 135.3 (5C, Bn-C^i), 128.7–126.6 (Ar–C), 100.0 (Gal-C1), 94.9 (Fuc-C1), 81.2 (Gal-C3), 79.7 (CH), 78.1 (CH), 77.2 (CH), 76.32 (CH), 76.28 (CH), 76.1 (PhCH_2), 74.9 (CH), 73.6 (PhCH_2), 73.3 (Gal-C5), 73.0 (PhCH_2), 71.4 (CH), 69.1 (CH_2), 67.1 (Gal-C4), 66.9 (Ph-CH_2–O–CO–), 66.1 (Fuc-C5), 47.8 (Lac-C3), 42.5 (3× Ad-C3), 36.8 (3× Ad-C2), 32.5 (Ad-C1), 29.9 (Cy-CH_2), 29.3 (Cy-CH_2), 28.5 (3× Ad-C4), 23.3 (2× Cy-CH_2), 16.6 (Fuc-C6); ESI-MS Calcd for $C_{66}H_{80}NaO_{13}$ $[M+Na]^+$: 1103.6; Found: 1103.8.

Benzyl (*S*)-3-(1-adamantyl)-2-fluoro-propionate (23). $[\alpha]_D^{20}$ −6.4 (*c* 2.3, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.39–7.33 (m, 5H, Ar–H), 5.23, 5.19 (A, B of AB, ^2J = 12.2 Hz, 2H, PhCH_2), 5.09 (ddd, ^2J(H–F) = 50.2, ^3J = 2.3, ^3J = 9.6 Hz, 1H, H2), 1.97 (br s, 3H, H6), 1.75–1.53 (m, 14H, H3a,b, 12H of Ad-CH_2); ESI-MS Calcd for $C_{20}H_{25}FNaO_2$ $[M+Na]^+$: 339.2; Found: 339.2.

4.11. Lactone derivative of benzyl (*2R*) 3-(1-adamantyl)-2-*O*-{1-*O*-[(*1R*,*2R*) 2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl) cyclohexyl] 6-*O*-benzyl-β-D-galactopyranos-3-yl}-propionate (24)

Compound **24** was prepared in analogy to **22** starting from 21 (51 mg, 65 μmol). Purification by column chromatography (PE/EE 9/1 > 0/10) yielded the pure lactone **24** (62 mg, 25%): $[\alpha]_D^{20}$ −62.4 (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.39–7.26 (m, 20 H, Ar–H), 4.95 (A of AB, ^2J = 13.0 Hz, 1H, $PhCH_2$), 4.93 (d, ^3J = 3.6 Hz, 1H, Fuc-H1), 4.84 (A′ of A′B′, ^2J = 11.7 Hz, 1H, $PhCH_2$), 4.76 (d, A″ of A″B″, ^2J = 11.9 Hz, 1H, $PhCH_2$), 4.70 (B′ of A′B′, ^2J = 12.9 Hz, 1H, $PhCH_2$), 4.67 (B″ of A″B″, ^2J = 12.1 Hz, 1H, $PhCH_2$), 4.61 (B of AB, ^2J = 11.6 Hz, 1H, $PhCH_2$), 4.56–4.50 (m, 2H, Gal-H1, Lac-H2), 4.49 (s, 2H, $PhCH_2$), 4.44 (q, ^3J = 7.1 Hz, 1H, Fuc-H5), 4.37 (t, ^3J = 9.7 Hz, 1H, Gal-H2), 4.15 (s, 1H, Gal-H4), 4.03 (dd, ^3J = 3.5, ^3J = 10.1 Hz, 1H, Fuc-H2), 3.97 (dd, ^3J = 2.7, ^3J = 10.1 Hz, 1H, Fuc-H3), 3.78–3.75 (m, 2H, Cy-CH, Gal-H6a), 3.68–3.59 (m, 4H, Cy-CH, Fuc-H4, Gal-H5/6b), 3.49 (dd, ^3J = 2.9, ^3J = 9.7 Hz, 1H, Gal-H3), 2.36 (br s, 1H, OH), 2.00–1.98 (m, 5H, 2× Cy-CH_2, 3× Ad-H3), 1.84 (dd, ^2J = 14.8, ^3J = 2.0 Hz, 1H, Lac-H3a), 1.73–1.51 (m, 15H, 2H of Cy-CH_2, 12H of Ad-CH_2, Lac-H3b), 1.49–1.17 (m, 4H, 4H of Cy-CH_2), 1.11 (d, ^3J = 6.5 Hz, 3H, Fuc-H6); ^{13}C NMR ($CDCl_3$): δ 169.6 (Lac-C1), 139.2, 138.9, 138.7, 137.5 (4C, Bn-C^i), 128.5–127.2 (Ar–C), 98.1 (Gal-C1), 94.5 (Fuc-C1), 79.7 (Fuc-C3), 78.5 (Cy-CH), 78.2 (Cy-CH), 76.7 (Fuc-C2), 76.4 (Gal-H2), 76.0 (Fuc-H4), 75.7 (Lac-C2), 74.82 (Gal-H3), 74.79 (PhCH_2), 73.7 (CH), 73.0 (2C, PhCH_2), 72.9 (PhCH_2), 68.4 (Gal-C6), 66.9 (Gal-C4), 66.0 (Fuc-C5), 46.9 (Lac-C3), 42.6 (3C, Ad-C3), 36.8 (3C, Ad-C2), 32.4 (Ad-C1), 29.5 (Cy-CH_2), 28.7 (Cy-CH_2), 28.5 (3× Ad-C4), 23.0 (2C, Cy-CH_2), 16.6 (Fuc-C6); ESI-MS Calcd for $C_{59}H_{72}NaO_{12}$ $[M+Na]^+$: 995.5; Found: 995.7.

4.12. Sodium (*2S*) 3-(1-adamantyl)-2-*O*-{1-*O*-[(*1R*,*2R*) 2-*O*-(α-L-fucopyranosyl) cyclohexyl] β-D-galactopyranos-3-yl}-propionate ((*S*)-7)

Compound **22** (26.3 mg, 24 μmol) and $Pd(OH)_2$/C (20 mg) were suspended in dioxane/water (4/1, 3 mL). This suspension was hydrogenated at rt for 3 d. The solvents were removed in vacuo and the residue taken up in MeOH. Filtration over Celite and evaporation of the solvent gave the crude product (22 mg). Purification by column chromatography on silica (DCM/MeOH/H_2O 10/4/0.8), Dowex 50 × 8 ion exchange chromatography (Na^+ form), Sephadex G-15 size exclusion chromatography, and microfiltration afforded (***S***)-**7** (14.8 mg, 92%) as white solid after a final lyophilization from ^{t}BuOH/H_2O. R_f (DCM/MeOH/H_2O 10/4.8/0.5) 0.34; $[\alpha]_D^{20}$ −64.5 (*c* 0.74, MeOH); ^1H NMR (MeOH-d_4): δ 4.86 (m, 1H, Fuc-H1), 4.58 (q, 1H, ^3J = 6.2 Hz, Fuc-H5), 4.32 (d, 1H, ^3J = 7.8 Hz, Gal-H1), 3.96 (d, 1H, ^3J = 8.9 Hz, Lac-H2), 3.89 (dd, 1H, ^3J = 3.3, ^3J = 10.1 Hz, Fuc-H3), 3.84 (d, 1H, ^3J = 2.3 Hz, Gal-H4), 3.76 (m, 1H, Gal-H6a), 3.73–3.65 (m, 4H, 1× Cy-CH, Fuc-H2/4, Gal-H6b), 3.58–3.52 (m, 2H, Gal-H2, 1× Cy-H), 3.47 (t, 1H, ^3J = 6.1 Hz, Gal-H5), 3.23 (dd, 1H, ^3J = 3.0, ^3J = 9.4 Hz, Gal-H3), 2.09–2.03 (m, 2H, Cy-CH_2), 1.93 (br s, 3H, Ad-H3), 1.74–1.61 (m, 14H, 2× Cy-CH_2, 12× Ad-CH_2), 1.60–1.41 (m, 2H, Lac-H3a,b), 1.39–1.25 (m, 4H, 4× Cy-CH_2), 1.18 (d, 3H, ^3J = 6.5 Hz, Fuc-H6); ^{13}C NMR (MeOH-d_4): δ 184.00 (Lac-C1), 102.6 (Gal-C1), 97.0 (Fuc-C1), 84.5 (Gal-C3), 80.2 (Lac-C2), 79.2 (CH), 77.2 (CH), 75.9 (Gal-C5), 73.8 (CH), 71.7 (CH), 71.5 (Fuc-C3), 69.9 (CH), 67.7 (Gal-C4), 67.4 (Fuc-C5), 63.2 (Gal-C6), 50.1 (Lac-C3), 43.9 (3× Ad-C3), 38.2 (3× Ad-C2), 33.5 (Ad-C1), 30.9 (Cy-CH_2), 30.3 (3× Ad-C4), 30.0 (Cy-CH_2), 24.5 (2× Cy-CH_2), 16.6 (Fuc-C6); HR-MS Calcd for $C_{31}H_{49}O_{13}$ $[M-H]^-$: 629.3173; Found: 629.3195.

4.13. Sodium (*2R*)-3-(1-adamantyl)-2-*O*-{1-*O*-[(*1R*,*2R*)-2-*O*-(α-L-fucopyranosyl) cyclohexyl] β-D-galactopyranos-3-yl}-propionate ((*R*)-7)

Hydrogenation was performed in analogy to (*S*)-7. The obtained lactone was opened by stirring in aqueous NaOH overnight at rt. After column chromatography on silica (DCM/MeOH/H_2O 10/4/0.8), (*R*)-7 (8.2 mg, 31%) was obtained as a white solid, which was taken up in MeOH (2 mL), microfiltered, dried, and lyophilized from ^{t}BuOH/H_2O: R_f (DCM/MeOH/H_2O 10/4.8/0.5) 0.58; $[\alpha]_D^{20}$ −31.9 (*c* 0.42, MeOH); ^{1}H NMR (MeOH-d_4): δ 4.89 (m, 1H, Fuc-H1), 4.53 (q, ^3J = 6.4 Hz, 1H, Fuc-H5), 4.33 (d, ^3J = 7.6 Hz, 1H, Gal-H1), 4.25 (d, ^3J = 5.9 Hz, 1H, Lac-H2), 4.09 (d, ^3J = 3.0 Hz, 1H, Gal-H4), 3.87 (dd, ^3J = 3.3, ^3J = 10.1 Hz, 1H, Fuc-H3), 3.80–3.62 (m, 6H, Cy-CH, Fuc-H2/4, Gal-H2/6a,b), 3.58 (dt, ^3J = 3.9, ^3J = 8.8 Hz, 1H, Cy-CH), 3.42 (t, ^3J = 5.7 Hz, 1H, Gal-H5), 3.37 (dd, ^3J = 3.1, ^3J = 9.8 Hz, 1H, Gal-H3), 2.04 (d, *J* = 12.8 Hz, 2H, Cy-CH_2), 1.95 (br s, 3H, Ad-H3), 1.75–1.64 (m, 14H, 2H of Cy-CH_2, 12H of Ad-CH_2), 1.57 (d, *J* = 5.8 Hz, 2H, Lac-H3a,b), 1.45–1.25 (m, 4H, 4H of Cy-CH_2), 1.18 (d, ^3J = 6.6 Hz, 3H, Fuc-H6); ^{13}C NMR (MeOH-d_4): δ 183.7 (Lac-C1), 102.9 (Gal-C1), 97.0 (Fuc-C1), 81.6 (Gal-C3), 79.2 (CH), 77.7 (Lac-C2), 77.0 (Cy-CH), 76.0 (Gal-C5), 73.8 (Fuc-C4), 71.6 (Fuc-C3), 71.5 (Fuc-C2), 70.0 (CH), 67.9 (Gal-C4), 67.4 (Fuc-C5), 62.9 (Gal-C6), 49.5 (Lac-C3), 43.9 (3× Ad-C3), 38.1 (3× Ad-C2), 33.5 (Ad-C1), 30.8 (Cy-CH_2), 30.3 (3C, Ad-C4), 29.7, 24.3, 24.2 (3C, Cy-CH_2), 16.6 (Fuc-C6); ESI-MS Calcd for $C_{31}H_{50}NaO_{13}$ $[M+H]^+$: 653.3; Found: 653.3.

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