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Design and Synthesis of *C*-Linked Fucosides as Inhibitors of E-Selectin

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Abstract—Two series of *C*-linked fucosides as mimetics for the tetrasaccharide sialyl Lewis X have been synthesized and tested as inhibitors of E-Selectin. The fucopeptides have been prepared from three key intermediates, including α-*C*-allyl fucose, natural and unnatural amino acids bearing hydroxyl groups and an α,ω-diacid moiety for the imitation of the essential three parts of SLe^x, i.e., the Fuc, Gal, and NeuAc. The nature and distance of the linkage of the fucose moiety to the amino acids as well as the distance between the amino acids and the terminal carboxylic acid group turned out to be crucial for the biological activity. In addition the necessity of both OH groups (4- and 6-OH) in the Gal part could be confirmed. Conformational NMR study of the most active mimetic supports the structure–activity relationship. A second series of mimetics was prepared, where Fuc and Gal moieties were purely *C*-linked. In the synthesis of β-*C*-allyl galactose an intramolecular 1,2-hydride shift led to an interesting side product. However, the substituted glycosidic oxygens led to a substantial loss of conformational constrain, which could not be compensated and resulted in low activity. Copyright © 1996 Elsevier Science Ltd

Introduction

Carbohydrate recognition was found to be a key step in inflammatory response to injury and infection. A terminal unit of cell surface glycoproteins and glycolipids was determined as the tetrasaccharide sialyl Lewis X (SLe^x, **1**), α-*N*-acetylneuraminyl-(2,3)-β-D-galactopyranosyl-(1,4)-[α-L-fucopyranosyl-(1,3)]-β-D-*N*-acetylglucosamine), which acts as a ligand for the endothelial leukocyte adhesion molecule-1 (E-Selectin). This carbohydrate/protein recognition mediates the early stage of the adhesion of leukocytes to activated endothelial cells and leads to leukocyte rolling on the vessel wall followed by firm attachment and extravasation of the blood cell.[1]

Overwhelming immune response however causes the excessive adherence of neutrophiles at the site of inflammation which is the reason for several acute or chronic diseases. The desire to block the carbohydrate E-Selectin recognition leads to the development of novel therapeutics imitating the role of SLe^x.

The natural ligand SLe^x itself has been prepared on large scale for clinical evaluation as an anti-inflammatory agent,[2] but due to its oral inactivity and its instability in the blood stream could only be used in intravenous application for acute symptoms.[3] Therefore the search for novel SLe^x mimetics has been focused on simpler structures with high affinity to E-Selectin and resistance to glycosidases (i.e., fucosidase and sialidase, respectively).[4]

The determination of the bioactive conformation of SLe^x has been intensively studied. The relatively weak interaction between SLe^x and E-Selectin on one hand prevents the isolation of the bound complex, but on the other hand suggests that the free and the bound conformation of SLe^x might essentially be the same. A hydrophilic surface stretching from the 2-, 3- and 4-OH groups of Fuc over the 4- and the 6-OH groups of Gal to the $-CO_2-$ group of NeuAc was proposed to be the E-Selectin binding domain of SLe^x.[5,6] The crystal structure of E-Selectin has been used in modeling the ligand binding,[7] and also the combination of transfer NOE studies with molecular modeling has been employed in investigating the bound conformation of SLe^x.[8,9] Most recent results indicate that the orientations of the *N*-acetylneuraminic acid and, to a smaller extent, also the fucose residue appear to be twisted in comparison to the conformation of free SLe^x in solution[2,10,11] upon binding to E-Selectin.[12] Furthermore, a SLe^x mimetic containing a conformationally fixed carboxylic acid group to imitate the orientation of NeuAc as in the solution conformation of SLe^x, proved to be biologically inactive.[13]

We have been particularly interested in the development of *C*-linked fucosides, which ensure an α-connection with an excellent stability towards glycosidases.

Although lacking the electronic contribution to the *exo*-anomeric effect it has been shown that *C*-glycosides adopt the same favorable gauche conformation as the *O*-linked analogues.[14]

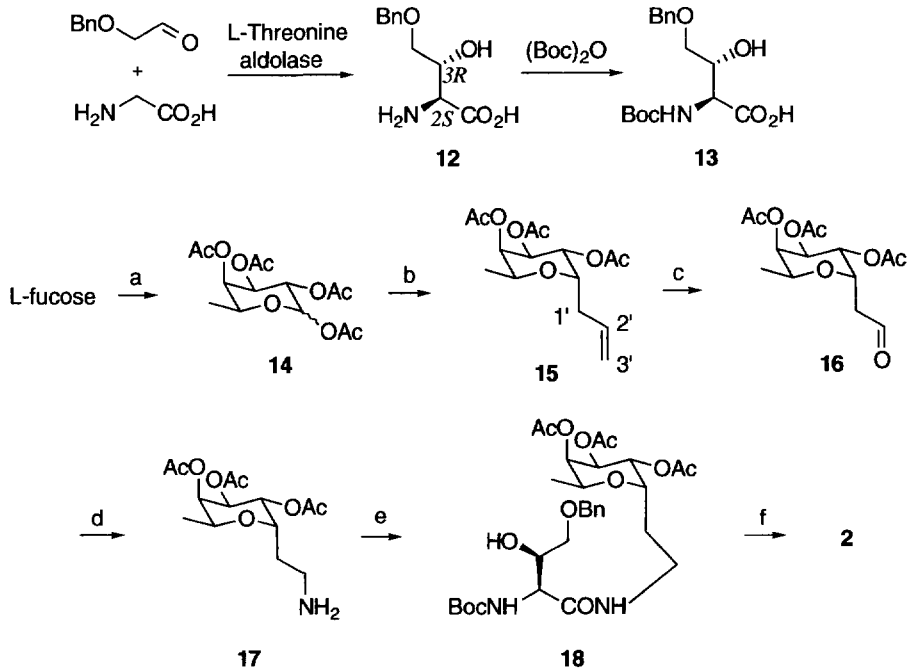
We have designed two series of small molecules (**2–10**) that contain these functional groups to mimic the active SLe^x conformation (Chart 1). In the fucopeptide series (**2–7**) the Gal residue is replaced by an amino acid, either 2*S*,3*R*-2-amino-3,4-dihydroxybutyric acid (4-hydroxy-L-*allo*-threonine) **12** or L-threonine (Scheme 1). A two- or three-carbon spacer group is designed to link the fucose and the amino acids via an amide or an ester bond. Model studies indicate that these *C*-glycopeptides resemble the active conformation of SLe^x and that the one or two OH groups of the amino acids in these analogues overlap with 4- and 6-OH groups of Gal in SLe^x or at least mimic one of them in the L-threonine containing compound. The second series (**8–10**) contains a fucose and a galactose residue linked by a four carbon spacer, where both glycosidic oxygens of the ethylene glycol tethered parent structure **11**[15] have been replaced. The employment of the *cis*-olefin as well as the corresponding epoxide as linkers in the compounds **8** and **10** were designed to have more constrained glycosidic torsion angles than the rather flexible all saturated linked **9**.

Results and Discussion

Mimetic **2** was initially synthesized as shown in Scheme 1,[4b] starting from tetraacetate **14**, which was converted to 3-(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-1-propene (**15**) by Luengo's procedure.[16] Ozonolysis in CH_2Cl_2 at −78 °C was followed by reductive work up with PPh_3 to give the aldehyde **16**. The reductive aminination with Pd–C in the presence of ammonium acetate (30 equiv) gave 1-(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-2-aminoethane (**17**) in 50% yield. The amino acid component (i.e., 2*S*,3*R*-γ-benzyloxythreonine) prepared from glycine and commercially available benzyloxyacetaldehyde catalysed by L-threonine aldolase,[17] was protected by *t*-butoxycarbonyl group (Boc) to provide the *N*-Boc derivative **13**. This was coupled to the α-*C*-fucosylethyl amine **17** using *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide (EDC) to afford fucopeptide **18** in 82% yield. After removal of the Boc group with HCl in EtOAc, the obtained amine hydrochloride was treated with glutaric anhydride in the presence of triethylamine (1 equiv) to yield the dipeptide derivative in 80% yield. Finally, deprotection of the benzyl and acetyl groups by successive hydrogenation on Pd–C and hydrolysis with 1.3 equiv of NaOMe in MeOH gave the target compound **2** (62%).

Although the procedure described in Scheme 1 was suitable for a small-scale synthesis, acyl migration to the primary amine was observed in the large-scale process. We therefore changed the acetyl protecting groups to benzyl groups and by recrystallization of the intermediate triol **19** from EtOAc any β-impurities from the *C*-allylation[18] could be removed effectively. The overall yield of the common starting material **20** for all the desired fucopeptide mimetics was 74% from L-fucose (Scheme 2).

For the synthesis of the two methylene spacer containing compounds (Scheme 3) tribenzylether **20** was ozonolyzed and treated with Me_2S to provide



Scheme 1. (a) Ac_2O, pyr, 96%; (b) allyl-TMS, TMSOTf, $MeNO_2$, −10 °C; (c) i. O_3, CH_2Cl_2, −78 °C, ii. Ph_3P, 76%; (d) NH_4OAc, H_2/Pd–C, MeOH, 60%; (e) **13**, EDC, $CHCl_3$, 82%; (f) i. H^+, ii. glutaric anhydride, TEA, MeOH, iii. H_2/Pd–C, MeOH–H_2O, iv. NaOMe, MeOH, 60%.

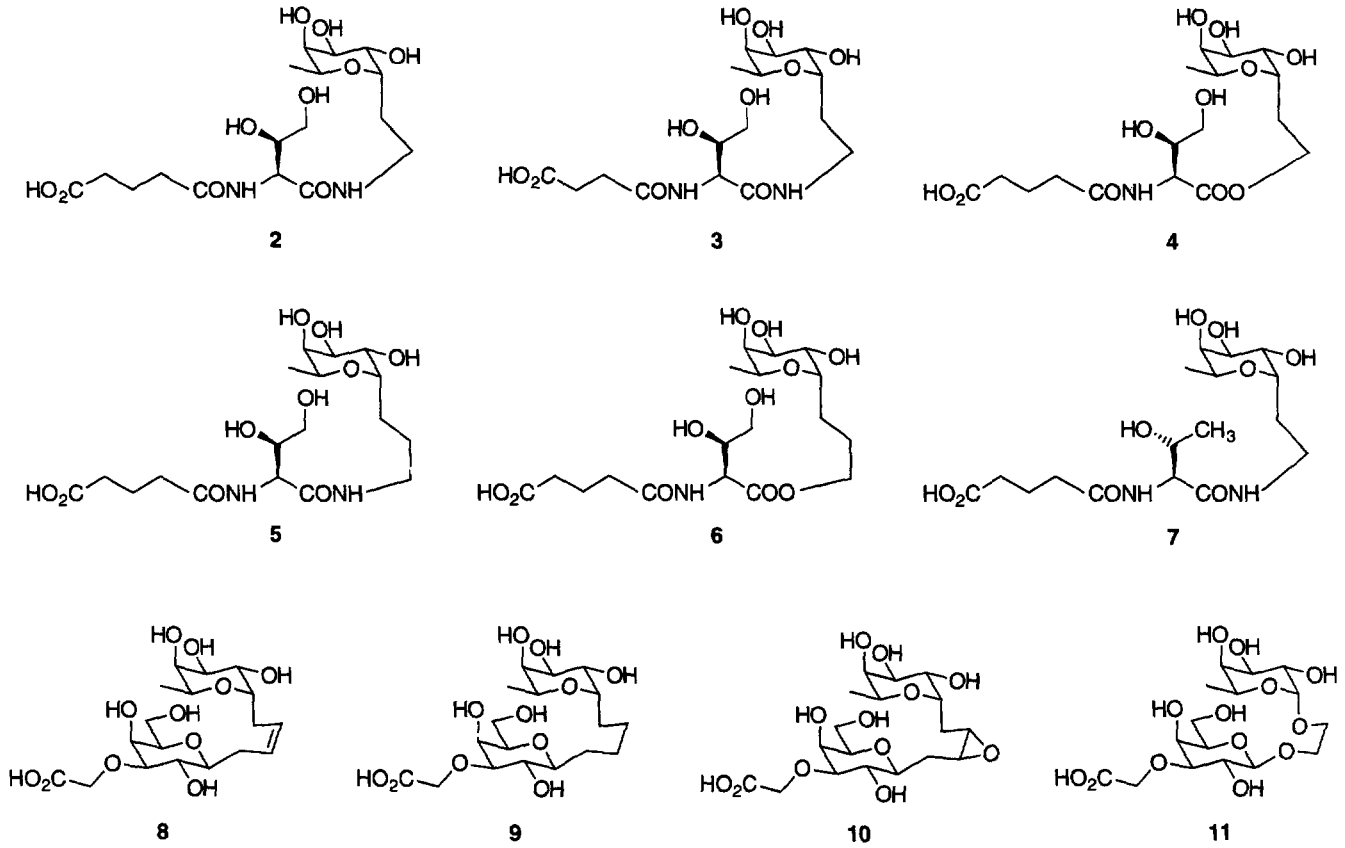


Chart 1.

aldehyde **22**. Reductive amination with $NaBH_3CN$ in the presence of excess NH_4OAc gave the amine **23** (60%), which was then coupled with *N*-Boc amino acid **13** to form peptide **24** (76%). After deprotection of the Boc group and treatment with glutaric anhydride, the following debenzylation with H_2/Pd–C gave **2** (70%) without any complication. The substitution of glutaric with succinic anhydride in the same synthesis yielded the analogous mimetic **3**, which carries the shorter four carbon moiety to resemble the sialic acid part.

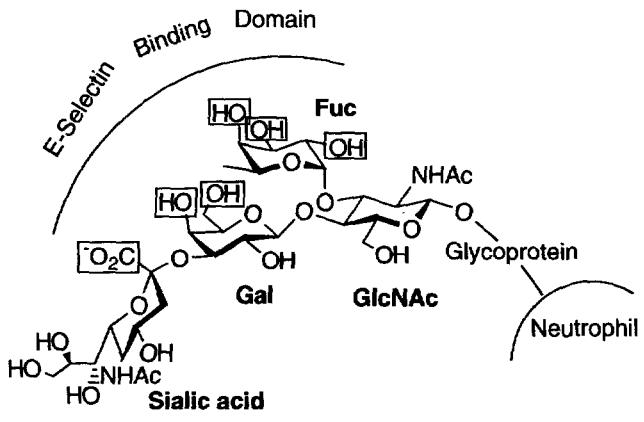


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Figure 1. The structure of sialyl Lewis X (**1**) and its six essential functional groups (highlighted) involved in E-Selectin binding.

Reductive work up of the ozonolysis of **20** with $NaBH_4$ afforded alcohol **25** (94%), which was converted to bromide **26** (75%) and coupled with *N*-Boc amino acid cesium salt **21** in warm DMF to form the ester **27** (65%). Attempting this ester formation, it was found that those coupling reagents (DCC(+DMAP), EDC(+DMAP), BOP, and BOP-Cl) activating the carboxylic acid functionality could not promote the desired esterification of the amino acid **13**, probably due to intramolecular interference of the free 3-OH group. Finally, compound **27** was treated as described in the synthesis of **2** from **24** to obtain the target ester **4** (71%).

For the synthesis of mimetics **5** and **6** (Scheme 4), tri-*O*-benzyl ether **20** was hydroborated with 9-BBN followed by oxidative work up with H_2O_2/NaOH to provide the alcohol **28** (87%). Chloromethane-sulfonyl ester[19] of **28** was then prepared and converted to the azide, which was reduced with H_2S gas in pyridine:H_2O (2:1) solution to give amine **29** (75% from **20**). This amine was also treated as described in the synthesis of **2** from **23** to obtain the target amide **5** (79% from **29**).

The synthesis of ester **6** from alcohol **28** was analogous to that from **25** to **4** as described above (39% from **28**).

The preparation of the L-threonine containing mimetic **7** (Scheme 5) started from the alcohol **25**, which was converted via the intermediate mesylate to the azide

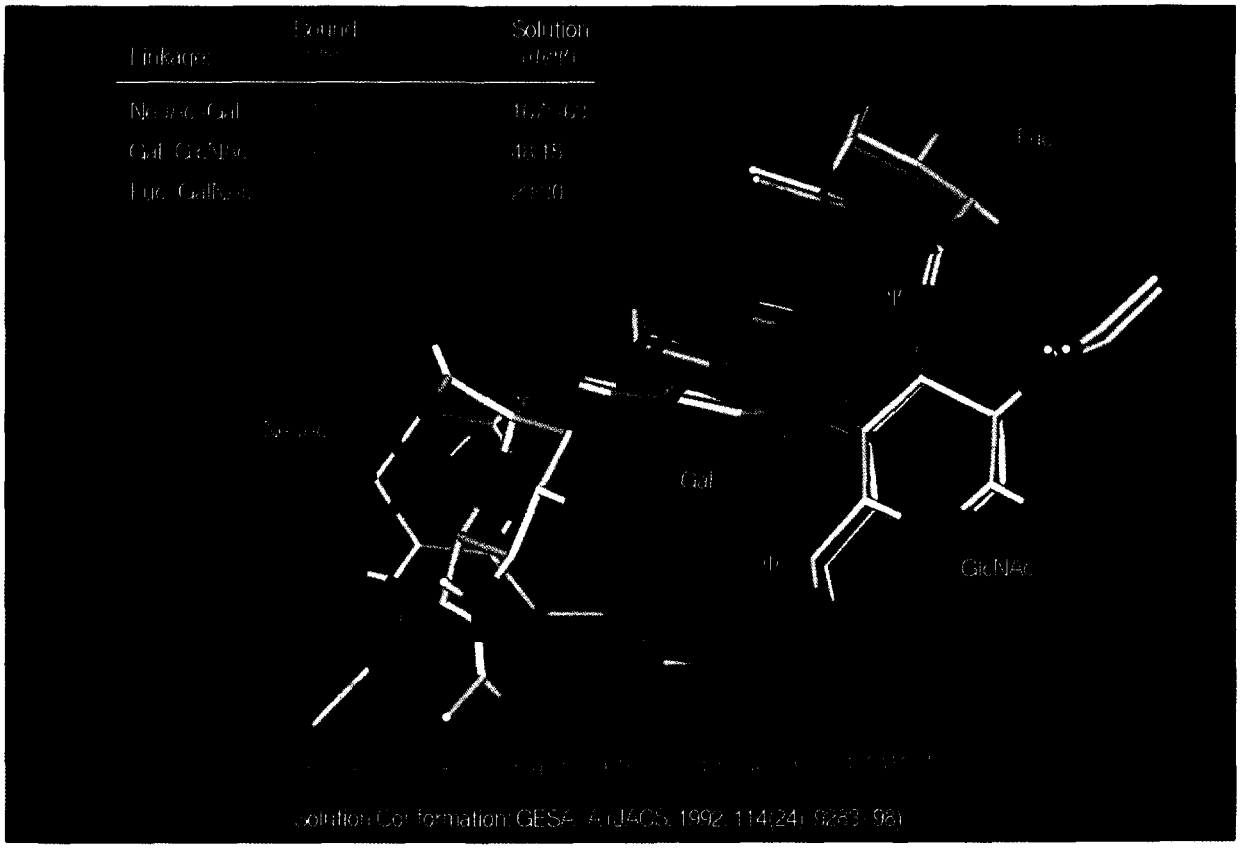
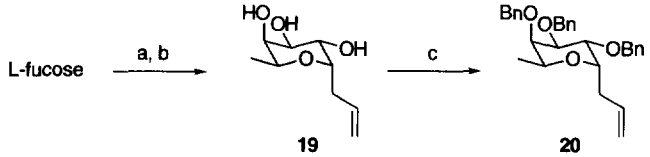


Figure 2. Overlay of the three conformations of SLe^x. White, free conformation determined by NMR.[2] Green, predicted free conformation (GESA).[2] Yellow, bond conformation determined by transfer NOE.[12] Listed are the three sets of glycosidic torsion angles.

and reduced under Staudinger-conditions (PPh_3, H_2O) to the amine **23**, resulting in a better overall yield (80%) than the previously described reductive amination (54%). Coupling with the commercially available *N*-Boc-*O*-benzyl-L-threonine using EDC afforded the peptide **33**, followed by the standard Boc-deprotection, coupling with glutaric anhydride and final debenzylation to give the desired mimetic **7**.

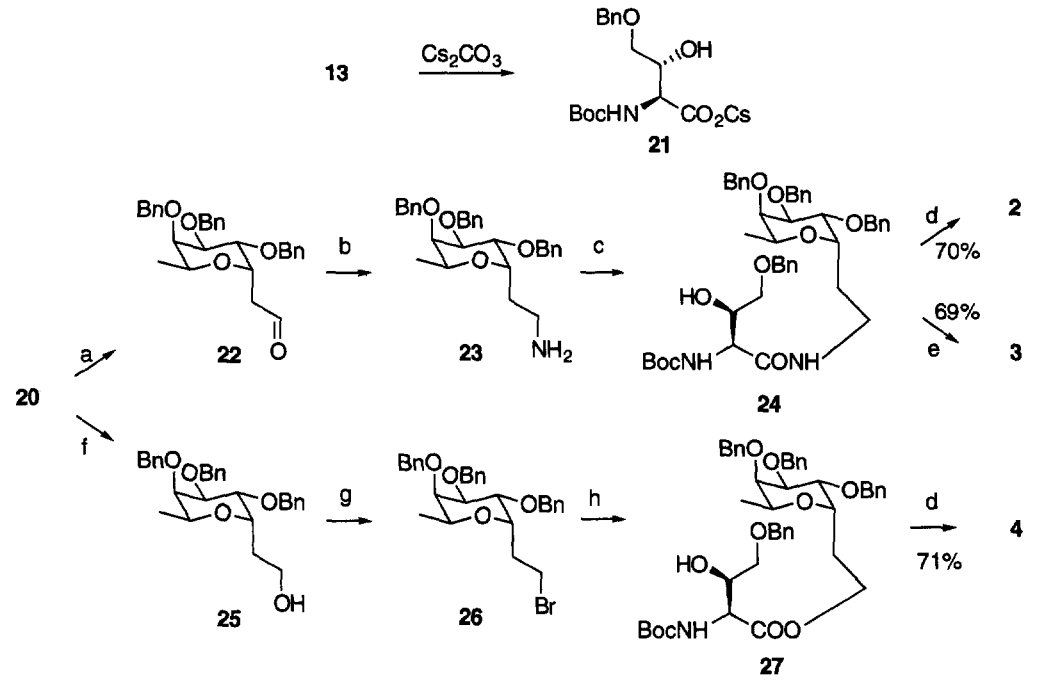
For the syntheses of the compounds **8–10**, the fucose part could be easily constructed from the above mentioned tri-*O*-acetyl-α-*C*-allyl-L-fucoside **15** (Scheme 6). Ozonolysis and reduction to the alcohol **34**, followed by conversion to the bromide **35** and treatment with PPh_3 afforded the Wittig reagent **36** (47% from **15**). The preparation of the necessary β-*C*-allyl-D-galactoside as the coupling counterpart for the planned Wittig reaction proved to be more difficult. Standard *C*-allylation procedures employing allyltrimethylsilane as nucleophile, galactose pentaacetate as



Scheme 2. (a) Ac_2O, pyr; (b) i. $H_2C{=}CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, TMSOTf, CH_3CN, 0 °C, ii. NaOMe, MeOH, iii. recrystallization from EtoAc, 74% from L-fucose; (c) NaH, BnBr, Bu_4NI, THF, 99%.

electrophile and $BF_3{\cdot}OEt_2$ as the Lewis acid, generally favor the undesired α-*C*-allyl-D-galctoside as the major product.[20] Several attempts to overcome this selectivity by varying the reaction conditions were undertaken, resulting in a remarkable dependency on the solvent (Table 1). The usually employed CH_3CN gave the highest ratio of undesired α-product (entry 1), whereas the less polar CH_2Cl_2 yielded an almost equal amount of α- and β-product (entry 2). In THF and benzene however, no reaction took place at 23 °C (entries 3 and 4) and only elevated temperature yielded again an unsatisfying anomeric ratio of 3:1 (entry 5). Using a mixed solvent system of CH_2Cl_2–benzene (1:3), the reaction proceeded, but failed to produce the desired product as the major isomer (entry 6). This allylation procedure appears to neglect the neighboring group participation.

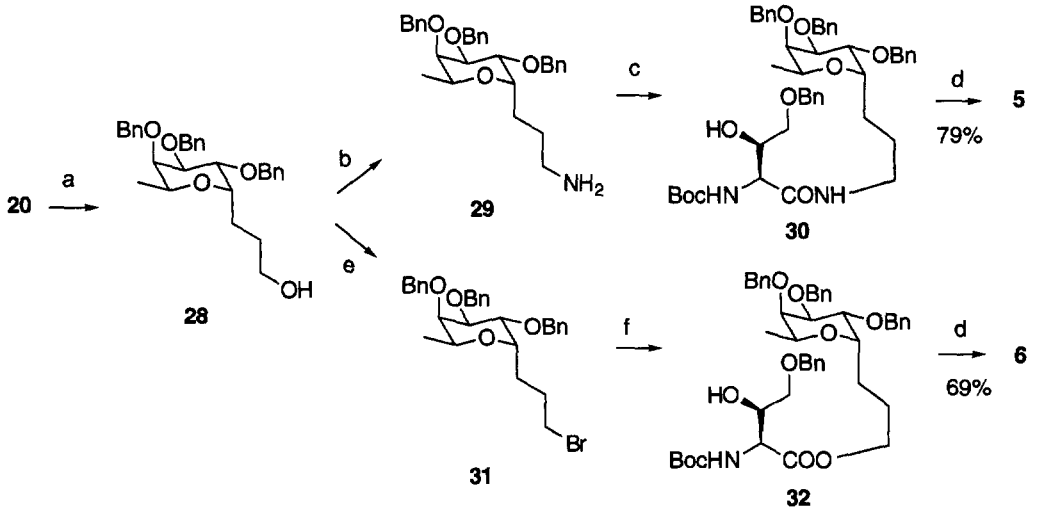
Therefore, our second approach to the construction of the β-*C*-allyl-D-galactoside was based on a strategy of an organometallic reaction with glycosyl bromide, a protocol known to afford good selectivity, depending on the participating group at C-2.[21] Treatment of tetra-acetyl-α-galactosyl bromide **37** with excess allylmagnesium bromide (10 equiv) resulted after aqueous work up and acetylation in the isolation of the desired β-*C*-allyl-D-galactoside **38** (60%) and the side product **39** (22%) (Scheme 7). The structure of **39** was confirmed by X-ray crystal structure analysis of the acetonide derivative **42**[4b] (Scheme 8). The formation of



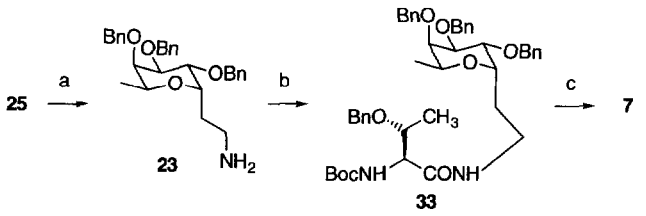
Scheme 3. (a) i. O_3, CH_2Cl_2–MeOH, −78 °C, ii. Me_2S, 90%; (b) NH_4OAc, $NaBH_3CN$, MeOH, 60%; (c) **13**, EDC, $CHCl_3$, 76%; (d) i. H^+, ii. glutaric anhydride, TEA, MEOH, iii. H_2/Pd–C, MeOH–H_2O; (e) i. H^+, ii. succinic anhydride, TEA, MEOH, iii. H_2/Pd–C, MeOH-H_2O; (f) i. O_3, CH_2Cl_2/MeOH, −78 °C, ii. $NaBH_4$, 94%; (g) CBr_4, PPh_3, CH_2Cl_2, 75%; (h) **21**, DMF, 40 °C, 65%.

39 may proceed through an epoxide intermediate, followed by an 1,2-hydride shift, as an analogous rearrangement was reported previously.[22] The tetraacetate **38** was deprotected and selectively reprotected to the 4:6-*p*-methoxybenzylidene acetal **40** (Scheme 7). Regioselective alkylation of the 3-OH group was achieved by activation via the intermediate dibutyltin acetal and subsequent treatment with methyl bromoacetate/Bu_4NI in refluxing toluene, which gave the lactonized compound. Final ozonolysis of the allyl moiety to the aldehyde **41** (22% from **37**) set the stage for the Wittig coupling with the fucose part. The phosphonium salt **36** was deprotonated with NaHMDS at −78 °C to the ylide and allowed to react with the aldehyde **41** to afford the desired *cis*-olefin **43** (29%) (Scheme 9). Deprotection of **43** by means of acidic acetal cleavage and saponification of the acetates as well as lactone ring opening gave mimetic **8** (80%), which could be hydrogenated to the butane linked mimetic **9** (100%). Epoxidation of **43** with mCPBA yielded a 1:1 diastereomeric mixture of epoxides, which were separated by HPLC and deprotected by subsequent hydrogenation (H_2/Pd(OH)(2)–C) and saponification (NaOH, aqueous THF) to give the epoxide mimetic **10** (80% from **43**).

All compounds **2**–**10** are resistant to α-fucosidase and β-galactosidase and were tested as inhibitors of SLe^X



Scheme 4. (a) i. 9-BBN, THF, ii. NaOH, H_2O_2, 87%; (b) i. $ClCH_2SO_2Cl$, pyr, ii. NaN_3, DMF, 50 °C, iii. H_2S, pyr-H_2O (2:1), 75%; (c) **13**, EDC, $CHCl_3$, 78%; (d) H^+, ii. glutaric anhydride, TEA, MeOH, iii. H_2/Pd–C, MeOH–H_2O; (e) CBr_4, PPh_3, CH_2Cl_2, 83%; (f) **21**, DMF, 40 °C, 68%.



Scheme 5. (a) i. $MeSO_2Cl$, TEA, CH_2Cl_2, 0 °C, ii. NaN_3, DMF, 65 °C, iii. PPh_3, H_2O, THF, 85%; (b) *N*-Boc-*O*-benzyl-L-threonine, EDC, HOBt, 4-methylmorpholine, DMF, −20 °C ≥ 23 °C, 98%; (c) i. TFA, CH_2Cl_2, ii. glutaric anhydride, MeOH, iii. $H_2/Pd(OH)_2$–C, HOAc–H_2O, 63%.

glycoconjugate in binding to immobilized recombinant E-Selectin.[23] The following IC_{50} values were measured: **1** (=SLe^X) 0.5 mM; **2**, 0.3 mM;[24] **3**, >5 mM; **4**, >10 mM; **5**, >10 mM; **6**, >10 mM; **7**, 1.0 mM; **8**, 15 mM; **9**, 20 mM; **10**, 5 mM; **11**, 1 mM.[25] Surprisingly none of the mimetics **4**, **5**, and **6** showed any inhibition of E-Selectin binding up to a 10 mM concentration. Therefore, not only the distance between the fucose and the amino acid part (two versus three methylene units), but also the nature of the connection is of importance (e.g., amide versus ester linkage). It is believed that the enhanced restriction of the conformationally more rigid amide bond in comparison to the more flexible ester moiety is responsible for the observed difference in the IC_{50} of **2** versus **4**. Although the mimetic **7** lacks one hydroxyl group imitating the Gal residue it primarily shows an IC_{50} of 1.0 mM. However the missing interaction causes the inhibition to drop to 9 mM in a further evaluation using the HL-60/E-Selectin assay.

A conformational study of the most active amide **2** in solution was performed, using NMR techniques (500 MHz, D_2O, 30 °C) as described for SLe^x in an earlier study (NOESY).[2] The intensities of NOE for the hydroxythreonine moiety are relatively weak compared to that of the *C*-fucoside moiety (Fig. 3). Energy minimization gave five conformations with slightly different orientation for the two OH groups of the hydroxythreonine part. The two-carbon linked *C*-fucoside moiety is, however, relatively stable. The *C*-glycosidic torsion angle (Φ=H1-C1-C1′-C2′) and also the dihedral angle (Ψ=C1-C1′-C2′-N) of the second C—C-bond in the connection of the fucose with the amino acid were thus determined (Fig. 4). Both dihedral angles indicate a basically staggered conformation in the ethylene linker of **2**, but also in both cases a clear gauche conformation was populated. These results and the additionally observed NOEs led to the complete modelling of **2**, in which the aglycon seems to be bended over to the left side of the molecule so that the two OH groups of the amino acid are positioned in the Gal space and the negative charge can reach that of the NeuAc position (top of Fig. 3). Therefore, the shorter two-carbon linkage in **2** resembles the Gal part better than the longer three-carbon unit in **5**, resulting in the better activity of the C-2 amide **2** versus the C-3 amide **5**. The distance between Fuc and the negative charge is apparently critical for binding as the succinic side chain bearing amide **3** is relatively inactive.

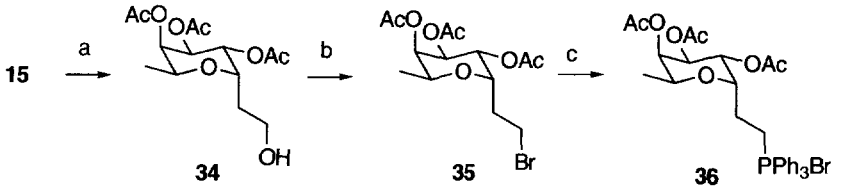
As for the series of four-carbon-linked Gal–Fuc mimetics, a general trend in the activity seems displayed. The highest flexiblity in the linkage (butane tethered **9**) goes along with the lowest inhibition. Increasing the conformational constrain with the *cis*-olefin linker in **8** or the rigid epoxide bearing tether in **10**, an improved activity is observed, but still remaining at low inhibition level (10-fold less active than SLe^X). However, none of them can compensate the double loss of *exo*-anomeric effect in comparison to the ethylene glycol tethered compound **11**, which exhibits the best activity in this series.

Overall, the *C*-fucopeptide concept appears to be a rather efficient approach towards the development of cell adhesion inhibitors. The synthesis of second generation mimetics is under investigation and results with regard to this aspect will be forthcoming.

Experimental

General procedures

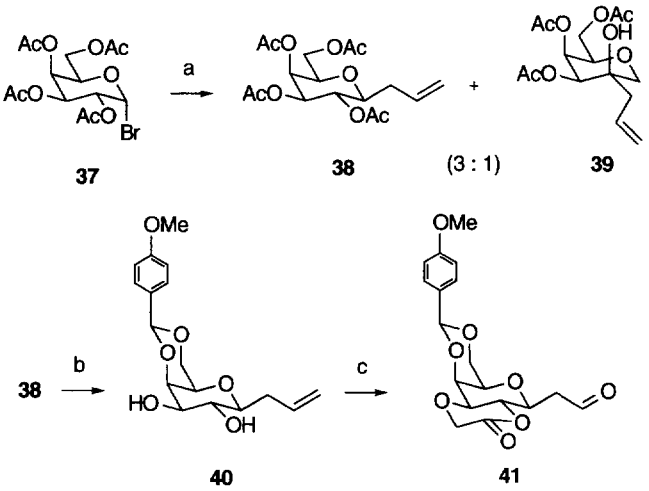
^1H and ^{13}C NMR spectra were recorded either on a Bruker AM-250, AMX-400 or AMX-500 spectrometer. Coupling constants were measured in Hertz (Hz). High resolution mass spectra (HRMS) were obtained on a VG ZAB-ZSE Mass Spectrometer using fast atom bombardment (FAB) method in a *m*-nitrobenzylalcohol (NBA) matrix doped with NaI or CsI. Infra-red spectra were recorded on a Perkin–Elmer FTIR 1620 spectrometer. Optical rotations were measured with an Optical Activity AA-1000 polarimeter. Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Column chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Analytical thin-layer chromatography was performed using precoated glass-backed plates (Merck Kieselgel F254) and visualised by cerium phosphomolybdate or ninhydrin. Diethyl ether and



Scheme 6. (a) i. O_3, CH_2Cl_2, −78 °C, ii. Me_2S, iii. $NaBH_4$, MeOH, 0 °C, 70%; (b) CBr_4, PPh_3, CH_2Cl_2, 90%; (c) PPh_3, DMF, 110 °C, 75%.

THF were distilled from sodium-benzophenone ketyl, dichloromethane from calcium hydride, toluene from sodium, acetonitrile from calcium hydride and methanol from magnesium. Other solvents and reagents were purified by standard procedures if necessary.

(2*S*,3*R*)-2-Amino-4-benzyloxy-*N*-(*tert*-butoxycarbonyl)-3-hydroxybutyric acid (13). To a suspension of (2*S*,3*R*)-2-amino-4-benzyloxy-3-hydroxybutyric acid (**12**) (100 mg, 0.444 mmol) in 1,4-dioxane (4 mL) and H_2O (2 mL) cooled to 0 °C, were added 1 N NaOH (0.5 mL) and di-*tert*-butyl dicarbonate (107 mg, 0.489 mmol) and the mixture stirred for 3 h at 23 °C. After the reaction, the mixture was adjusted to pH 2.5 with 5% $KHSO_4$ and extracted with EtOAc (3 × 6 mL). The combined organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated. The residue (147 mg) was used for the next reaction without purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (9H, s, CO_2tBu), 3.61 and 3.66 (each: 1H, dd, J=9.9, 4.9, CH_2OBn), 4.20 (1H, dd, J=7.6, 4.9, C*H*OH), 4.43 (1H, t, J=7.6, NHC*H*CO), 4.50 and 4.56 (each: 1H, d, J=11.9, OCH_2Ph), 5.71 (1H, d, J=7.6, $CHNHCO_2$), 7.30 (5H, m, aromatic). HRMS calcd for $C_{16}H_{23}NO_6$ ($M+H^+$) 326.1604, found 326.1640.



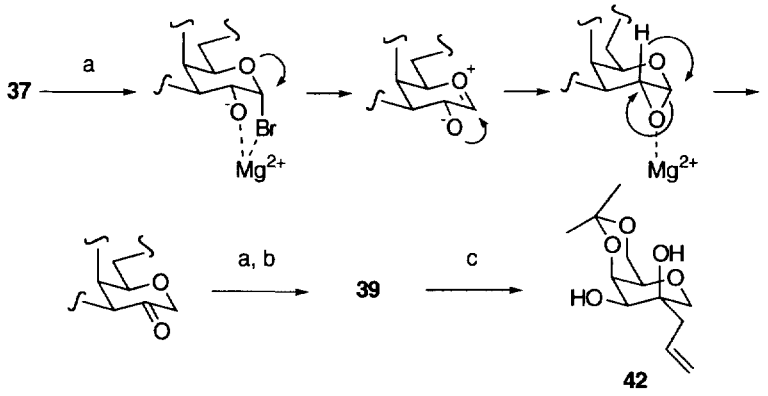
Scheme 7. (a) i. 10 equiv of allyl-MgBr, THF, −78 °C, ii. Ac_2O, pyr, DMAP 80%; (b) i. Amberlite IR 400 (OH^-), MeOH, ii. *p*-methoxybenzaldehyde dimethyl acetal, TsOH, 65%; (c) i. Bu_2SnO, toluene, 110 °C, ii. $MeOCOCH_2Br$, Bu_4NI, toluene, 110 °C, iii. O_3, CH_2Cl_2, −78 °C, iv. PPh_3, 60%.

Tetra-*O*-acetyl-α-L-fucopyranose (14).[26] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (3H, d, J=6.6, H-6), 2.01, 2.02, 2.15 and 2.18 (each: 3H, s, OAc), 4.28 (1H, q, J=6.6, H-5), 5.34 (3H, m, H-2,3,4), 6.34 (1H, d, J=2.3, H-1); TOFMS *m/z* 355 ($M+Na^+$).

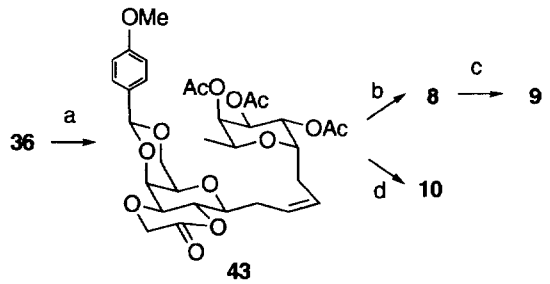
3- (Tri- *O*-acetyl- α-L-fucopyranosyl) -1- propene (15).[16] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (3H, d, J=6.3, H-6), 2.01, 2.05, and 2.16 (each: 3H, s, OAc), 2.29 (1H, ddd, J=15.2, 6.9, 5.4, H-1′a), 2.52 (1H, ddd, J=15.2, 6.9, 5.4, H-1′b), 3.97 (1H, dq, J=2.0, 6.3, H-5), 4.28 (1H, dt, J=10.8, 5.4, H-1), 5.00 (1H, dd, J=10.2, 2.7, H-3′a), 5.12 (1H, dd, J=15.8, 2.7, H-3′b), 5.23 (1H, dd, J=9.9, 3.3, H-3), 5.27 (1H, dd, J=3.3, 2.0, H-4), 5.32 (1H, dd, J=9.9, 5.4, H-2), 5.78 (1H, ddt, J=15.8, 10.2, 6.9, H-2′). HRMS calcd for $C_{16}H_{23}O_7$ ($M+H^+$) 315.1444, found 315.1444.

2-(Tri-*O*-acetyl-α-L-fucopyranosyl)acetaldehyde (16). A solution of **15** (200 mg, 0.637 mmol) in CH_2Cl_2 (15 mL) was cooled to −78 °C, O_3 was bubbled through the solution until a blue color was observed then N_2 was bubbled through the solution until it became colorless. A solution of triphenylphosphine (167 mg, 0.637 mmol) in CH_2Cl_2 (2 mL) was successively added to the reaction and the mixture was then stirred for 14 h at 23 °C. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (*n*-hexane:EtOAc, 2:1) to obtain **16** (153 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (3H, d, J=6.6, H-6), 2.02, 2.04, and 2.16 (each: 3H, s, OAc), 2.76 (2H, m, H-1′), 3.97 (1H, dq, J=1.6, 6.6, H-5), 4.87 (1H, dt, J=7.6, 5.6, H-1), 5.15 (1H, dd, J=9.6, 2.3, H-3), 5.28 (1H, dd, J=2.3, 1.6, H-4), 5.36 (1H, dd, J=9.6, 5.6, H-2), 9.74 (1H, dd, J=2.6, 1.6, C*H*O); FABMS *m/z* 317 ($M+H^+$).

2-(Tri-*O*-acetyl-α-fucopyranosyl)ethylamine (17). P–C (50 mg) was added to a solution of **16** (200 mg, 0.633 mmol) and ammonium acetate (487 mg, 6.33 mmol) in



Scheme 8. (a) allyl-MgBr; (b) i. H_3O^+, ii. Ac_2O, pyr, DMAP, 22%; (c) i. Amberlite IR 400 (OH^-), MeOH, ii. dimethoxypropane, CSA, iii. H_3O^+, 72%.

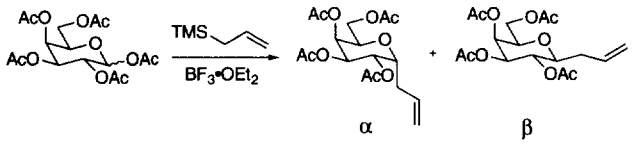


Scheme 9. (a) NaHMDS, THF, −78 °C, then **41**, 29%; (b) i. 80% HOAc, ii. NaOH, H_2O, THF, 80%; (c) H_2/Pd–C, MeOH, 100%; (d) i. mCPBA, CH_2Cl_2, ii. H_2/$Pd(OH)_2$–C, MeOH, iii. NaOH, H_2O, THF, 80%.

MeOH (5 mL) at 23 °C. The solution was stirred under H_2 for 3 h. After filtration, the filtrate was concentrated and the residue was extracted with $CHCl_3$ (20 mL). The organic layer was washed with H_2O (5 mL × 5), dried over $MgSO_4$ and evaporated. The residue was purified by silica gel flash column chromatography ($CHCl_3$:MeOH:H_2O, 8:2:0.2) to obtain **17** (120 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (3H, d, J=6.3, H-6), 1.59 and 1.90 (each: 1H, m, H-1′), 2.01, 2.06 and 2.16 (each: 3H, s, OAc), 2.82 (2H, m, H-2′), 3.99 (1H, dq, J=6.3, 1.6, H-5), 4.33 (1H, ddd, J=11.5, 5.6, 3.6, H-1), 5.19 (1H, dd, J=9.9, 3.3, H-3), 5.27 (1H, m, H-4), 5.31 (1H, dd, J=9.9, 5.6, H-2). HRMS calcd for $C_{14}H_{24}NO_7$ ($M+H^+$) 318.1553, found 318.1553.

1-{(2*S*,3*R*)-2-Amino-4-benzyloxy-*N*-(*tert*-butoxycarbonyl)-3-hydroxybutyramide}-2-(tri-*O*-acetyl-α-L-fucopyranosyl)ethane (18). A solution of **17** (12 mg, 0.038 mmol) and **13** (15 mg, 0.046 mmol) in $CHCl_3$ (1 mL) was cooled to 0 °C. 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) (9 mg, 0.046 mmol) was added to the solution, and the mixture was stirred for 14 h. After the reaction, the mixture was evaporated and the residue purified by preparative TLC (*n*-hexane:EtOAc, 1:3) to obtain **18** (19 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (3H, d, J=6.3, H-6), 1.44 (9H, s, $COOC(CH_3)_3$), 1.68, 1.89 (each: 1H, m, H-1′), 2.00, 2.04, and 2.14 (each: 3H, s, OAc), 3.22–3.40 (2H, m, H-2′), 3.58 and 3.65 (each: 1H, dd, J=9.9, 5.6, CH_2OCH_2Ph), 3.97 (1H, dq, J=2.5, 6.3, H-5), 4.17 (1H, t, J=7.3, NHC*H*CO), 4.23 (1H, dt, J=12.4, 5.3, H-1), 4.52 and 4.57 (each: 1H, d, J=12.2, OCH_2Ph), 5.14 (1H, dd, J=9.6, 3.0, H-3), 5.27 (1H, m, H-4), 5.29 (1H, dd, J=9.6, 5.3, H-2), 5.58 (1H, d, J=7.3, CHN*H*CO), 6.65 (1H, t, J=5.5, CH_2NHCO), 7.33 (5H, m, aromatic). HRMS calcd for $C_{30}H_{45}N_2O_{12}$ ($M+H^+$) 625.2973, found 625.2972.

Table 1.



Entry	Solvent	Reaction Temp	α:β
1	CH_3CN	23 °C	6:1
2	CH_2Cl_2	23 °C	1.4:1
3	THF	23 °C	n.r.
4	C_6H_6	23 °C	n.r.
5	C_6H_6	23 °C	3:1
6	CH_2Cl_2:C_6H_6 (1:3)	23 °C	1.6:1

1-{(2*S*,3*R*)-3,4-dihydroxybutyramide-2-monoglutaramidyl}-2-(α-L-fucopyranosyl)ethane (2).

Method A (from 18)—H$^+$-form. One mL of 4 N HCl/EtOAc (from KOKUSAN KAGAKU Co.) was added to a solution of **18** (15 mg, 0.024 mmol) in EtOAc (1 mL) at 0 °C, and the mixture stirred for 12 h. After the reaction, the solvent was evaporated and the residue dissolved in MeOH (1 mL) containing TEA (3.3 mL) at 0 °C. Glutaric anhydride (3 mg, 0.024 mmol) was added to the solution and the mixture stirred for 1 h. The reaction mixture was evaporated and purified by preparative TLC ($CHCl_3$:MeOH:H_2O, 9:1:0.1) to obtain monocarboxylic acid. This compound was debenzylated with P–C (10 mg) in MeOH (3 mL) under H_2 for 14 h. The reaction mixture was filtered, evaporated, dissolved in 1 mL of MeOH and 0.1 M NaOMe (166 mL) in MeOH was added. The mixture was stirred for 1 h, then the solvent was evaporated. The residue was dissolved in cold water (5 mL), neutralized with Muromac 50WX8 (H$^+$, 100–200 mesh), filtered through Celite 545, and the filtrate was lyophilized to obtain **2** (6 mg, 60%). ^{1}H NMR (500 MHz, D_2O) δ 1.16 (3H, d, J=6.3, H-6), 1.75–1.92 (4H, m, CH_2CH_2NHCO, $HNOCCH_2CH_2CH_2CO_2H$), 2.35 (4H, m, $CH_2CH_2CH_2CO_2H$), 3.20 and 3.43 (each: 1H, m, CH_2CH_2NHCO), 3.55 (1H, dd, J=12.0, 6.0, CH_2aOH), 3.67 (1H, dd, J=12.0, 3.0, CH_2bOH), 3.73 (2H, m, H-3,4), 3.84–4.02 (4H, m, H-1, 2, 5, *C*HOH), 4.35 (1H, d, J=7.6, HNCOC*H*NHCO); ^{13}C NMR (125 MHz, D_2O) δ 16.60, 21.61, 24.45, 34.30, 35.41, 37.46, 56.51, 63.39, 68.17, 68.66, 70.81, 71.75, 72.61, 74.39, 166.76, 172.45, 176.97. ESIMS *m/z* 423 ($M+H^+$).

Method B (from 24)—sodium salt. Compound **24** (1.14 g, 1.48 mmol) was added to 10 mL of 4 N HCl/EtOAc at 0 °C and stirred for 2 h. After the reaction, the solvent was evaporated and the residue was dissolved in MeOH (10 mL) containing TEA (149 mg, 1.48 mmol) at 0 °C. Glutaric anhydride (168 mg, 1.48 mmol) was added to the solution followed by stirring for 1 h. The reaction mixture was evaporated and the residue purified by silica gel column chromatography (*n*-hexane:EtOAc, 1:1) to obtain the monocarboxylic acid. This compound was debenzylated with P–C (10 mg) in MeOH (3 mL) under H_2 for 24 h. The reaction mixture was filtered, evaporated and the residue purified by silica gel column chromatography ($CHCl_3$:MeOH:H_2O, 6:4:1) to obtain **2** (460 mg, 70%).

3-(α-L-Fucopyranosyl)-1-propene (19).[18] To a solution of L-fucose tetraacetate **14** (20.3 g, 61.1 mmol) and trimethylallylsilane (19.4 mL, 122.2 mmol) in dry acetonitrile (110 mL) at 0 °C were added $BF_3 \cdot Et_2O$ (7.75

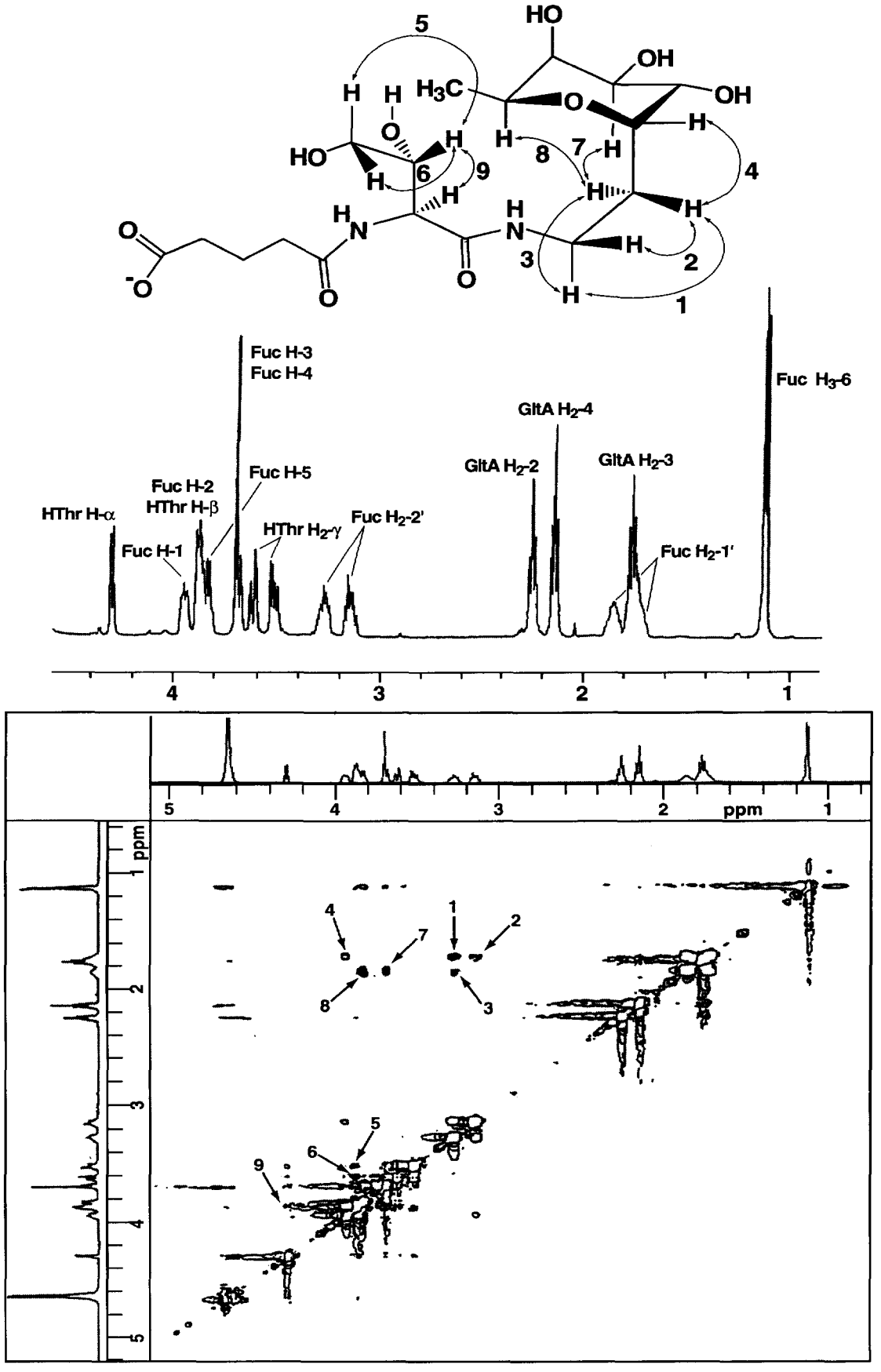


Figure 3. 2-D analysis of **2** using NOESY (500 MHz, D_2O, 30 °C). The numbers indicate NOE.

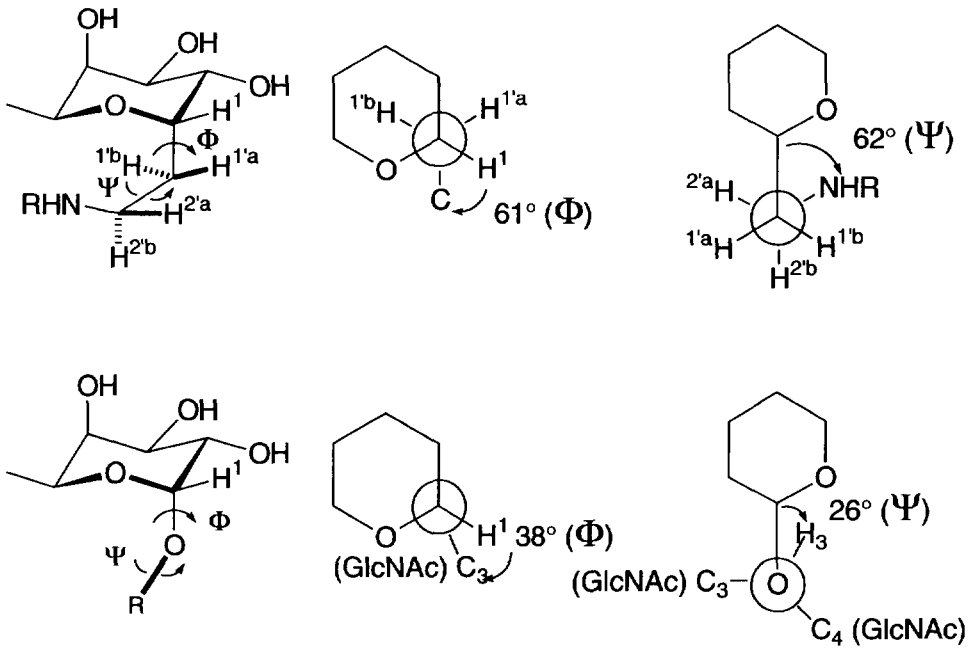


Figure 4. Glycosidic torsion angles of **2** and SLe^x determined by NOESY followed by energy minimization.

mL, 122.2 mmol) and TMSOTf (2.36 mL, 12.2 mmol) simultaneously within 25 min and the reaction mixture stirred for 10 h at 0 °C. After quenching with ice water, the mixture was taken up in ether and extracted with satd $NaHCO_3$ soln and brine, the aqueous layer was reextracted with ether (2 × 40 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (gradient elution 20%→30%→50% ethyl acetate in hexanes) to give **15** (18.4 g, 95%) as a slightly yellow oil. This material was dissolved in dry MeOH (100 mL), treated with 1 mL NaOMe soln (25% w/w in dry MeOH) and stirred at 23 °C for 15 h. The solution was neutralized by addition of Dowex 50WX8–100 H^+-form resin, filtered, and evaporated to dryness under reduced pressure. The remaining white solid was recrystallized from boiling ethyl acetate to yield two fractions (8.1 g and 0.7 g) of equally pure title compound **19** (74% from L-fucose) as colorless plates (mp 153 °C, αD_2O −115.6° (*c* 1.01, MeOH)). ^1H NMR (400 MHz, D_2O) δ 0.98 (3H, d, *J* = 6.5, H-6), 2.17 (1H, ddt, *J* = 14.9, 3.8, 1.7, H-1′a), 2.35 (1H, ddd, *J* = 14.9, 11.6, 8.4, H-1′b), 3.60 (1H, dd, *J* = 3.5, 1.2, H-4), 3.63 (1H, dd, *J* = 9.8, 3.5, H-3), 3.77 (1H, br m, H-5), 3.78 (1H, dd, *J* = 9.8, 6.2, H-2), 3.87 (1H, ddd, *J* = 11.5, 6.1, 3.7, H-1), 4.95 (1H, br dd, *J* = 10.1, 1.2, H-3′a), 5.01 (1H, br dd, *J* = 17.2, 1.2, H-3′b), 5.64 (1H, dddd, *J* = 17.2, 10.1, 8.3, 5.8, H-2′); ^{13}C NMR (100 MHz, D_2O) δ (as CH_3CN: 1.7) 16.34, 29.51, 67.72, 68.72, 70.64, 72.66, 76.07, 118.24, 135.92; HRMS calcd for $NaC_9H_{16}O_4$ (M + Na) 211.0946, found 211.0954.

3-(Tri-*O*-benzyl-α-L-fucopyranosyl)-1-propene (20). A solution of **19** (4.7 g, 25 mmol), Bu_4NI (460 mg, 1.3 mmol) and benzylbromide (14.9 mL, 125.3 mmol) in dry THF (50 mL) was cooled to 0 °C and NaH (4.0 g, 100 mmol, 60% w/w in mineral oil) added followed by stirring at 23 °C for 17 h. The reaction was quenched with ice water, taken up in ether and the mixture acidified with 1 N HCl. The aqueous layer was extracted with ether (2 × 40 mL) and the combined organic layer was neutralized with satd $NaHCO_3$ soln, treated with brine and dried over $MgSO_4$. Removal of the solvent in vacuo left a yellow oil, which was purified by silica gel flash column chromatography (gradient elution 0%→30%→50% ethyl acetate in hexanes) to yield the title compound **20** (11.3 g, 99%) as a waxy solid. ^1H NMR (250 MHz, $CDCl_3$) δ 1.29 (3H, d, *J* = 6.7, H-6), 2.27–2.44 (2H, m, H-1′), 3.78 (3H, m, H-2,3,4), 3.96 (1H, dq, *J* = 6.6, 3.4, H-5), 4.07 (1H, td, *J* = 5.5, 2.3, H-1), 4.50–4.78 (6H, m, OCH_2Ph), 5.02 (1H, dd, *J* = 10.2, 1.3, H-3′a), 5.06 (1H, dd, *J* = 17.1, 1.3, H-3′b), 5.76 (1H, ddt, *J* = 17.0, 10.2, 6.9, H-2′), 7.23–7.35 (15H, m, aromatic); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 15.12, 32.40, 68.62, 70.14, 72.91, 73.00, 75.74, 76.80, 116.55, 127.44, 127.52, 127.58, 127.67, 127.72, 127.90, 128.23, 128.28, 135.29, 138.28, 138.52, 138.76; HRMS calcd for $CsC_{30}H_{34}O_4$ (M + Cs) 591.1511, found 591.1530.

Cesium (2*S*, 3*R*)-2-amino-4-benzyloxy-*N*-(*tert*-butoxycarbonyl)-3-hydroxybutyrate (21). Cesium carbonate was added to a solution of **13** in ethanol/H_2O until pH 7.0 was reached, the solution was concentrated and toluene (3 mL) was added to the residue. This solution was evaporated in vacuo and the procedure was repeated three to four times to obtain **21** as a powder, which was used for the next coupling without further purification.

2-(Tri-*O*-benzyl-α-L-fucopyranosyl)acetaldehyde (22). A solution of **20** (2.00 g, 4.36 mmol) in CH_2Cl_2 (18 mL) and MeOH (3.6 mL) was cooled to −78 °C. O_3 was bubbled through the solution until a blue color

appeared, and then N_2 was bubbled until it became colorless. $NaHCO_3$ (733 mg, 8.72 mmol) and dimethylsulfide (3.2 mL, 43.6 mmol) were successively added to the reaction, and the mixture was stirred for 22 h at 23 °C. The reaction was taken up in Et_2O, washed with water and brine, and dried over $MgSO_4$. After removal of the solvent in vacuo the residual oil was purified by silica gel column chromatography (gradient elution 20%→30% ethyl acetate in hexanes) to give the title aldehyde **22** (1.81 g, 90%) as a slightly yellow oil. ^1H NMR (400 MHz, $CDCl_3$) 1.26 (3H, d, $J=6.6$, H-6), 2.59 (1H, ddd, $J=16.3$, 5.9, 1.9, H-1′a), 2.64 (1H, ddd, $J=16.3$, 7.9, 2.9, H-1′b), 3.73 (1H, dd, $J=6.9$, 2.9, H-3), 3.76 (1H, t, $J=3.2$, H-4), 3.84 (1H, dd, $J=6.8$, 4.2, H-2), 3.90 (1H, dq, $J=6.6$, 4.1, H-5), 4.47–4.76 (7H, m, H-1 and OCH_2Ph), 7.24–7.46 (15H, m, aromatic), 9.66 (1H, dd, $J=2.7$, 1.9, *CH*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.30, 42.86, 66.81, 69.30, 73.04, 73.22, 73.28, 75.50, 76.11, 77.01, 127.57, 127.69, 127.99, 128.13, 128.33, 128.42, 128.46, 137.85, 138.39, 138.47, 200.90; IR (neat) ν 2732, 1724, 1096, 733, 697 cm^{-1}; HRMS calcd for $CsC_{29}H_{32}O_5$ (M+Cs) 593.1304, found 593.1286.

2-(Tri-*O*-benzyl-α-L-fucopyranosyl)ethylamine (23). Ammonium acetate was added to a solution of aldehyde **22** (1.0 g) in MeOH (20 mL) until saturation, then sodium cyanoborohydride (145 mg, 2.18 mmol) was added to the solution at 23 °C. The mixture was stirred for 14 h, then concentrated and extracted with $CHCl_3$ (30 mL). The organic layer was washed with satd $NaHCO_3$ and H_2O, dried over $MgSO_4$ and then concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH:NH_4OH, 9:1:0.1) to obtain amine **23** (600 mg, 60%).

Alternative synthesis via 25→mesylate→azide→23

2-(Tri-*O*-benzyl-α-L-fucopyranosyl)ethyl azide. A solution of alcohol **25** (2.83 g, 6.12 mmol) and Et_3N (1.71 mL, 9.17 mmol) in dry CH_2Cl_2 (12.5 mL) was cooled to 0 °C, MesCl (0.71 mL, 9.17 mmol) was added and the mixture was stirred for 1 h at 0 °C. The reaction was taken up in ether and washed successively with ice cold 0.5 N HCl (2×50 mL), satd $NaHCO_3$ soln and brine followed by drying over $MgSO_4$. The solvent was removed in vacuo and the residual yellow oil (3.28 g, 99%) was treated with NaN_3 (1.99 g, 30.6 mmol) in dry DMF (20 mL) at 65 °C for 13 h. After reaching 23 °C the reaction was diluted with ether and washed with water (2×30 mL) and brine, then dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (gradient elution 10%≥30% ethyl acetate in hexanes) to yield the title azide (2.53 g, 85%) as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (3H, d, $J=6.6$, H-6), 1.70 (1H, ddt, $J=14.3$, 6.5, 3.6, H-1′a), 1.90 (1H, ddt, $J=14.3$, 10.3, 5.6, H-1′b), 3.31 (2H, br t, $J=6.4$, H-2′), 3.76 (3H, m, H-2,3,4), 3.92 (1H, dq, $J=6.5$, 3.4, H-5), 4.08 (1H, dt, $J=10.3$, 3.2, H-1), 4.50–4.78 (6H, m, OCH_2Ph), 7.23–7.35 (15H, m, aromatic); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 15.09, 27.30, 48.47, 67.60, 68.84, 72.97, 73.04, 75.59, 76.56, 127.49, 127.81, 127.87, 127.99, 128.23, 128.34, 138.02, 138.43, 138.61; IR (neat) η 2091, 1097, 699 cm^{-1}; HRMS calcd for $CsC_{29}H_{33}N_3O_4$ (M+Cs) 620.1525, found 620.1550.

2-(Tri-*O*-benzyl-α-L-fucopyranosyl)ethylamine (23). A solution of 2-(tri-*O*-benzyl-α-L-fucopyranosyl)ethyl azide (2.53 g, 5.19 mmol) and PPh_3 (1.50 g, 5.72 mmol) in THF (26 mL) and H_2O (0.25 mL) was stirred at 23 °C for 2 days. The reaction mixture was concentrated in vacuo and the residual oil was purified by silica gel column chromatography (gradient elution CH_2Cl_2:MeOH, 8:1≥CH_2Cl_2:MeOH:NH_4OH, 1:1:0.1) to give the desired amine **23** (2.40 g, 99%) as a yellow oil. ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (3H, d, $J=6.6$, H-6), 1.55 (2H, br s, NH_2), 1.60 (1H, ddt, $J=14.3$, 7.1, 3.6, H-1′a), 1.82 (1H, ddt, $J=14.2$, 10.4, 6.3, H-1′b), 2.74 (2H, m, H-2′), 3.79 (3H, m, H-2, 3, and 4), 3.90 (1H, dq, $J=6.6$, 2.8, H-5), 4.10 (1H, dt, $J=10.5$, 3.7, H-1), 4.51–4.81 (6H, m, OCH_2Ph), 7.26–7.35 (15H, m, aromatic); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 15.26, 30.35, 39.40, 68.35, 69.68, 72.98, 73.22, 76.06, 76.76, 77.34, 127.14, 127.29, 127.53, 127.61, 127.87, 127.95, 138.03, 138.23, 138.40; IR (neat) ν 3364, 1097, 697 cm^{-1}; HRMS calcd for $C_{29}H_{34}N_3O_4$ (M+H) 462.2644, found 462.2656.

1-{(2*S*,3*R*)-2-Amino-4-benzyloxy-*N*-(*tert*-butoxycarbonyl)-3-hydroxybutyramide}-2-(tri-*O*-benzyl-α-L-fucopyranosyl)ethane (24). A solution of **23** (900 mg, 1.95 mmol) and **13** (634 mg, 1.95 mmol) in $CHCl_3$ (5 mL) was cooled to 0 °C. EDC (412 mg, 2.147 mmol) was added to the solution, and the mixture stirred for 14 h. The reaction mixture was then evaporated and the residue purified by silica gel column chromatography (*n*-hexane:EtOAc, 1:1) to obtain **24** (1.14 g, 76%). ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (3H, d, $J=6.3$, H-6), 1.42 (9H, s, $COOC(CH_3)_3$), 1.57–1.90 (2H, m, H-1′), 3.18–3.44 (2H, m, H-2′), 3.54 and 3.62 (each: 1H, dd, $J=9.9$, 5.6, CH_2OCH_2Ph), 3.73 (3H, m, H-2,3,4), 3.92–4.07 (3H, m, H-1,5, *CH*(OH)CH_2O), 4.18 (1H, dd, $J=6.3$, 5.6, COC*H*NH), 4.45–4.76 (8H, m, OCH_2Ph), 5.57 (1H, d, $J=6.3$, CON*H*CH), 6.79 (1H, t, $J=5.2$, CH_2NHCO), 7.23–7.36 (20H, m, aromatic); HRMS calcd for $CsC_{45}H_{56}N_2O_9$ (M+Cs) 901.3040, found 901.3082.

1-{(2*S*,3*R*)-3,4-Dihydroxybutyramide-2-monosuccinamidyl}-2-(α-L-fucopyranosyl)ethane (3). The procedure to obtain **3** (32 mg, 69% from 87 mg of **24**) was analogous to that for **2** (method B), besides using succinic instead of glutaric anhydride. ^1H NMR (400 MHz, D_2O) δ 1.18 (3H, d, $J=6.4$, H-6), 1.74–1.81 (1H, m, H-1′a), 1.87–1.96 (1H, m, H-1′b), 2.55–2.64 (4H, m, $HO_2CCH_2CH_2CONH$), 3.16–3.22 (1H, m, H-2′a), 3.30–3.37 (1H, m, H-2′b), 3.58 (1H, dd, $J=12.1$, 6.2, CH_2aOH), 3.68 (1H, dd, $J=12.1$, 3.2, CH_2bOH), 3.73–3.76 (2H, m, H-3,4), 3.86–4.03 (4H, m, H-1,2,5 and *CH*OH), 4.36 (1H, d, $J=7.2$, HNCOC*H*NHCO), 8.11 (ca. 1H, t, $J=5.3$, CON*H*CH_2); ^{13}C NMR (100 MHz, D_2O) δ 18.08, 25.67, 32.85, 38.88, 39.01, 58.02, 64.83, 69.61, 72.23, 73.32, 74.08, 75.84, 173.86, 177.54,

180.10; HRMS calcd for $NaC_{16}H_{28}N_2O_{10}$ (M+Na) 431.1642, found 431.1646.

2-(Tri-*O*-benzyl-α-L-fucopyranosyl)ethanol (25). Ozone was bubbled through a solution of **20** (5.00 g, 10.9 mmol) in dry CH_2Cl_2 (45 mL) and dry MeOH (9 mL) cooled to −78 °C until a blue color persisted. The excess O_3 was expelled by a stream of N_2 and the ozonide was reduced by addition of $NaBH_4$ (2.06 g, 54.5 mmol) at −78 °C followed by slowly warming up to 23 °C and additional stirring for 1 h. The mixture was quenched cautiously with 1 N HCl at 0 °C, taken up in ether, washed with satd $NaHCO_3$ soln and brine. The aqueous layers were reextracted with ether (2 × 40 mL) and the combined organic phases were dried over $MgSO_4$. After removal of the solvent in vacuo the residue was purified by silica gel colum chromatography (gradient elution 40% ≥ 66% ethyl acetate in hexanes) to give the title alcohol **25** (4.76 g, 94%) as a slightly yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.29 (3H, d, *J* = 6.6, H-6), 1.67 (1H, ddt, *J* = 14.7, 5.6, 3.7, H-1′a), 1.97 (1H, ddt, *J* = 15.0, 10.2, 5.8, H-1′b), 2.50 (1H, br s, O*H*), 3.71 (2H, t, *J* = 5.9, H-2′), 3.76 (3H, m, H-2,3,4), 3.98 (1H, dq, *J* = 6.6, 3.4, H-5), 4.20 (1H, br d, *J* = 10, H-1), 4.50–4.78 (6H, m, OC*H*$_2$Ph), 7.23–7.36 (15H, m, aromatic); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 15.33, 29.91, 61.46, 68.85, 70.76, 73.00, 73.08, 75.63, 76.65, 76.92, 127.46, 127.54, 127.74, 127.93, 128.22, 128.30, 138.01, 138.34, 138.55; HRMS calcd for $CsC_{29}H_{34}O_5$ (M+Cs) 595.1461, found 595.1448.

2-(Tri-*O*-benzyl-α-L-fucopyranosyl)ethyl bromide (26). Tetrabromomethane (105 mg, 0.318 mmol) and triphenylphosphine (28 mg, 0.106 mmol) were added to a solution of **25** (49 mg, 0.106 mmol) at 23 °C, and the mixture was stirred for 4 h. After the reaction, the mixture was evaporated and purified by silica gel column chromatography (*n*-hexane:EtOAc, 10:1) to obtain bromide **26** (42 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (3H, d, *J* = 6.6, H-6), 1.94 (1H, m, H-1′a), 2.22 (1H, m, H-1′b), 3.43 (2H, dd, *J* = 8.0, 5.7, H-3′), 3.75 (3H, m, H-2,3,4), 3.92 (1H, dq, *J* = 4.0, 6.6, H-5), 4.19 (1H, dd, *J* = 10.2, 3.3, H-1), 4.46–4.78 (6H, m, OC*H*$_2$Ph), 7.23–7.35 (15H, m, aromatic). HRMS calcd for $C_{29}H_{34}O_4Br$ (M+H$^+$) 525.1640, found 525.1609.

1-{(2*S*,3*R*)-2-Amino-4-benzyloxy-*N*-(*tert*-butoxycarbonyl)-3-hydroxybutyryloxy}-2-(tri-*O*-benzyl-α-L-fucopyranosyl)ethane (27). A solution of **21** (44 mg, 96 μmol) and **26** (42 mg, 80 μmol) in DMF (1 mL) was heated at 40 °C for 12 h. The reaction mixture was then evaporated and the residue was purified by silica gel column chromatography (*n*-hexane:EtOAc, 1:1) to obtain ester **27** (40 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (3H, d, *J* = 6.3, H-6), 1.43 (9H, s, COO(C*H*$_3$)$_3$), 1.70–2.02 (2H, m, H-1′), 3.51 (2H, d, *J* = 5.6, C*H*$_2$OCH$_2$Ph), 3.72 (3H, m, H-2,3,4), 3.90 (1H, dq, *J* = 3.3, 6.3, H-5), 4.06 (1H, dt, *J* = 10.6, 2.9, H-1), 4.17 (3H, m, H-2′, C*H*(OH)CH$_2$O), 4.43–4.78 (9H, m, COC*H*NH, OC*H*$_2$Ph), 5.54 (1H, d, *J* = 6.3, CHN*H*CO), 7.23–7.36 (20H, m, aromatic). HRMS calcd for $C_{45}H_{56}NO_{10}$ (M+H$^+$) 770.3904, found 770.3868.

1-{(2*S*,3*R*)-3,4-Dihydroxybutyryloxy-2-monoglutaramidyl}-2-(α-L-fucopyranosyl)ethane sodium salt (4). The procedure to obtain **4** (16 mg, 71% from 40 mg of **27**) was identical to that for **2** (method B). ^{1}H NMR (500 MHz, D_2O) δ (as HOD; 4.70) 1.11 (3H, d, *J* = 6.3, H-6), 1.76 (2H, dt, *J* = 7.5, 7.5, NHCOCH$_2$C*H*$_2$-CH$_2$CO$_2$), 1.85–2.10 (2H, m, H-1′), 2.15 (2H, t, *J* = 7.5, NHCOC*H*$_2$CH$_2$CH$_2$CO$_2$), 2.26 (2H, t, *J* = 7.5, NHCOCH$_2$CH$_2$C*H*$_2$CO$_2$), 3.54 (1H, dd, *J* = 12.4, 7.4, C*H*$_2$aOH), 3.63 (1H, dd, *J* = 12.4, 4.0, C*H*$_2$bOH), 3.70 (2H, m, H-3,4), 3.85 (2H, m, H-2,5), 3.96 (1H, ddd, *J* = 7.4, 5.9, 4.0, C*H*(OH)CH$_2$OH), 4.05 (1H, dt, *J* = 11.9, 3.9, H-1), 4.21 (2H, m, H-2′), 4.49 (1H, d, COC*H*NH); ^{13}C NMR (125 MHz, D_2O) δ (as *C*H$_3$CN; 1.3): 16.05, 22.52, 23.37, 35.37, 36.65, 55.48, 62.70, 63.53, 67.80, 67.97, 70.21, 71.81, 72.08, 72.96, 171.89, 176.98, 182.38; HRMS calcd for $C_{17}H_{30}NO_{11}$ (M+H$^+$) 424.1819, found 424.1816.

3-(Tri-*O*-benzyl-α-L-fucopyranosyl)-1-propanol (28). A solution of **20** (500 mg, 1.09 mmol) in tetrahydrofurane (THF) was cooled to 0 °C. 9-Borabicyclo[3,3,1]nonane (9-BBN) in THF solution (0.5 M, 2.84 mL) was added to the solution, and the mixture was warmed to 23 °C then heated at reflux for 3 h. The reaction mixture was cooled to 23 °C, then EtOH (300 μL) and 1 N NaOH (2.18 mL) were added successively. To this reaction mixture at 0 °C 600 μL of 30% H_2O_2 was added, and the mixture stirred for 14 h at 23 °C. The reaction mixture was extracted with EtOAc (20 mL), and the organic layer washed with brine (3 × 5 mL), dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc, 2:1) to obtain alcohol **28** (450 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (3H, d, *J* = 6.6, H-6), 1.60 (4H, m, H-1′,2′), 2.05 (1H, br t, *J* = 5.6, O*H*), 3.61 (2H, m, H-3′), 3.77 (5H, m, H-2,3,4), 3.97 (2H, m, H-1,5), 4.49–4.78 (6H, m, OC*H*$_2$Ph), 7.26–7.37 (15H, m, aromatic). HRMS calcd for $C_{30}H_{37}O_5$ (M+H$^+$) 477.2641, found 477.2640.

3-(Tri-*O*-benzyl-α-L-fucopyranosyl)-1-propylamine (29). TEA (25 mg, 0.252 mmol) and chloromethanesulfonyl chloride (37 mg, 0.252 mmol) were added to a solution of **28** (100 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The mixture was stirred for 2 h, then extracted with CH_2Cl_2 (10 mL) and the organic layer washed with H_2O (4 × 5 mL), dried over $MgSO_4$ and evaporated. Sodium azide (16 mg, 0.252 mmol) was added to a solution of this residue in DMF (2 mL), and the mixture heated to 50 °C for 1 h. After the reaction, the mixture was extracted with CH_2Cl_2 (15 mL) and the organic layer washed with H_2O (3 × 5 mL) and brine (2 × 5 ml), dried over $MgSO_4$ and evaporated to obtain the crude azide. H_2S gas was then bubbled through a solution of this azide in pyridine (4 mL) and H_2O (2 mL) until saturation. The resulting mixture was stirred for 16 h at 23 °C. The reaction mixture was evaporated and the residue was purified by silica gel column

chromatography ($CHCl_3$:MeOH:NH_4OH, 9:1:0.1) to obtain amine **29** (75 mg, 75%). ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (3H, d, $J=6.6$, H-6), 1.48–1.75 (4H, m, H-1′,2′), 2.68 (1H, t, $J=5.8$, H-3′), 3.76 (3H, m, H-2,3,4), 3.87 (1H, dq, $J=3.0$, 6.6, H-5), 3.95 (1H, dt, $J=9.9$, 3.3, H-1), 4.48–4.79 (6H, m, OCH_2Ph), 7.28–7.35 (15H, m, aromatic).

1-{(2*S*,3*R*)-2-Amino-4-benzyloxy-*N*-(*tert*-butoxycarbonyl)-3-hydroxybutyramide}-3-(tri-*O*-benzyl-α-L-fucopyranosyl)propane (30). The procedure to obtain **30** (38 mg, 78% from 30 mg of **29**) was identical to that for **24**. ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (3H, d, $J=6.6$, H-6), 1.40–1.60 (4H, m, H-1′,2′), 1.42 (9H, s, $COO(CH_3)_3$), 3.19 (2H, dt, $J=5.6$, 5.6, H-3′), 3.53 (1H, dd, $J=9.9$, 5.6, CH_2aOCH_2Ph), 3.63 (1H, dd, $J=9.9$, 5.3, OCH_2bOCH_2Ph), 3.75 (3H, m, H-2,3,4), 3.83–4.01 (3H, m, H-1,5, $CH(OH)CH_2O$), 4.17 (1H, dd, $J=6.9$, 5.3, $COCHNH$), 4.47–4.77 (8H, m, OCH_2Ph), 5.63 (1H, d, $J=6.9$, $CHNHCO$), 6.49 (1H, t, $J=5.6$, CH_2NHCO), 7.25–7.34 (20H, m, aromatic).

1-{(2*S*,3*R*)-3,4-Dihydroxybutyramide-2-monoglutaramidyl}-3-(α-L-fucopyranosyl)propane sodium salt (5). The procedure to obtain **5** (17 mg, 79% from 38 mg of **30**) was identical to that for **2** (method B). ^1H NMR (500 MHz, D_2O) δ (as HOD; 4.70): 1.20 (3H, d, $J=6.3$, H-6), 1.45–1.75 (4H, m, H-1′,2′), 1.85 (2H, t, $J=7.5$, $HNOCCH_2CH_2CH_2CO_2$), 2.22 (2H, t, $J=7.5$, $HNOCCH_2CH_2CH_2CO_2$), 2.34 (2H, t, $J=7.5$, $HNOCH_2CH_2CH_2CO_2$), 3.27 (1H, dd, $J=13.5$, 7.3, H-3′a), 3.32 (1H, dd, $J=13.5$, 7.3, H-3′b), 3.62 (1H, dd, $J=12.1$, 6.2, $CH2aOH$), 3.73 (1H, dd, $J=12.1$, 3.3, CH_2bOH), 3.79 (2H, m, H-3,4), 3.88 (1H, q, $J=6.3$, H-5), 3.97 (3H, m, H-1,2, $CH(OH)CH_2OH$), 4.38 (2H, d, $J=7.3$, $COCHNH$); ^{13}C NMR (125 MHz, D_2O) δ (as CH_3CN; 1.3): 16.09, 21.30, 22.61, 25.33, 35.50, 37.10, 39.54, 56.16, 62.88, 67.21, 68.42, 70.27, 71.20, 72.28, 75.93, 171.95, 176.77, 182.91; HRMS calcd for $C_{18}H_{33}N_2O_{10}$ ($M+H^+$) 437.2135, found 437.2112.

3-(Tri-*O*-benzyl-α-L-fucopyranosyl)-1-propyl bromide (31). The procedure to obtain **31** (43 mg, 83% from 43 mg of **28**) was identical to that for **26**. ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (3H, d, $J=6.6$, H-6), 1.55–2.00 (4H, m, H-1′,2′), 3.42 (2H, t, $J=6.3$, H-3′), 3.78 (3H, m, H-2,3,4), 3.88 (1H, dq, $J=3.0$, 6.6, H-5), 3.97 (1H, dt, $J=9.9$, 4.0, H-1), 4.50–4.80 (6H, m, OCH_2Ph), 7.25–7.35 (15H, m, aromatic). FABMS *m/z* 539 ($M+H^+$).

1-{(2*S*,3*R*)-2-Amino-4-benzyloxy-*N*-(*tert*-butoxycarbonyl)-3-hydroxybutyryloxy}-3-(tri-*O*-benzyl-α-L-fucopyranosyl)propane (32). The procedure to obtain **32** (42 mg, 68% from 43 mg of **31**) was identical to that for **27**. ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (3H, d, $J=6.3$, H-6), 1.43 (9H, s, $COOC(CH_3)_3$), 1.45–1.72 (4H, m, H-1′,2′), 3.53 (2H, d, J = 5.6, CH_2OCH_2Ph), 3.75 (3H, m, H-2,3,4), 3.85 (1H, m, $CH(OH)CH_2O$), 3.93 (1H, dt, $J=9.3$, 3.3, H-1), 4.08 (2H, m, H-3′), 4.18 (1H, m, $CH(OH)CH_2OCH_2Ph$), 4.45–4.77 (9H, m, $COCHNH$, OCH_2Ph), 5.57 (1H, d, $J=5.9$, $CHNHCO$), 7.25–7.34 (20H, m, aromatic). HRMS calcd for $C_{46}H_{58}NO_4$ ($M+H^+$) 784.4061, found 784.4062.

1-{(2*S*,3*R*)-3,4-Dihydroxybutyryloxy-2-monoglutaramidyl}-3-(α-L-fucopyranosyl)propane sodium salt (6). The procedure to obtain **6** (17 mg, 69% from 42 mg of **32**) was identical to that for **2** (method B). ^1H NMR (500 MHz, D_2O) δ (as HOD; 4.70) 1.10 (3H, d, $J=6.6$, H-6), 1.52–1.82 (6H, m, H-1′,2′), $HNOCCH_2CH_2CH_2CH_2CO_2$), 2.15 (2H, t, $J=7.3$, $HNOCCH_2CH_2CH_2CH_2CO_2$), 2.25 (2H, t, $J=7.3$, $HNOCCH_2CH_2CH_2CO_2$), 3.56 (1H, dd, $J=12.3$, 6.6, CH_2aOH), 3.65 (1H, dd, $J=12.0$, 5.0, CH_2bOH), 3.68 (2H, m, H-3, 4), 3.78 (1H, q, $J=6.6$, H-5), 3.90 (3H, m, H-1,2, $CHOH$), 4.17 (2H, br t, $J=4.9$, H-3′), 4.48 (1H, d, $J=6.6$, $COCHNH$); ^{13}C NMR (125 MHz, D_2O) δ (as CH_3CN: 1.3): 16.09, 20.47, 22.49, 24.93, 35.37, 36.56, 55.53, 62.75, 66.49, 67.28, 68.38, 70.27, 71.79, 72.26, 75.98, 172.08, 176.93, 182.25; HRMS calcd for $C_{18}H_{32}NO_{11}$ ($M+H^+$) 438.1975, found 438.1984.

1-(*O*-Benzyl-*N*-*tert*-butoxycarbonyl-L-threonine)-2-(tri-*O*-benzyl-α-L-fucopyranosyl)ethane (33). A solution of **23** (110 mg, 238 μmol), HOBt (36.0 mg, 266 μmol), *N*-Boc-*O*-benzyl-L-threonine (81.7 mg, 264 μmol) and 4-methyl morpholine (55 μL, 500 μmol) in dry DMF (2.9 mL) was cooled to −20 °C and EDC (50.3 mg, 262 μmol) was added in one portion. The reaction mixture was stirred at −20 °C for 1 h and then allowed to reach 23 °C slowly. After 29 h the reaction was taken up in ethyl acetate and extracted with 5% w/v citric acid solution (25 mL). The aqueous layer was further extracted with ethyl acetate (4 × 25 mL) and the combined organic layers were washed with satd $NaHCO_3$ soln (40 mL) and brine (40 mL) followed by drying over $MgSO_4$. After evaporation under reduced pressure the residual oil was purified by silica gel column chromatography (gradient elution 40% ≥ 50% ethyl acetate in hexanes) to give the title compound **33** (175.7 mg, 98%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, d, $J=6.2$, Me-thr), 1.27 (3H, d, $J=6.6$, H-6), 1.44 (9H, s, Boc), 1.64 (1H, m, H-1′a), 1.83 (1H, m, H-1′b), 3.25 (1H, dq, $J=12.7$, 6.3, H-2′a), 3.43 (1H, dq, $J=12.7$, 6.2, H-2′b), 3.71 (3H, m, H-2,3,4), 3.88 (1H, br m, H-5), 4.02 (1H, dt, $J=10.7$, 2.9, H-1), 4.20 (2H, m, $BnOCHCHNHBoc$), 4.45–4.73 (8H, m, OCH_2Ph), 5.42 (1H, br d, $J=7.3$, $BocNH$), 6.94 (1H, br t, $J=$ca. 6, $CONHCH_2$), 7.19–7.37 (20H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.15, 15.84, 27.31, 28.33, 37.76. 57.92, 68.93, 69.72, 71.67, 72.85, 73.08, 74.88, 75.46, 76.48, 76.96, 79.94, 127.12, 127.53, 127.56, 127.61, 127.64, 127.74, 127.76, 127.85, 127.89, 128.05, 128.08, 128.15, 128.26, 128.32, 128.40, 138.13, 138.17, 138.53, 138.67, 155.84, 169.77; HRMS calcd for $CsC_{45}H_{56}N_2O_8$ (M + Cs) 885.3091, found 885.3067.

1-(*O*-Benzyl-L-threonine)-2-(tri-*O*-benzyl-α-L-fucopyranosyl)ethane. A solution of **33** (175 mg, 232 μmol) in dry CH_2Cl_2 (1 mL) was treated with TFA (1 mL) at 0 °C and stirred for 90 min. The reaction mixture was evaporated under reduced pressure, taken up in MeOH (10 mL) and Dowex-1X8–50 (OH)- resin was

added until pH 8 was reached. The resin was filtered off and washed with MeOH. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH:NH_4OH, 19:1:0.1) to give the title compound (153 mg, 100%) as a slightly yellow oil. ^1H NMR (250 MHz, $CDCl_3$) δ 1.19 (3H, d, J=6.3, Me-thr), 1.25 (3H, d, J=6.6, H-6), 1.60 (2H, br s, NH_2), 1.67–1.86 (2H, m, H-1′), 3.13 (1H, br m, $CHNH_2$), 3.34 (2H, m, H-2′), 3.66–3.86 (4H, m, H-2,3,4,5), 4.06 (1H, dt, J=10.2, 3.6, H-1), 4.18 (1H, br dq, J=6.3, 2.1, BnOC*H*CHNH$_2$), 4.38–4.76 (8H, m, OCH_2Ph), 7.16–7.34 (20H, m, aromatic), 7.76 (1H, br t, J=5.5, CON*H*CH2); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 15.28, 16.77, 26.60, 36.81, 59.03, 69.85, 71.15, 72.74, 72.88, 72.98, 75.06, 75.71, 76.50, 127.26, 127.32, 127.40, 127.49, 127.71, 127.84, 128.05, 128.14, 138.05, 138.36, 138.49, 173.05; HRMS calcd for $CsC_{40}H_{48}N_2O_6$ (M+Cs) 785.2567, found 785.2548.

1-(3-*O*-Benzyl-2-monoglutaramidyl-L-threonine)-2-(tri-*O*-benzyl-α-L-fucopyranosyl)ethane. To a solution of 1-(*O*-benzyl-L-threonine)-2-(tri-*O*-benzyl-α-L-fucopyranosyl)ethane (152 mg, 232 μmol) in dry MeOH (2 mL) was added glutaric anhydride (28.3 mg, 246 μmol) and the mixture was stirred for 1 h at 23 °C. After removal of the solvent in vacuo the residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH:HOAc, 19:1:0.1) to yield the title compound (148 mg, 83%) as a slightly yellow solid. ^1H NMR (250 MHz, CD_3OD) δ 1.18 (3H, d, J=6.3, Me-thr), 1.27 (3H, d, J=6.6, H-6), 1.85 (2H, m, H-1′), 1.89 (2H, qui, J=7.3, $CH_2CH_2CH_2$), 2.33 and 2.36 (each: 2H, t, J=7.5, $CH_2CH_2CH_2$), 3.21 (2H, m, H-2′), 3.77–3.88 (4H, m, H-2,3,4,5), 4.02–4.08 (2H, m, H-1 and BnOC*H*CH), 4.40–4.77 (9H, m, OCH_2Ph and BnOCHC*H*CO), 7.20–7.33 (20H, m, aromatic), 7.90 (1H, m, CON*H*CH$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 15.01, 15.28, 20.34, 26.93, 32.72, 34.75, 37.36, 55.77, 68.71, 69.16, 71.38, 72.87, 74.48, 75.41, 76.59, 127.37, 127.45, 127.65, 127.73, 127.84, 128.14, 128.22, 128.28, 137.72, 137.93, 138.22, 138.46, 169.64, 172.86, 176.19; HRMS calcd for $CsC_{45}H_{54}N_2O_9$ (M+Cs) 899.2884, found 899.2850.

1-(2-Monoglutaramidyl-L-threonine)-2-(α-L-fucopyranosyl)ethane (7). A solution of 1-(3-*O*-benzyl-2-monoglutaramidyl-L-threonine)-2-(tri-*O*-benzyl-α-L-fucopyranosyl)ethane (148 mg, 193 μmol) in *tert*-butanol (3 mL), HOAc (1.5 mL) and H_2O (1.5 mL) was hydrogenated at 50 psi in the presence of $Pd(OH)_2$–C (ca. 20 mg) for 20 h at 23 °C. The reaction was filtered through Celite, washed with MeOH and the solvent removed under reduced pressure. The residue was purified by BioGel column chromatography (H_2O) and lyophilized to give the title compound **7** (59.7 mg, 76%) as a white solid. ^1H NMR (400 MHz, D_2O) δ 1.18 (3H, d, J=6.4, H-6), 1.19 (3H, d, J=6.1, Me-thr), 1.85 (2H, qui, J=7.5, $HO_2CCH_2CH_2CH_2CONH$), 1.74–1.97 (2H, m, H-1′), 2.22 (2H, t, J=7.5, CH_2CO_2H), 3.19 (1H, dt, J =13.6, 7.5, H-2′a), 3.36 (1H, ddd, J=13.5, 8.2, 5.1, H-2′b), 3.72 (1H, dd, J=9.2, 5.8, H-3), 3.80 (1H, br s, H-4), 3.89 (1H, br q, J=6.5, H-5), 3.94 (1H, dd, J=9.1, 6.1, H-2), 4.00 (1H, ddd, J=11.2, 6.1, 3.4, H-1), 4.19 (1H, dq, J=6.2, 4.5, H_3CHOH), 4.22 (1H, d, J=4.4, CONHC*H*CONH); ^{13}C NMR (100 MHz, D_2O) δ (206 as Me_2C=O) 6.30, 9.54, 12.73, 13.91, 20.90, 25.63, 27.12, 50.12, 57.54, 57.82, 58.29, 60.44, 62.26, 64.09, 162.66, 167.52, 172.77; HRMS calcd for $CsC_{17}H_{30}N_2O_9$ (M+Cs) 539.1006, found 539.0987.

2-(Tri-*O*-acetyl-α-L-fucopyranosyl)ethanol (34). Ozone was bubbled into a solution of **15** (15.7 g, 50.0 mmol) in dry dichloromethane (100 mL) at −78 °C until the solution turned the blue. The solution was purged with argon until blue color disappeared. Dimethyl sulfide (20 mL) was added to this cold solution and the resulting mixture was gradually warmed up to 23 °C while stirring. To this solution methanol (100 mL) was added followed by sodium borohydride in excess. The suspension was stirred at 23 °C for 1 h and the reaction mixture was filtered and concentrated. The residue was diluted with diethyl ether (600 mL), washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated. Flash column chromatography (ethyl acetate: hexane, 1:4) gave **34** (11.1 g, 70%) as a colorless oil. $[\alpha]_D^{25}$ −7.2° (*c* 4.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (3H, d, J=6.4), 1.66–1.73 (1H, m), 1.95–2.09 (1H, m), 1.96 (1H, br s), 2.02 (3H, s), 2.07 (3H, s), 2.16 (3H, s), 3.74–3.82 (2H, m), 4.05 (1H, dq, J=2.1, 6.4), 4.41 (1H, ddd, J=3.2, 5.6, 11.5), 5.19 (1H, dd, J=3.3, 9.8), 5.28 (1H, dd, J=2.1, 3.3), 5.30 (1H, dd, J=5.6, 9.8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.86, 20.64, 20.70, 20.77, 27.73, 60.10, 66.05, 67.97, 68.49, 70.33, 70.86, 169.89, 170.12, 170.49; HRMS *m/z* 451.0380 [(M+Cs)$^+$; calcd for $CsC_{14}H_{22}O8$: 451.0369].

2-(Tri-*O*-acetyl-α-L-fucopyranosyl)ethyl bromide (35). To a stirred, cooled (0 °C) solution of **34** (1.59 g, 5.0 mmol) and triphenyl phosphine (3.38 g, 15.0 mmol) in dichloromethane (10 mL), was slowly added carbon tetrabromide (3.98 g, 12.0 mmol). The resulting suspension was stirred for 10 h at 23 °C and the reaction mixture diluted with diethyl ether (30 mL), washed with satd $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic layer was dried over $MgSO_4$ and concentrated. Flash column chromatography (ethyl acetate: hexane, 1:9) gave **35** (1.71 g, 90%) as a colorless oil. $[\alpha]_D^{25}$ −6.0° (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 (3H, d, J=6.5), 1.92–2.00 (2H, m), 2.02 (3H, s), 2.08 (3H, s), 2.16 (3H, s), 2.26–2.36 (1H, m), 3.39–3.52 (2H, m), 3.37 (1H, dq, J=2.3, 6.5), 4.38 (1H, ddd, J=3.2, 5.5, 11.3), 5.16 (1H, dd, J=3,3, 9.7), 5.27 (1H, dd, J=2.3, 3.3), 5.32 (1H, dd, J=dd, 5.5, 9.7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.79, 20.66, 20.71, 20.79, 28.88, 29.02, 66.19, 67.85, 68.54, 70.13, 70.31, 169.78, 170.08, 170.46; HRMS *m/z* 381.0556 [(M+H)$^+$; calcd for $C_{14}H_{21}O_7Br$: 381.0549].

(2-(Tri-*O*-acetyl-α-L-fucopyranosyl) ethyl) triphenylphosphonium bromide (36). To a solution of **35** (1.52 g, 4.0 mmol) in dry DMF under argon was added triphenyl phosphine (3.14 g, 12 mmol). The resulting solution was heated at 110 °C for 3 h. DMF was

removed under reduced pressure and the residue chromatographed (methanol:chloroform, 5:95) to give Wittig reagent **36** (1.93 g, 75%) as a colorless oil. ^{1}H NMR (500 MHz, CD_3OD) δ 1.38 (3H, d, J=6.4), 1.92–2.04 (1H, m), 2.46–2.59 (1H, m), 3.46–3.58 (1H, m), 3.68–3.80 (1H, m), 4.32 (1H, dt, J=2.1, 6.4), 4.56 (1H, ddd, J=3.3, 5.0, 11.0), 5.72 (1H, dd, J=2.1, 3.3), 5.76 (1H, dd, J=3.3, 9.5), 5.82 (1H, dd, J=5.0, 9.5), 7.15–8.05 (36H, m); ^{13}C NMR (125 MHz, CD_3OD) δ 16.13, 19.85 (J=53.1), 20.18, 20.50, 20.59, 20.62, 67.67, 69.26, 69.52, 71.51, 73.45 (J=15.3), 119.68 (J=86.4), 131.62 (J=12.8), 134.89 (J=13.3), 136.43, 171.18, 171.47, 172.93 HRMS *m/z* 563.2218 [(M-Br)$^+$; calcd for $C_{32}H_{36}O_7P$: 563.2199].

3-(Tetra-*O*-acetyl-β-D-galactopyranosyl)-1-propene (38) and 2-allyl-3,4,6-tri-*O*-acetyl-1-deoxy-D-mannose (39). Allyl magnesium bromide (34.5 mL of a 1 M soln in THF) was added to a solution of α-bromo-2,3,4,6-tetra-acetyl-galactose **37** (1.29 g, 3.1 mmol) in THF (15 mL) at −78 °C. The mixture was warmed up to 23 °C within 0.5 h, then poured into H_2O (60 mL). Glacial acetic acid (6 mL) was added to dissolve the magnesium salts and the mixture was shaken with Et_2O until two separate layers were observed. The aqueous layer was evaporated to dryness and the residue was stirred overnight with Ac_2O (30 mL), pyridine (30 mL) and catalytic amount of DMAP. After removal of the solvent, the remaining oil was diluted with EtOAc, washed with satd $NaHCO_3$ soln, brine and dried over $MgSO_4$. The concentrated crude product was purified by silica gel column chromatography (hexanes:EtOAc, 3:1) to afford the compounds **38** (694 mg, 60%) and **39** (225 mg, 22%). Data for **38**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.96 (3H, s), 2.02 (6H, s), 2.13 (3H, s) all AcO, 2.28–2.30 (2H, m, H-1′), 3.44 (1H, td, J=5.9, 10.1, H-1), 3.83 (1H, dt, J=1.0, 6.7, H-5), 4.03 (1H, dd, J=6.7, 11.3, H-6a), 4.12 (1H, dd, J=6.7, 11.3, H-6b), 4.98 (1H, dd, J=3.4, 10.1, H-2), 5.04–5.12 (3H, m, H-3 and H-3′), 5.39 (1H, dd, J=1.0, 3.4, H-4), 5.80 (1H, tdd, J=6.8, 10.3, 17.1, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 20.7, 20.8, 36.0, 61.6, 67.7, 69.2, 72.2, 74.0, 77.7, 117.4, 133.3, 169.8, 170.3, 170.4, 170.5; HRMS *m/z* 373.1492 [(M+H)$^+$; calcd for $C_{17}H_{25}O_9$: 373.1499]. Data for **39**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03 (3H, s), 2.06 (3H, s), 2.14 (3H, s) all AcO, 2.14–2.19 (1H, m, H-1′a), 2.26–2.31 (1H, m, H-1′b), 3.47 (1H, d, J=12.3, H-1a), 3.77 (1H, dt, J=1.4, 6.3, H-5), 3.86 (1H, d, J=12.3, H-1b), 4.09–4.11 (2H, m, H-6), 4.88 (1H, d, J=3.6, H-3), 5.02–5.11 (2H, m, H-3′), 5.36 (1H, dd, J=1.4,3.6, H-4), 5.73 (1H, dddd, J=7.5, 8.0, 10.5, 18.0, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9 (2×), 38.8, 67.0, 68.0, 70.7, 71.5, 74.9, 75.4, 119.3, 131.4, 169.6, 170.2, 170.5; HRMS *m/z* 463.0360 [(M+Cs)$^+$; calcd for $CsC_{15}H_{22}O_8$: 463.0369].

3-(β-D-Galactopyranosyl)-1-propene. A solution of **38** (4.0 g, 12.1 mmol) in MeOH (50 mL) was stirred overnight at 23 °C in the presence of Amberlite IR 400 (OH-) resin (7 g). The polymer was filtered off, washed with MeOH and the filtrate was concentrated to give a solid (1.76 g, 91%), which was used without further purification. ^{1}H NMR (500 MHz, CD_3OD) δ 2.24 (1H, ddddd, J=1.3, 1.3, 6.8, 8.4, 14.8, H-1′a), 2.58 (1H, ddddd, J=1.3, 1.3, 2.8, 7.0, 14.8, H-1′b), 3.11–3.15 (1H, m, H-1), 3.38–3.43 (3H, m, H-2,3,5), 3.65 (1H, dd, J=6.7, 11.3, H-6a), 3.69 (1H, dd, J=6.7, 11.3, H-6b), 3.85 (1H, dd, J=1.0, 2.7, H-4), 4.99–5.01 (1H, m, H-3′a), 5.06–5.10 (1H, m, H-3′b), 5.97 (1H, dddd, J=6.9, 10.2, 13.8, 17.1, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.2, 67.7, 70.8, 72.3, 76.4, 80.2, 81.3, 116.7, 136.7; HRMS *m/z* 227.0891 [(M+Na)$^+$; calcd for $NaC_9H_{16}O_5$: 227.0895].

3-(4:6-*p*-Methoxybenzylidene-β-D-galactopyranosyl)-1-propene (40). A solution of 3-(β-D-galactopyranosyl)-1-propene (5.0 g, 25.7 mmol), 4-methoxybenzaldehyde dimethyl acetal (12.0 g, 65.8 mmol), and toluene-*p*-sulphonic acid monohydrate (10.0 mg) in DMF (10 mL) was stirred under aspirator pressure at 50 °C overnight. The mixture was poured into a stirred solution of cold water (100 mL) containing NaOH (10.0 mg). After 1 h, the mixture was kept at 4 °C for 24 h. The crystals which had formed were filtered off, washed successively with cold water (10×25 mL) and hexane (5×25 mL), and dried in vacuo to give the title compound **40** (5.2 g, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (2H, br, OH), 3.50 (1H, bs, H-5), 3.60 (3H, s, OCH_3), 3.69 (1H, dd, J=9.3, 3.8, H-3), 3.75 (1H, dd, J=9.3, 7.5, H-2), 3.81 (3H, s, OCH_3), 4.10 (1H, dd, J=12.5, 1.9, H-6a), 4.21 (1H, d, J=3.8, H-4), 4.22 (1H, d, J=7.5, H-1), 4.35 (1H, dd, J=12.6, 1.3, H-6b), 5.52 (1H, s, CH), 6.89 (2H, m, Ar), 7.43 (2H, m, Ar); HRMS *m/z* 455.0465 [(M+Cs)$^+$; calcd for $CsC_{17}H_{22}O_6$: 455.0471].

3-(4:6-*p*-Methoxybenzylidene-2:3-carbonylmethylene-β-D-galactopyranosyl)-1-propene. A mixture of **40** (757.8 mg, 2.35 mmol) and dibutyltin oxide (585.8 mg, 2.35 mmol) in toluene (10 mL) was heated under reflux for 16 h to remove water azeotropically. The solution was evaporated to ca. 25 mL, and methyl bromoacetate (0.33 mL, 3.52 mmol) and Bu_4NI (869.3 mg, 2.35 mmol) were added. The mixture was then heated under reflux for 3 h. The solvent was removed in vacuo and purified by column chromatography (ethyl acetate:hexane, 1:3) to give the title compound (626.1 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49–2.43 (1H, m), 2.72–2.78 (1H, m), 3.47 (1H, br s), 3.53 (1H, ddd, J=9.5, 7.5, 2.5), 3.67 (1H, dd, J=9.5, 3.5), 4.05 (1H, br d, J=12.5), 3.80 (3H, s), 4.32 (1H, br d, J=12.5), 4.41 (1H, br d, J=3.5), 4.43 (1H, d, J=17.5), 4.61 (1H, dd, J=9.5, 9.5), 4.62 (1H, d, J=17.5), 5.24–5.15 (2H, m), 5.52 (1H, s), 6.02–5.97 (1H, m), 6.89 (2H, d, J=10.0), 7.42 (2H, d, J=10); HRMS *m/z* 495.0431 [(M+Cs)$^+$; calcd for $CsC_{19}H_{22}O_7$: 495.0420].

2-(4:6-*p*-Methoxybenzylidene-2:3-carbonylmethylene-β-D-galactopyranosyl)acetaldehyde (41). Ozone was bubbled into a solution of the preceding lactone (600.0 mg, 1.6 mmol) in CH_2Cl_2 at −78 °C. After excess O_3 was purged by argon, PPh_3 was added at −78 °C and the reaction was gradually warmed to 23 °C while

stirring. The concentrated crude product was purified by flash chromatography (ethyl acetate:hexane:MeOH, 10:10:1) to yield **41** (421.0 mg, 70%) as a colorless oil. $[\alpha]_D^{25}+1.0°$ (*c* 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.91 (1H, m), 3.00 (1 H, m), 3.57 (1H, m), 3.71 (1H, dd, *J*=11.0, 3.0), 3.80 (3H, s), 4.05 (1H, dd, *J*=12.5), 4.10 (1H, m), 4.28 (1H, dd, *J*=12.5, 1.0), 4.45 (1H, d, *J*=3.0), 4.63 (1H, dd, *J*=11.0, 11.0), 4.63 (1H, d, *J*=18.0), 5.52 (1H, s), 6.89 (2H, d, *J*=8.8), 7.48 (2H, d, *J*=8.8), 9.85 (1H, s); MS (FAB) *m/z* 497 $[(M+Cs)^+$; calcd for $CsC_{18}H_{20}O_8$: 497].

2-Allyl-4:6-isopropylidene-1-deoxy-D-mannose (42). Triacetate **39** was deprotected as described for tetraacetate **38**. The crude material (0.12 g, 0.59 mmol) was dissolved in dimethoxypropane (6 mL) and stirred for 2 h at 23 °C in the presence of a catalytic amount of camphor sulphonic acid. The reaction mixture was diluted with Et_2O, washed with satd $NaHCO_3$ soln and brine, dried over $MgSO_4$ and concentrated. The residue was dissolved in 75% aqueous HOAc and stirred at 23 °C for 5 min. The acetic acid was removed in vacuo and the crude product was purified by silica gel column chromatography (hexanes:EtOAc, 1:1) to afford the title compound **42** (0.10 g, 72%). ^1H NMR (500 MHz, CD_3OD) δ 1.41 (3H, s), 1.47 (3H, s), 2.25 (1H, dd, *J*=8.3, 14.0, H-1′a), 2.40 (1H, dd, *J*=6.6, 14.0, H-1′b), 3.28 (1H, br, H-5), 3.40 (1H, d, *J*=12.0, H-1a), 3.51 (1H, d, *J*=3.4, H-3), 3.71 (1H, d, *J*=12.0, H-1b), 3.80 (1H, dd, *J*=1.5, 12.9, H-6a), 4.09 (1H, dd, *J*=1.6, 12.9, H-6b), 4.23–4.24 (1H, m, H-4), 5.06–5.11 (2H, m, H-3′), 5.83 (1H, dddd, *J*=6.6, 8.3, 10.1, 18.3, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 29.9, 39.7, 64.4, 71.1, 71.4, 71.6, 73.8, 74.7, 102.7, 118.8, 134.2; HRMS *m/z* 267.1204 $[(M+Na)^+$; calcd for $NaC_{12}H_{22}O_5$: 267.1208].

(Z)-1-(4:6-*p*-Methoxybenzylidene-2:3-carbonylmethylene-β-D-galactopyranosyl)-4-(tri-*O*-acetyl-α-L-fucopyranosyl)-2-butene (43). To a solution of Wittig reagent **36** (385.2 mg, 0.6 mmol) in THF (2 mL) was added NaHMDS (0.5 mL, 1.0 M in THF) at −78 °C and the resulting yellow solution was stirred for 1 h. A solution of aldehyde **41** (72.0 mg, 0.2 mmol) in THF (1 mL) was added dropwise and the resulting solution was stirred at this temperature for 30 min. The reaction mixture was poured into satd NH_4Cl (1 mL), extracted with ethyl acetate (10 mL), and dried ($MgSO_4$). Flash column chromatography (EtOAc:hexane, 1:1) gave the coupled product **43** (35.0 mg, 29%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (3H, d, *J*=6.4), 2.00 (3H, s), 2.05 (3H, s), 2.15 (3H, s), 2.35–2.42 (1H, m), 2.45–2.70 (3H, m), 3.46–3.50 (1H, m), 3.52–3.57 (1H, m), 3.67 (1H, dd, *J*=3.4, 10.4), 3.80 (3H, s), 3.90–3.96 (1H, m), 4.05 (1H, dd, *J*=1.3, 12.6), 4.21–4.27 (1H, m), 4.29 (1H, dd, *J* =1.3, 12.6), 4.39–4.45 (2H, m), 4.61–4.65 (2H, m), 5.21–5.27 (2H, m), 5.33 (1H, dd, *J*=5.7, 9.8), 5.58–5.65 (1H, m), 5.70–5.76 (1H, m), 6.88 (2H, d, *J*=8.7), 7.40 (2H, d, *J*=8.7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.05, 21.02, 21.04, 24.38, 28.25, 55.05, 65.54, 66.04, 68.00, 68.23, 69.30, 70.05, 72.00, 73.95, 74.90, 101.20, 113.35, 126.45, 127.50, 127.65, 128.10, 128.25, 129.50, 132.05, 133.45, 160.05, 165.15, 170.15, 170.95; HRMS *m/z* 781.1480 $[(M+Cs)^+$; calcd for $CsC_{32}H_{40}O_{14}$: 781.1472].

(Z)-1-(3-Carboxylmethylene-β-D-galactopyranosyl)-4-(α-L-fucopyranosyl)-2-butene (8). Compound **43** (30.0 mg, 0.05 mmol) in 80% acetic acid (1 mL) was stirred at 23 °C for 0.5 h. The acetic acid was removed, the residue redissolved in THF (1 mL) and 1 N NaOH (200 mL, 0.2 mmol) was added to it. The resulting solution was stirred for 1 h and THF removed. The residue was redissolved in H_2O and then passed through a Bio Gel column to furnish compound **8** as a white solid (16.0 mg, 80%). ^1H NMR (500 MHz, D_2O) δ 1.00 (3H, d, *J*=6.4), 2.11–2.21 (m, 2H), 2.38–2.50 (m, 2H), 3.09–3.16 (m, 1H), 3.26 (1H, dd, *J*=3.3, 9.5), 3.39–3.46 (m, 2H), 3.52 (1H, dd, *J*=4.3, 11.7), 3.58 (1H, dd, *J*=7.8, 11.7), 3.61 (1H, d, *J*=3.4), 3.67 (1H, dd, *J*=3.4, 10.1), 3.74 (1H, q, *J*=6.4), 3.81 (1H, dd, *J*=6.1, 10.1), 3.86–3.96 (4H, m), 5.34–5.43 (1H, m), 5.51–5.60 (1H, m); ^{13}C NMR (125 MHz, D_2O) δ 16.00, 22.72, 29.44, 61.72, 66.22, 67.50, 68.25, 68.42, 69.68, 70.09, 72.11, 76.09, 78.65, 80.07, 83.60, 127.98, 128.56, 179.01; electrospray negative ion mass (declustering potential = −80 V) *m/z* 421 $[(M-H)^-$; calcd for $C_{18}H_{29}O_{11}$: 421].

1-(3-Carboxylmethylene-β-D-galactopyranosyl)-4-(α-L-fucopyranosyl)butane (9). To compound **8** (16.0 mg, 0.04 mmol) in MeOH 10% Pd–C was added and the mixture stirred under hydrogen at 23 °C for 30 min. The catalyst was filtered off and the solvent was removed to give compound **9** as a white solid (16.0 mg, 100%). ^1H NMR (500 MHz, D_2O) δ 1.14 (3H, d, *J*=6.5), 1.25–1.57 (6H, m), 1.66–1.85 (2H, m), 3.19–3.25 (1H, m), 3.39 (1H, dd, *J*=3.3, 9.5), 3.52 (1H, dd, *J*=9.5, 9.5), 3.54 (1H, dd, *J*=4.4, 7.8), 3.65 (1H, dd, *J*=4.4, 11.7), 3.71 (1H, dd, *J*=7.8, 11.7), 3.72 (1H, d, *J*=3.5), 3.76 (1H, dd, *J*=3.3, 9.8), 3.86 (1H, q, *J*=6.5), 3.89 (1H, dd, *J*=6.1, 9.8), 3.90–3.97 (1H, m), 4.02–4.10 (3H, m); ^{13}C NMR (125 MHz, D_2O) δ 15.96, 23.52, 24.57, 25.27, 31.13, 61.71, 66.23, 67.04, 68.25, 68.52, 70.14, 70.20, 72.22, 76.07, 78.62, 79.93, 83.76, 178.63; electrospray negative ion mass (declustering potential = −80 V) *m/z* 423 $[(M-H)^-$; calcd for $C_{18}H_{31}O_{11}$: 423].

1-(3-Carboxylmethylene-β-D-galactopyranosyl)-4-(α-L-fucopyranosyl)-2,3-epoxybutane (10). Compound **43** (30 mg, 0.05 mmol) in dichloromethane (1 mL) was treated with mCPBA and the resulting solution was stirred at 23 °C overnight. The resulting epoxide was purified by HPLC (ethyl acetate:hexane, 1:1) to give two diastereomers of 1:1 ratio. One of the diastereomers was dissolved in MeOH and hydrogenated by using $Pd(OH)_2$ (Degussa type) as catalyst for 0.5 h. The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated. The residue was redissolved in THF (1 mL) and 1 N NaOH (0.2 mL, 0.2 mmol) was added and the resulting mixture stirred for 1 h. The purification was the same as for compound **8** and the epoxide **10** was isolated as a white solid (9.0 mg, 40%). ^1H NMR (500 MHz, D_2O) δ 1.14 (3H, d, *J*=6.5), 1.61–1.69 (1H, m), 1.84–1.92 (1H, m), 1.96–2.05 (1H, m), 2.09–2.18 (1H, m), 3.37 (1H, dd,

J=3.0, 9.6), 3.51 (1H, dd, J=9.6, 9.6), 3.57–3.58 (1H, m), 3.61 (1H, dd, J=5.1, 12.0), 3.67 (1H, dd, J=9.2, 12.0), 3.69–3.72 (1H, m), 3.75 (1H, dd, J=3.4, 8.8), 3.77–3.82 (1H, m), 3.92–4.05 (4H, m), 4.16–4.21 (1H, m), 4.54 (1H, br q, J=7.1); ^{13}C NMR (125 MHz, D_2O) δ 15.4, 29.3, 34.9, 61.5, 65.8, 68.1, 68.9, 69.4, 69.9, 70.3, 71.2, 73.0, 77.5, 78.1, 78,1, 78.7, 82.8, 178.6; electrospray negative ion mass (declustering potential = −80 V) *m/z* 421 [(M-H)$^-$; calcd for $C_{18}H_{29}O_{12}$: 437].

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