Potent E-Selectin Antagonists

by **Rolf Bänteli**[a]), **Peter Herold**[a]), **Christian Bruns**[a]), **John T. Patton**[b]), **John L. Magnani**[b]), and **Gebhard Thoma***[a])[1])

[a]) *Novartis Pharma AG*, P.O. Box, CH-4002 Basel
[b]) *GlycoTech Corporation*, 14915 Broschart Road, Rockville, Maryland 10850, USA

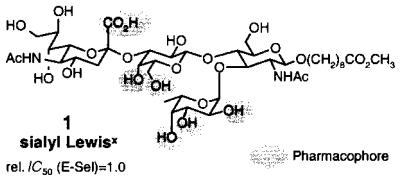
In the search for drugs that could control excessive leukocyte extravasation, we now report on modifications of the already known potent E-selectin antagonist **3** containing a cyclohexyllactic acid residue and a glucal-derived building block. Thus, we describe the synthesis and biological evaluation of a series of derivatives **6** with modified glucal-derived moieties ($CH_2NR^1R^2$ instead of CH_2OH in **3**) to explore a hypothetical potential complementary interaction with E-selectin. However, similar activity profiles of most derivatives **6** and compound **3** do not support such an interaction, but rather indicate topological-structure changes of **6** (and **3**) in the orientation of the neighboring fucose and galactose due to intramolecular steric interactions. The most potent E-selectin antagonist **6v** showed >50-fold improved E-selectin inhibition compared to the weak selectin ligand sialyl Lewis^x (sLe^x, **1**; $IC_{50} = 1000-1500$ μM), but only a 2-fold improvement compared to **3**. Compound **6x** was tested *in vivo* in a murine model of acute inflammation and found to be as potent as **3** ($ED_{50} = 15$ mg/kg).

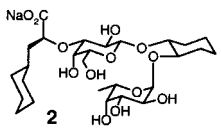
Introduction. – Excessive infiltration of leukocytes from blood vessels into surrounding tissues, mediated by cell-adhesion molecules (CAM) and extracellular matrix proteins, can cause both acute and chronic inflammatory disorders such as reperfusion injuries, psoriasis, rheumatoid arthritis, or respiratory diseases [1]. E- and P-selectin – prominent members of the CAM family – that are expressed on endothelial cells upon stimulation, are involved in an early step of the cascade of events that finally leads to the extravasation of leukocytes [2]. E-Selectin recognizes complex glycoproteins on the leukocyte surface by interacting with the carbohydrate part of the physiological ligand [3]. For P-selectin, additional interactions with sulfated tyrosines have been discussed [4]. It has been indicated that the tetrasaccharide sialyl Lewis^x (sLe^x; **1**) is an epitope of the physiological selectin ligands and is a weak selectin inhibitor itself (E-selectin, $IC_{50} = 1000-1500$ μM) [5]. Simplified, more-potent analogs of the complex tetrasaccharide **1** could be used to control inflammatory disorders and, therefore, are of pharmaceutical interest.

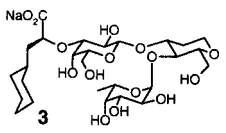
Extensive work elucidated that the essential pharmacophores of sLe^x required to bind to E-selectin are the carboxylic acid function, all three OH groups of the fucose, and the 4-OH and 6-OH groups of galactose. Based on this knowledge, a multitude of small-molecule selectin antagonists have been designed during the last few years. The efforts of the various research groups involved have been summarized in an excellent review [6]. The E-selectin antagonist **2** with 10-fold improved activity compared to sLe^x (**1**) was obtained by concomitant replacement of sialic acid by cyclohexyllactic acid and

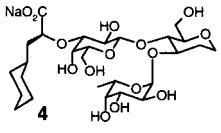
[1]) E-mail: gebhard.thoma@pharma.novartis.com

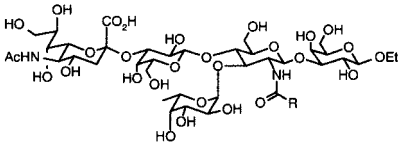
of N-acetylglucosamine by cyclohexanediol [7]. Upon incorporation of a glucal-derived building block instead of the expensive chiral cyclohexanediol, we discovered compound **3**, which was even more potent than **2** (3-fold improvement in a static assay; 6-fold improvement in a dynamic flow assay) [8]. Possible explanations are additional direct interactions with E-selectin or conformational changes of **3** compared to **2**. Interestingly, the regioisomer **4** of antagonist **3** did not show improved potency as compared to **2** [9].



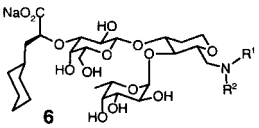








5 a R = 2-napthyl
b R = Ph
c R = cyclohexyl



Recently, *Ramphal et al.* have reported on *N*-acylglucosamine derivatives **5** of sLe^x [10]. Aromatic residues such as 2-naphthyl in **5a** and phenyl in **5b** led to 10- and 3-fold improved affinities, respectively, compared to sLe^x, whereas the corresponding cyclohexyl derivative **5c** was less active than sLe^x. Since these compounds showed essentially the same topological-structure as sLe^x, the effect was attributed to an additional interaction between aromatic residues and a new binding site on E-selectin [10]. Current models of ligand binding on E-selectin do not account for a complementary lipophilic binding site but, due to the lack of an X-ray crystal structure of a ligand/E-selectin complex, these models are mainly based on indirect evidence obtained from the X-ray structure of the lectin domain of E-selectin, molecular modeling, and NMR studies [11].

It has been shown that the bound conformations of sLe^x and antagonist **2** on E-selectin are very similar [11c, d]. Assuming related bioactive conformations of **3** and **2** and of sLe^x and **5**, we concluded that the CH_2OH group of the glucal-derived moiety of **3** and the aromatic residues of sLe^x derivatives **5** point in the same direction and address the same area of the protein. Thus, suitable substituents at this position of **3** could lead

to compounds with improved affinity. Since **3** seems to be more potent than **5a**[2]), derivatives of **3** could be expected to be highly active E-selectin antagonists. To explore the hypothesis of a potential complementary binding site of E-selectin, we decided to prepare a series of compounds **6** with various substituents in the glucal-derived portion.

In this paper, we describe the synthesis of antagonists **6** and their biological evaluation in both static and dynamic E-selectin *in vitro* assays. Most compounds **6** showed a similar activity profile to that of **3**. The best antagonist **6v** exhibited a >50-fold improved E-selectin inhibition compared to sLe^x (**1**), but only a 2-fold improvement compared to **3**. These findings do not support the hypothesis of a complementary hydrophobic binding site of E-selectin, but rather indicate topolocial-structure changes in the orientation of the neighboring fucose and galactose due to intramolecular steric interactions in **3** and **6**.

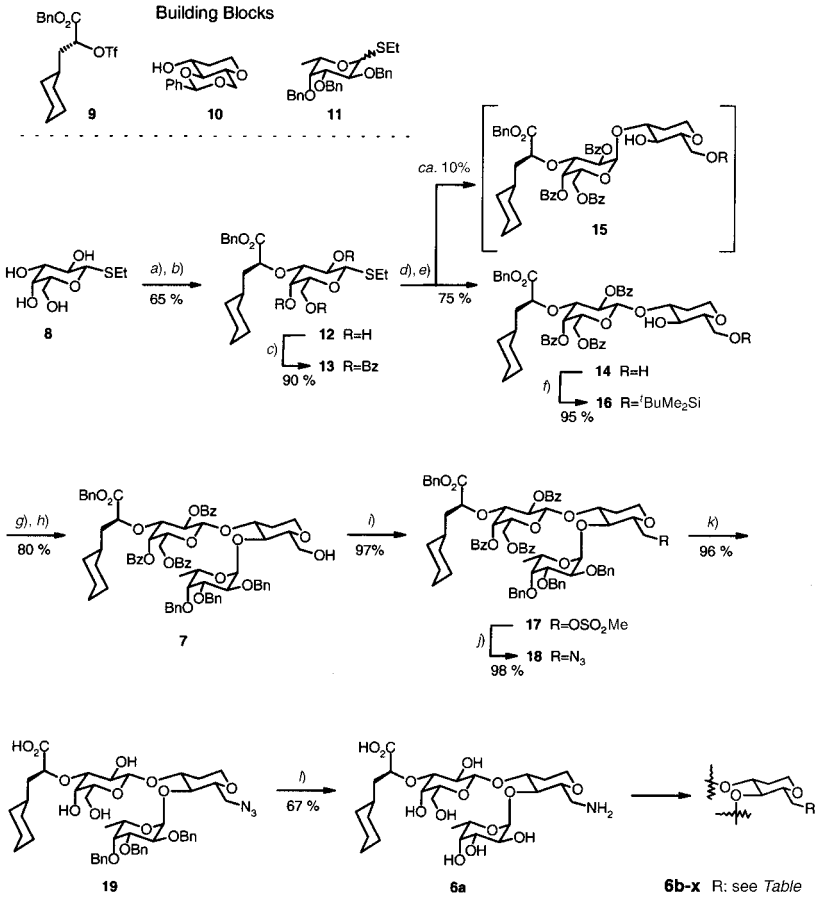
Synthesis. – To modify the glucal-derived portion of compound **3** in a convergent manner, we required a selectively protected advanced intermediate with a free primary OH group, such as **7**. Thus, the previously developed synthesis that readily gave access to antagonist **3** could not be applied [8]. The newly developed synthesis is depicted in the *Scheme*. Compound **7** was prepared from thiogalactoside **8** [12], cyclohexyllactic acid derivative **9** [8], glucal-derived building block **10** [8], and thiofucoside **11** [13] (*Scheme*). Tin-mediated alkylation of **8** with **9**, followed by benzoylation of intermediate **12**, gave the modified galactose donor **13**. Glycosylation of acceptor **10** and subsequent removal of the benzylidene acetal afforded disaccharide **14**. Surprisingly, in addition to the desired product **14**, we isolated 10–15% of the corresponding α-D-anomer **15**. This was unexpected since the neighboring-group participation of the benzoate in the 2-position of donor **13** should selectively lead to the β-D-glycosidic linkage. The stereoisomers were separated by chromatography. Next, the primary OH group of **14** was silyl-protected to give **16**, which was fucosylated using thioglycoside **11**. Donor **11** was transformed into the corresponding glycosyl bromide, which gave, under *in situ* anomerization conditions in the presence of Et_4NBr, exclusively the α-L-fucoside. Desilylation of the crude material with Bu_4NF led to partial cleavage of the sensitive α-L-glycosidic bond between fucose and galactose, but treatment with H_2SiF_6 [14] furnished compound **7** in 80% yield over 2 steps. Comparable yields were obtained using α- or β-L-thiofucoside **11**. The selectively protected, advanced intermediate **7** was readily available in multi-gram quantities.

The unprotected primary OH group of **7** was converted to an amino function by preparing mesylate **17**, which was subsequently transformed into azide **18**. Saponification gave **19** which was completely deprotected by subsequent hydrogenation to furnish amino acid **6a**. Compound **6a** is available from thiogalactoside **8** in 12 steps with an overall yield of 20%. Several analogs such as amines **6b** and **6c**, derivatives with negatively charged residues **6d** and **6e**, amides with aromatic residues **6f**–**p**, aliphatic amides **6q** and **6r**, sulfonamide **6s**, ureas **6t** and **6u**, and carbamates **6v**–**x** were prepared from **6a**. The yields of **6b**–**x** are given in the *Table*, and the conditions for the individual transformations are described in detail in the *Exper. Part.*

---

[2]) It is worth noting that compounds **5** and **3** have been tested in different assays. Comparison of affinities could be misleading, even though sLe^x was used as a reference in both assay formats.

Scheme



a) Bu_2SnO, MeOH, *Δ*. *b*) **9**, CsF, $MeOCH_2CH_2OMe$. *c*) BzCl, *N*,*N*-dimethylpyridin-4-amine (DMAP), Py. *d*) **10** *N*-iodosuccinimide (NIS), TfOH, CH_2Cl_2. *e*) AcOH, H_2O, *Δ*. *f*) ^{t}BuMe$_2$SiCl, Py. *g*) **11**, Br_2, Et_4NBr, CH_2Cl_2/DMF. *h*) $H_2SiF_6Et_3N$, MeCN. *i*) $MeSO_2Cl$, Py. *j*) NaN_3, DMF. *k*) LiOH, H_2O, MeOH. *l*) H_2, 10% Pd/C, dioxane, H_2O.

Biological Evaluation. – All compounds **6** were tested at least twice in a competitive, cell-free assay that measures E-selectin inhibition under equilibrium conditions [15]. E-Selectin/hIg chimera is immobilized on microtiter plates and incubated with a biotinylated polylysine-sLe^a conjugate. The displacement of this multivalent ligand by E-selectin inhibitors was monitored and quantified to determine their IC_{50} values (concentration to achieve 50% displacement of the polymer). To compare the data for different compounds obtained on different test plates, sLe^x (**1**) was assayed on each plate as a reference. This allows the determination of IC_{50} values relative to sLe^x, which are defined as rel. $IC_{50} = IC_{50}$(test compound)/IC_{50}(sLe^x).

Since E-selectin-mediated rolling of leucocytes on activated endothelium is expected to be a nonequilibrium process, we also used a cell-based flow assay to

Table. *Compositon and E-Selectin Inhibition Data of Compounds* **3** *and* **6a–x**

	6-Substituent of the glucal-derived moiety	Yield [%]	Static assay rel. IC_{50}[a])	Flow assay [% red. of *NIC*][b]) at 50 μM (rel. red. *NIC*)[c])
3	OH		0.032	60% (1.36)
6a	NH_2	78	0.404	n.d.
6b	$NHCH_2Ph$	14	0.693	n.d.
6c	$N(CH_2Ph)_2$	36	0.520	n.d.
6d	$NHSO_3Na$	46	0.046	36% (0.68)
6e	NHCO-C_6H_4–COOH (*ortho*)	27	0.032	66% (1.30)
6f	NHCOPh	40	0.034	n.d.
6g	NHCO–C_6H_4–Cl (*para*)	55	0.031	78% (1.03)
6h	NHCO–C_6H_4–OMe (*para*)	40	0.031	85% (1.12)
6i	NHCO–C_6H_4–NO_2 (*para*)	51	0.057	78% (1.04)
6j	NHCO–C_6H_4–Ph (*para*)	46	0.065	70% (1.43)
6k	NHCO–$C_6H_3(OMe)_2$ (*meta*, *para*)	82	0.024	62% (0.84)
6l	NHCO(2-naphthyl)	78	0.028	70% (1.00)
6m	NHCO–C_6H_4–OCH_2Ph (*para*)	79	0.075	n.d.
6n	$N(CH_2Ph)COPh$	48	0.084	n.d.
6o	$NHCOCH_2CH_2Ph$	49	0.094	n.d.
6p	$NHCOCHPh_2$	79	0.028	70% (0.95)
6q	NHCOMe	46	0.038	41% (0.57)
6r	NHCO(cyclo-C_6H_{11})	89	0.044	38% (0.71)
6s	$NHSO_2$–C_6H_4–Me (*para*)	42	0.039	74% (1.20)
6t	NHCONHEt	64	0.053	51% (0.82)
6u	NHCONHPh	42	0.045	68% (0.88)
6v	$NHCOOCH_2$–C_6H_4–NO_2 (*para*)	50	0.017	87% (0.98)
6w	$NHCOOCH_2$(2-naphthyl)	30	0.021	92% (1.03)
6x	$NHCOOCH_2Ph$	72	0.034	82% (1.06)

[a]) Relative IC_{50} values are defined as rel. $IC_{50} = IC_{50}$(test compound)/$IC_{50}(sLe^x)$; sLe^x (**1**) was tested as a reference on each plate to allow direct comparison of data from different test plates; compounds were tested at least twice (mean value). [b]) Reduction of the number of interacting cells (*NIC*). [c]) Relative reductions of the number of interacting cells (*NIC*) are defined as rel. red. *NIC* = red. (compound at 50 μM)/reduction (**2** at 200 μM). On each test day, **2** was tested as a reference to be able to compare data from individual test days and different cell cultures.

characterize antagonists **6** (*Fig.*) [16]. This dynamic *in vitro* assay monitors the rolling of polymorphonuclear neutrophils (PMN) on stimulated human umbilical vein endothelium cells (HUVEC) under hydrodynamic shear stress and, thus, mimics *in vivo* conditions. The reduction of the number of interacting cells (*NIC*) serves as a measure to determine the inhibitory potential of a test compound. The assay is labor-intensive, and only 4–5 compounds can be tested on a single day. New HUVECs from different sources are used on each test day. This can affect the E-selectin expression levels and, consequently, causes different assay sensitivities on individual test days. To allow a more accurate comparison of the data obtained on individual test days, compound **2** was used as a reference and assayed on each test day at 200 μM along with the test compounds. The test compounds were assayed at 50 μM. The relative reduction of the number of interacting cells (rel. red. *NIC*) of an antagonist with respect to **2** is defined as rel. red. *NIC* = red. *NIC*(test compound at 50 μM)/red. *NIC*(**2** at 200 μM). The dynamic cell assay was performed for the compounds that showed promising

affinities in the primary, static assay. The *in vitro* data for E-selectin inhibitors **6a**–**x** are given in the *Table* and are compared to **3**.

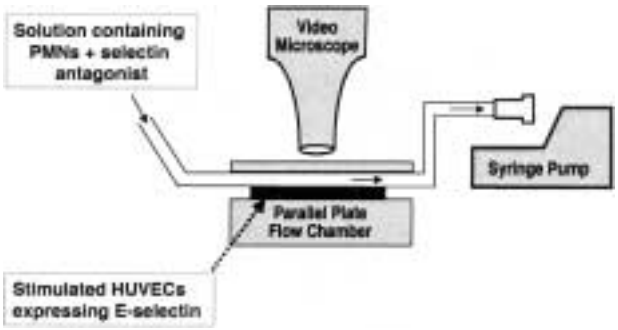


Figure. *Cell-based E-selectin flow assay*

The amines **6a**–**c** showed similar activities in the static assay (rel. $IC_{50} = 0.4-0.7$), despite of their different substitution patterns. They were more potent than sLe^x (2-fold), but significantly less active than **3** (10-fold). Unfavorable steric and/or electronic interactions of the substituents with E-selectin are not probable since, in case of direct contact with the protein, the different steric demands of the substituents should be reflected by less-uniform bioactivities. It is more likely that intramolecular electrostatic interactions between the amine and the carboxylic acid unfavorably affect the conformations of these antagonists. The dependence of the potency of E-selectin antagonists on their conformation in solution has been outlined earlier [7]. Due to their relatively weak affinities, these compounds have not been tested in the flow assay. Interestingly, analogs with an additional negatively charged substituent, such as **6d** and **6e** (rel. $IC_{50} = 0.046$ and 0.032, resp.), were much more potent than the amines but did not exhibit improved affinities compared to **3** (rel. $IC_{50} = 0.032$). In the flow assay, antagonist **6e** was as potent as **3**, whereas **6d** was less active.

The amides **6f**–**p** with various aromatic substituents showed good affinities to E-selectin within a relatively narrow range (rel. $IC_{50} = 0.024-0.094$), but compared to **3** (rel. $IC_{50} = 0.032$), no substantial improvement could be achieved. Surprisingly, the aliphatic amides **6q** and **6r** were found to be as active as the aromatic derivatives. Comparable affinities were observed for naphthalene-2-carboxamide **6l** (rel. $IC_{50} = 0.028$) and cyclohexanecarboxamide **6r** (rel. $IC_{50} = 0.044$), contrary to the results for the corresponding sLe^x derivatives **5**. In the flow assay, the aliphatic amides **6q** and **6r** were found to be slightly less-potent than **3**, whereas the compounds with aromatic substituents showed very similar activities. Our findings seem to contradict the results reported by *Ramphal et al.*, but it has to be considered that we investigated substantially modified sLe^x mimics that could behave differently than the *N*-acyl-substituted sLe^x pentasaccharides **5**. For example, in **6**, the amide function is separated from the six-membered ring by a CH_2 group inducing a higher degree of flexibility than in **5** where it is directly attached to the ring.

The aromatic sulfonamide **6s** (rel. $IC_{50} = 0.039$), and the ureas **6t** and **6u** (rel. $IC_{50} = 0.045-0.053$) were found to be similarly as potent as **3**. The most-active compounds obtained were among the carbamates. Antagonist **6v** showed 2-fold-improved potency

(rel. $IC_{50} = 0.017$) compared to **3**, while **6w** (rel. $IC_{50} = 0.021$) was slightly more active than **3**, and **6x** was equally active (rel. $IC_{50} = 0.034$). Generally, the data from the static assay could be confirmed by the flow assay.

The *in vivo* efficacy of carbamate **6x** was tested in a murine peritonitis model and compared to the more hydrophilic compound **3** [17]. The migration of leukocytes in response to an acute inflammatory stimulus was assessed by intraperitoneal injection of thioglycollate followed by an appropriate incubation. Peritonitis was induced in female NMRI mice (22–25 g) by intraperitoneal (i.p.) injection of 1 ml of 3% thioglycolate in 0.9% (*w*/*v*) NaCl solution. Negative-control mice received an injection of sterile saline only. The total number of PMNs in the peritoneal exudates increased 13-fold within 3 h of thioglycolate treatment. Animals were killed 3 h post injection and the peritoneal cavity lavaged with 5 ml of ice-cold PBS (containing 188 U/ml of heparin). Total cell counts were performed and cytospins prepared for differential cell counting to determine the number of neutrophils transmigrated into the peritoneum. Neutrophil infiltration of the inflamed peritoneum was dose-dependently inhibited by the *anti*-E-selectin antibody 10E9.6, resulting in a complete inhibition of the thioglycolate-induced peritonitis at 30 μg/mouse ($ED_{50} = 5$ μg/mouse). In contrast, injection of a negative IgG control antibody (10 μg/mouse) did not alter thioglycolate-induced neutrophil influx. The demonstration that thioglycolate-induced cell influx can be inhibited by a specific *anti*-E-selectin antibody provides proof-of-concept that the peritonitis model can be used to test small-molecular-weight selectin inhibitors. Test compounds were administered i.p. at the time of thioglycolate stimulation. Compound **3** showed promising activity in this model earlier ($ED_{50} = 15$ mg/kg) [8]. Compound **6x** was found to inhibit the transmigration of PMNs into the peritoneum during thioglycolate-induced acute inflammation with equal efficacy ($ED_{50} = 15$ mg/kg), whereas sLe^x was ineffective at doses up to 100 mg/kg.

Conclusion. – Similar affinity profiles of E-selectin antagonist **3** and a series of derivatives **6** with modifications in the glucal-derived moiety do not support the hypothesis of an additional interaction of the substituent with a complementary lipophilic binding site. It is more likely that a steric interaction of the CH_2R substituent of compounds **3** and **6** with the neighboring fucose may affect the solution conformation of these compounds, as suggested by a strong NOE between the CH_2 protons of the CH_2R substituent and H–C(1) of the fucose. We are currently investigating this hypothesis. Antagonist **6v** showed >50-fold improved potency compared to sLe^x, but only 2-fold improved potency compared to compound **3**. A variety of substituents are tolerated without losing affinity, allowing for the modification of pharmacokinetic properties.

Experimental Part

General. All reactions were carried out under dry Ar. Commercially available abs. solvents were used. Column chromatography = CC, flash chromatography = FC. NMR Spectra: *Bruker-Avance-DPX-400* spectrometer; assignments by 2-D $^1H,^1H$ correlation (COSY) and $^1H,^{13}C$ correlation (HSQC); δ in ppm rel. to $SiMe_4$, *J* in Hz; Chx = cyclohexyl, Hex = *arabino*-D-hexitol. MS: *Finnigan-MAT-90* mass spectrometer.

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-6-amino-1,5-anhydro-2,6-dideoxy*-D-arabino-*hexitol* (**6a**). To a soln. of **19** (8.45 g, 9.33 mmol) in dioxane (250 ml) and H_2O (50 ml), 10% Pd/C (3.4 g) was added. The suspension was stirred vigorously for 20 h

under H_2 and then filtered through *Celite*® (washing with dioxane). The pH of the filtrate was brought from 6 to 5 by adding AcOH (4 ml). After addition of fresh catalyst (10% Pd/C (3.4 g) suspended in H_2O (20 ml)), hydrogenation was continued for 20 h. Filtration (*Celite*®), evaporation and CC (silica gel (300 g), AcOEt/^{i}PrOH/H_2O 2:2:1) yielded 3.82 g (67%) of **6a**. ^{1}H-NMR (400 MHz, D_2O): 0.7–0.95 (*m*, 2 H); 0.95–1.2 (*m*, 3 H) and 1.35–1.75 (*m*, 9 H) (H_{ax}–C(2)(Hex), CH_2(Chx)); 1.10 (*d*, *J* = 6.5, Me(6)(Fuc)); 2.07–2.2 (*m*, H_{eq}–C(2)(Hex)); 3.0–3.15 (*m*, 1 H–C(6)(Hex)); 3.29 (*dd*, *J* = 10.0, 3.5, H–C(3)(Gal)); 3.3–3.6 (*m*, 1 H–C(1)(Hex), H–C(4)(Hex), H–C(5)(Hex), 1 H–C(6)(Hex), H–C(2)(Gal), H–C(5)(Gal)); 3.6–3.65 (*m*, 2 H–C(6)(Gal)); 3.65–3.73 (*m*, H–C(2)(Fuc), H–C(4)(Fuc)[3])); 3.73–3.83 (*m*, H–C(4)(Gal), H–C(3)(Fuc)); 3.83–3.9 (*m*, OC*H*CO_2H); 3.9–4.02 (*m*, 1 H–C(1)(Hex), H–C(3)(Hex)); 4.42 (*d*, *J* = 8.0, H–C(1)(Gal)); 4.58 (*q*, *J* = 6.5, H–C(5)(Fuc)); 4.80 (*d*, *J* = 3.5, H–C(1)(Fuc)). HR-MS: 610.3079 ($C_{27}H_{48}NO_{14}^+$, $[M+H]^+$; calc. 610.3075).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1→3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1→4)]-1,5-anhydro-2,6-dideoxy-6-[(phenylmethyl)amino]*-D-arabino-*hexitol* (**6b**) *and* O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1→3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1→4)]-1,5-anhydro-6-[bis(phenylmethyl)amino]-2,6-dideoxy*-D-arabino-*hexitol* (**6c**). To a mixture of **6a** (40 mg, 0.066 mmol), benzaldehyde (0.033 ml, 0.328 mmol), and freshly dried 4-Å molecular sieves (*ca.* 500 mg) in dry MeOH (0.5 ml), borane-pyridine complex ($BH_3 \cdot C_5H_5N$; 0.013 ml, 0.131 mmol) was added. After 20 h, the mixture (2 new products) was filtered and evaporated and the residue separated by FC (silica gel, AcOEt/^{i}PrOH/H_2O 4:2.1): **6c** and then **6b**. Each was separately further purified by gel filtration (*P2*, H_2O) and by ion-exchange chromatography (*Dowex* (Na^+ form), H_2O) and then freeze-dried: **6c** (17 mg, 36%) and **6b** (6.4 mg, 14%), resp., both as white foams.

Data of **6b**: ^{1}H-NMR (400 MHz, D_2O): 0.72–0.92 (*m*, 2 H); 0.95–1.21 (*m*, 6 H, including a *d* at 1.09, *J* = 7, Me(6)(Fuc)); 1.38–1.72 (*m*, 8 H); 1.65–1.73 (*m*, 1 H); 2.08–2.18 (*m*, 1 H); 3.18 (*dd*, *J* = 10, 12, 1 H); 3.29 (*dd*, *J* = 10, 3, H–C(3)(Gal)); 3.32–3.44 (*m*, 2 H); 3.45–3.59 (*m*, 4 H); 3.59–3.68 (*m*, 3 H); 3.69 (*d*, 1 H); 3.73 (*dd*, *J* = 3, 11, H–C(3)(Fuc)); 3.81 (*d*, *J* = 3, H–C(4)(Gal)); 3.48–4.00 (*m*, 3 H); 4.14 (*d*, *J* = 12, 1 H, PhCH_2); 4.19 (*d*, *J* = 12, 1 H, PhCH_2); 4.41 (*d*, *J* = 8, H–C(1)(Gal)); 4.52 (*q*, *J* = 7, H–C(5)(Fuc)); 4.72 (*d*, *J* = 4, H–C(1)(Fuc)); 7.38 (*m*, 5 H). HR-MS: 698.3380 ($C_{34}H_{52}NO_{14}^-$, $[M-Na]^-$; calc. 698.3388).

Data of **6c**: The ^{1}H-NMR showed broad signals that were shifted in different measurements; a total of 2 H were missing in the region 3.0–4.7 ppm, probably due to signal broadening. ^{1}H-NMR (400 MHz, D_2O): 0.75–0.92 (*m*, 2 H); 0.97–1.22 (*m*, 6 H, including a *d* at 1.08, *J* = 7, Me(6)(Fuc)); 1.38–1.73 (*m*, 8 H); 1.65–1.74 (*m*, 1 H); 2.02–2.12 (*m*, 1 H); 3.19–3.37 (*m*, 3 H); 3.37–3.58 (*m*, 3 H); 3.58–3.78 (*m*, 7 H); 3.81 (*d*, *J* = 3, H–C(4)(Gal)); 3.83–3.93 (*m*, 2 H); 4.12–4.46 (*m*, 3 H); 4.37 (*d*, *J* = 8, H–C(1)(Gal)); 4.43 (*q*, *J* = 7, H–C(5)(Fuc)); 4.64 (*d*, *J* = 4, H–C(1)(Fuc)); 7.41 (*m*, 10 H). HR-MS: 788.3862 ($C_{41}H_{58}NO_{14}^-$, $[M-Na]^-$; calc. 788.3857).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1→3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1→4)]-1,5-anhydro-2,6-dideoxy-6-(sulfoamino)*-D-arabino-*hexitol Sodium Salt* (**6d**). To a soln. of **6a** (20 mg, 0.033 mmol) in H_2O (2 ml) with enough 2N NaOH to obtain a pH > 11, commercially available sulfur trioxide pyridine complex (7.8 mg, 0.049 mmol, 1.5 equiv.) was added. After 16 h, another portion of sulfur trioxide pyridine complex (7.8 mg, 0.049 mmol, 1.5 equiv.) was added. After 40 h, the mixture was evaporated and the residue purified by gel filtration (*P2*, *BioRad*, H_2O) and CC (*RP C18*, *SepPack* syringe adapter, step gradient MeCN/H_2O 1:9, 2:8, 3:7, 4:6, 5:5, 7:3, and 9:1) and freeze-dried: **6d** (10.6 mg, 46%). White foam. ^{1}H-NMR (400 MHz, D_2O): 0.75–0.92 (*m*, 2 H); 1.00–1.21 (*m*, 6 H, including a *d* at 1.12, *J* = 7, Me(6)(Fuc)); 1.39–1.63 (*m*, 8 H); 1.66–1.74 (*m*, 1 H); 2.08–2.17 (*m*, 1 H); 3.12 (*dd*, *J* = 7, 12, 1 H); 3.30 (*dd*, *J* = 10, 3, H–C(3)(Gal)); 3.32–3.48 (*m*, 4 H); 3.48–3.58 (*m*, 2 H); 3.59–3.67 (*m*, 2 H); 3.67–3.73 (*m*, H–C(4)(Fuc), H–C(2)(Fuc)); 3.78 (*dd*, *J* = 3, 11, H–C(3)(Fuc)); 3.82 (*d*, *J* = 3, H–C(4)(Gal)); 3.86–3.99 (*m*, 3 H); 4.42 (*d*, *J* = 8, H–C(1)(Gal)); 4.68 (*q*, *J* = 7, H–C(5)(Fuc)); 4.98 (*d*, *J* = 4, H–C(1)(Fuc)). HR-MS: 688.2491 ($C_{27}H_{46}NO_{17}S^-$, $[M-2\,Na+H]^-$; calc. 688.2486).

General Procedure (*G.P.*) *for the Synthesis of Amides* **6e**–**r** *and Carbamates* **6v**–**x**. To a soln. of **6a** (20 mg, 0.033 mmol) in THF/H_2O 1:1 (2 ml) at 0°, a soln. of commercially available acid chloride (0.049 mmol, 1.5 equiv.) in THF (0.5 ml) was added. The pH of the mixture was adjusted to 8–10 by the addition of 1N NaOH and maintained at 8–10 throughout the reaction. If necessary, additional acid chloride (0.016 mmol, 0.5 equiv.) was added after 1–4 h, and after a total of 2–42 h, the mixture was partially evaporated to remove THF. The now aq. soln. was purified by applying one or more of the following three purification methods, as needed, to get

[3] 6-Deoxy-α-L-galactopyranose refers to α-L-fucopyranose (Fuc).

a pure product: FC (silica gel, AcOEt/^{i}PrOH/H_2O 4:2:1) and/or CC (*RP C18*, column 1 × 10 cm, MeCN/H_2O 3:7, then MeCN/H_2O 4:6), and/or gel filtration (*P2*, *BioRad*, H_2O). The product obtained was freeze dried: white foam.

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-6-[(2-carboxybenzoyl)amino]-2,6-dideoxy*-D-arabino-*hexitol* (**6e**). According to the *G.P.* FC, gel filtration, and CC gave 10.3 mg (27%) of **6e**. ^{1}H-NMR (400 MHz, D_2O): 0.75–0.90 (*m*, 2 H); 1.00–1.2 (*m*, 6 H, including a *d* at 1.12, *J* = 7, Me(6)(Fuc)); 1.39–1.65 (*m*, 8 H); 1.65–1.73 (*m*, 1 H); 2.10–2.18 (*m*, 1 H); 3.30 (*dd*, *J* = 10, 3, H–C(3)(Gal)); 3.36–3.58 (*m*, 6 H); 3.58–3.65 (*m*, 2 H); 3.68–3.75 (*m*, H–C(4)(Fuc), H–C(2)(Fuc)); 3.75–3.83 (*m*, 3 H); 3.83–4.04 (*m*, 3 H); 4.42 (*d*, *J* = 8, H–C(1)(Gal)); 4.64 (*q*, *J* = 7, H–C(5)(Fuc)); 4.91 (*d*, *J* = 4, H–C(1)(Fuc)); 7.35–7.44 (*m*, 3 H); 7.49 (*d*, *J* = 7, 1 H). HR-MS: 756.3080 ($C_{35}H_{50}NO_{17}^-$, $[M-Na]^-$; calc. 756.3079).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-6-(benzoylamino)-2,6-dideoxy*-D-arabino-*hexitol* (**6f**). According to the *G.P.* FC followed by gel filtration gave 9.7 mg (40%) of **6f**. ^{1}H-NMR (400 MHz, D_2O): 0.73–0.92 (*m*, 2 H); 1.00–1.21 (*m*, 6 H, including a *d* at 1.13, *J* = 7, Me(6)(Fuc)); 1.39–1.65 (*m*, 8 H); 1.65–1.73 (*m*, 1 H); 2.10–2.18 (*m*, 1 H); 3.32 (*dd*, *J* = 10, 3, H–C(3)(Gal)); 3.36–3.69 (*m*, 8 H); 3.68–3.75 (*m*, H–C(4)(Fuc), H–C(2)(Fuc)); 3.80 (*dd*, *J* = 3, 11, H–C(3)(Fuc)); 3.75–3.88 (*m*, 2 H, including a *d* at 3.85, *J* = 3, H–C(4)(Gal)); 3.90–4.04 (*m*, 3 H); 4.42 (*d*, *J* = 8, H–C(1)(Gal)); 4.64 (*q*, *J* = 7, H–C(5)(Fuc)); 4.93 (*d*, *J* = 4, H–C(1)(Fuc)); 7.42 (*t*, *J* = 7, 2 H); 7.52 (*m*, 1 H); 7.66 (*d*, *J* = 7, 2 H). HR-MS: 712.3178 ($C_{34}H_{50}NO_{15}^-$, $[M-Na]^-$, calc. 712.3180).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-6-[(4-chlorobenzoyl)amino]-2,6-dideoxy*-D-arabino-*hexitol* (**6g**). According to the *G.P.* FC gave 13.8 mg (55%) of **6g**. ^{1}H-NMR (400 MHz, D_2O): 0.72–0.92 (*m*, 2 H); 1.00–1.21 (*m*, 6 H, including a *d* at 1.10, *J* = 7, Me(6)(Fuc)); 1.37–1.65 (*m*, 8 H); 1.65–1.73 (*m*, 1 H); 2.10–2.18 (*m*, 1 H); 3.30 (*dd*, *J* = 10, 3, H–C(3)(Gal)); 3.35–3.68 (*m*, 8 H); 3.68–3.73 (*m*, H–C(4)(Fuc), H–C(2)(Fuc)); 3.78 (*dd*, *J* = 3, 11, H–C(3)(Fuc)); 3.75–3.83 (*m*, 2 H, including a *d* at 3.81, *J* = 3, H–C(4)(Gal)); 3.84–4.04 (*m*, 3 H); 4.42 (*d*, *J* = 8, H–C(1)(Gal)); 4.63 (*q*, *J* = 7, H–C(5)(Fuc)); 4.92 (*d*, *J* = 4, H–C(1)(Fuc)); 7.42 (*m*, 2 H); 7.62 (*m*, 2 H). HR-MS: 746.2789 ($C_{34}H_{49}ClNO_{15}^-$, $[M-Na]^-$; calc. 746.2791).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-2,6-dideoxy-6-[(4-methoxybenzoyl)amino]*-D-arabino-*hexitol* (**6h**). According to the *G.P.* FC gave 10.3 mg (40%) of **6h**.^{1}H-NMR (400 MHz, D_2O): 0.75–0.92 (*m*, 2 H); 1.00–1.21 (*m*, 6 H, including a *d* at 1.10, *J* = 7, H–C(6)(Fuc)); 1.39–1.65 (*m*, 8 H); 1.65–1.73 (*m*, 1 H); 2.11–2.18 (*m*, 1 H); 3.30 (*dd*, *J* = 10, 3, H–C(3)(Gal)); 3.35–3.68 (*m*, 8 H); 3.68–3.73 (*m*, H–C(4)(Fuc), H–C(2)(Fuc)); 3.78 (*dd*, *J* = 3, 11, H–C(3)(Fuc)); 3.79 (*s*, MeO); 3.75–3.83 (*m*, 2 H, including a *d* at 3.81, *J* = 3, H–C(4)(Gal)); 3.85–4.04 (*m*, 3 H); 4.42 (*d*, *J* = 8, H–C(1)(Gal)); 4.63 (*q*, *J* = 7, H–C(5)(Fuc)); 4.92 (*d*, *J* = 4, H–C(1)(Fuc)); 6.98 (*m*, 2 H); 7.66 (*m*, 2 H). HR-MS: 742.3282 ($C_{35}H_{52}NNaO_{16}^-$, $[M-Na]^-$; calc. 742.3286).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-2,6-dideoxy-6-[(4-nitrobenzoyl)amino]*-D-arabino-*hexitol* (**6i**). According to the *G.P.* FC gave 13 mg (51%) of **6i**. ^{1}H-NMR (400 MHz, D_2O): 0.75–0.90 (*m*, 2 H); 0.96–1.21 (*m*, 6 H, including a *d* at 1.10, *J* = 7, Me(6)(Fuc)); 1.36–1.64 (*m*, 8 H); 1.64–1.72 (*m*, 1 H); 2.08–2.18 (*m*, 1 H); 3.29 (*dd*, *J* = 10, 3, H–C(3)(Gal)); 3.35–3.68 (*m*, 5 H); 3.58–3.74 (*m*, 5 H); 3.76–3.83 (*m*, 2 H, H–C(4)(Gal)); 3.84–4.04 (*m*, 4 H); 4.42 (*d*, *J* = 8, H–C(1)(Gal)); 4.63 (*q*, *J* = 7, H–C(5)(Fuc)); 4.92 (*d*, *J* = 4, H–C(1)(Fuc)); 7.83 (*m*, 2 H); 8.25 (*m*, 2 H). HR-MS: 757.3026 ($C_{34}H_{49}N_2O_{17}^-$, $[M-Na]^-$; calc. 757.3031).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-6-([1,1′-biphenyl]-4-ylamino)-2,6-dideoxy*-D-arabino-*hexitol* (**6j**). According to the *G.P.* FC followed by gel filtration gave 12 mg (46%) of **6j**. ^{1}H-NMR (400 MHz, D_2O): 0.78–0.95 (*m*, 2 H); 1.00–1.22 (*m*, 6 H, including a *d* at 1.13, *J* = 7, Me(6)(Fuc)); 1.40–1.68 (*m*, 8 H); 1.68–1.76 (*m*, 1 H); 2.13–2.21 (*m*, 1 H); 3.32 (*dd*, *J* = 10, 3, H–C(3)(Gal)); 3.38–3.62 (*m*, 5 H); 3.62–3.72 (*m*, 3 H); 3.72–3.80 (*m*, H–C(4)(Fuc), H–C(2)(Fuc)); 3.80–4.08 (*m*, 6 H); 4.45 (*d*, *J* = 8, H–C(1)(Gal)); 4.66 (*q*, *J* = 7, H–C(5)(Fuc)); 4.97 (*d*, *J* = 4, H–C(1)(Fuc)); 7.42 (*m*, 1 H); 7.48 (*t*, *J* = 7, 2 H); 7.65–7.75 (*m*, 4 H); 7.78 (*d*, *J* = 7, 2 H). HR-MS: 812.3471 ($C_{40}H_{55}NNaO_{15}^+$, $[M+H]^+$; calc. 812.3469).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-6-[(3,4-dimethoxybenzoyl)amino]-2,6-dideoxy*-D-arabino-*hexitol* (**6k**). According to the *G.P.* CC followed by FC gave 21.5 mg (82%) of **6k**. ^{1}H-NMR (500 MHz, D_2O): 0.82–0.96 (*m*, 2 H); 1.08–1.24 (*m*, 6 H, including a *d* at 1.17, *J* = 6.5, Me(6)(Fuc)); 1.45–1.69 (*m*, 8 H); 1.72–1.78 (*m*, 1 H); 2.19–2.24 (*m*, 1 H); 3.36 (*dd*, *J* = 9.3, 3.1, H–C(3)(Gal)); 3.44–3.54 (*m*, 2 H); 3.54–3.74 (*m*, 6 H); 3.75–3.80 (*m*, H–C(4)(Fuc), H–C(2)(Fuc)); 3.75 (*dd*, *J* = 9.5, 3.0, H–C(3)(Fuc)); 3.81–3.90 (*m*, 8 H, including a *s* at

3.86, MeO); 3.87 (*s*, MeO); 3.93 (*m*, 1 H); 3.99 (*m*, 1 H); 4.05 (*m*, 1 H); 4.49 (*d*, *J* = 7.8, H–C(1)(Gal)); 4.69 (*q*, *J* = 6.8, H–C(5)(Fuc)); 4.98 (*d*, *J* = 3.7, H–C(1)(Fuc)); 7.06 (*d*, *J* = 8.6, 1 H); 7.35 (*d*, *J* = 2.2, 1 H); 7.40 (*dd*, *J* = 2.2, 8.6, 1 H). HR-MS: ($C_{36}H_{55}NNaO_{17}^{+}$, $[M+H]^+$; calc. 796.3368).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-2,6-dideoxy-6-[(naphthalen-2-ylcarbonyl)amino]*-D-arabino-*hexitol* (**6l**). According to the *G.P.* CC followed by FC gave 20.4 mg (78%) of **6l**. ^{1}H-NMR (500 MHz, D_2O): 0.81 – 1.00 (*m*, 2 H); 1.06 – 1.24 (*m*, 6 H, including a *d* at 1.10, *J* = 6.3, Me(6)(Fuc)); 1.46 – 1.72 (*m*, 8 H); 1.72 – 1.79 (*m*, 1 H); 2.18 – 2.24 (*m*, 1 H); 3.36 (*dd*, *J* = 9.5, 3.3, H–C(3)(Gal)); 3.45 – 3.65 (*m*, 5 H); 3.68 – 3.76 (*m*, 3 H); 3.76 – 3.81 (*m*, H–C(4)(Fuc), H–C(2)(Fuc)); 3.85 – 3.96 (*m*, 4 H, including H–C(4)(Gal), H–C(3)(Fuc)); 3.97 – 4.01 (*m*, 2 H); 4.49 (*d*, *J* = 7.8, H–C(1)(Gal)); 4.70 (*q*, *J* = 6.3, H–C(5)(Fuc)); 5.01 (*d*, *J* = 3.9, H–C(1)(Fuc)); 7.58 – 7.65 (*m*, 2 H); 7.74 – 7.78 (*m*, 1 H); 7.93 – 8.02 (*m*, 3 H); 8.28 (*s*, 1 H). HR-MS: 762.3334 ($C_{38}H_{52}NO_{15}^{-}$, $[M-Na]^-$; calc. 762.3337).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-2,6-dideoxy-6-[[4-(phenylmethoxy)benzoyl]amino]*-D-arabino-*hexitol* (**6m**). According to the *G.P.* FC gave 21.9 mg (79%) of **6m**. ^{1}H-NMR (400 MHz, D_2O): 0.72 – 0.90 (*m*, 2 H); 1.00 – 1.20 (*m*, 6 H, including a *d* at 1.10, *J* = 7, Me(6)(Fuc)); 1.35 – 1.62 (*m*, 8 H); 1.65 – 1.72 (*m*, 1 H); 2.08 – 2.18 (*m*, 1 H); 3.29 (*dd*, *J* = 10,3, Me(3)(Gal)); 3.33 – 3.65 (*m*, 8 H); 3.65 – 3.72 (*m*, H–C(4)(Fuc), H–C(2)(Fuc)); 3.72 – 4.03 (*m*, 6 H); 4.42 (*d*, *J* = 8, H–C(1)(Gal)); 4.60 (*q*, *J* = 7, H–C(5)(Fuc)); 4.90 (*d*, *J* = 4, H–C(1)(Fuc)); 5.10 (*s*, 2 H); 7.00 (*d*, *J* = 8, 2 H); 7.25 – 7.43 (*m*, 5 H); 7.62 (*d*, *J* = 8, 2 H). HR-MS: 818.3604 ($C_{41}H_{56}NO_{16}^{-}$, $[M-Na]^-$; calc. 818.3599).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-6-[benzoyl(phenylmethyl)amino]-2,6-dideoxy*-D-arabino-*hexitol* (**6n**). According to the *G.P.* FC gave 11.6 mg (48%) of **6n**. ^{1}H-NMR (400 MHz, D_2O; 2 rotamers): 0.72 – 0.92 (*m*, 2 H); 0.95 – 1.21 (*m*, 6 H); 1.38 – 1.72 (*m*, 8 H); 1.65 – 1.73 (*m*, 1 H); 1.95 – 2.18 (*m*, 1 H); 3.05 – 3.99 (*m*, 17 H); 4.28 – 4.90 (*m*, 5 H); 7.07 – 7.45 (*m*, 10 H). HR-MS: 802.3648 ($C_{41}H_{56}NO_{15}^{-}$, $[M-Na]^-$; calc. 802.3650).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-2,6-dideoxy-6-[(1-oxo-3-phenylpropyl)amino]*-D-arabino-*hexitol* (**6o**). According to the *G.P.* FC gave 17.3 mg (49%) of **6o**. ^{1}H-NMR (400 MHz, D_2O): 0.73 – 0.92 (*m*, 2 H); 1.00 – 1.21 (*m*, 6 H, including a *d* at 1.13, *J* = 7, Me(6)(Fuc)); 1.39 – 1.65 (*m*, 8 H); 1.65 – 1.73 (*m*, 1 H); 2.06 – 2.12 (*m*, 1 H); 2.49 (*t*, *J* = 7, 2 H); 2.82 (*t*, *J* = 7, 2 H); 3.18 – 3.35 (*m*, 5 H); 3.50 – 3.58 (*m*, 3 H); 3.62 – 3.95 (*m*, 9 H, including a *dd* at 3.78, *J* = 3, 11, H–C(3)(Fuc)); 4.41 (*d*, *J* = 8, H–C(1)(Gal)); 4.59 (*q*, *J* = 7, H–C(5)(Fuc)); 4.78 (*d*, *J* = 4, H–C(1)(Fuc)); 7.20 (*t*, *J* = 8, 3 H); 7.30 (*t*, *J* = 8, 2 H). HR-MS: 740.3486 ($C_{36}H_{55}NO_{15}^{-}$, $[M-Na]^-$; calc. 740.3493).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-2,6-dideoxy-6-[(1-oxo-2,2-diphenylethyl)amino]*-D-arabino-*hexitol* (**6p**). According to the *G.P.* CC followed by FC gave 21.5 mg (79%) of **6p**. ^{1}H-NMR (500 MHz, D_2O): 0.82 – 0.96 (*m*, 2 H); 1.08 – 1.22 (*m*, 6 H, including a *d* at 1.15, *J* = 6.5, Me(6)(Fuc)); 1.46 – 1.68 (*m*, 8 H); 1.72 – 1.79 (*m*, 1 H); 2.11 – 2.19 (*m*, 1 H); 3.45 – 3.32 (*m*, 4 H); 3.62 – 3.49 (*m*, 3 H); 3.65 – 3.78 (*m*, 5 H); 3.82 (*dd*, *J* = 3.4, 10.0, H–C(3)(Fuc)); 3.87 (*d*, *J* = 3.0, H–C(4)(Gal)); 3.88 – 4.02 (*m*, 3 H); 4.46 (*d*, *J* = 8.0, H–C(1)(Gal)); 4.64 (*q*, *J* = 6.6, H–C(5)(Fuc)); 4.78 (*d*, *J* = 4.0, H–C(1)(Fuc)); 5.16 (*s*, Ph_2CH); 7.42 – 7.22 (*m*, 10 H). HR-MS: 802.3651 ($C_{41}H_{56}NO_{15}^{-}$, $[M-Na]^-$; calc. 802.3650).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-6-(acetylamino)-1,5-anhydro-2,6-dideoxy*-D-arabino-*hexitol* (**6q**). According to the *G.P.* FC gave 15.2 mg (46%) of **6q**. ^{1}H-NMR (400 MHz, D_2O): 0.73 – 0.92 (*m*, 2 H); 1.00 – 1.21 (*m*, 6 H, including a *d* at 1.13, *J* = 7, Me(6)(Fuc)); 1.39 – 1.65 (*m*, 8 H); 1.65 – 1.73 (*m*, 1 H); 1.90 (*s*, MeCO); 2.10 – 2.18 (*m*, 1 H); 3.28 (*dd*, *J* = 10, 3, H–C(3)(Gal)); 3.32 – 3.45 (*m*, 4 H); 3.48 – 3.57 (*m*, 3 H); 3.60 – 3.72 (*m*, 4 H); 3.78 (*dd*, *J* = 3, 1, H–C(3)(Fuc)); 3.81 (*d*, *J* = 3, H–C(4)(Gal)); 3.83 – 3.97 (*m*, 3 H); 4.40 (*d*, *J* = 8, H–C(1)(Gal)); 4.62 (*q*, *J* = 7, H–C(5)(Fuc)); 4.80 (*d*, *J* = 4, H–C(1)(Fuc)). HR-MS: 674.3002 ($C_{29}H_{49}NNaO_{15}^{+}$, $[M+H]^+$; calc. 674.3000).

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-6-[(cyclohexylcarbonyl)amino]-2,6-dideoxy*-D-arabino-*hexitol* (**6r**). According to the *G.P.* FC gave 21.4 mg (89%) of **6r**. ^{1}H-NMR (500 MHz, D_2O): 0.83 – 0.97 (*m*, 2 H); 1.08 – 1.37 (*m*, 11 H, including a *d* at 1.17, *J* = 6.7, Me(6)(Fuc)); 1.47 – 1.68 (*m*, 9 H); 1.79 – 1.68 (*m*, 5 H); 2.16 – 2.27 (*m*, 2 H); 3.36 (*dd*, *J* = 9.5, 3.2, H–C(3)(Gal)); 3.53 – 3.40 (*m*, 4 H); 3.63 – 3.55 (*m*, 3 H); 3.72 – 3.68 (*m*, 2 H); 3.74 (*dd*, *J* = 10.5, 4.0, H–C(2)(Fuc)); 3.77 (*d*, *J* = 3.2, H–C(4)(Fuc)); 3.83 (*dd*, *J* = 3.2, 10.5, H–C(3)(Fuc)); 3.87 (*d*, *J* = 3.0, H–C(4)(Gal)); 3.91 – 4.05 (*m*, 3 H); 4.48 (*d*, *J* = 8.0, H–C(1)(Gal)); 4.67 (*q*, *J* = 7.0, H–C(5)(Fuc)); 4.86 (*d*, *J* = 4.0, H–C(1)(Fuc)). HR-MS: 718.3650 ($C_{34}H_{56}NO_{15}^{-}$, $[M-Na]^-$; calc. 718.3650).

*O-3-O-[(1S)-1-Carboxy-2-cyclohexylethyl]-β-*D*-galactopyranosyl-(1 → 3)-O-[6-deoxy-α-*L*-galactopyranosyl-(1 → 4)]-1,5-anhydro-2,6-dideoxy-6-{[(4-methylphenyl)sulfonyl]amino}-*D*-arabino-hexitol* (**6s**). To a soln. of **6a** (30 mg, 0.049 mmol) in sat. aq. $NaHCO_3$ soln. (0.3 ml), 1.1M 4-methlybenzenesulfonyl chloride (TsCl) in toluene (50 µl, 0.054 mmol, 1.1 equiv.) was added. After 3 d, another portion of 1.1M TsCl in toluene (50 µl, 0.054 mmol, 1.1 equiv.) was added. After 6 d, the mixture was evaporated and the residue purified subsequently by gel filtration (*P2*, *BioRad*, H_2O), FC (silica gel, AcOEt/^{i}PrOH/H_2O 4:2:1), CC (*RP C18*, column 1 × 10 cm, MeCN/H_2O 3:7, then 4:6), and gel filtration (*P2*, *BioRad*, H_2O) and freeze-dried: **5w** (16 mg, 42%). White foam. ^{1}H-NMR (400 MHz, D_2O): 0.75–0.92 (*m*, 2 H); 1.00–1.18 (*m*, 6 H, including a *d* at 1.08, *J* = 7, Me(6)(Fuc)); 1.35–1.60 (*m*, 8 H); 1.64–1.72 (*m*, 1 H); 2.02–2.08 (*m*, 1 H); 2.32 (*s*, 3 H); 3.12 (*dd*, *J* = 7, 12, 1 H); 3.15–3.35 (*m*, 4 H); 3.48–3.53 (*m*, 2 H); 3.55–3.62 (*m*, 3 H); 3.65–3.73 (*m*, H–C(4)(Fuc), H–C(2)(Fuc)); 3.72–3.80 (*m*, H–C(3)(Fuc), H–C(4)(Gal)); 3.82–3.88 (*m*, 2 H); 4.46 (*d*, *J* = 8, H–C(1)(Gal)); 4.53 (*q*, *J* = 7, H–C(5)(Fuc)); 4.75 (*d*, *J* = 4, H–C(1)(Fuc)); 7.34 (*d*, *J* = 8, 2 H); 7.04 (*d*, *J* = 8, 2 H). HR-MS: 762.2998 ($C_{34}H_{52}NO_{16}S^-$, $[M-Na]^-$; calc. 762.3007).

*O-3-O-[(1S)-1-Carboxy-2-cyclohexylethyl]-β-*D*-galactopyranosyl-(1 → 3)-O-[6-deoxy-α-*L*-galactopyranosyl-(1 → 4)]-1,5-anhydro-2,6-dideoxy-6-{[(ethylamino)carbonyl]amino}-*D*-arabino-hexitol* (**6t**). As described for **6u**, from **6a** (30 mg, 0.049 mmol) and ethyl isocyanate instead of phenyl isocyanate. FC (silica gel) gave **6t** (21.7 mg, 64%). White foam. ^{1}H-NMR (400 MHz, D_2O): 0.75–0.92 (*m*, 2 H); 0.98 (*t*, *J* = 7, 3 H); 1.00–1.18 (*m*, 6 H, including a *d* at 1.09, *J* = 7, Me(6)(Fuc)); 1.38–1.62 (*m*, 8 H); 1.63–1.73 (*m*, 1 H); 2.08–2.16 (*m*, 1 H); 3.04 (*q*, *J* = 7, 2 H); 3.28–3.44 (*m*, 5 H); 3.46–3.58 (*m*, 3 H); 3.64–3.74 (*m*, 4 H, including H–C(4)(Fuc), H–C(2)(Fuc)); 3.78 (*dd*, *J* = 3, 11, H–C(3)(Fuc)); 3.81 (*d*, *J* = 3, H–C(4)(Gal)); 3.84–3.98 (*m*, 3 H); 4.41 (*d*, *J* = 8, H–C(1)(Gal)); 4.63 (*q*, *J* = 7, H–C(5)(Fuc)); 4.83 (*d*, *J* = 4, H–C(1)(Fuc)). HR-MS: 679.3288 ($C_{30}H_{51}N_2O_{15}^-$, $[M-Na]^-$; calc. 679.3289).

*O-3-O-[(1S)-1-Carboxy-2-cyclohexylethyl]-β-*D*-galactopyranosyl-(1 → 3)-O-[6-deoxy-α-*L*-galactopyranosyl-(1 → 4)]-1,5-anhydro-2,6-dideoxy-6-{[(phenylamino)carbonyl]amino}-*D*-arabino-hexitol* (**6u**). To a soln. of **6a** (17 mg, 0.027 mmol) in 0.5N NaOH (1 ml) at 0°, a soln. of commercially available phenyl isocyanate (4 mg, 0.033 mmol, 1.2 equiv.) in 0.5N NaOH was added. Additional phenyl isocyanate (4 mg, 0.033 mmol, 1.2 equiv.) was added after 1 h, and the mixture was warmed to r.t. Addition of phenyl isocyanate was continued until after 11 d, a total amount of 6 equiv. was added. The product was purified by FC (silica gel; AcOEt/^{i}PrOH/H_2O 4:2:1), ion exchange (*Dowex* (Na^+ form), H_2O), gel filtration (*P2*, *BioRad*, H_2O), and again ion exchange (*Dowex* (Na^+ form), H_2O) and freeze-dried: **6u** (8.4 mg, 42%). White foam. ^{1}H-NMR (400 MHz, D_2O): 0.72–0.92 (*m*, 2 H); 0.97–1.21 (*m*, 6 H, including a *d* at 1.09, *J* = 7, Me(6)(Fuc)); 1.38–1.62 (*m*, 8 H); 1.63–1.73 (*m*, 1 H); 2.06–2.16 (*m*, 1 H); 3.28–3.46 (*m*, 4 H); 3.46–3.63 (*m*, 6 H); 3.64–3.72 (*m*, 2 H, H–C(4)(Fuc), H–C(2)(Fuc)); 3.76 (*dd*, *J* = 3, 11, H–C(3)(Fuc)); 3.84 (*s*, H–C(4)(Gal)); 3.85–4.08 (*m*, 3 H); 4.39 (*d*, *J* = 8, H–C(1)(Gal)); 4.64 (*q*, *J* = 7, H–C(5)(Fuc)); 4.86 (*d*, *J* = 4, H–C(1)(Fuc)); 7.03 (*t*, 1 H); 7.18 (*d*, 2 H); 7.27 (*m*, 2 H). HR-MS: 727.3292 ($C_{34}H_{51}N_2O_{15}^+$, $[M-Na]^-$; calc. 727.3289).

*3-O-3-[(1S)-1-Carboxy-2-cyclohexylethyl]-β-*D*-galactopyranosyl-(1 → 3)-O-[6-deoxy-α-*L*-galactopyranosyl-(1 → 4)]-1,5-anhydro-2,6-dideoxy-6-{[[(4-nitrophenyl)methoxy]carbonyl]amino}-*D*-arabino-hexitol* (**6v**). According to the *G.P.* from **6a** (30 mg). FC followed by gel filtration gave **6v** (20 mg, 50%). ^{1}H-NMR (400 MHz, D_2O): 0.73–0.90 (*m*, 2 H); 1.03–1.21 (*m*, 6 H, including a *d* at 1.13, *J* = 7, Me(6)(Fuc)); 1.39–1.60 (*m*, 8 H); 1.65–1.72 (*m*, 1 H); 2.08–2.15 (*m*, 1 H); 3.28–3.42 (*m*, 5 H); 3.48–3.58 (*m*, 3 H); 3.59–3.78 (*m*, 5 H); 3.81 (*dd*, *J* = 3, 10, H–C(3)(Fuc)); 3.84–3.98 (*m*, 3 H); 4.40 (*d*, *J* = 8, H–C(1)(Gal)); 4.58 (*q*, *J* = 7, H–C(5)(Fuc)); 4.80 (*d*, *J* = 4, H–C(1)(Fuc)); 5.12 (*m*, PhCH_2); 7.48 (*d*, *J* = 8, 2 H); 8.16 (*d*, *J* = 7, 2 H). HR-MS: 787.3136 ($C_{35}H_{51}N_2O_{18}^-$, $[M-Na]^-$; calc. 787.3137).

*3-O-3-[(1S)-1-Carboxy-2-cyclohexylethyl]-β-*D*-galactopyranosyl-(1 → 3)-O-[6-deoxy-α-*L*-galactopyranosyl-(1 → 4)]-1,5-anhydro-2,6-dideoxy-6-{[(naphthalen-2-ylmethoxy)carbonyl]amino}-*D*-arabino-hexitol* (**6w**). According to the *G.P.* FC followed by gel filtration gave 12 mg (30%) of **6w**. ^{1}H-NMR (400 MHz, D_2O): 0.74–0.94 (*m*, 2 H); 0.95–1.18 (*m*, 6 H, including a *d* at 1.08, *J* = 7, Me(6)(Fuc)); 1.38–1.60 (*m*, 8 H); 1.64–1.72 (*m*, 1 H); 2.05–2.14 (*m*, 1 H); 3.28–3.42 (*m*, 5 H); 3.48–3.58 (*m*, 3 H); 3.59–3.78 (*m*, 5 H); 3.78–3.98 (*m*, 4 H); 4.38 (*d*, *J* = 8.0, H–C(1)(Gal)); 4.59 (*q*, *J* = 6.3, H–C(5)(Fuc)); 4.81 (*d*, *J* = 3.8, H–C(1)(Fuc)); 5.18 (*m*, PhCH_2); 7.38–7.52 (*m*, 3 H); 7.78–7.88 (*m*, 4 H). HR-MS: 816.3422 ($C_{39}H_{55}NNaO_{16}^+$, $[M+H]^+$; calc. 816.3419).

*3-O-3-[(1S)-1-Carboxy-2-cyclohexylethyl]-β-*D*-galactopyranosyl-(1 → 3)-O-[6-deoxy-α-*L*-galactopyranosyl-(1 → 4)]-1,5-anhydro-2,6-dideoxy-6-{[(phenylmethoxy)carbonyl]amino}-*D*-arabino-hexitol* (**6x**). According to the *G.P.* CC followed by FC gave 18 mg (72%) of **6x**. ^{1}H-NMR (500 MHz, D_2O): 0.80–0.94 (*m*, 2 H); 1.03–1.21 (*m*, 6 H, including a *d* at 1.13, *J* = 6.4, Me(6)(Fuc)); 1.44–1.65 (*m*, 8 H); 1.71–1.76 (*m*, 1 H); 2.12–2.18 (*m*, 1 H); 3.33 (*dd*, *J* = 9.6, 3.6, H–C(3)(Gal)); 3.35–3.44 (*m*, 4 H); 3.54–3.62 (*m*, 3 H); 3.66–3.76 (*m*, 4 H);

3.81 (*dd*, *J* = 3.0, 10.4, H–C(3)(Fuc)); 3.85 (*d*, *J* = 3.0, H–C(4)(Gal)); 3.89–3.95 (*m*, 2 H); 3.95–4.01 (*m*, 1 H); 4.45 (*d*, *J* = 8.0, H–C(1)(Gal)); 4.66 (*q*, *J* = 6.3, H–C(5)(Fuc)); 4.86 (*d*, *J* = 3.8, H–C(1)(Fuc)); 5.06 (*m*, PhCH_2); 7.42–7.33 (*m*, 5 H). HR-MS: 742.3282 ($C_{35}H_{52}NO_{16}^-$, $[M-Na]^-$; calc. 742.3286).

O-*3*-O-*[(1*S*)-1-Cyclohexylmethyl)-2-oxo-2-(phenylmethoxy)ethyl]-2,4,6-tris*-O-*(phenylmethyl)-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-2,3,4-tris*-O-*(phenylmethyl)-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-2-deoxy*-D-arabino-*hexitol* (**7**). A soln. of Br_2 (1.90 g, 11.8 mmol) in CH_2Cl_2 (11 ml) was added dropwise at 0° to a soln. of **11** (4.5 g, 9.45 mmol) in CH_2Cl_2 (11 ml). After stirring for 30 min at 0°, cyclohexene (2.5 ml) was added to consume excessive Br_2. The soln. was added within 10 min to a mixture of **16** (7.71 g, 7.87 mmol), Et_4NBr (2.00 g, 9.45 mmol; dried for 2 h at 200°), and molecular sieves (12 g; dried for 24 h at 300°) in DMF/CH_2Cl_2 1:1 (60 ml). The mixture was stirred for 65 h at 20°, diluted with CH_2Cl_2 (250 ml), and filtered. The resulting soln. was washed with $NaHCO_3$ soln. (2 × 50 ml), H_2O (2 × 250 ml), (0.5M HCl, 2 × 250 ml), and brine (250 ml), dried (Na_2SO_4) and evaporated. To the residue dissolved in MeCN (85 ml) at 20°, a soln. of Et_3N (0.21 ml) and H_2SiF_6 (1.3 ml, 35%) in MeCN (17 ml) was added within 10 min. After stirring for 2 h, the mixture was diluted with CH_2Cl_2 (250 ml), washed with $NaHCO_3$ soln. (3 × 250 ml) and brine (250 ml), dried (Na_2SO_4), and evaporated, and the residue subjected to CC (silica gel, hexane/AcOEt 1:1 → 1:2): **7** (7.88 g, 78%). Colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.45–1.44 (*m*, 14 H, H_{ax}–C(2)(Hex), CH_2(Chx)); 1.39 (*d*, *J* = 6.5, Me(6)(Fuc)); 1.89 (*m*, H_{eq}–C(2)(Chx)); 2.25 (*t*, *J* = 6.5, OH–C(6)(Hex)); 3.03 (*dt*, *J* = 9.0, 3.5, H–C(5)(Hex)); 3.20 (br. *t*, *J* = 12.0, H_{ax}–C(1)(Hex)); 3.52 (br. *d*, *J* = 3.0, H–C(4)(Fuc)); 3.55 (*t*, *J* = 9.0, H–C(4)(Hex)); 3.74 (*m*, H_{eq}–C(1)(Hex), H–C(3)(Hex), 2 H–C(6)(Hex)); 3.87 (*dd*, *J* = 10.0, 3.5, H–C(3)(Gal)); 3.94 (br. *t*, *J* = 6.5, H–C(5)(Gal)); 3.99 (*dd*, *J* = 10.0, 2.5, Me(3)(Fuc)); 4.07 (*dd*, *J* = 10.0, 3.5, H–C(2)(Fuc)); 4.15 (*dd*, *J* = 8.0, 4.5, OC*H*CO_2Bn); 4.32 (*dd*, *J* = 11.5, 7.5, H_a–C(6)(Gal)); 4.34 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.42 (*dd*, *J* = 11.5, 5.5, H_b–C(6)(Gal)); 4.55 (*d*, *J* = 12.0, 1 H, PhCH_2); 4.61 (*d*, *J* = 8.0, H–C(1)(Gal)); 4.63 (*d*, *J* = 12.0, 1 H, PhCH_2); 4.69 (br. *q*, *J* = 6.5, H–C(5)(Fuc)); 4.69 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.79 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.83 (*d*, *J* = 11.5, 1 H, PhCH_2); 5.04 (*d*, *J* = 3.5, H–C(1)(Fuc)); 5.07 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.14 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.62 (*dd*, *J* = 10.0, 8.0, H–C(2)(Gal)); 5.87 (*dd*, *J* = 3.5, 0.5, H–C(4)(Gal)); 7.17–8.14 (*m*, 35 arom. H). HR-MS: 1305.5389 ($C_{76}H_{82}NaO_{18}^+$; $[M+Na]^+$; calc. 1305.5399).

Ethyl 3-O-*[(1*S*)-1-(Cyclohexylmethyl)-2-oxo-2-(phenylmethoxy)ethyl]-1-thio-β*-D-*galactopyranoside* (**12**). A suspension of **8** (15.0 g, 66.9 mmol) and Bu_2SnO (20.0 g, 80.3 mmol) in MeOH (450 ml) was refluxed for 2 h (→ clear soln.). Evaporation and the repeated co-evaporation with pentane gave a colorless foam, which was dried under vacuum for 1 h. $MeOCH_2CH_2OMe$ (120 ml), **9** (39.6 g, 100.3 mmol) dissolved in $MeOCH_2$-CH_2OMe (60 ml), and CsF (12.2 g, 80.3 mmol; dried) were added, and the suspension was stirred for 2 h at 20°. Then 1M KH_2PO_4 (700 ml) and KF (25 g) were added, followed by extraction with AcOEt (3 × 250 ml). The combined org. extract was washed with 10% KF soln. (2 × 250 ml) and brine (1 × 250 ml), dried (Na_2SO_4), and evaporated, and the residue subjected to FC (silica gel, hexane/acetone 4:1 → 2:1): **12** (20.4 g, 65%). Colorless solid. ^{1}H-NMR (400 MHz, CD_3OD): 0.82–1.88 (*m*, 13 H, CH_2(Chx)); 1.28 (*t*, *J* = 7.5, *Me*CH_2S); 2.74 (*m*, MeCH_2S); 3.25 (*dd*, *J* = 9.0, 3.0, H–C(3)(Gal)); 3.45 (*ddd*, *J* = 7.0, 5.0, 1.0, H–C(5)(Gal)); 3.61 (*dd*, *J* = 11.5, 5.0, H_a–C(6)(Gal)); 3.66 (*t*, *J* = 9.5, H–C(2)(Gal)); 3.71 (*dd*, *J* = 11.5, 7.0, H_b–C(6)(Gal)); 3.92 (*dd*, *J* = 3.0, 1.0, H–C(4)(Gal)); 4.28 (*d*, *J* = 10.0, H–C(1)(Gal)); 4.48 (*dd*, *J* = 8.5, 4.0, OC*H*CO_2Bn); 5.14 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.25 (*d*, *J* = 12.0, 1 H, PhCH_2); 7.34–7.40 (*m*, 5 arom. H). ES-MS: 486 ($[M+NH_4]^+$).

Ethyl 3-O-*[(1*S*)-1-(Cyclohexylmethyl)-2-oxo-2-(phenylmethoxy)ethyl]-1-thio-β*-D-*galactopyranoside 2,4,6-Tribenzoate* (**13**). At 0°, benzoyl chloride (52.1 g, 370.7 mmol) was added to a soln. of **12** (19.3 g, 41.2 mmol) and DMAP (1.51 g) in pyridine (210 ml). The mixture was stirred at 20° for 6 h, the solvent removed, and the residue dissolved in AcOEt (500 ml). The soln. was extracted with 0.1M HCl (2 × 250 ml), $NaHCO_3$ soln. (2 × 250 ml), and brine (250 ml), dried (Na_2SO_4), and evaporated, and the residue subjected to FC (silica gel, hexane/AcOEt 6:1 → 4:1): **13** (28.9 g, 90%). Colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.44–1.43 (*m*, 13 H, CH_2(Chx)); 1.26 (*t*, *J* = 7.5, *Me*CH_2S); 2.77 (*m*, MeCH_2S); 3.93 (*dd*, *J* = 9.5, 3.5, H–C(3)(Gal)); 4.02 (*ddd*, *J* = 7.0, 5.0, 1.0, H–C(5)(Gal)); 4.21 (*dd*, *J* = 8.0, 5.0, OC*H*CO_2Bn); 4.42 (*dd*, *J* = 11.5, 5.0, H_a–C(6)(Gal)); 4.49 (*dd*, *J* = 11.5, 7.0, H_b–C(6)(Gal)); 4.62 (*d*, *J* = 10.0, H–C(1)(Gal)); 5.08 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.21 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.69 (*t*, *J* = 9.5, H–C(2)(Gal)); 6.00 (*dd*, *J* = 3.5, 1.0, H–C(4)(Gal)); 7.30–8.17 (*m*, 20 arom. H). HR-MS: 803.2857 ($C_{45}H_{48}NaO_{10}S^+$, $[M+Na]^+$; calc. 803.2866).

1,5-Anhydro-2-deoxy-3-O-*[2,4,6-tri*-O-*benzoyl-3*-O-*[(1*S*)-1-(cyclohexylmethyl)-2-oxo-2-(phenylmethoxy)-ethyl]-β*-D-*galactopyranosyl]*-D-arabino-*hexitol* (**14**). At −10°, 0.15M CF_3SO_3H soln. in CH_2Cl_2 was added to a soln. of **10** (6.05 g, 25.64 mmol) and **13** (10.0 g, 12.82 mmol) in CH_2Cl_2 (75 ml). The addition was stopped when the orange soln. turned brown. AcOEt was added (500 ml), the mixture extracted with $NaHCO_3$ soln. (4 × 250 ml) and brine (250 ml), dried (Na_2SO_4), and evaporated, and the residue subjected to FC (silica gel, Et_2O):

14 (9.03 g, 81%). Colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.47–1.46 (*m*, 13 H, CH_2(Chx)); 1.52–1.68 (*m*, 2 H–C(2)(Hex)); 2.12 (br. *t*, *J* = 6.0, OH–C(6)(Hex)); 3.13 (*ddd*, *J* = 9.0, 5.5, 4.0, H–C(5)(Hex)); 3.30 (*td*, *J* = 12.0, 2.0, H_{ax}–C(1)(Hex)); 3.42 (*t*, *J* = 9.0, H–C(4)(Hex)); 3.47 (*m*, H–C(3)(Hex)); 3.68 (*dt*, *J* = 11.0, 5.5, H_a–C(6)(Hex)); 3.83 (*m*, H_{eq}–C(1)(Hex), H_b–C(6)(Hex)); 3.91 (*dd*, *J* = 10.0, 3.5, H–C(3)(Gal)); 4.03 (br. *dd*, *J* = 9.0, 3.0, H–C(5)(Gal)); 4.21 (*dd*, *J* = 8.0, 5.0, OC*H*CO_2Bn); 4.25 (br. *s*, OH–C(4)(Hex)); 4.28 (*dd*, *J* = 12.0, 9.0, H_a–C(6)(Gal)); 4.64 (*d*, *J* = 8.0, H–C(1)(Gal)); 4.68 (*dd*, *J* = 12.0, 3.0, H_b–C(6)(Gal)); 5.10 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.23 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.67 (*dd*, *J* = 10.0, 8.0, H–C(2)(Gal)); 5.91 (br. *d*, *J* = 3.5, H–C(4)(Gal)); 7.33–8.17 (*m*, 20 arom. H). HR-MS: 889.3409 ($C_{49}H_{54}NaO_{14}^+$, $[M+Na]^+$; calc. 889.3411).

In addition to **14**, 10% of the α-D-epimer **15** was isolated. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.48–1.68 (*m*, 14 H, H_{ax}–C(2)(Hex), CH_2(Chx)); 1.90 (*m*, OH–C(6)(Hex)); 2.03 (*m*, H_{eq}–C(2)(Hex)); 2.23 (*d*, *J* = 1.0, OH–C(4)(Hex)); 3.12 (*m*, H–C(5)(Hex)); 3.23 (*td*, *J* = 12.0, 2.0, H_{ax}–C(1)(Hex)); 3.45–3.58 (*m*, H_{eq}–C(1)(Hex), H–C(3)(Hex), H–C(4)(Hex)); 3.67 (br. *d*, *J* = 11.0, H_a–C(6)(Hex)); 3.78 (br. *d*, *J* = 11.0, H_b–C(6)(Hex)); 4.15 (*dd*, *J* = 9.5, 3.5, H–C(3)(Gal)); 4.36 (*dd*, *J* = 8.0, 5.0, OC*H*CO_2Bn); 4.39–4.45 (*m*, H–C(5)(Gal), H_a–C(6)(Gal)); 4.48 (*dd*, *J* = 10.0, 2.0, H_b–C(6)(Gal)); 5.18 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.32 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.55 (*m*, H–C(1)(Gal), H–C(2)(Gal); 5.99 (br. *d*, *J* = 3.5, H–C(4)(Gal)); 7.34–8.15 (*m*, 20 arom. H). ESI-MS: 884 ($[M+NH_4]^+$).

*1,5-Anhydro-2-deoxy-6-*O*-[(1,1-dimethylethyl)dimethylsilyl]-3-*O*-{2,4,6-tri-*O*-benzoyl-3-*O*-[(1*S*)-1-(cyclohexylmethyl)-2-oxo-2-(phenylmethoxy)ethyl]-β-*D*-galactopyranosyl}-*D*-arabino-hexitol* (**16**). A soln. of **14** (7.96 g, 9.19 mmol), ^{t}BuMe$_2$SiCl (1.52 g, 10.1 mmol) and 1*H*-imidazol (0.94 g, 13.8 mmol) in DMF (55 ml) was stirred for 1 h at 20°. The mixture was diluted with AcOEt (250 ml), washed with $NaHCO_3$ soln. (5 × 250 ml) and brine (250 ml), dried (Na_2SO_4), and evaporated, and the residue subjected to FC (silica gel, hexane/AcOEt 4:1 → 1:1): **16** (8.38 g, 93%). Colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.01, 0.03 (2*s*, Me_2Si); 0.45–1.64 (*m*, 15 H, 2 H–C(2)(Hex), CH_2(Chx)); 0.87 (*s*, ^{t}BuSi); 3.05 (*ddd*, *J* = 9.0, 5.5, 1.5, H–C(5)(Hex)); 3.23 (*td*, *J* = 12.0, 2.0, H_{ax}–C(1)(Hex)); 3.39 (*t*, *J* = 9.0, H–C(4)(Hex)); 3.45 (*m*, H–C(3)(Hex)); 3.73 (*dt*, *J* = 11.5, 5.5, H_a–C(6)(Hex)); 3.82 (br. *dd*, *J* = 12.0, 3.5, H_{eq}–C(1)(Hex)); 3.89 (*dd*, *J* = 10.0, 3.5, H–C(3)(Gal)); 3.90 (*dd*, *J* = 11.5, 1.5, H_b–C(6)(Hex)); 3.96 (br. *s*, OH–C(4)(Hex)); 4.02 (br. *dd*, *J* = 8.5, 3.5, H–C(5)(Gal)); 4.19 (*dd*, *J* = 8.0, 4.5, OC*H*CO_2Bn); 4.31 (*dd*, *J* = 12.0, 8.5, H_a–C(6)(Gal)); 4.62 (*dd*, *J* = 12.0, 3.5, H_b–C(6)(Gal)); 4.64 (*d*, *J* = 8.0, H–C(1)(Gal)); 5.08 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.21 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.66 (*dd*, *J* = 10.0, 8.0, H–C(2)(Gal)); 5.91 (*d*, *J* = 3.5, H–C(4)(Gal)); 7.29–8.17 (*m*, 20 arom. H). HR-MS: 1003.4289 ($C_{55}H_{68}NaO_{14}Si^+$, $[M+Na]^+$; calc. 1003.4276).

O-*3*-O-*{2,4,6-Tri*-O-*benzoyl-3*-O-*[(1*S*)-1-(cyclohexylmethyl)-2-oxo-2-(phenylmethoxy)ethyl]-β-*D*-galacto-pyranosyl-(1 → 3)*-O-*[6-deoxy-2,3,4-tris*-O-*(phenylmethyl)-α-*L*-galactopyranosyl-(1 → 4)]-1,5-anhydro-2-de-oxy-6*-O-*(methylsulfonyl)*-*D*-arabino-*hexitol* (**17**). To a soln. of **7** (12.5 g, 9.75 mmol) in dry pyridine (80 ml), methanesulfonyl chloride (3.35 g, 29.2 mmol) was added dropwise with magnetic stirring within 5 min (Ar, r.t.). After 30 min, the mixture was diluted with AcOEt (500 ml) and extracted with 1N HCl (250 ml). The aq. phase was extracted twice with AcOEt (300 ml), the combined org. phase (Na_2SO_4) dried and evaporated, and the residue submitted to FC (silica gel (500 g), hexanes/AcOEt 6:4): 12.98 g (97%) of **17**. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.4–1.4 (*m*, 14 H, H_{ax}–C(2)(Hex), CH_2(Chx)); 1.39 (*d*, *J* = 6.5, H–C(6)(Fuc)); 1.85–1.95 (*m*, H_{eq}–C(2)(Hex)); 2.89 (*s*, $MeSO_3$–C(6)); 3.08 (*m*, H–C(5)(Hex)); 3.15 (*t*, *J* = 11, H_{ax}–C(1)(Hex)); 3.45–3.52 (*m*, H–C(4)(Hex), H–C(4)(Fuc)); 3.6–3.7 (*m*, H–C(3)(Hex)); 3.75 (br. *d*, *J* = 11, H_{eq}–C(1)(Hex)); 3.85 (*dd*, *J* = 10.0, 3.5, H–C(3)(Gal)); 3.9–4.0 (*m*, H–C(5)(Gal), H–C(3)(Fuc)); 4.03 (*dd*, *J* = 10.0, 3.5, H–C(2)(Fuc)); 4.12 (*dd*, *J* = 8.0, 4.5, OC*H*CO_2Bn); 4.27–4.37 (*m*, H_a–C(6)(Hex), 1 H of PhCH_2); 4.37–4.45 (*m*, H_b–C(6)(Hex), H_a–C(6)(Gal)); 4.48 (*dd*, *J* = 11.5, 5.5, H_b–C(6)(Gal)); 4.52–4.68 (5 H, H–C(1)(Gal), H–C(5)(Fuc), PhCH_2); 4.78, 4.83 (2*d*, 2 H, PhCH_2); 4.93 (*d*, *J* = 3.5, H–C(1)(Fuc)); 5.05, 5.13 (2*d*, *J* = 12, CO_2CH_2Ph); 5.60 (*dd*, *J* = 10.0, 8.0, H–C(2)(Gal)); 5.83 (*d*, *J* = 3.5, H–C(4)(Gal)); 7.13–7.35 (*m*, 22 H); 7.35–7.42 (*m*, 5 H); 7.45–7.5 (*m*, 2 H); 8.0–8.13 (*m*, 6 arom. H). HR-MS: 1383.5168 ($C_{77}H_{84}NaO_{20}S^+$, $[M+Na]^+$; calc. 1383.5174).

O-*3*-O-*{2,4,6-Tri*-O-*benzoyl-3*-O-*[(1*S*)-1-(cyclohexylmethyl)-2-oxo-2-(phenylmethoxy)ethyl]-β-*D*-galacto-pyranosyl-(1 → 3)*-O-*[6-deoxy-2,3,4-tris*-O-*(phenylmethyl)-α-*L*-galactopyranosyl-(1 → 4)]-1,5-anhydro-6-azido-2,6-dideoxy*-*D*-arabino-*hexitol* (**18**). To a soln. of **17** (12.95 g, 9.52 mmol) in DMF (40 ml), NaN_3 (4.64 g, 74.4 mmol) was added. The mixture was heated to 65° under Ar and stirred for 35 h. After cooling, the soln. was diluted with AcOEt (500 ml) and washed with H_2O (300 ml) and saturated brine (150 ml). The aq. phases were extracted with AcOEt (2 × 300 ml). The combined org. phase was dried (Na_2SO_4) and evaporated and the residue submitted to FC (silica gel (500 g), hexanes/AcOEt 1:1): 12.2 g (98%) of **18**. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.4–1.5 (*m*, 14 H, H_{ax}–C(2)(Hex), Ch_2(Chx)); 1.40 (*d*, *J* = 6.5, H–C(6)(Fuc)); 1.85–1.95 (*m*, H_{eq}–C(2)(Hex)); 3.05–3.13 (*m*, H–C(5)(Hex)); 3.17 (br. *t*, *J* = 11, H_{ax}–C(1)(Hex)); 3.42 (*dd*, *J* = 12, 5,

H_a–C(6)(Hex)); 3.45–3.55 (*m*, H–C(4)(Hex), H_b–C(6)(Hex), H–C(4)(Fuc)); 3.6–3.7 (*m*, H–C(3)(Hex)); 3.78 (br. *d*, *J* = 11, H_{eq}–C(1)(Hex)); 3.86 (*dd*, *J* = 10.0, 3.5, H–C(3)(Gal)); 3.9–4.0 (*m*, H–C(5)(Gal), H–C(3)(Fuc)); 4.03 (*dd*, *J* = 10.0, 2.5, H–C(2)(Fuc)); 4.13 (*dd*, *J* = 8.0, 4.5, OC*H*CO_2Bn); 4.33 (*dd*, *J* = 11.5, 7.5, H_a–C(6)(Gal)); 4.33 (*d*, *J* = 11.5, 1 H); 4.77 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.40 (*dd*, *J* = 11.5, 5.5, H_b–C(6)(Gal)); 4.54, 4.62 (2 *d*, each *J* = 11.5, PhCH_2); 4.58 (*d*, *J* = 8, H–C(1)(Gal)); 4.63, 4.83 (2*d*, each *J* = 11.5, PhCH_2); 4.65–4.73 (*m*, H–C(5)(Fuc)); 4.87 (*d*, *J* = 3.5, H–C(1)(Fuc)); 5.07, 5.15 (2*d*, each *J* = 11.5, CO_2CH_2Ph); 5.63 (*dd*, *J* = 10.0, 8.0, H–C(2)(Gal)); 5.86 (*d*, *J* = 3.5, H–C(4)(Gal)); 7.17–7.4 (*m*, 22 arom. H); 7.4–7.5 (*m*, 5 arom. H); 7.55–7.65 (*m*, 2 arom. H); 8.0–8.15 (*m*, 6 arom. H). HR-MS: 1330.5460 ($C_{76}H_{81}NaN_3O_{17}^+$, $[M+Na]^+$; calc. 1330.5464).

O-*3*-O-*[(1*S*)-1-Carboxy-2-cyclohexylethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-2,3,4-tri*-O-*(phenylmethyl)-α*-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-6-azido-2,6-dideoxy*-D-arabino-*hexitol* (**19**). A soln./suspension of **18** (12.2 g, 9.33 mmol) and LiOH · H_2O (5.1 g, 121.3 mmol) in MeOH (200 ml) and H_2O (20 ml) was stirred and heated to 65° under Ar under reflux. After 20 h, the mixture was concentrated under vacuum to 1/3 of the volume. After addition of Et_2O (500 ml) and sat. brine (200 ml), the aq. phase was extracted with Et_2O (2 × 300 ml). The org. phases were washed with brine (150 ml), dried (Na_2SO_4), and evaporated. FC (silica gel (350 g) hexanes/AcOEt 7:3, then $CHCl_3$/MeOH/AcOH 94:5:1) of the residue (12.2 g) gave 8.10 g (96%) of **19**. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.8–1.05 (*m*, 2 H), 1.05–1.35 (*m*, 3 H), and 1.55–1.9 (*m*, 9 H, H_{ax}–C(2)(Hex), CH_2(Chx)); 1.17 (*d*, *J* = 6.5, Me(6)(Fuc)); 2.03–2.16 (*m*, H_{eq}–C(2)(Hex)); 3.23–3.4 (*m*, 3 H), 3.4–3.6 (*m*, 4 H), and 3.7–4.05 (*m*, 11 H, H–C(1)(Hex), H–C(3)(Hex), H–C(4)(Hex), H–C(5)(Hex, 2 H–C(6)(Hex), H–C(2)(Gal), H–C(3)(Gal), H–C(4)(Gal), H–C(5)(Gal), OH–C(2)(Gal), OH–C(4)(Gal), OH–C(6)(Gal), H–C(3)(Fuc), H–C(4)(Fuc)); 4.26–4.44 (*m*, H–C(1)(Gal), OC*H*CO_2H); 4.45 (*q*, *J* = 6.5, H–C(5)(Fuc)); 4.55–5.0 (*m*, 6 H, PhCH_2); 4.95 (*d*, *J* = 3.5, H–C(1)(Fuc)); 7.2–7.4 (*m*, 15 arom. H). HR-MS: 928.4203 ($C_{48}H_{63}NaN_3O_{14}^+$, $[M+Na]^+$; calc. 928.4208).

We wish to thank Mrs. *Christine Bourquin*, Mrs. *Brigitte Furrer*, Mr. *Kurt Martin*, and Mr. *Franz Schwarzenbach* for excellent technical support.

REFERENCES

[1] S. A. Mousa, *Drugs Fut.* **1996**, *21*, 283; S. A. Mousa, D. A. Cheresh, *Drug Discovery Today* **1997**, *2*, 187; D. B. Cines, E. S. Pollak, C. A. Buck, J. Loscalzo, G. A. Zimmermann, R. P. McEver, J. S. Pober, T. M. Wick, B. A. Konkle, B. S. Schwartz, E. S. Barnathan, K. R. McCrae, B. A. Hug, A.-M. Schmidt, D. M. Stern, *Blood* **1998**, *91*, 3527.

[2] G. S. Kansas, *Blood* **1996**, *88*, 3259; A. Varki, *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 7390.

[3] A. Levinovitz, J. Muhloff, S. Isenmann, D. Vestweber, *J. Cell Biol.* **1993**, *121*, 449; M. Lenter, A. Levinovitz, S. Isenmann, D. Vestweber, *J. Cell Biol.* **1994**, *125*, 471; K. L. Moore, N. L. Stults, S. Diaz, D. F. Smith, R. D. Cummings, A. Varki, R. P. McEver, *J. Cell Biol.* **1992**, *118*, 445.

[4] D. Sako, K. M. Commess, K. M. Barone, R. T. Camphausen, D. A. Cumming, G. D. Shaw, *Cell* **1995**, *83*, 323; P. P. Wilkins, K. L. Moore, R. P. McEver, R. D. Cummings, *J. Biol. Chem.* **1995**, *270*, 22677; K. E. Norgard, K. L. Moore, S. Diaz, N. L. Stults, S. Ushiyama, R. P. McEver, R. D. Cummings, A. Varki, *J. Biol. Chem.* **1993**, *268*, 12764; T. Pouyani, B. Seed, *Cell* **1995**, *83*, 333.

[5] E. L. Berg, M. K. Robinson, O. Mansson, E. C. Butcher, J. L. Magnani, *J. Biol. Chem.* **1991**, *266*, 14869; M. L. Phillips, E. Nudelman, F. C. A. Gaeta, M. Perez, A. K. Singhal, S.-I. Hakomori, J. C. Paulson, *Science (Washington, D.C.)* **1990**, *250*, 1130; D. Tyrell, P. James, N. Rao, C. Foxall, S. Abbas, F. Dasgupta, M. Nashed, A. Hasegawa, M. Kiso, D. Asa, J. Kidd, B. K. Brandley, *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 10372; G. Walz, A. Aruffo, W. Kolanus, M. Bevilacqua, B. Seed, *Science (Washington, D.C.)* **1990**, *250*, 1132; K. L. Moore, S. F. Eaton, D. E. Lyons, H. S. Lichenstein, R. D. Cummings, R. P. McEver, *J. Biol. Chem.* **1994**, *269*, 23318.

[6] E. E. Simanek, G. J. McGarvey, J. A. Jablonowski, C.-H. Wong, *Chem. Rev.* **1998**, *98*, 833.

[7] H. C. Kolb, B. Ernst, *Chem. Eur. J.* **1997**, 1571; H. C. Kolb, B. Ernst, *Pure Appl. Chem.* **1997**, *69*, 1879.

[8] G. Thoma, W. Kinzy, C. Bruns, J. T. Patton, J. L. Magnani, R. Bänteli, *J. Med. Chem.* **1999**, *42*, 4909.

[9] G. Thoma, W. Kinzy, J. L. Magnani, unpublished results.

[10] J. Y. Ramphal, M. Hiroshige, B. Lou, J. J. Gaudino, M. Hayashi, S. M. Chen, L. C. Chiang, F. C. A. Gaeta, S. A. DeFrees, *J. Med. Chem.* **1996**, *39*, 1357.

[11] a) J. Graves, R. L. Crowther, C. Chandran, J. M. Rumberger, S. Li, K.-S. Huang, D. H. Presky, P. C. Familletti, B. Z. Wolitzky, D. K. Burns, *Nature (London)* **1994**, *367*, 532; b) K. Scheffler, B. Ernst, A.

Katopodis, J. L. Magnani, W. T. Wang, R. Wiesemann, T. Peters, *Angew. Chem., Int. Ed.* **1995**, *34*, 1841; c) W. Jahnke, H. C. Kolb, M. J. J. Blommers, J. L. Magnani, B. Ernst, *Angew. Chem., Int. Ed.* **1997**, *36*, 2603; d) K. Scheffler, J.-R. Brisson, R. Weisemann, J. L. Magnani, W. T. Wang, B. Ernst, T. Peters, *J. Biol. NMR* **1997**, *9*, 423; e) L. Poppe, G. S. Brown, J. S. Philo, P. V. Nikrad, B. H. Shah, *J. Am. Chem. Soc.* **1997**, *119*, 1727; f) R. M. Cooke, R. S. Hale, S. G. Lister, G. Shah, M. P. Weir, *Biochemistry* **1994**, *33*, 10591; g) P. Hensley, P. J. McDevitt, I. Brooks, J. J. Trill, J. A. Feild, D. E. McNulty, J. R. Connor, D. E. Griswold, N. V. Kumar, K. D. Kopple, S. A. Carr, B. J. Dalton, K. Johanson, *J. Biol. Chem.* **1994**, *269*, 23949; h) R. Harris, G. R. Kiddle, R. A. Field, B. Ernst, J. L. Magnani, S. W. Homans, *J. Am. Chem. Soc.* **1999**, *121*, 2546.

[12] M. O. Contour, J. Defaye, M. Little, E. Wong, *Carbohydr. Res.* **1989**, *193*, 283.

[13] F. Yamazaki, T. Kitajima, T. Numata, T. Ito, T. Ogawa, *Carbohydr. Res.* **1990**, *201*, 15.

[14] S. Pilcher, P. DeShong, *J. Org. Chem.* **1993**, *58*, 5130.

[15] G. Thoma, J. L. Magnani, R. Oehrlein, B. Ernst, F. Schwarzenbach, R. O. Duthaler, *J. Am. Chem. Soc.* **1997**, *119*, 7414.

[16] T. Thoma, R. O. Duthaler, B. Ernst, J. L. Magnani, J. T. Patton, PCT Int. Appl., WO 97/19105, **1997**; b) G. Thoma, J. T. Patton, J. L. Magnani, B. Ernst, R. Oehrlein, R. O. Duthaler, *J. Am. Chem. Soc.* **1999**, *121*, 5919.

[17] R. Bosse, D. Vestweber, *Eur. J. Immunol.* **1994**, *24*, 3019.

Received April 10, 2000