Simplified Sialyl Lewis^x Analogues with Improved E-Selectin Inhibition

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The simplified sialyl Lewis^x mimic **5** containing a D-arabinose, a 3-cyclohexyl-2-hydroxypropanoate, and a tetrahydropyran building block instead of L-fucose, sialic acid, and *N*-acetylglucosamine, respectively was synthesized. Compound **5** was 10-fold more potent than sLe^x in a static E-selectin binding assay and showed at 50 μM 75% inhibition in a dynamic-flow assay in which sLe^x did not inhibit neutrophil rolling at up to 1000 μM. Compound **7** with a lactic acid instead of sialic acid building block showed threefold improved potency compared to sLe^x.

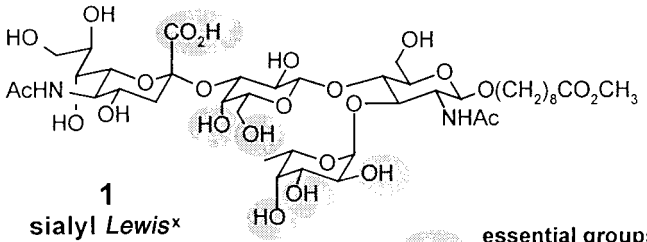
Introduction. – The initial interaction (tethering and rolling) of leukocytes with the endothelium is mediated by the selectin family of adhesion molecules (E-, P-, and L-selectin) [1]. Although their physiological ligands are emerging as a diverse group of glycosylated proteins recognizing one or more of the selectins [2], it has been shown that the minimal carbohydrate epitope recognized by all three selectins is the tetrasaccharide sialyl Lewis^x (sLe^x) **1** (*Fig.*) [1].

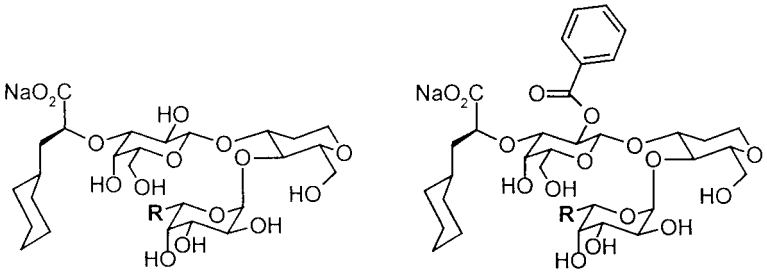
The carbohydrate/selectin-mediated rolling is a prerequisite for leukocyte extravasation, and thus, inhibition of this process is a possible therapy for adverse effects caused by accumulating leukocytes [3]. Evidence stems from experiments with knockout mice, antibodies, and soluble carbohydrates recognized by the selectins [4]. Patients with the LAD-2 syndrome (leukocyte adhesion deficiency 2) indicate the importance of selectins in humans [5]. They have an impaired ability to synthesize the physiological ligands of the selectins, show markedly reduced leukocyte recruitment to sites of inflammation, and consequently suffer from frequent bacterial infections.

The sialyl Lewis^x tetrasaccharide **1**, which is a weak E-selectin inhibitor (K_D = 1060 μM)[1]) [6] became a lead structure to identify simplified but more-potent selectin antagonists. Extensive work elucidated that the essential groups required for binding to E-selectin are the three OH groups of the fucose, the 4- and the 6-OH groups of the galactose, and the carboxylic acid function [7]. Based on this knowledge, a multitude of E-selectin antagonists have been prepared [7].

Earlier, we reported the simplified sLe^x analogue **2**, which is 30-fold more potent than sLe^x in an E-selectin binding assay and can be prepared from commercially available starting materials in ten linear steps in an overall yield of 18% [8a] (for an alternative synthesis of **2**, see [8b]. Compound **2** was designed from sLe^x by replacing sialic acid and *N*-acetylglucosamine by 3-cyclohexyl-2-hydroxypropanoate and a tetrahydropyran building block derived from D-glucal, respectively. We also described

[1]) Individual protein-carbohydrate interactions are generally weak ($K_D = 10^{-3} - 10^{-4}$ M^{-1}), see [6].





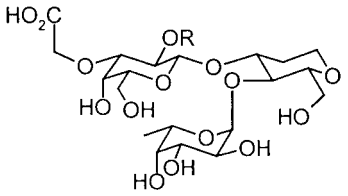


Figure. *Sialyl Lewis^x* **1** *and analogs* **2**–**7**

compound **3**, which is similar to **2** but contains a benzoate at the 2-position of the galactose [9]. It was found to be 100-fold more potent than sLe^x **1** in the binding assay and showed an IC_{50} value of 1–2 μM in a cell-based *in vitro* flow assay. The high potencies of sLe^x analogues **2** and **3** cannot be explained by additional interactions of the methyl substituent or the benzoyl group with E-selectin but are most probably due to improved preorganization of the bioactive conformation in solution compared to sLe^x **1** [10]. Both compounds **2** and **3** contain costly residues such as L-fucose and 3-cyclohexyl-2-hydroxypropanoate. It would be desirable to replace these groups by inexpensive ones such as arabinose and readily available carboxylic acids.

Sialyl Lewis^x analogues with D-arabinose instead of L-fucose[2])[3]) or (*S*)-lactic acid instead of sialic acid[4]) have been described but showed unsatisfying E-selectin inhibition (four- and fivefold less potent than sLe^x **1**, resp.). We reasoned that performing similar modifications on highly potent inhibitors **2** and **3** could – although a drop of activity has to be expected– lead to derivatives with good potency compared to sLe^x **1**.

Here we report on the synthesis and biological evaluation of the novel E-selectin antagonists **4**–**7** (see *Fig.*) which are based on highly potent inhibitors **2** and **3** but contain D-arabinose instead of L-fucose (see **4** and **5**) or glycolic acid instead of 3-cyclohexyl-2-hydroxypropanoate (see **6** and **7**). Compounds **4** and **5** were less potent than **2** and **3** but still showed 3- and 10-fold improved inhibition of E-selectin binding compared to sLe^x **1**. Furthermore antagonist **5** gave 75% inhibition in the flow assay at 50 μM. Compound **6** did not inhibit E-selectin but its galactose-2-benzoate derivative **7** was found to be three times more potent than sLe^x **1**.

Syntheses. – Compounds **4** and **5** were prepared from advanced intermediate **8**, the synthesis of which we reported earlier (*Scheme 1*) [14]. Selective tritylation of the primary OH group gave **9**. D-Arabinose was stereoselectively introduced by means of donor **10**, which was transformed into the corresponding glycosyl bromide by slow addition of a small excess of Br_2. Hydrolysis of the reaction mixture led to the cleavage of the trityl group, and the modified trisaccharide **11** was isolated in 61% yield. The corresponding α-D-glycoside could not be isolated. Hydrogenolysis followed by mild transesterification at room temperature gave compound **5**, which still contains the benzoate at the 2-position of the D-galactose unit. To obtain compound **4**, we removed the benzoate by applying harsher conditions and elevated temperatures. With related compounds, we had observed this selective deprotection earlier [9]. The sodium salt **4** was obtained by passing the lithium salt through an ion-exchange-resin (Na^+) column[5]) [15].

Thioarabinoside **10** was prepared from glycosyl bromide **12**, which was reacted with thiourea in acetone and, subsequently, with bromoethane to give acetylated thioarabinoside **13** (*Scheme 1*). Removal of the acetate groups and introduction of benzyl protecting groups afforded the required arabinose donor **10**.

Compounds **6** and **7** were prepared starting from thiogalactoside **14** [16] by tin-mediated regioselective alkylation[6]) with ethyl iodoacetate (*Scheme 2*). Intermediate **15** was benzoylated ($\rightarrow$**16**) and, subsequently, treated with tetrahydropyran building block **17** [8] to give the desired β-D-linked disaccharide **18** (76%) along with small

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[2]) Replacement of fucose by arabinose in a sLe^x pentasaccharide resulted in a fivefold less potent E-selectin inhibitor [11].

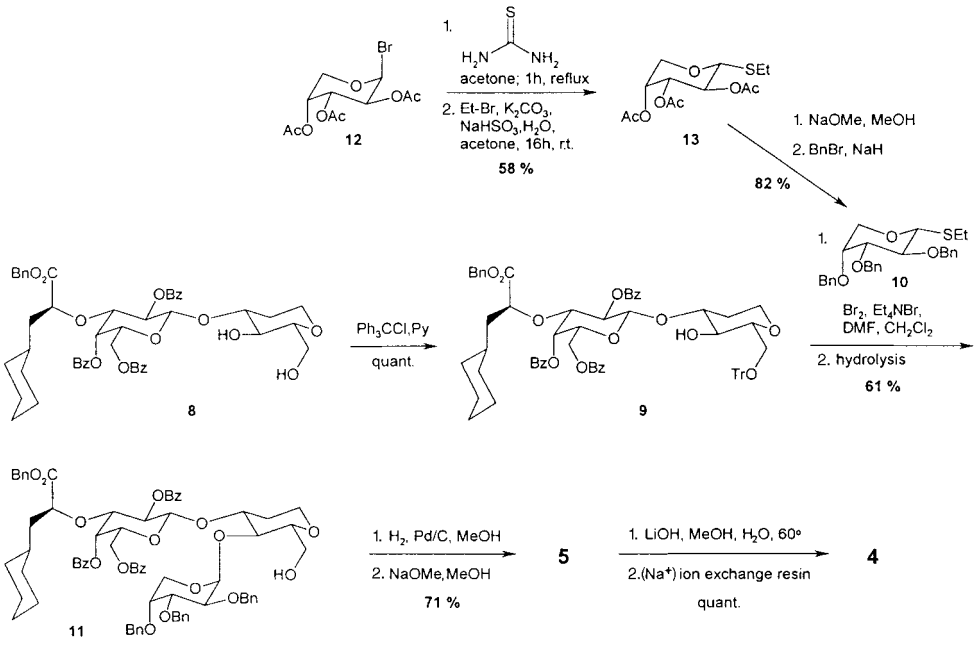
[3]) Very recently, a complex glycopeptide from E-selectin ligand 1 (ESL-1) with the arabino sLe^x structure was reported that showed ninefold improved E-selectin inhibition compared to sLe^x [12]; synthesis and biological evaluation of the corresponding glycopeptide with the fuco sLe^x was not included.

[4]) The corresponding (*R*)-lactic acid derivative was inactive up to 10 mM [13]. An sLe^x mimetic containing glycolic acid instead of sialic acid was 4.5-fold less potent than sLe^x **1** [13].

[5]) It has been reported that compounds contaminated with trace amounts of polyanions released from ion-exchange resins can give false positive test results in selectin assays [15]. To exclude such effects, we tested several compounds that were not treated with ion-exchange resin as sodium salts and as free acids. The biological results in our assays were not affected.

[6]) For regioselective manipulations of OH groups *via* organotin derivatives, see [17].

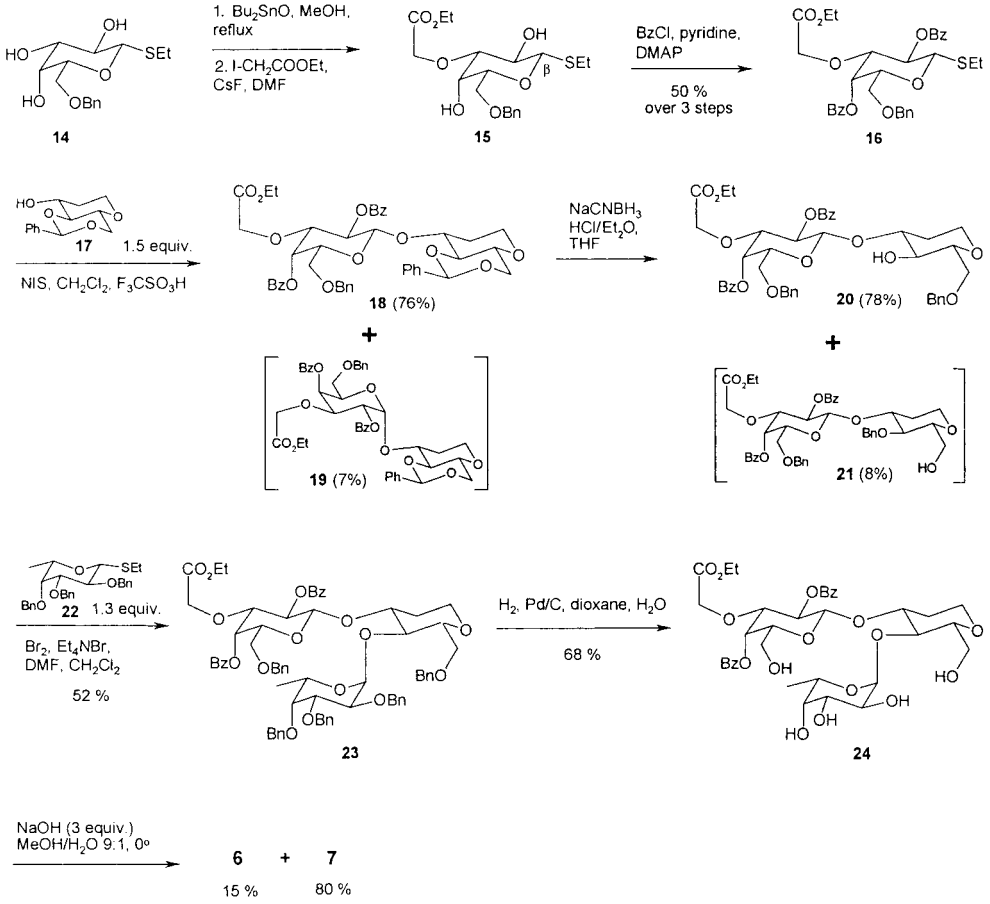
Scheme 1



quantities of its α-D-anomer **19** (7%). This was unexpected since neighboring-group participation of the benzoate at the 2-position of donor **16** should selectively lead to the β-D-glycosidic linkage. In related transformations of acceptor **17** and galactosyl donors having an ether group at the 3-position and a benzoate at the 2-position, we have observed incomplete stereo-induction before [14]. The stereoisomers were separated by chromatography. Reductive opening of the benzylidene acetal afforded regioisomers **20** and **21** as a separable 10:1 mixture (86%). Compound **20** was reacted with fucosyl donor **22** [8] applying similar conditions as described for the arabinosylation of **9**. The fully protected trisaccharide **23** was obtained in 52% yield. Hydrogenolytic removal of the benzyl protecting groups gave pentol **24**, which was treated with NaOH (3 equiv.) in MeOH/H_2O 9:1 at 0° for 2 h. The reaction mixture was quenched with AcOH, and the products **6** (80%) and **7** (15%) were separated by reversed-phase chromatography. The 2-benzoate of the galactose unit in **24** was clearly less stable under basic conditions than the 2-benzoate in **11**, most probably due to shielding by the adjacent bulky 3-cyclohexyl-2-hydroxypropanoate in **11**.

Biological Evaluation. Compounds **4**–**7** were tested in a static, cell-free ligand-binding assay that measures E-selectin inhibition under equilibrium conditions [18]. To compare the data for different compounds obtained on different test plates, sLe^x **1** ($IC_{50} = 1000-1500$ μM) was assayed on each plate as a reference. This allows the determination of IC_{50} values relative to sLe^x **1**, which are defined as relative $IC_{50} = IC_{50}$ (test compound)/IC_{50}(sLe^x **1**). All compounds were tested at least twice. Compounds **4**,

Scheme 2



5, and **7** were found to be significantly more active than sLe^x **1**, showing relative IC_{50} values of 0.31, 0.09, and 0.29, respectively. Compound **6** did not inhibit E-selectin binding at concentrations up to 5000 μM. The most potent antagonist, compound **5**, was also profiled in a dynamic *in vitro* assay which allows monitoring of E-selectin-dependent rolling of neutrophils on activated endothelial cells and, hence, mimics the non-equilibrium *in vivo* conditions [19]. It inhibited rolling by 75% at 50 μM, whereas sLe^x **1** did not show any inhibition in this more relevant assay at up to 1000 μM.

Conclusions. – Based on our highly active E-selectin antagonist **3**, we designed compounds **5** and **7** with inexpensive replacements for the costly L-fucose and 3-cyclohexyl-2-hydroxypropanoate, which were less potent than **3** but 10- and 3-fold more potent than sLe^x **1**.

Experimental Part

General. All reactions were carried out under dry Ar. Commercially available abs. solvents were used. CC = column chromatography, FC = flash chromatography. NMR Spectra: *Bruker Avance-DPX-400* spectrometer; assignments by 2D ^{1}H,^{1}H correlation (COSY) and ^{1}H,^{13}C correlation (HSQC); δ in ppm rel. to $SiMe_4$, J in Hz; Gal = β-D-galactopyranosyl, Ara = β-D-arabinopyranosyl, Fuc = 6-deoxy-α-L-galactopyranosyl, Hex = D-*arabino*-hexitol), cC_6H_{11} = cyclohexyl. MS: *Finnigan MAT-90* mass spectrometer.

O-*3*-O-*[(1S)-1-Carboxy-2-cyclohexylethyl]-*β-D-*galactopyranosyl-(1 → 3)*-O-*[*β-D-*arabinopyranosyl-(1 → 4)]-1,5-anhydro-2-deoxy*-D-arabino-*hexitol Sodium Salt* (**4**). A mixture of **5** (12 mg, 0.021 mmol), LiOH (13 mg, 0.312 mmol), MeOH (1.5 ml), and H_2O (0.5 ml) was stirred at 25° for 24 h. AcOH (0.02 ml) was added, and the solvents were evaporated. The residue was passed through an ion-exchange column (Na^+) and then subjected to CC (*RP-18*, H_2O/MeOH 5:1 → 2:1): **4** (11 mg, quant.). ^{1}H-NMR (400 MHz, D_2O): 0.75–1.72 (*m*, $cC_6H_{11}CH_2$, H_{ax}–C(2) (Hex)); 2.15 (br. *dd*, *J* = 13.0, 5.9, H_{eq}–C(2) (Hex)); 3.31 (*dd*, *J* = 9.5, 3.5, H–C(3) (Gal)); 3.32 (*m*, H–C(5) (Hex)); 3.40 (br. *t*, *J* = 12.0, H_{ax}–C(1) (Hex)); 3.46 (*t*, *J* = 9.5, H–C(4) (Hex)); 3.49 (*d*, *J* = 12.0, H_{ax}–C(5) (Ara)); 3.52 (*t*, *J* = 9.0, H–C(2) (Gal)); 3.54 (*t*, *J* = 6.0, H–C(5) (Gal)); 3.65 (*m*, CH_2(6) (Gal)); 3.74 (*dd*, *J* = 8.0, 3.5, H–C(2) (Ara)); 3.75 (*m*, CH_2(6) (Hex)); 3.82 (*dd*, *J* = 9.0, 3.0, H–C(3) (Ara)); 3.83 (*m*, H–C(4) (Gal)); 3.85–3.95 (*m*, $CHCO_2Na$, H_{eq}–C(1) (Hex), H–C(4) (Ara)); 4.00 (*m*, H–C(3) (Hex)); 4.44 (*d*, *J* = 8.0, H–C(1) (Gal)); 4.47 (*d*, *J* = 12.0, H_{eq}–C(5) (Ara)); 4.93 (*d*, *J* = 3.5, H–C(1) (Ara)). HR-MS: 595.2604 ($C_{26}H_{43}O_{15}^-$, $[M - Na]^-$; calc. 595.2602).

O-*2*-O-*Benzoyl-3*-O-*[(1S)-1-carboxy-2-cyclohexylethyl]-*β-D-*galactopyranosyl-(1 → 3)*-O-*[*β-D-*arabinopyranosyl)-(1 → 4)]-1,5-anhydro-2-deoxy*-D-arabino-*hexitol Sodium Salt* (**5**). A mixture of **11** (200 mg, 0.158 mmol), 10% Pd/C (400 mg) and MeOH (15 ml) was hydrogenated at 25° for 16 h at 1 atm. The catalyst was filtered off and the solvent evaporated. The residue was dissolved in MeOH (10 ml). NaOMe (0.169 mmol) was added, and the mixture was stirred at 25° for 16 h. AcOH (0.02 ml) was added, and the solvent was evaporated. The residue was passed through an ion-exchange column (Na^+) and then subjected to CC (*RP-18*, H_2O/MeOH 3:1 → 1:2): **5** (81 mg, 71%). ^{1}H-NMR (400 MHz, D_2O): 0.27–1.47 (*m*, $cC_6H_{11}CH_2$, H_{ax}–C(2) (Hex)); 2.08 (*m*, H_{eq}–C(2) (Hex)); 3.27 (*m*, H–C(5) (Hex)); 3.34 (*m*, H_{ax}–C(1) (Hex)); 3.35 (*t*, *J* = 9.0, H–C(4) (Hex)); 3.55 (*dd*, *J* = 13.0, 2.0, H_{ax}–C(5) (Ara)); 3.64–3.82 (*m*, 8 H); 3.92 (br. *d*, *J* = 3.0, H–C(4) (Gal)); 3.95 (br. *d*, *J* = 2.0, H–C(4) (Ara)); 3.96 (*m*, H–C(3) (Hex)); 4.49 (*d*, *J* = 13.0, H_{eq}–C(5) (Ara)); 4.86 (*d*, *J* = 8.0, H–C(1) (Gal)); 4.87 (*d*, *J* = 3.0, H–C(1) (Ara)); 5.17 (br. *t*, *J* = 9.0, H–C(2) (Gal)); 7.48 (*t*, *J* = 8.0, 2 arom. H); 7.62 (br. *t*, *J* = 8.0, 1 arom. H); 8.05 (*dd*, *J* = 8.0, 1.0, 2 arom. H). HR-MS: 699.2865 ($C_{33}H_{47}O_{16}^-$, $[M - Na]^-$; calc. 699.2864).

O-*3*-O-*(Carboxymethyl)-*β-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-*α-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-2-deoxy*-D-arabino-*hexitol* (**6**) *and* O-*2*-O-*Benzoyl-3*-O-*(carboxymethyl)-*β-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-*α-L-*galactopyranosyl-(1 → 4)]-1,5-anhydro-2-deoxy*-D-arabino-*hexitol* (**7**). A mixture of **24** (98 mg, 0.131 mmol), NaOH (0.39 mmol), MeOH (25 ml), and H_2O (0.1 ml) was stirred at 0° for 2 h. AcOH (0.1 ml) was added, and the solvents were evaporated. The residue was subjected to CC (*RP-18*, H_2O/MeOH 9:1 → 1:1): **6** (13 mg, 19%) followed by **7** (65 mg, 80%).

Data of **6**: ^{1}H-NMR (400 MHz, D_2O) 1.10 (*J* = 6.5, Me(6) (Fuc)); 1.54 (*qd*, *J* = 12.5, 5.0, H_{ax}–C(2)); 2.13 (*dd*, *J* = 12.5, 5.0, H_{eq}–C(2) (Hex)); 3.29 (*m*, H–C(5) (Hex)); 3.37 (*dd*, *J* = 9.5, 3.0, H–C(3) (Gal)); 3.40 (br. *t*, *J* = 12.0, H_{ex}–C(1) (Hex)); 3.49 (*t*, *J* = 9.0, H–C(4) (Hex)); 3.52 (*dd*, *J* = 7.0, 4.5, H–C(5) (Gal)); 3.65 (*m*, CH_2(6) (Gal)); 3.68 (*dd*, *J* = 10.5, 4.0, H–C(2) (Fuc)); 3.71 (*d*, *J* = 3.5, H–C(4) (Fuc)); 3.73 (*dd*, *J* = 12.0, 5.0, H–C(6) (Hex)); 3.79 (*dd*, *J* = 10.5, 3.5, H–C(3) (Fuc)); 3.83 (*dd*, *J* = 12.0, 2.0, 1 H–C(6) (Hex)); 3.91 (br. *dd*, *J* = 12.0, 5.0, H_{eq}–C(1) (Hex)); 3.96 (*m*, H–C(3) (Hex)); 3.97 (*s*, CH_2CO_2H); 3.98 (*d*, *J* = 3.0, H–C(4) (Gal)); 4.45 (*d*, *J* = 8.0, H–C(1) (Gal)); 4.67 (*q*, *J* = 6.5, H–C(5) (Fuc)); 4.87 (*d*, *J* = 4.0, H–C(1) (Fuc)). HR-MS: 513.1816 ($C_{20}H_{33}O_{15}^-$, $[M - H]^-$; calc. 513.1819).

Data of **7**: ^{1}H-NMR (400 MHz, D_2O): 1.21 (*m*, H_{ax}–C(2) (Hex)); 1.23 (*d*, *J* = 6.5, Me(6) (Fuc)); 2.03 (*m*, H_{eq}–C(2) (Hex)); 3.26 (*m*, H–C(5) (Hex)); 3.33 (*td*, *J* = 12.0, 1.5, H_{ax}–C(1) (Hex)); 3.37 (*t*, *J* = 9.0, H–C(4) (Hex)); 3.65 (br. *t*, *J* = 6.0, H–C(5) (Gal)); 3.66–3.79 (*m*, 8 H); 3.82 (*dd*, *J* = 10.0, 3.0, H–C(3) (Gal)); 3.88 (*m*, H–C(3) (Hex)); 3.89 (*d*, *J* = 16, 1 H, CH_2CO_2H); 3.97 (*d*, *J* = 16, 1 H, CH_2CO_2H); 4.10 (*d*, *J* = 3.0, H–C(4) (Gal)); 4.76 (br. *q*, *J* = 6.5, H–C(5) (Fuc)); 4.81 (*d*, *J* = 8.0, H–C(1) (Gal)); 4.83 (*d*, *J* = 4.0, H–C(1) (Fuc)); 5.24 (*dd*, *J* = 10.0, 8.0, H–C(2) (Gal)); 7.49 (*t*, *J* = 8.0, 2 arom. H); 7.64 (*t*, *J* = 8.0, 1 arom. H); 8.03 (*t*, *J* = 8.0, 2 arom. H). HR-MS: 617.2091 ($C_{27}H_{37}O_{16}^-$, $[M - H]^-$; calc. 617.2082).

1,5-Anhydro-2-deoxy-3-O-*[2,4,6-tri*-O-*benzoyl-3*-O-*[(1S)-1-(cyclohexylmethyl)-2-oxo-2-(phenylmethoxy)-ethyl]-*β-D-*galactopyranosyl]-6*-O-*(triphenylmethyl)*-D-arabino-*hexitol* (**9**). A soln. of **8** [14] (177 mg, 0.204 mol) and chlorotriphenylmethane (114 mg, 0.408 mmol) in pyridine (5 ml) was heated at 70° for 16 h. The solvent

was evaporated and the residue subjected to FC (SiO_2, hexane/AcOEt 3:1 → 2:1): **9** (226 mg, quant.). Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.45–1.70 (*m*, $cC_6H_{11}CH_2$, H_{ax}–C(2) (Hex), H_{eq}–C(2) (Hex)); 3.20 (*m*, H–C(5) (Hex), 1 H–C(6) (Hex)); 3.26 (*td*, *J* = 11.5, 2.0, H_{ax}–C(1) (Hex)); 3.41 (*m*, H–C(3) (Hex), 1 H–C(6), Hex)); 3.49 (br. *t*, *J* = 9.0, H–C(4) (Hex)); 3.85 (*d*, *J* = 1.0, OH–C(4) (Hex)); 3.87 (*m*, H–C(1) (Hex)); 3.88 (*dd*, *J* = 10.0, 3.5, H–C(3) (Gal)); 3.96 (*ddd*, *J* = 8.5, 3.5, 1.0, H–C(5) (Gal)); 4.17 (*dd*, *J* = 8.0, 4.5, C*H*CO_2Bn); 4.24 (*dd*, *J* = 12.0, 8.5, 1 H–C(6) (Gal)); 4.61 (*d*, *J* = 8.0, H–C(1) (Gal)); 4.63 (*dd*, *J* = 12.0, 3.5, 1 H–C(6) (Gal)); 5.07 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.21 (*d*, *J* = 12.0, 1 H, PhCH_2); 5.63 (*dd*, *J* = 10.0, 8.0, H–C(2) (Gal)); 5.88 (*dd*, *J* = 3.5, 1.0, H–C(4) (Gal)); 7.13–8.14 (*m*, 35 arom. H). ESI-MS: 1126 ($[M + NH_4]^+$).

S-*Ethyl 2,3,4-Tris*-O-*(phenylmethyl)-1-thio-α*-D-*arabinopyranoside* (**10**). A mixture of **13** (13.2 g, 41.3 mmol) and $NaOCH_3$ (4.13 mmol) in MeOH (150 ml) was stirred for 16 h at 25°. The mixture was neutralized with *Amberlyst 15* (H^+ form) and filtered and the solvent evaporated to give the corresponding triol as a colorless oil (7.34 g, quant.), which was used without further purification. ^{1}H-NMR (400 MHz, D_2O): 1.04 (*t*, *J* = 7.0, *Me*CH_2S); 2.48 (*m*, MeCH_2S); 3.31 (*m*, 2 H–C(5)); 3.37 (*t*, *J* = 9.5, H–C(2)); 3.64 (*m*, H–C(4)); 3.70 (*dd*, *J* = 10.0, 3.0, H–C(3)); 4.10 (*d*, *J* = 9.0, H–C(1)).

To a soln. of this triol (1.00 g, 5.15 mmol) in DMF (15 ml) was added NaH (0.50 g, 20.8 mmol) in small portions. Benzyl bromide (2.82 g, 16.5 mmol) was added within 45 min, and the mixture was stirred at 25° for additional 30 min. MeOH (0.25 ml) and 2M NaOMe/MeOH (1 ml) and then H_2O (30 ml) were added. The mixture was extracted with Et_2O, the org. phase dried (Na_2SO_4) and evaporated, and the residue subjected to FC (SiO_2, hexane/AcOEt 7:1 → 4:1): **10** (1.96 g, 82%). Colorless foam. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.31 (*t*, *J* = 7.0, *Me*CH_2S); 2.72 (*m*, MeCH_2S); 3.38 (*d*, *J* = 12.0, 1.5, 1 H–C(5)); 3.62 (*m*, H–C(4)); 3.82 (*m*, H–C(2), H–C(3)); 4.20 (*dd*, *J* = 12.0, 3.0, 1 H–C(5)); 4.52 (*d*, *J* = 9.0, H–C(1)); 4.60–4.82 (*m*, H–C(1), 3 PhCH_2); 7.28–7.41 (*m*, 15 arom. H). ESI-MS: 482 ($[M + NH_4]^+$).

O-*2,4,6-Tri*-O-*benzyl-3*-O-*[(1*S*)-1-(cyclohexylmethyl)-2-oxo-2-(phenylmethoxy)ethyl]-β*-D-*galactopyranosyl-(1 → 3)*-O-*[2,3,4-tris*-O-*(phenylmethyl)-β*-D-*arabinopyranosyl-(1 → 4)]-1,5-anhydro-2-deoxy*-D-arabino-*hexitol* (**11**). A soln. of Br_2 (332 mg, 2.08 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise at 0° to a soln. of **10** (840 mg, 1.81 mmol) in CH_2Cl_2 (1.5 ml). After stirring for 30 min at 0°, cyclohexene (0.25 ml) was added to consume excessive Br_2. The soln. was added within 20 min to a mixture of **9** (1000 mg, 0.90 mmol), Et_4NBr (377 mg, 1.81 mmol; dried for 2 h at 200°), and molecular sieves (3 Å, 1.0 g; dried for 24 h at 300°) in DMF/CH_2Cl_2 1:1 (9 ml). The mixture was stirred for 40 h at 25°, diluted with AcOEt and filtered. The resulting soln. was washed with H_2O and brine and dried (Na_2SO_4). The solvent was evaporated and the residue dissolved in Et_2O (40 ml). Formic acid (15 ml) was added, and the mixture was stirred at 25° for 2 h, washed with 1N NaOH, H_2O, and brine. The org. phase was dried (Na_2SO_4) and evaporated and the residue subjected to FC (SiO_2, toluene/AcOEt 4:1 → 3:1): **11** (690 mg, 61%). Colorless foam. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.43–1.42 (*m*, $cC_6H_{11}CH_2$, H_{ax}–C(2) (Hex)); 1.90 (br. *dd*, *J* = 13.0, 5.0, H_{eq}–C(2) (Hex)); 2.35 (br. *s*, OH–C(6) (Hex)); 3.03 (*dt*, *J* = 9.0, 3.5, H–C(5) (Hex)); 3.16 (*t*, *J* = 12.0, H_{ax}–C(1) (Hex)); 3.49 (*t*, *J* = 9.0, 1 H–C(6) (Hex)); 3.64 (br. *s*, H–C(4) (Ara)); 3.66–3.80 (*m*, H_{eq}–C(1) (Hex), H–C(3) (Hex), H–C(4) (Hex), 1 H–C(6) (Hex), 1 H–C(6) (Gal)); 3.82 (br. *d*, *J* = 12.5, 1 H–C(5) (Ara)); 3.87 (*dd*, *J* = 10.0, 3.0, H–C(3) (Gal)); 3.93 (*t*, *J* = 6.5, H–C(5) (Gal)); 3.95 (*dd*, *J* = 10.0, 3.0, H–C(3) (Ara)); 4.08 (*dd*, *J* = 10.0, 3.5, H–C(2) (Ara)); 4.13 (*dd*, *J* = 8.0, 4.5, OC*H*CO_2Bn); 4.34 (*d*, *J* = 6.5, 1 H–C(6) (Gal), 4.38 (br. *d*, *J* = 12.5, 1 H–C(5) (Ara)); 4.40 (*d*, *J* = 12.0, 1 H, PhCH_2); 4.45 (*d*, *J* = 12.0, 1 H, PhCH_2); 4.50 (*d*, *J* = 12.0, 1 H, PhCH_2); 4.57 (*d*, *J* = 12.0, 1 H, PhCH_2); 4.67 (*d*, *J* = 8.0, H–C(1) (Gal)); 4.69 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.86 (*d*, *J* = 11.5, 1 H, PhCH_2); 5.04 (*d*, *J* = 12.0, 1 H, CO_2CH_2Ph); 5.09 (*d*, *J* = 3.5, H–C(1) (Ara)); 5.13 (*d*, *J* = 12.0, 1 H, CO_2CH_2Ph); 5.62 (br. *t*, *J* = 9.0, H–C(2) (Gal)); 5.87 (br. *d*, *J* = 3.0, H–C(4) (Gal)); 7.14–8.13 (*m*, 35 arom. H). ESI-MS: 1286 ($[M + NH_4]^+$).

S-*Ethyl 2,3,4-Tri*-O-*acetyl-1-thio-α*-D-*arabinopyranoside* (**13**). A soln. of **12** (24.0 g, 70.8 mmol) and thiourea (6.30 g, 83.3 mmol) in acetone (96 ml) was stirred and heated under reflux for 1 h. To the grey suspension, acetone (500 ml), H_2O (600 ml), bromoethane (8.54 g, 78.5 mmol), K_2CO_3 (10.1 g, 73.1 mmol), and $NaHCO_3$ (6.72 mg, 64.7 mmol) were added, and the mixture was stirred at 25° for 16 h. The mixture was extracted with CH_2Cl_2, the org. phase dried (Na_2SO_4) and evaporated, and the residue subjected to FC (SiO_2, hexane/AcOEt 4:1 → 1:1): **13** (13.2 g, 58%). Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.29 (*t*, *J* = 7.0, *Me*CH_2S); 2.05 (*s*, 1 AcO); 2.09 (*s*, 1 AcO); 2.04 (*s*, 1 AcO); 2.71 (*m*, MeCH_2S); 3.67 (*dd*, *J* = 12.0, 1.5, 1 H–C(5)); 4.11 (*dd*, *J* = 12.0, 3.0, 1 H–C(5)); 4.52 (*d*, *J* = 9.0, H–C(1)); 5.08 (*dd*, *J* = 10.0, 3.0, H–C(3)); 5.24 (*t*, *J* = 9.5, H–C(2)); 5.20 (*m*, H–C(4)). ESI-MS: 343 ($[M + Na]^+$).

S-*Ethyl 3*-O-*(2-Ethoxy-2-oxoethyl)-6*-O-*(phenylmethyl)-1-thio-β*-D-*galactopyranoside* (**15**). A suspension of **14** [16] (2.54 g, 8.06 mmol) and Bu_2SnO (2.21 g, 8.87 mmol) in MeOH (100 ml) was heated under reflux for 2 h. The solvent was removed and the resulting colorless foam dried *in vacuo* for 16 h. The residue was dissolved in DMF (40 ml). At 0°, iodoacetic acid ethyl ester (8.83 g, 40.3 mmol) and CsF (2.45 g, 16.1 mmol) were added.

The resulting suspension was stirred at 0° for 20 h. The mixture was diluted with AcOEt, washed with H_2O and brine, dried (Na_2SO_4), and evaporated and the crude **15** used without further purification in the next step.

S-*Ethyl 2,4-Di*-O-*benzoyl-3*-O-*(2-ethoxy-2-oxoethyl)-6*-O-*(phenylmethyl)-1-thio-β*-D-*galactopyranoside* (**16**). At 0°, benzoyl chloride (4.54 g, 32.2 mmol) was slowly added to a soln. of crude **15** (8.06 mmol) and *N,N*-dimethylpyridin-4-amine (DMAP; 0.39 g, 3.22 mmol) in pyridine (30 ml). The mixture was stirred at 25° for 16 h. The mixture was diluted with AcOEt and washed with 0.2N, HCl, $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated and the residue subjected to FC (SiO_2, toluene/AcOEt 20:1): **16** (2.44 g, 50%). Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.11 (*t*, *J* = 7.0, *Me*CH_2O); 1.31 (*t*, *J* = 7.5, *Me*CH_2S); 2.74–2.90 (*m*, MeCH_2S); 3.61 (*dd*, *J* = 9.5, 7.0, 1 H–C(6)); 3.70 (*dd*, *J* = 9.5, 6.0, 1 H–C(6)); 3.99 (br. *t*, *J* = 6.5, H–C(5)); 4.00–4.09 (*m*, MeCH_2O); 4.10 (*dd*, *J* = 10.0, 3.5, H–C(3)); 4.15 (*d*, *J* = 17, 1 H, OCC$H_2$$CO_2$Et); 4.26 (*d*, *J* = 17, 1 H, OC$H_2$$CO_2$Et); 4.46 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.54 (*d*, *J* = 11.5,1 H, PhCH_2); 4.71 (*d*, *J* = 10.0, H–C(1)); 5.58 (*t*, *J* = 10.0, H–C(2)); 5.98 (*d*, *J* = 3.5, H–C(4)); 7.20–8.14 (*m*, 15 arom. H). ESI-MS: 631 ([*M* + Na]$^+$).

1,5-Anhydro-2-deoxy-3-O-*[2,4-di*-O-*benzoyl-3*-O-*(2-ethoxy-2-oxoethyl)-6*-O-*(phenylmethyl)-β*-D-*galacto-pyranosyl]-4,6*-O-*(phenylmethylene)*-D-arabino-*hexitol* (**18**) *and 1,5-Anhydro-2-deoxy-3*-O-*[2,4-di*-O-*benzoyl-3*-O-*(2-ethoxy-2-oxoethyl)-6*-O-*(phenylmethyl)-α*-D-*galactopyranosyl]-4,6*-O-*(phenylmethylene)*-D-arabino-*hexitol* (**19**). At 0°, trifluoromethanesulfonic acid (3 drops) was added to a soln. of **16** (1.40 g, 2.30 mmol), **17** [8] (0.81 g, 3.45 mmol), and *N*-iodosuccinimide (NIS; 0.65 g, 2.88 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred for 30 min. Solid $NaHCO_3$ (0.2 g) was added. The mixture was diluted with CH_2Cl_2 and extracted with $NaHCO_3$ soln. and brine. The solvent was evaporated and the residue subjected to FC (SiO_2, toluene/AcOEt 9:1 → 5:1): **19** (0.13 g, 7%) followed by **18** (1.36 g, 76%).

Data of **19**: Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.15 (*t*, *J* = 7.0, *Me*CH_2O); 1.90 (*qd*, *J* = 12.0, 5.0, H_{ax}–C(2) (Hex)); 2.08 (*dd*, *J* = 12.0, 5.0, H_{eq}–C(2) (Hex)); 3.27 (*td*, *J* = 9.5, 5.0, H–C(5) (Hex)); 3.45–3.65 (*m*, H_{ax}–C(1) (Hex), H–C(4) (Hex), 1 H–C(6) (Hex), CH_2(6) (Gal)); 3.92 (*dd*, *J* = 12.0,5.0, H_{eq}–C(1) (Hex)); 3.98 (*m*, H–C(3) (Hex)); 4.08 (*q*, *J* = 7.0, MeCH_2O); 4.17 (*dd*, *J* = 10.5, 5.0, 1 H–C(6) (Hex)); 4.21 (br. *s*, C$H_2$$CO_2$Et); 4.30 (*dd*, *J* = 10.5, 3.5, H–C(3) (Gal)); 4.39 (br. *t*, *J* = 6.0, H–C(5) (Gal)); 4.42 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.51 (*d*, *J* = 11.5, 1 H, PhCH_2); 5.04 (*s*, PhC*H*(O)$_2$); 5.47 (*dd*, *J* = 10.5, 3.5, H–C(2) (Gal)); 5.64 (*d*, *J* = 3.5, H–C(1) (Gal)); 5.97 (*d*, *J* = 3.5, H–C(4) (Gal)); 7.10–8.12 (*m*, 20 arom. H). ESI-MS: 805 ([*M* + Na]$^+$).

Data of **18**: Colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.09 (3 H, *t*, *J* = 7.0, *Me*CH_2O); 1.80 (*m*, H_{ax}–C(2) (Hex), H_{eq}–C(2) (Hex)); 3.28 (*td*, *J* = 9.5, 5.0, H–C(5) (Hex)); 3.38 (*td*, *J* = 12.0, 3.0, H_{ax}–C(1) (Hex)); 3.48 (*dd*, *J* = 9.0, 5.5, 1 H–C(6) (Gal)); 3.56 (br. *t*, *J* = 8.5, 1 H–C(6) (Gal)); 3.67 (*t*, *J* = 9.0, H–C(4) (Hex)); 3.70 (*t*, *J* = 10.0, 1 H–C(6) (Hex)); 3.78 (br. *t*, *J* = 7.0, H–C(5) (Gal)); 3.86 (*m*, H_{eq}–C(1) (Hex)); 3.90 (*m*, H–C(3) (Hex)); 3.94–4.09 (*m*, H–C(3) (Gal), MeCH_2O); 4.12 (*d*, *J* = 17.0, 1 H, C$H_2$$CO_2$Et); 4.23 (*d*, *J* = 17.0, 1 H, C$H_2$$CO_2$Et); 4.26 (*dd*, *J* = 10.0, 5.0, 1 H–C(6) (Hex)); 4.31 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.40 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.89 (*d*, *J* = 8.0, H–C(1) (Gal)); 5.48 (*dd*, *J* = 10.0, 8.0, H–C(2) (Gal)); 5.58 (*s*, PhC*H*(O)$_2$); 5.85 (br. *d*, *J* = 3.0, H–C(4) (Gal)); 7.16–8.14 (*m*, 20 arom. H). ESI-MS: 805 ([*M* + Na]$^+$).

1,5-Anhydro-2-deoxy-3-O-*[2,4-di*-O-*benzoyl-3*-O-*(2-ethoxy-2-oxoethyl)-6*-O-*(phenylmethyl)-β*-D-*galacto-pyranosyl]-6*-O-*(phenylmethyl)*-D-arabino-*hexitol* (**20**) *and 1,5-Anhydro-2-deoxy-3*-O-*[2,4-di*-O-*benzoyl-3*-O-*(2-ethoxy-2-oxoethyl)-6*-O-*(phenylmethyl)-β*-D-*galactopyranosyl]-4*-O-*(phenylmethyl)*-D-arabino-*hexitol* (**21**). At 0°, a sat. HCl soln. in Et_2O (freshly prepared) was slowly added in small portions to a mixture of **18** (1.36 g, 1.74 mmol) and $NaCNBH_3$ (1.09 g, 17.4 mmol) in THF (30 ml). The addition was stopped (11 ml) when TLC (toluene/AcOEt 4:1) indicated complete consumption of **18**. $NaHCO_3$ (solid, 0.75 g) and AcOEt were added. The mixture was washed with $NaHCO_3$ soln. and brine dried (Na_2SO_4), and evaporated, and the residue subjected to FC (SiO_2, toluene/acetone 9:1 → 5:1): **20** (1.06 g, 78%) followed by **21** (0.12 g, 8%).

Data of **20**: Colorless foam. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.11 (*t*, *J* = 7.0, *Me*CH_2O); 1.63–1.74 (*m*, CH_2(2) (Hex)); 3.29–3.37 (*m*, H_{ax}–C(1) (Hex), H–C(5) (Hex)); 3.45 (*td*, *J* = 9.0, 1.5, H–C(4) (Hex)); 3.52 (*m*, H–C(3) (Hex)); 3.59–3.67 (*m*, H–C(6) (Hex), CH_2(6) (Gal)); 3.82 (*dd*, *J* = 10.5, 2.0, 1 H–C(6) (Hex)); 3.90 (*m*, H_{eq}–C(1) (Hex)); 3.98–4.10 (*m*, MeCH_2O, OH–C(4), H–C(3) (Gal), H–C(5) (Gal)); 4.12 (*d*, *J* = 17.0, 1 H, C$H_2$$CO_2$Et); 4.21 (*d*, *J* = 17.0, 1 H, C$H_2$$CO_2$Et); 4.43 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.52 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.59 (*m*, PhCH_2); 4.74 (*d*, *J* = 8.0, H–C(1) (Gal)); 5.53 (*dd*, *J* = 10.0, 8.0, H–C(2) (Gal)); 5.87 (*d*, *J* = 3.0, H–C(4) (Gal)); 7.20–8.11 (*m*, 20 arom. H). ESI-MS: 807 ([*M* + Na]$^+$).

Data of **21**: Colorless foam. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.11 (*t*, *J* = 7.0, *Me*CH_2O); 1.46 (*qd*, *J* = 12.0, 5.0, H–C(2) (Hex)); 1.85 (*m*, OH–C(6)); 1.95 (*dd*, *J* = 12.0, 5.0, H_{eq}–C(2) (Hex)); 3.23 (*ddd*, *J* = 9.5, 5.0, 3.0, H–C(5) (Hex)); 3.33 (*td*, *J* = 12.0, 1.5, H_{ax}–C(1) (Hex)); 3.37 (*t*, *J* = 9.0, H–C(4) (Hex)); 3.60 (*m*, CH_2(6) (Gal)); 3.68 (*m*, 1 H–C(6) (Hex)); 3.81–3.89 (*m*, H_{eq}–C(1) (Hex), 1 H–C(6) (Hex)); 3.94 (br. *t*, *J* = 6.5, H–C(5) (Gal)); 3.97–4.09 (*m*, H–C(3) (Hex), MeCH_2O); 4.11 (*dd*, *J* = 10.0, 3.0, H–C(3) (Gal)); 4.17 (*d*, *J* =

17.0, 1 H, CH_2CO$_2$Et); 4.27 (*d*, *J* = 17.0, 1 H, CH_2CO$_2$Et); 4.39 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.49 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.66 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.85 (*d*, *J* = 8.0, H–C(1) (Gal)); 5.16 (*d*, *J* = 11.5, 1 H, PhCH_2); 5.54 (*dd*, *J* = 10.0, 8.0, H–C(2) (Gal)); 5.93 (br. *d*, *J* = 3.0, H–C(4) (Gal)); 7.20–8.15 (*m*, 20 arom. H). ESI-MS: 807 ([*M* + Na]$^+$).

O-*2,4-Di*-O-*benzoyl-3*-O-*(2-ethoxy-2-oxoethyl)-6*-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-6*-O-*(phenylmethyl)*-D-arabino-*hexitol* (**23**). A soln. of Br_2 (307 mg, 1.92 mmol) in CH_2Cl_2 (2 ml) was added dropwise at 0° to a soln. of **22** [8] (840 mg, 1.81 mmol) in CH_2Cl_2 (2 ml). After stirring for 30 min at 0°, cyclohexene (0.20 ml) was added to consume excessive Br_2. The soln. was added within 10 min to a mixture of **20** (1050 mg, 1.34 mmol) and Et_4NBr (335 mg, 1.61 mmol; dried for 2 h at 200°) in DMF/CH_2Cl_2 1:1 (10 ml). The mixture was stirred for 70 h at 25°, diluted with AcOEt and filtered. The resulting soln. was washed with H_2O and brine, dried (Na_2SO_4), and evaporated and the residue subjected to FC (SiO_2, hexane/AcOEt 1:1 → 1:2): **23** (838 mg, 52%). Colorless foam. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.10 (*t*, *J* = 7.0, *Me*CH$_2$O); 1.41 (*d*, *J* = 6.5, Me(6) (Fuc)); 1.49 (*qd*, *J* = 12.0, 5.0, H_{ax}–C(2) (Hex)); 2.03 (br. *dd*, *J* = 12.0, 5.0, H_{eq}–C(2) (Hex)); 3.29–3.37 (*m*, H_{ax}–C(1) (Hex), H–C(5) (Hex)); 3.56–3.65 (*m*, 1 H–C(6) (Hex), CH_2(6) (Gal)); 3.66 (br. *d*, *J* = 2.5, H–C(4) (Fuc)); 3.76 (*dd*, *J* = 10.5, 4.0, 1 H–C(6) (Hex)); 3.79 (*t*, *J* = 9.0, H–C(4) (Hex)); 3.86–3.97 (*m*, H_{eq}–C(1) (Hex), H–C(3) (Hex), H–C(3) (Fuc), H–C(5) (Gal)); 3.97–4.09 (*m*, MeCH_2O, H–C(2) (Fuc), H–C(3) (Gal)); 4.13 (*d*, *J* = 17.0, 1 H, CH_2CO$_2$Et); 4.23 (*d*, *J* = 17.0, 1 H, CH_2CO$_2$Et); 4.41 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.42 (*s*, PhCH_2); 4.49 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.52 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.57 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.58 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.63 (*d*, *J* = 11.5, PhCH_2); 4.73 (br. *q*, *J* = 6.5, H–C(5) (Fuc)); 4.75 (*d*, *J* = 11.5, 1 H, PhCH_2); 4.78 (*d*, *J* = 8.0, H–C(1) (Gal)); 4.93 (*d*, *J* = 11.5, 1 H, PhCH_2); 5.06 (*d*, *J* = 3.5, H–C(1) (Fuc)); 5.49 (*dd*, *J* = 10.0, 8.0, H–C(2) (Gal)); 5.93 (br. *d*, *J* = 3.0, H–C(4) (Gal)); 7.16–8.12 (*m*, 35 arom. H). ESI-MS: 1223 ([*M* + Na]$^+$).

O-*2,4-Di*-O-*benzoyl-3*-O-*(2-ethoxy-2-oxoethyl)-6*-O-*(phenylmethyl)-β*-D-*galactopyranosyl-(1 → 3)*-O-*[6-deoxy-α*-L-*galactopyranosyl)-(1 → 4)]-1,5-anhydro-2-deoxy*-D-arabino-*hexitol* (**24**). A mixture of **23** (300 mg, 0.250 mmol), 10% Pd/C (150 mg), dioxan (10 ml), and H_2O (2 ml) was hydrogenated at 25° for 16 h at 1 atm. The catalyst was filtered off and the solvent evaporated. The residue was subjected to CC (SiO_2, ^{i}PrOH/AcOEt/H_2O 1:1:0.05 → 1:1:0.1): **24** (127 mg, 68%). Colorless solid. ^{1}H-NMR (400 MHz, CD_3OD):1.07 (*t*, *J* = 7.0, *Me*CH$_2$O); 1.30 (*m*, H_{ax}–C(2) (Hex)); 1.38 (*d*, *J* = 6.5, Me(6) (Fuc)); 2.13 (*m*, H_{eq}–C(2) (Hex)); 3.19 (br. *d*, *J* = 9.0, H–C(5) (Hex)); 3.38 (*t*, *J* = 12.0, H_{ax}–C(1) (Hex)); 3.58 (*t*, *J* = 9.0, H–C(4) (Hex)); 3.63–3.72 (*m*, 1 H–C(6) (Hex), CH_2(6) (Gal)); 3.47 (*dd*, *J* = 10.0, 3.0, H–C(2) (Fuc)); 3.76–3.86 (*m*, H_{eq}–C(1) (Hex), 1 H–C(6) (Hex), H–C(3) (Fuc), H–C(4) (Fuc)); 3.86–4.03 (*m*, MeCH_2O, H–C(3) (Hex), H–C(5) (Gal)); 4.13–4.25 (*m*, CH_2CO$_2$Et, H–C(3) (Gal)); 4.89 (*m*, H–C(5) (Fuc), H–C(1) (Gal)); 4.97 (*d*, *J* = 3.0, H–C(1) (Fuc)); 5.44 (br. *t*, *J* = 9.0, H–C(2) (Gal)); 5.85 (br. *d*, *J* = 2.5, H–C(4) (Gal)); 7.47–8.13 (*m*, 10 arom. H). ESI-MS: 773 ([*M* + Na]$^+$).

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