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The Design, Synthesis, and Evaluation of Novel Conformationally Rigid Analogues of Sialyl Lewis^x

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Abstract—The design and synthesis of a series of analogues of sialyl Lewis^x (**1**) which incorporate conformationally rigid tetralin and naphthalene ring systems (**2–4**) has led to novel compounds which have similar potency to **1** as inhibitors of cell adhesion. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Introduction

The interactions between the selectin proteins (E, P, and L) and their corresponding natural carbohydrate ligands are important recognition events in cell adhesion that eventually results in migration of the white blood cells (leukocytes) to sites of injury and infection.[1] Excessive recruitment of leukocytes can lead to a number of disease states such as rheumatoid arthritis, septic shock, asthma, diabetes, reperfusion injury, and psoriasis. Cell adhesion involving carbohydrates could also have an important role in tumor metastasis.

L-Selectin is found on the surface of leukocytes, P-selectin is stored within endothelial cells and is released immediately on exposure to inflammatory mediators, whereas E-selectin is expressed on the surface of endothelial cells after stimulation by cytokines approximately 4 h after injury or infection.[2] The relative importance of each selectin protein is still unclear. Sialyl Lewis^x (sLe^x, **1**), which is a carbohydrate present on the surface of leukocytes, has been shown to be a ligand for E-selectin and P-selectin and also recognizes L-selectin.[3]

Various structure–activity studies have indicated that the essential features which are important for the recognition of E-selectin by its ligand are the fucose hydroxyl groups and the carboxylic acid group of sLe^x.[4] The galactosyl 4- and 6-hydroxyl groups have also been implicated. The determination of the X-ray diffraction structure of E-selectin by Graves and co-workers,[5] and NMR studies of the conformation of sLe^x which is bound to E-selectin,[6] have been used as a basis for the generation of a model of the E-selectin/sLe^x interaction.[7] This model is based on the structural homology which exists in the calcium binding domains of the rat mannose binding protein (rMBP)[8] and E-selectin and the authors have used a series of superimpositions and energy minimizations in the docking of sLe^x to the active site of E-selectin.[7] This model can be used to explain the requirement of the fucose and carboxyl groups for biological activity in that the fucose is coordinated to calcium and the carboxyl group of sLe^x can form a charged interaction with the Arg 97 residue of the protein. There is also the suggestion that the galactose 6-OH can hydrogen bond with Tyr 94 and account for its role in ligand binding.

These structure–activity results, NMR determinations of the bound conformation of sLe^x and molecular modeling studies have been used in the rational design of sLe^x mimics which inhibit cell adhesion and have potential as therapeutics in the treatment of inflammatory disease and cancer metastasis.[9] Indeed, sLe^x itself is currently in clinical trials for the treatment of reperfusion injury and heart attack but is costly to synthesize and has relatively weak binding affinity in vitro (1.0 mmol). Therefore, the search for novel mimics of

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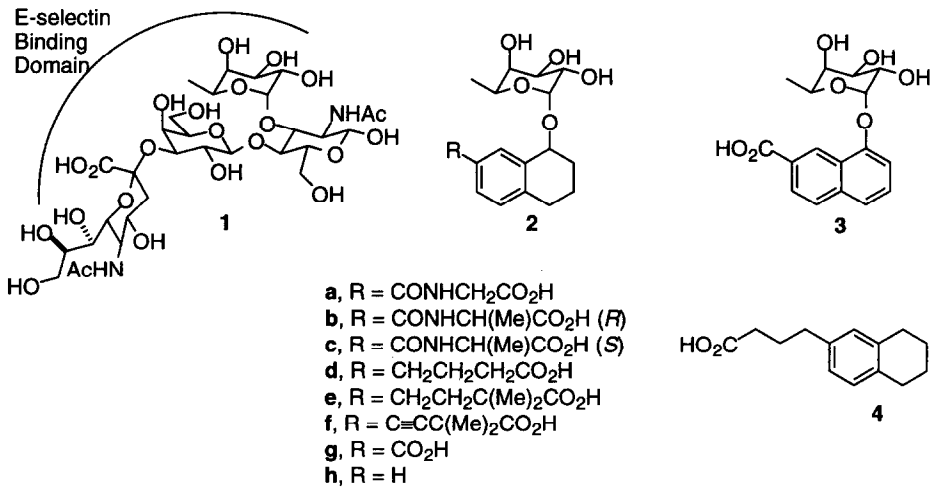
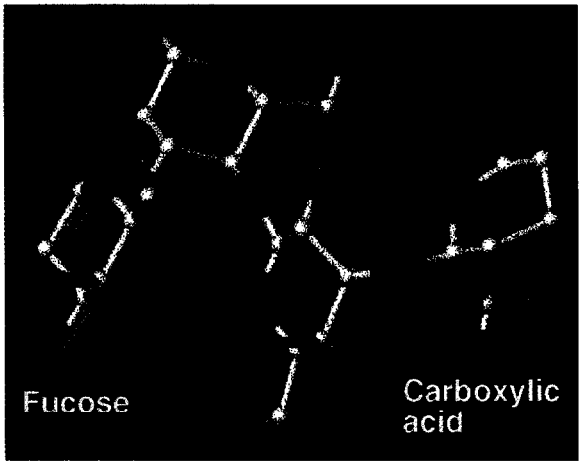


sLe^x, with lower costs of synthesis and improved affinities for E-selectin, is currently an important goal for researchers in this area.[10] Many of the compounds that have been synthesized as selectin inhibitors still have relatively weak potency and this could in part be due to their flexible nature. Moreover, many of these compounds are largely carbohydrate in nature and are thus susceptible to rapid metabolism.

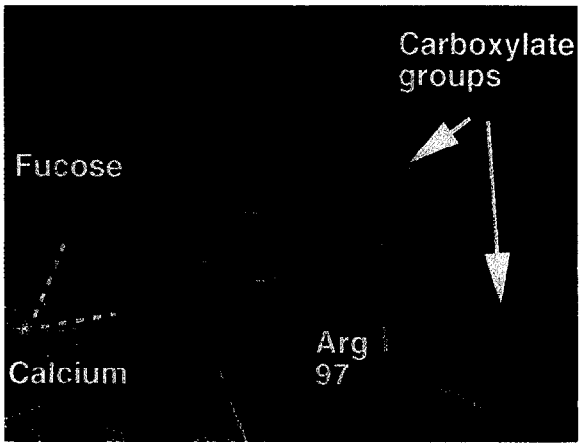
Thus, we have been interested in the design and synthesis of compounds that contain the fucose sugar bound to an appropriate conformationally rigid scaffold to which a carboxyl group is attached via a relatively short side chain. These compounds contain only the minimal structural elements necessary for E-selectin recognition as we chose to ignore, in the first instance, the role of the galactose hydroxyl groups. Herein we describe the design, synthesis and biological properties of conformationally rigid analogues of sLe^x which contain fucose bound to tetralin (**2a–h**), and naphthalene ring systems (**3**). These compounds are much reduced in carbohydrate character compared to sLe^x.[11] Molecular modeling was instrumental in the design of these compounds in ensuring that they had the correct spatial arrangement of the fucose and carboxyl groups necessary for binding and that they would not exhibit any unfavorable steric interactions with the protein when placed in the active site.

Results and Discussion

The molecular modeling procedures used in this study began with an examination of the bioactive conformation of sLe^x as determined using NMR by Peters and co-workers.[12] We removed the NHAc group of the GlcNAc residue to prevent the formation of bonding artifacts of the type described by Kogan and co-workers.[7] This conformation was docked into the active site and energy minimization was performed using CHARMM with the protein and fucose resides immobilized and dihedral constraints suggested by the work of Peters imposed on the various glycosidic torsion angles ($\varnothing_{N-G}$ $-76°+/-10°$, Ψ_{N-G} $+6°+/-10°$; $\varnothing_{G-GN}$ $+39°+/-10°$, Ψ_{G-GN} $+12°+/-6°$; $\varnothing_{F-GN}$ $+38°+/-7°$, Ψ_{F-GN} $+26°+/-6°$).[11] A low energy structure was obtained ($\varnothing_{N-G}$ $-69°$, Ψ_{N-G} $+12°$; $\varnothing_{G-GN}$ $+39°$, Ψ_{G-GN} $+13°$; $\varnothing_{F-GN}$ $+42°$, Ψ_{F-GN} $+29°$, see Figure 1(a)). Our observations were essentially the same as those of Kogan and co-workers and placed the carboxylic acid group in a position close to the guanidino group of Arg 97. The model also predicted hydrogen bonding interactions of the ligand with various residues of the protein, including that of the galactosyl 6-OH with Tyr 94 which has also been implicated in ligand binding.[7] Initially, we chose to ignore the apparent role of the galactose sugar and to concentrate our efforts on the design of mimics with increased conformational rigidity, which are much reduced in carbohydrate character, and which would hold the fucose and carboxylic acid residues, essential for ligand binding in the optimum position based on this model. Molecular modeling of the tetralin derivative **2d** indicated that it was feasible for a relatively low energy conformation to hold the fucose and carboxyl groups in the correct spatial orientation for selectin binding based on the sLe^x model. The modeling was carried out by performing a conformational grid search, using QUANTA, on the glycosidic bonds of **2d**. This analysis revealed a number of low energy conformations and one of these, when docked in the active site, placed the carboxylic acid group near to Arg 97. Some minor unfavorable steric interactions were removed by an energy minimization using constraints that immobilized the fucose and the protein residues. Having determined that it was a reasonable hypothesis for **2d** to take up a conformation suitable for binding, we set about the



(a)



(b)

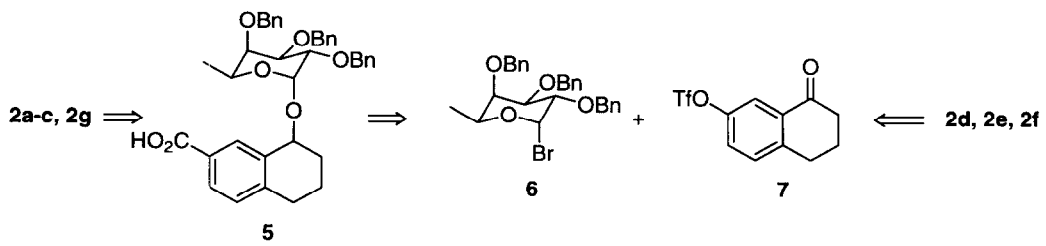
Figure 1. (a) The relationship between the fucose and carboxyl groups of tetralin **2d** (colored in purple) and sLe^x **1** (colored in white, with oxygen atoms displayed in red) is shown, illustrating the good overlap of the fucose and carboxylic acid groups. (b) Diagram showing the energy minimized structures of tetralins **2d** (colored in purple) and **2g** (colored in blue-green) docked into the E-selectin active site. The calcium atom and Arg 97 residues of E-selectin are highlighted. The carboxylate group of **2g** has been placed next to Arg 97 in an alternative location to **2d**, suggesting a second site capable of interacting with this residue.

synthesis of **2d** and other analogues which have a fucose–tetralin backbone but varying degrees of conformational freedom in the acid side chain. Molecular modeling had indicated that all of the compounds (**2a–f**) could also orient the fucose and carboxyl groups in a spatial orientation close to that of sLe^x.

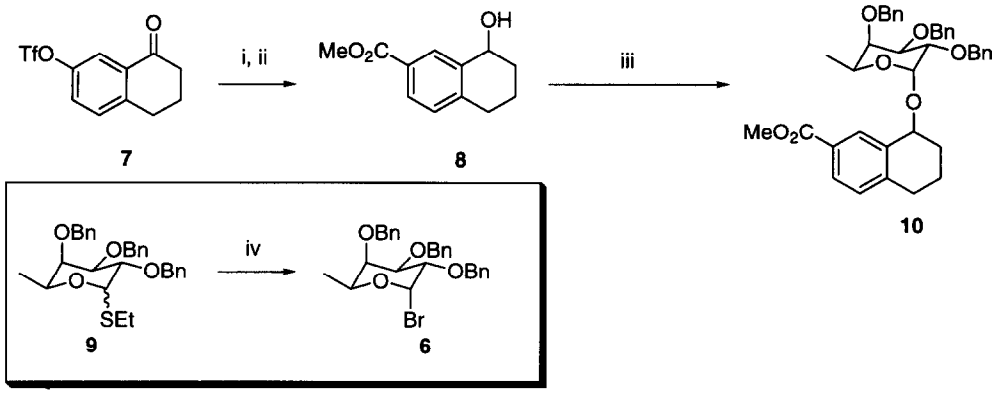
Retrosynthetic analysis of compounds **2** is outlined in Scheme 1. We envisaged that the alkyl and acetylene side chains for **2d–f** could be introduced by palladium coupling reactions of suitable acetylene derivatives with the known triflate **7**,[13] and that the acid **5** would prove a useful intermediate in the synthesis of the amide derivatives (**2a–c**). The bromide **6** was envisaged as the fucose donor in the synthesis.[14] We also thought that with **5** in hand it would be interesting to prepare **2g** for a comparison with the other derivatives, despite the carboxyl and fucose not having the spatial requirements to match that of sLe^x or **2d**.

The syntheses of derivatives **2a–c** and **2g** were carried out as described in Scheme 2. The aryl triflate (**7**) was prepared in two steps from commercially available 7-methoxy-1-tetralone as previously described.[13] Palladium catalyzed carbonylation of **7** using palladium (II) acetate, 1,3-bis(diphenylphosphino)propane (dppp), with triethylamine as base in DMF/MeOH,[13] followed by reduction of the product with sodium borohydride, gave the required alcohol (**8**) in an excellent overall yield. Halide ion catalyzed glycosylation[15] of the alcohol **8** using the bromide **6**, which was freshly prepared from a mixture of the thiofucosides (**9**),[14] stereoselectively gave the α-fucoside (**10**) as a 1/1 mixture of tetralin diastereoisomers.

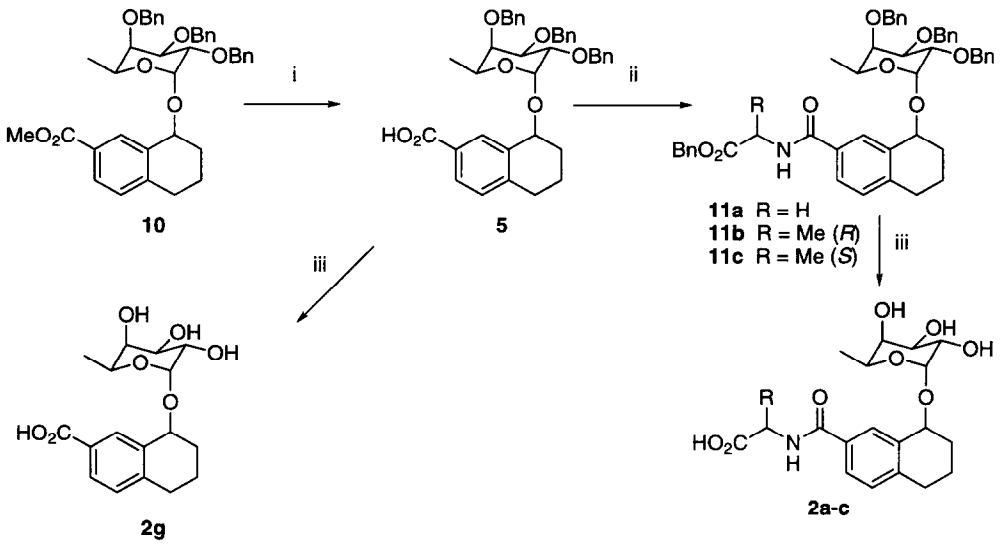
The required intermediate **5** was isolated after saponification of **10** using lithium hydroxide in THF–water (Scheme 3). We found that the BOP-Cl[16] reagent coupled the corresponding amino acid benzyl esters with the acid **5** to give the target compounds in their protected form (**11a–c**). Catalytic hydrogenation of **11a–c** removed the benzyl groups and gave **2a–c** respectively. With **5** in hand, **2g** was prepared simply by catalytic hydrogenation (Scheme 3).



Scheme 1.



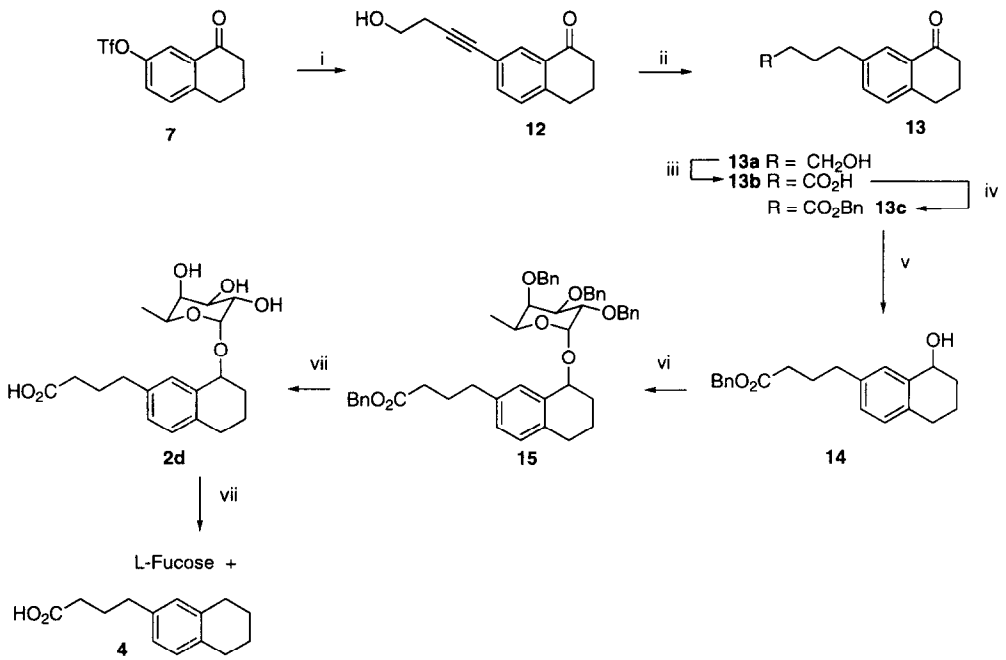
Scheme 2. Reagents and conditions: (i) $Pd(OAc)_2$, CO, MeOH, DMF, NEt_3, dppp, 95%; (ii) $NaBH_4$, MeOH, 80%; (iii) **6**, Et_4NBr, CH_2Cl_2, mol. sieves, 61%; (iv) Br_2, CH_2Cl_2.



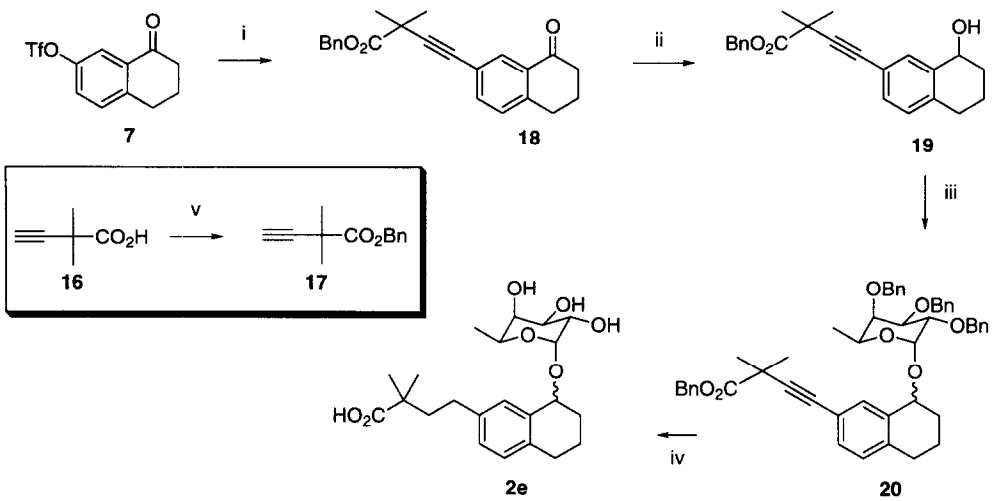
Scheme 3. Reagents and conditions: (i) LiOH, THF–H_2O, 92%; (ii) BOP-Cl, Et_3N, $NH_2CH(R)CO_2Bn$, 66–71%; (iii) H_2, 5% Pd-C, EtOH, 72–95%.

The aryl triflate **7** proved to be a useful intermediate in the preparation of the alkyl analogue **2d** (Scheme 4). Palladium catalyzed coupling of 3-butyn-1-ol with the triflate **7** gave the acetylene **12** in 77% yield. We found that the highest yields for this transformation were obtained when bis(triphenylphosphine)palladium(II) chloride was used to effect the transformation in DMF with triethylamine as base.[17] This acetylene **12** was then converted into the ester **13c** in three steps (catalytic hydrogenation, oxidation of the primary alcohol to the carboxylic acid using Jones' reagent, and benzylation of the acid with DCC/DMAP and benzyl alcohol). Reduction of the ketone group of **13c** with sodium borohydride gave the alcohol **14** which was fucosylated using the bromide **6** as described above and gave the desired α-anomer (**15**) as a 1/1 mixture of tetralin diastereoisomers in 42% yield. Compound **2d** was obtained in 72% yield when the benzyl groups were removed from **15** by catalytic hydrogenation using 5% palladium on activated carbon in ethanol. The reaction required careful monitoring as prolonged exposure gave the tetralin **4** and L-fucose because of competing hydrogenolysis of the secondary benzylic ether linkage of the tetralin ring.

We were interested in preparing analogues of **2d** that contained a multiple bond. We first attempted to utilize the chemistry similar to that used in the preparation of **2d** to prepare the alkyne **2f**. The precursor **19** was prepared without difficulty by the methods already outlined. Thus, as is shown in Scheme 5, the acetylene **17** was obtained by benzylation of the known acid **16**[20]



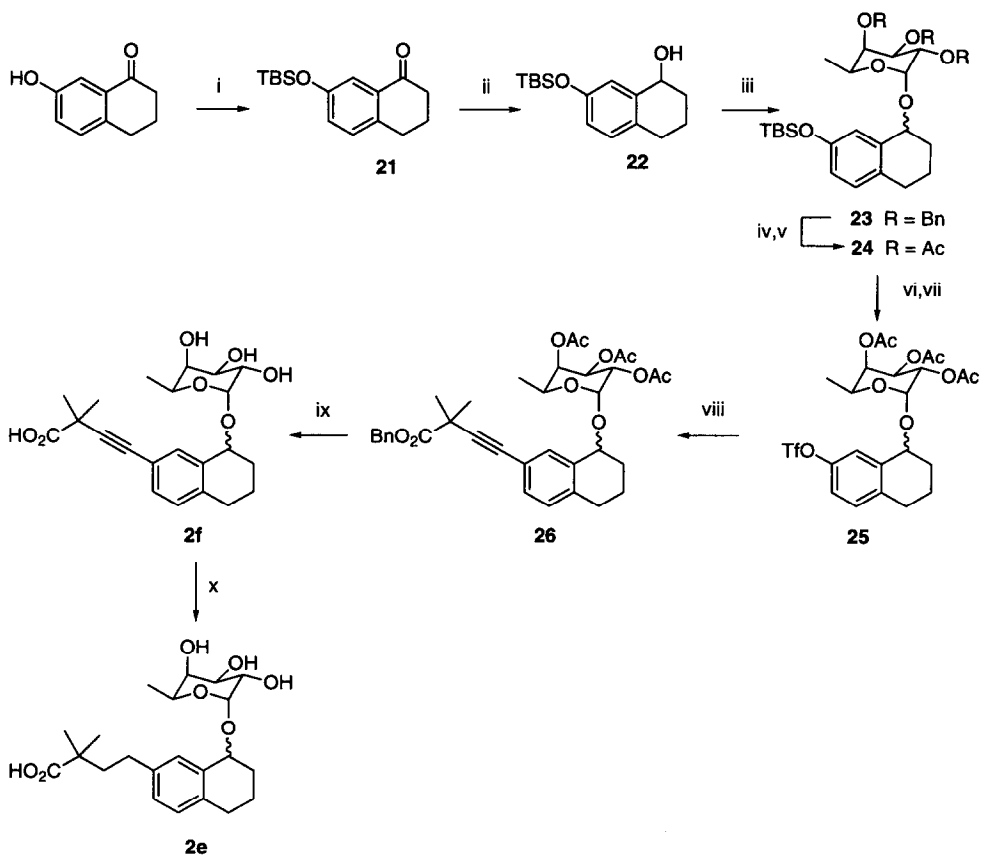
Scheme 4. Reagents and conditions: (i) $PdCl_2(PPh_3)_2$, 3-butyn-1-ol, DMF, Et_3N, 77%; (ii) 5% Pd-C, H_2, EtOH, 96%; (iii) Jones Reagent, acetone, 61%; (iv) BnOH, DCC, DMAP, CH_2Cl_2, 88%; (v) $NaBH_4$, MeOH, 78%; (vi) **6**, Et_4NBr, CH_2Cl_2, mol. sieves, 42%; (vii), 5% Pd-C, H_2, EtOH.



Scheme 5. Reagents and conditions: (i) $PdCl_2(PPh_3)_2$, **17**, DMF, Et_3N, 56%; (ii) $NaBH_4$, MeOH, 80%; (iii) **6**, Et_4NBr, CH_2Cl_2, mol. sieves, 25%; (iv) 5% Pd-C, H_2 EtOH; (v) DCC, DMAP, BnOH, 74%.

using DCC, DMAP, and benzyl alcohol. Palladium catalyzed coupling of the alkyne **17** with the triflate **7** followed by reduction of the ketone **18** with sodium borohydride gave the alcohol **19**. Glycosylation with total α-stereocontrol gave the ester **20** as a 1/1 mixture of diastereoisomers. Hydrogenation removed the benzyl groups and simultaneously reduced the alkyne to give the acid **2e**. We were not able to remove the benzyl groups and leave the acetylene group intact. Methods tried included Na/NH_3, TMSI, $FeCl_3$, and $BCl_3{\cdot}SMe_2$ which have been reported to be efficient reagents for the removal of benzyl groups, but these methods all gave complex mixtures of products.[18]

We therefore developed the alternative approach, shown in Scheme 6, for the preparation of unsaturated analo-

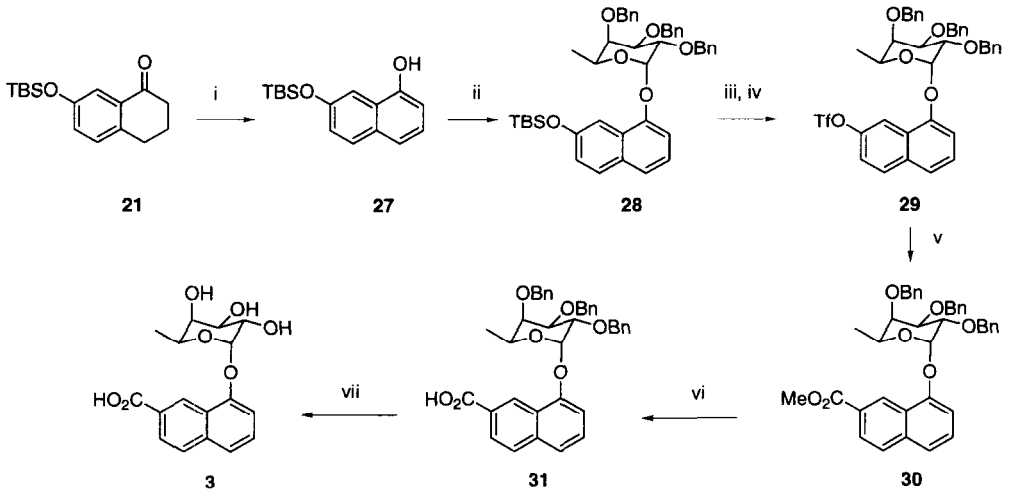


Scheme 6. Reagents and conditions: (i) TBSCl, Im., DMF, 92%; (ii) $NaBH_4$, MeOH, 77%, (iii) **6**, Et_4NBr, CH_2Cl_2, mol. sieves, 73%; (iv) 5% Pd-C, H_2, EtOH; (v) Ac_2O, Py., 91%, two steps; (vi) TBAF, THF; (vii) Tf_2O, 2,6-lutidine, DMAP (cat.), CH_2Cl_2, 79%, two steps; (viii) $PdCl_2(PPh_3)_2$, **17**, DMF, Et_3N, 56%; (ix) NaOMe, MeOH (1 h), then LiOH, H_2O (12 h), 55%; (x) 5% Pd-C, H_2, 95%.

gues. Thus the required *tert*-butyldimethylsilyl (TBS) derivative (**22**) was prepared in two steps from 7-hydroxy-1-tetralone and, after stereoselective glycosylation, gave the α-fucoside **23** as a 1/1 mixture of diastereoisomers. The removal of the benzyl groups was effected by hydrogenation and the fucose hydroxyl groups were then protected as the acetate esters (**24**) by treatment with acetic anhydride pyridine. The silyl group of **24** was then removed with TBAF in THF and subsequent reaction of the product with trifluoromethanesulfonic anhydride in the presence of 2,6-lutidine and catalytic DMAP gave the triflate **25**. Palladium catalyzed coupling of the triflate **25** with the acetylene **17** gave the ester **26** in 55% yield. When adduct **26** was treated with catalytic sodium methoxide in methanol followed by LiOH the sLe^x analogue **2f** was obtained in 50% yield over two steps. Analogue **2e** could be obtained from **2f** after catalytic hydrogenation. Triflate **25** is thus a potentially useful intermediate for the synthesis of other multiple-bond analogues via palladium coupling reactions, and for saturated analogues after reduction of the multiple bonds.

We decided to develop a method for synthesis of compounds which contain a naphthalene scaffold to investigate what effect this structural motif would have on the biological activity of sLe^x mimics of this type. The synthesis of **3** is outlined in Scheme 7 and starts from the TBS protected phenol **27**, which is also prepared from 7-hydroxytetralone. Aromatization of the ketone **21** using palladium catalyzed dehydrogenation in cumene provided the naphthol **27** in 55% yield. Glycosylation of **27** introduced the fucose group with the correct α-stereochemistry to give **28** in 71% yield. The TBS group in **28** was removed using TBAF in THF and the reaction of the resulting phenol with trifluoromethanesulfonic anhydride in the presence of 2,6-lutidine and DMAP gave the triflate **29** in 44% over two steps. Palladium catalyzed carbonylation of the triflate **29** gave the ester **30** which was converted into the target compound **3** in two steps (saponification with lithium hydroxide and hydrogenolysis of the benzyl groups with 5% Pd-C).

Finally, we prepared the tetralin **2h** as a control compound with a view to confirming the requirement of the



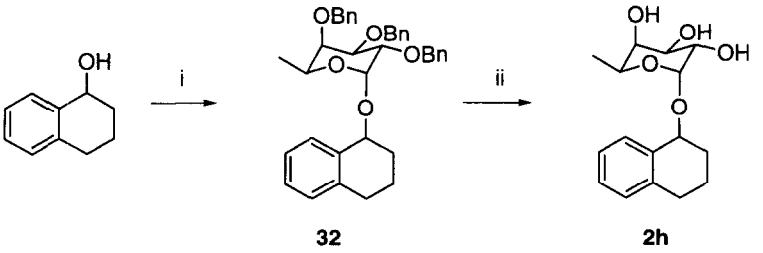
Scheme 7. Reagents and conditions: (i) 5% Pd-C, cumene, 55%; (ii) **6**, Et_4NBr, CH_2Cl_2, mol. sieves, 71%; (iii) TBAF, THF; (iv) Tf_2O, 2,6-lutidine, DMAP, CH_2Cl_2, 44% over two steps, (v) $Pd(OAc)_2$, CO, NEt_3, MeOH, DMF 65%; (vi) LiOH, THF, H_2O 74%; (vii) 5% Pd-C, H_2, EtOH, 35%.

acid group for activity. Glycosylation of commercially available 1,2,3,4-tetrahydro-1-naphthol gave **32**, which was converted into the tetralin **2h** by hydrogenation (Scheme 8).

Compounds **2a–h**, **3**, and **4** were evaluated for their effects on the adhesion of resting HL60 cells on TNFα-HUVEC[19] and the results are displayed in Table 1. Selected compounds were also tested in an assay of HL-60 cell adhesion to plates coated with recombinant soluble E-selectin and the results are shown in Table 2.

Results from the TNFα-stimulated HUVEC cell assay show that the acid **2d** was the most potent of these compounds with 90% inhibition of adhesion of resting HL60 cells at a concentration of 1.0 mM (Table 1). Indeed, **2d** demonstrated an IC_{50} of 1.7 mM in the E-selectin coated plate assay (Table 2), consolidating the result seen in Table 1. The amide analogues (**2a–c**) were less active than the acid **2d** with the D-alanine and glycine derivatives (**2b**, **2c**) showing no activity at 1.0 mM concentration in contrast to moderate activity observed for the L-alanine analogue **2c** (26% inhibition at 1.0 mM; Tables 1 and 2). The dimethylalkyl analogue **2e** was less active than **2d**. While the acetylene analogue **2f** was inactive in the HUVEC cell assay (Table 1), it demonstrated the same potency as **2d** in the E-selectin coated plate assay. The reason for the inconsistent results for **2f** were not clear and this may be a result of the difficulties of comparing single point results with full IC_{50}s, particularly when the slope of the inhibition curve is very steep as was seen with these compounds.

The biological activity of **2g** was an unexpected result as the carboxyl group and the fucose residue are at a much shorter distance than in sLe^x and would not appear to meet the spatial arrangement required for selectin recognition. Interestingly, modeling studies showed that **2g** could occupy the active site with a potential interaction between the acid group and the guanidino group of Arg 97 by an approach from the opposite side to that modeled for sLe^x (see Figure 1(b)). This suggests a second potential binding position for a carboxylic acid or



Scheme 8. Reagents and conditions: (i) **6**, Et_4NBr, CH_2Cl_2, mol. sieves; (ii) 5% Pd-C, H_2, EtOH.

Table 1. Effects of compounds **2–4** on the adhesion of resting HL60 cells on TNFα-stimulated HUVEC cells[19a]

Compound	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**	**3**	**4**
% Inhibition	< 10	< 10	26	90	39	< 10	48	< 10	< 10	< 10

[a]Results are either from a single determination or the mean of 2 determinations, % inhibition was determined at 1.0 mM concentration for a 1:1 mixture of diastereoisomers except for the naphthalene **3**. Compounds **2a** and **2g** were tested at a concentration of 0.1 mM. 3-Isopropoxybenzo[*b*]thiophene-2-carboxyamide (**33**) was evaluated in this assay (IC_{50} = 2.0 mM; literature value = 3.8 μM) as it is a known inhibitor of ICAM-1 and E-selectin mediated neutrophil adhesion.[19b] The IC_{50} for sLe^x was not determined in this case; sLe^x has an IC_{50} of 0.8 mM for the inhibition of adhesion of HL60 cells to E-selectin coated plates.[19c]

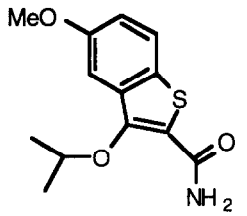


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Table 2. Effects of compounds **2b–2g** on the adhesion of resting HL-60 cells to recombinant soluble E-selectin [a]

Compound	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**
IC_{50}	> 5 mM	> 5 mM	1.7 mM	3.7 mM	1.7 mM	≈4 mM

[a]Results are a mean of 2 determinations. Percent inhibition was determined at 7 compound doses and dose response curves were constructed to determine IC_{50}s. A monoclonal antibody against human E-selectin (R&D Systems clone BBIG-E4) blocked adhesion of HL-60s in this assay with an IC_{50} of 0.32 ± 0.1 μg/mL (n = 8). sLe^x had an IC_{50} of 3.2 mM (n = 2) in this assay.

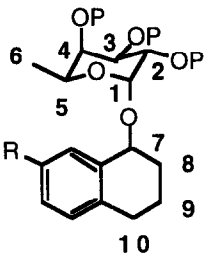
hydrogen-bonding group in the active site. Compounds **2h** and **4** were inactive, thus confirming the requirement of the fucose and carboxylic acid groups for activity in the tetralin series. The naphthalene derivative (**3**) was also inactive under the conditions of this assay and thus it would appear that the flexibility of the tetralin ring is important for the binding of this family of compounds.

Conclusions

In summary, we have described the design, synthesis and evaluation of conformationally rigid glycomimetics which use a substituted tetralin or naphthalene ring system as replacements for the glucosamine, galactose and sialic acid residues of sialyl Lewis^x. The acid **2d** is the most potent of these compounds in inhibition of adhesion of HL60 cells to TNFα-stimulated HUVEC (90% inhibition at 1.0 mM). The activity of the benzoic acid **2g** indicates a second orientation in which a carboxylate can bind to E-selectin. We are currently looking at the determination of the specific binding affinity of these compounds for E-, P- and L-selectins and at further structural modifications to increase their potency and thus their potential for treatment of inflammatory related diseases and cancer metastasis.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Jeol JNM-GX 270 spectrometer or Bruker AM500. Tetramethylsilane (TMS), $CDCl_3/CHCl_3$, HOD, or ACETN-d_6 was used as internal standard. Carbon spectral assignments were verified by DEPT experiments. NMR data assignments for tetrahydronaphthalene compounds are given for both diastereoisomers and the numbering used in NMR assignments is shown below in structure **A**. The $[\alpha]_D$ values were recorded using a JASCO DIP-370 digital polarimeter using a sodium lamp (λ = 589 nm) at 20 °C. Petroleum ether is the fraction bp 40–60 °C. EtOAc is ethyl acetate. All reagents were used as supplied. Column chromatography was performed on silica gel (ICN Biomedicals, 32–63, 60 Å) with flash elution. Analytical TLC was performed on Merck aluminum backed silica gel sheets (silica gel 60 F_{254}). Elemental analyses were carried out at the University of East Anglia, Norwich. Low-resolution electron impact (EI) mass spectra were recorded on a Kratos MS 25 spectrometer. Chemical ionization (CI), fast atom bombardment (FAB), and high-resolution mass spectra were recorded on a Micromass Autospec spectrometer. Melting points were recorded on an Electrothermal IA9100 digital melting point apparatus and were uncorrected.



P = H, Ac or Bn

A

Molecular modeling

The bioactive conformation of sLe^x was constructed in QUANTA from the individual monosaccharides (the coordinates of which were obtained from the Cambridge Database) using the glycosidic torsional angles determined by Peters and co-workers.[12] The NHAc group of GlcNAc was removed to avoid generation of bonding artifacts.[7] Coordinates for E-selectin and Mannose binding protein (MBP) were obtained from the Brookhaven databank (1ESL and 2MSB, respectively). Polar hydrogen atoms were added to the E-selectin structure. The procedure described by Kogan and co-workers was then followed with minor modifications.[7] Thus the calcium ion, Glu 185, Asn 187, Asn 205, and Asp 206 of MBP were superimposed on the calcium ion and Glu 80, Asn 82, Asn 105, and Asp 106 of the E-selectin structure. The mannose residue was then used as a template for docking sLe^x to the active site. The ring oxygen, C-2 and C-3 hydroxyls of fucose were superimposed on the ring oxygen and the C-4 and C-3 hydroxyl groups, respectively, of mannose. The mannose template was then removed. When this modeling procedure was carried out, there were some steric interactions between the ligand and the protein, specifically of the carbohydrate with the guanidino group of Arginine 97 as observed by Kogan. The protein and the fucose residue were immobilized and dihedral constraints were employed as indicated by the NMR structure of Peters[12] ensuring that the resulting conformation of the tetrasaccharide agreed with the NMR structure. Energy minimization was carried out using CHARMM (conjugate gradient method) and the resulting glycosidic torsion angles (Ø/Ψ) were −77°/9° (NeuAc–Gal), 47°/1° (Gal–GlcNAc), and 49°/35° (Fuc–GlcNAc). This model also predicted charge interactions of the guanidino group of Arg 97 and the carboxyl group of sLe^x and also hydrogen bonding of the galactosyl 6-OH with Tyr 94 and also possibly with Glu 80.

The following procedure was employed for the tetralin derivative **2d** to determine if a conformation required for activity would be accessible for the molecule. The compounds were constructed in QUANTA and minimized with CHARMM (conjugate gradient method). A conformational search using Grid Scan was then employed about the two glycosidic torsion angles (30° intervals from 30–360° were chosen for each bond, thus energy was calculated for 144 conformations). The fucose residue of one of the low energy conformers of **2d** was superimposed on that of the corresponding sLe^x structure obtained above. This particular conformation when docked in E-selectin held the carboxylic acid group close to that occupied by that of the carboxyl group of sLe^x and thus close to Arg 97. Energy minimization using CHARMM (conjugate gradient method) was then carried out in the active site to remove some minor unfavorable steric interactions. The protein and the fucose residue were immobilized during the energy minimization. The overall conclusion was that it was reasonable to assume that **2d** could have a conformation where the carboxylic acid and the fucose groups had the correct spatial orientation required for biological activity. A similar procedure was used for docking all of the tetralin molecules and the naphthalene derivative.

Method for biological assay[19]

1. After 4 h stimulation of HUVEC by TNFα, in the presence or in the absence of drug, cells were washed, and fluorescent dye-labeled HL-60 cells were added to HUVEC for 30 min at 37 °C, always in the presence or absence of drug. At the end of incubation, HUVEC were washed three times to remove nonadherent HL-60 cells. Spectrofluorimetric measurements were performed with a multiple reader (Cytofluor 2350, Millipore).
2. 96-well plates (Nunc Maxisorp) were coated with 2 μg/mL recombinant soluble E-selectin (R&D Systems) in phosphate buffered saline (PBS) overnight at 4 °C. Plates were washed three times with PBS then nonspecific binding sites were blocked by incubation in a solution of 1% (w/v) bovine serum albumin in PBS for 1 h at room temperature followed by further washing. 4×10^5 HL-60 cells were added to each well in the presence or absence of drug and the plates incubated for 1 h at 37 °C in an atmosphere of 5% CO_2. Plates were washed twice to remove nonadhered cells and the number of adherent cells quantitated using CellTiter96® or CytoTox96® kits (Promega).

Synthetic procedures

General procedure for reduction of tetralones with sodium borohydride. Sodium borohydride (1 equiv) was added to a solution of the tetralone (1 equiv) in metha-

nol (10 mL/mmol). The mixture was left to stir for 1 h and then the methanol was removed. The product was partitioned between EtOAc and water and the aqueous layer was further washed with EtOAc. The organic layers were combined and dried ($MgSO_4$). The solvent was removed and the product was purified by silica gel chromatography.

General method for glycosylation of alcohols and phenol[15]

Bromine (0.05 mL/mmol) was added dropwise to a mixture of thiofucosides (**9**, 1 equiv) in dichloromethane (5 mL/mmol) at 0 °C and the solution was stirred for 20 min. The solvent was then removed and toluene was distilled from the residue using a rotary evaporator (2×25 mL) and the residue was dried at high vacuum. This product was taken up in dichloromethane and added to a flask containing alcohol (0.2–1.0 equiv), tetraethylammonium bromide (TEABr, 1 equiv) and 4 Å molecular sieves and the resulting mixture was stirred for 24 h under an atmosphere of N_2 and at RT. The product was filtered through Celite washing thoroughly with EtOAc. The filtrate was washed with saturated sodium hydrogencarbonate, water, and dried ($MgSO_4$). The solvent was removed and the product was purified by silica gel chromatography.

General method for palladium catalyzed acetylene coupling with aryl triflates

The aryl triflate (1 equiv), $PdCl_2(PPh_3)_2$ (10–20 mol%), triethylamine (excess), the acetylene (2–3 equiv) and DMF (2.0 mL/mmol) were added to a 2-necked flask under an atmosphere of N_2 and the mixture was purged with N_2 for 10 min and was then heated at 70 °C and stirred at this temperature overnight maintaining an atmosphere of N_2. Ethyl acetate was added and the organic layer was washed with satd NH_4Cl and water and was then dried over anhydrous $MgSO_4$. The solvent was removed and the product was purified by silica gel chromatography.

General method for coupling amino acids to 5

The acid **5**, BOP-Cl (1.2 equiv) and the amino acid, benzyl ester, *p*-toluenesulfonate or hydrochloride salt (1.1 equiv) were added to dichloromethane and the mixture was stirred at rt. Then triethylamine (2.0 equiv) was added dropwise over 30 min and the mixture was stirred for 2 h. The solvent was removed and the product purified by silica gel chromatography.

General method for removal of benzyl groups

The benzylated compound was stirred in EtOH in the presence of an equal weight of 5% Pd-C until by TLC analysis the product had formed. The mixture was then filtered through Celite and the solvent was removed. The product was purified by chromatography on silica gel.

Ethyl 2,3,4-tri-*O*-benzyl-1-thio-α- and β-L-fucopyranose (9)[15]. L-Fucose (10 g, 0.061 mol) was treated with acetic anhydride/pyridine (300 mL, 2/1) at 100 °C for 3 h. The solution was concentrated and xylene was distilled from the residue (2×50 mL). The residue was taken up in dichloromethane (300 mL). Ethanethiol (6 mL) and tin(IV) chloride (3.0 mL) were added at 0 °C and the mixture was left to stir overnight. The product was washed with 10% sulfuric acid, saturated sodium hydrogencarbonate and water, dried ($MgSO_4$) and the solvent was removed. The residue was taken up in methanol (50 mL) and a freshly prepared solution of sodium methoxide in methanol (0.03 g Na/5 mL MeOH) was added and the mixture stirred until TLC analysis (acetone/chloroform, 1/2) revealed one fraction (R_f = 0.1). The methanol was then removed and the product in DMF (150 mL) was added to sodium hydride (14.7 g, 60% dispersion in mineral oil) with external ice cooling. After 1 h, benzyl bromide (32 mL) was added carefully and the mixture was left to stir overnight under nitrogen. Methanol was then added (20 mL) and the mixture was partitioned between toluene and water. The organic layer was washed with water and solvent was then removed. Column chromatography (EtOAc/petroleum ether, gradient) of the product gave in order of elution 7α and 7β (17.9 g; yield 61%; α/β, 1/3). The compounds crystallize on standing; the β-anomer (mp 49–51 °C: lit[15] 52 °C; $[\alpha]_D$ +11.5° (*c*, 0.2, $CHCl_3$: lit.[15] −16° (*c*, 1.5; CH_2Cl_2)) had NMR data in excellent agreement with that previously reported;[14] α anomer: mp 74–76 °C; $[\alpha]_D$ −142° (*c*, 0.7; $CHCl_3$); δ_H 7.25–7.28 (21H, ms, Ar-H), 5.46 (1H, d, *J* 5.5 Hz, H-1), 4.63–5.00 (6H, ms, CH_2Ph), 4.26 (1H, dd, *J* 5.5, 10.0 Hz, H-2), 4.19 (1H, q, *J* 6.5 Hz, H-5) 3.78 (1H, dd, *J* 10.0 Hz, 2.0 Hz, H-3), 2.44–2.61 (2H, ms, CH_2), 1.26 (3H, t, *J* 7.2 Hz, CH_3) 1.12 (3H, d, *J* 6.5 Hz, H-6): δ_C 139.3, 139.0, 138.8 (C, Ar), 128.9, 128.8, 128.6, 128.4, 128.0, 127.9 (CH, Ar), 83.9 (C-1), 80.3, (C-2), 78.1 (C-4), 76.5 (C-3), 75.3, 73.9, 72.8 (CH_2Ph), 67.1 (C-5), 24.2 (CH_2), 17.0 (CH_3), 15.3 (C-6): *m/z* (CI) 496 ($M+NH_4$) [Found: C, 72.8; H, 7.1; S, 6.8. $C_{29}H_{34}O_4S$ requires C, 72.8; H, 6.7; S, 6.7%].

7-Methoxycarbonyl-1,2,3,4-tetrahydro-1-naphthol (8). Treatment of 7-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene-1-one[13] (0.97 g, 4.8 mmol) with sodium borohydride as described above gave the title compound **8** (0.802 g, 80%): δ_H 8.50 (1H, d, *J* 1.5 Hz, Ar-H), 7.81 (1H, dd, *J* 1.5 and 8.0 Hz, Ar-H), 7.14 (1H, d, J 8.0 Hz, Ar-H), 4.79 (1H, m, CH), 3.89 (3H, s, OCH3), 2.89–2.62 (2H, m, CH2), 2.41 (1H, br s, OH), 1.65–2.03 (4H, ms, CH_2): δ_C 197.2 (C=O, ketone), 166.2 (C=O, ester),

149.1, 132.5, 128.7 (C, Ar), 133.6, 129.1, 128.5 (CH, Ar), 52.1 (OCH_3), 38.8, 29.7, 22.7 (CH_2): *m/z* (EI) 206 (M).

1-[7-Methoxycarbonyl-1,2,3,4-tetrahydro-1(*R,S*)-naphthyl]-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (10). The glycosylation procedure was followed as above for **8** (0.309 g, 1.5 mmol) and the thiofucoside **9** (2 equiv) and gave the title compound **10** as a colorless oil (0.57 g): δ_H 8.26 (1H, br s, Ar-H), 7.92 (1H, d, *J* 1.5, Ar-H), 7.87 (1H, dd, *J* 1.5 and 8.0 Hz, Ar-H), 7.82 (1H, dd, *J* 1.5 and 8.0 Hz, Ar-H), 7.15 (2H, d, *J* 8.0 Hz), 7.21–7.38 (30H, ms, Ar-H), 5.16 (1H, d, *J* 3.5 Hz, H-1), 5.12 (1H, d, *J* 3.5 Hz, H-1), 4.62–5.00 (14H, ms, CH_2Ph and H-7), 3.78–4.10 (6H, ms, H-2,3,5), 3.77 and 3.86 (each 3H, each s, OCH_3), 3.68 and 3.71 (each 1H, each br s, H-4), 2.73–2.85 (4H, m, H-10), 1.60–2.06 (8H, ms, H-8,9), 1.15 and 1.21 (each 3H, d, *J* 6.0 Hz, H-6): δ_C 167.1, 167.0 (C=O), 143.5, 143.1, 139.0, 138.9, 138.8, 138.6 (2C), 136.7, 136.1 (C, Ar), 131.5, 130.5, 129.1 (2C), 128.7, 128.5, 128.4, 128.3 (2C), 128.2 (2C), 128.0, 127.8, 127.7, 127.5 (2C), 127.4, 127.3 (CH, Ar), 98.1, 96.0 (C-1), 79.5, 79.4, 77.7, 76.6, 76.3 (2C), 75.0, 72.3, 66.8, 66.7 (C-2,3,4,5,7), 74.8 (2C), 73.2, 73.0, 72.7 (CH_2Ph), 51.9, 51.8 (OMe), 30.1, 29.3, 29.0, 27.7, 18.9, 18.0 (C-8,9,10), 16.7, 16.6 (C-6): *m/z* (CI) 640 (M + NH_4) [Found: C, 75.0; H; 6.7. $C_{39}H_{42}O_7$ requires C, 75.2; H, 6.8%].

1-[7-Carboxy-1,2,3,4-tetrahydro-1(*R,S*)-naphthyl]-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (5). Compound **10** (0.32 g, 0.49 mmol) was dissolved in THF/H_2O (5 mL, 4/1) and excess LiOH added (0.15 g). The solution was heated at reflux for 24 h. The THF was removed, water was added, and the aqueous layer was adjusted to pH 7 using KH_2PO_4. The product was washed with EtOAc (4×25 mL) and dried ($MgSO_4$) and the solvent removed to give title compound (**5**, 0.29 g, 92%, R_f = 0.53 and 0.46, EtOAc): δ_H 8.32 (1H, s, Ar-H), 8.00 (1H, s, Ar-H), 7.88–7.93 (2H, apparent dd, *J* 1.5, 8.0 Hz, Ar-H), 7.14–7.38 (44H, ms, Ar-H), 5.15 (2H, 2d, *J* 4.4 Hz, H-1), 4.61–5.02 (14H, ms, CH_2Ph and C-7), 3.87–4.13 (6H, ms, H-2,3,5), 3.66 (2H, br s, H-4), 2.69–2.91 (4H, m, H-10), 1.74–2.01 (8H, ms, H-8,9), 1.20 (3H, d, *J* 6.5 Hz, H-6), 1.17 (3H, d, *J* 6.5 Hz, H-6): δ_C 172.0 (C=O), 144.4, 144.1, 139.1, 139.0, 138.9, 138.7, (2C), 137.2, 137.0, (C, Ar), 132.2, 132.0, 131.3, 129.5, 129.2, 129.1, 128.9, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.5 (2C), 127.4, 127.2, 127.1, 126.9 (CH, Ar), 98.2, 96.1 (C-1), 79.5, 79.4, 78.1, 76.6, 76.4, 75.2, 72.3, 67.0, 66.8 (C-2,3,4,5,7), 74.9, 73.2, 73.1 (CH_2Ph), 30.1, 29.5, 29.2, 27.7, 18.8, 18.0 (C-8,9,10), 16.7, 16.6 (C-6); Found: *m/z* (CI) 626 (M + NH_4). $C_{38}H_{40}O_7$ requires M + NH_4 626.

1-[7-(*N*-Benzyloxycarbonylmethyl)-aminocarbonyl)-1,2,3,4-tetrahydro-1(*R,S*)-naphthyl]-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (11a). The coupling procedure above for **5** (0.15 g, 0.25 mmol) and glycine benzyl ester gave the title compound (**11a**, 0.125 g, 66%, R_f = 0.6, EtOAc/petroleum ether, 1/1): δ_H 8.03 (1H, br s, Ar-H), 7.73–7.75 (2H, ms, Ar-H), 7.59 (1H, dd, *J* 8.0, 2.0 Hz, Ar-H), 7.11–7.35 (58H, ms, Ar-H), 6.67 and 6.40 (each 1H, each t, *J* 1.5 Hz, NH), 5.20 (1H, d, *J* 3.6 Hz, H-1), 5.18 (2H, s, CH_2Ph), 5.13 (1H, d, *J* 3.5 Hz, H-1), 5.09 (2H, s, CH_2Ph), 4.63–5.01 (14H, ms, CH_2Ph and H-7), 3.81–4.24 (10H, ms, H-2,3,5, $NHCH_2$), 3.69 and 3.73 (each 1H, each d, *J* 1.0 Hz, H-4), 2.75–2.87 (4H, m, H-10), 1.70–2.05 (8H, ms, H-8,9), 1.19 (3H, d, *J* 6.6 Hz, H-6), 1.16 (3H, d, *J* 6.8 Hz, H-6): δ_C 169.9, 169.6 (C=O, ester), 167.2, 167.1 (C=O, amide), 142.1, 141.4, 138.9, 138.8 (2C), 138.6, 137.2, 137.0, 135.2, 135.1, 131.1 (C, Ar), 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 127.3, 126.9, 126.4, 125.7 (CH, Ar), 99.2, 95.4 (C-1), 79.6, 79.5 , 77.7, 77.2, 76.9, 76.2, 71.9, 66.8 (C-2,3,4,5,7), 74.8, 73.2, 73.0 (2C), 67.2, 66.9 (CH_2Ph), 41.7, 41.5 ($NHCH_2$), 30.4, 29.2, 28.8, 27.4, 19.5 18.1 (C-8,9,10), 16.7 (C-6). Found: *m/z* (CI) 756.3548 (M + H). $C_{47}H_9NO_8$ requires M + H 756.3536.

1-[7-((*R*)-*N*-1-Benzyloxycarbonylethyl)-aminocarbonyl)-1,2,3,4-tetrahydro-1(*R,S*)-naphthyl)-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (11b). The procedure for D-alanine benzyl ester and **5** (0.22 g, 0.3 mmol) in CH_2Cl_2 (5 mL) gave **11b** (0.22 g, 70%, R_f = 0.45–0.50, EtOAc/petroleum ether, 1/1): δ_H 8.11 (1H, s, Ar-H), 7.70–7.72 (2H, ms, Ar-H), 7.57 (1H, d, *J* 8.0 Hz, Ar-H), 7.13–7.37 (58H, ms, Ar-H), 6.74 and 6.72 (each 1H, each s, NH), 5.18–5.18 (6H, ms, CH_2Ph and H-1), 4.64–4.96, (16H, ms, CH_2Ph, H-7 and NHCH), 3.95–4.07 (6H, ms, H-2,3,5), 3.66 and 3.71 (each 1H, each br s, H-4), 2.75–2.87 (4H, m, H-10), 1.69–2.06 (8H, ms, H-8,9), 1.49 (3H, d, *J* 7.2 Hz, CH_3), 1.31 (3H, d, *J* 7.2 Hz, CH_3), 1.17 (3H, d, *J* 6.8 Hz, H-6), 1.14 (3H, d, *J* 6.8 Hz, H-6): δ_C 173.1, 172.9 (C=O, ester), 166.8, 166.7, (C=O, amide), 142.1, 141.5, 139.1, 139.0, 138.8 (2C), 138.7, 138.6, 137.4, 137.0, 135.4, 131.4 (2C) (C, Ar), 129.2, 128.6, 128.5, 128.4 (2C), 128.2, 128.1 (2C), 128.0, 127.7, 127.5 (2C), 127.4, 127.3, 127.0, 126.8, 126.6, 125.8 (CH, Ar), 98.9, 95.7 (C-1), 79.6, 79.5, 77.8, 77.5, 76.8, 76.6 72.1, 66.8 (2C) (C-2,3,4,5,7), 74.5, 73.2, 73.1, 73.0 (2C) 67.2, 67.0 (CH_2Ph), 48.5 (NHCH), 30.2, 29.1, 28.8, 27.5, 19.4 (C-8,9,10), 18.8, 18.3 (CH_3), 16.7 (C-6). Found: *m/z* (CI) 770.3697 (M + H). $C_{48}H_{51}NO_8$ requires M + H 770.3693]. [Found: C, 74.9; H, 6.7; N 1.8%. $C_{48}H_{51}NO_8$ requires C, 74.8; H, 6.7; N, 1.8%]

1-[7-((*S*)-*N*-1-Benzyloxycarbonylethyl)-aminocarbonyl)-1,2,3,4-tetrahydro-1(*R,S*)-naphthyl]-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (11c). Coupling of L-alanine benzyl ester and the acid **5** (0.22 g, 0.3 mmol) as described above gave **11c** (0.18 g, 67%, R_f = 0.34–0.36, ether): δ_H 8.00 (1H, d, *J* 1.5 Hz, Ar-H), 7.71–7.72 (2H, dd and s overlapping, *J* 1.5 Hz, Ar-H), 7.57 (1H, dd, *J* 8.0, 1.5 Hz, Ar-H), 7.12–7.37 (58H, ms, Ar-H), 6.71 and 6.68

(each 1H, each d, J 1.0 Hz, NH), 5.18 (2H, ABd, J 13.0 Hz, CH_2Ph), 5.12 (3H, overlapping ABd, J 13.0 Hz, CH_2Ph and H-1), 5.08 (1H, d, J 3.6 Hz, H-1), 4.59–5.00 (16H, ms, CH_2Ph, H-7 and NHCH), 3.94–4.10 (6H, ms, H-2,3,5), 3.66 and 3.71 (each 1H, each d, J 1.0 Hz, H-4), 2.75–2.87 (4H, m, H-10), 1.69–2.06 (8H, ms, H-8,9), 1.50 (3H, d, J 7.0 Hz, CH_3), 1.37 (3H, d, J 7.2 Hz, CH_3), 1.19 (3H, d, J 6.5 Hz, H-6), 1.14 (3H, d, J 6.5 Hz, H-6): δ_C 173.1, 172.9 (C=O, ester), 166.7, 166.6 (C=O, amide), 142.1, 141.7, 139.0 (2C), 138.8, 138.7, 138.6, 135.4, 135.3, 131.4 (C, Ar), 129.3, 129.2, 128.7, 128.6 (2C), 128.4, 128.3, 128.2 (2C), 128.1, 127.8, 127.7, 127.5 (2C), 127.4, 127.3, 127.0, 126.8, 125.7 (CH, Ar), 98.3, 95.5 (C-1), 79.5, 79.4, 77.8, 77.2, 76.8, 76.2, 75.7, 71.9, 66.9, 66.7 (C-2,3,4,5,7), 74.8, 73.2 (2C), 73.0, 72.8, 67.2, 67.1 (CH_2Ph), 48.5 (NHCH), 30.2, 29.2, 28.8, 27.4, 19.1 18.1 (C-8,9,10), 18.8, 18.3 (CH_3), 16.7 (C-6). [Found: m/z (CI) 770.3694 ($M+NH_4$). $C_{48}H_{51}NO_8$ requires M + NH4 770.3693]. [Found: C, 74.9; H, 6.7; N 1.82. $C_{48}H_{51}NO_8$ requires C, 74.8; H, 6.7; N, 1.8%]

1-[7-(*N*-Carboxymethyl)-aminocarbonyl)-1,2,3,4-tetrahydro-1 (*R*,*S*)-naphthyl]-α-L-fucopyranose (2a). The benzyl groups were removed from **11a** (0.110 g, 0.37 mmol) as described above and chromatography of the residue (EtOAc/MeOH, gradient) gave **2a** (39 mg, 95%, R_f = 0.3–0.4, EtOAc/MeOH, 1/1); δ_H (Acetone-d_6/D_2O) 7.96 (1H, d, J 1.5 Hz, Ar-H), 7.80 (1H, br s, Ar-H), 7.70–7.75 (2H, m, Ar-H), 7.29 and 7.33 (each 1H, each d, J 8.0 Hz, Ar-H), 5.28 and 5.21 (each 1H, each d, J 3.4 Hz, H-1), 4.80 (2H, m overlapping with HOD, H-7), 4.18 and 4.14 (each 1H, each q, J 6.4 Hz, H-5), 3.97 (4H, s, CH_2NH), 3.80–3.87 (6H, m, H-2,3,4), 2.79–2.88 (4H, m, H-10), 1.81–2.08 (8H, ms, H-8,9), 1.30 and 1.28 (each 3H, each d, J 6.4 Hz, H-6): δ_C 170.1, 169.8 (C=O), 143.6, 143.1, 137.4, 137.2, 132.0, 131.8 (C, Ar), 130.5, 130.4, 129.7, 128.9, 127.4, 127.0 (CH, Ar), 101.0, 97.7 (C-1), 77.6, 73.8, 72.8 (2C), 70.5 (2C), 69.4, 68.9, 67.9, 67.8 (C-2,3,4,5,7), 44.7, 44.5 ($NHCH_2$), 30.1, 29.4, 28.7, 27.9, 19.4, 18.4 (C-8,9,10), 16.7, 16.4 (C-6). [Found: m/z (FAB) 418.1482 (M + Na). $C_{19}H_{25}NO_8$ requires M + Na 418.1478].

1-[7-((*R*)-*N*-1-Carboxyethyl)-aminocarbonyl)-1,2,3,4-tetrahydro-1(*R*,*S*)-naphthyl]-α-L-fucopyranose (2b). An identical procedure for **11b** (0.29 g, 0.37 mmol) as for **11a** gave **2b** (0.14 g, 95%, R_f = 0.3–0.4, MeOH/EtOAc, 1/1): δ_H (Acetone-d_6/D_2O) 8.00 (1H, br s, Ar-H), 7.85 (1H, br s, Ar-H), 7.76–7.81 (2H, m, Ar-H), 7.36 and 7.33 (each 1H, each d, J 8.0 Hz, Ar-H), 5.32 and 5.26 (each 1H, each d, J 3.0 and 3.6 Hz, H-1), 4.84 (2H, m overlapping with HOD, H-7), 4.48 (2H, apparent q, J 7.0 Hz, NHCH), 4.22 and 4.15 (each H, each q, J 6.6 Hz, H-5), 3.84–3.94 (6H, m, H-2,3,4), 2.78–2.93 (4H, m, H-10), 1.89–2.10 (8H, ms, H-8,9), 1.54 (6H, d, J 7.0 Hz, CH_3), 1.36 and 1.33 (each 3H, each d, J 6.6 Hz, H-6): δ_C 170.1, 170.2 (C=O), 143.3, 142.9, 136.5, 136.1, 130.2, 130.0 (C, Ar), 129.9, 129.8, 129.2, 128.3, 126.8, 126.6 (CH, Ar), 100.3, 97.1 (C-1), 77.2 (2C), 73.4, 72.0, 69.6, 68.7, 68.2, 67.3, 67.2 (C-2,3,4,5,7), 50.7 (NHCH), 29.9, 28.7, 27.1, 18.5, 17.5 (C-8,9,10), 17.1, 17.0 (CH_3), 15.6, 15.5 (C-6) [Found: m/z (FAB) 432.1629 (M + Na). $C_{22}H_{27}NO_8$ requires M + Na 432.1634].

1-[7-((*S*)-*N*-1-carboxyethyl)-aminocarbonyl)-1,2,3,4-tetrahydro-1-naphthyl]-α-L-fucopyranose (2c). Removal of the benzyl groups from **11c** (240 mg, 0.30 mmol) as described for **11a** gave a residue which was then adsorbed on silica gel. Elution with EtOAc removed traces of impurities, further elution with methanol gave **2c** (0.12 g, 95%, R_f = 0.3–0.4, MeOH/EtOAc, 1/1): δ_H (Acetone-d_6/D_2O) 8.15 (1H, br s, Ar-H), 8.05 (1H, br s, Ar-H), 7.84–7.95 (2H, m, Ar-H), 7.42 and 7.40 (each H, each d, J 8.0 Hz, Ar-H), 5.37 and 5.32 (each 1H, d, J 3.0 and 3.6 Hz, H-1), 4.89 (2H, m overlapping with HOD, H-7), 4.64 (2H, apparent q, J 7.4 Hz, NHCH), 4.29 and 4.23 (each 1H, each q, J 6.9, 6.4 Hz, H-5), 3.91–4.01 (6H, m, H-2,3,4), 2.93–3.07 (4H, m, H-10), 1.93–2.19 (8H, ms, H-8,9), 1.64 (6H, d, J 7.4 Hz, CH_3), 1.43 and 1.40 (each 3H, each d, J 6.4 Hz, H-6): δ_C 170.1, 169.8 (C=O), 143.9, 143.3, 137.5, 137.2, 131.7, 131.5 (C, Ar), 130.5, 130.4, 130.0, 129.0, 127.5, 127.2 (CH, Ar), 100.9, 97.7 (C-1), 77.5 (2C), 74.0, 72.8, 70.6, 69.5, 69.0, 68.0, 67.8 (C-2,3,4,5,7) 50.2 (NHCH), 30.7, 29.5, 28.1, 19.2, 18.3 (C-8,9,10), 17.5, 17.4 (CH_3), 16.8, 15.8 (C-6) [Found: m/z (FAB) 432.1654 (M + Na). $C_{20}H_{27}NO_8$ requires M + Na 432.1634].

1-[7-Carboxy-1,2,3,4-tetrahydro-1(*R*,*S*)-naphthyl]-α-L-fucopyranose (2g). The benzyl groups were removed from **5** (300 mg, 0.49 mmol) as described for **11a** and gave **2g** (0.17 g, 91%, R_f = 0.0–0.1, MeOH/EtOAc, 1/5): δ_H (Acetone-d_6/D_2O) 8.12 (1H, br s, Ar-H), 8.02 (1H, br s, Ar-H), 7.87 (2H, d, J 8.0 Hz, Ar-H), 7.31 and 7.28 (each 1H, each d, J 8.0 Hz, Ar-H), 5.36 (1H, br s, H-1), 5.30 (1H, d, J 3.0 Hz, H-1), 4.86 (2H, overlapping with HOD, H-7), 4.26 (2H, apparent q, J 6.5 Hz, H-5), 3.91–3.96 (6H, m, H-2,3,4), 2.77–2.95 (4H, m, H-10), 1.61–2.16 (8H, ms, H-8,9), 1.42 and 1.37 (each 3H, each d, J 6.5 Hz, H-6): δ_C 173.6 (2C, C=O), 142.3, 141.7, 136.8, 136.6 (C, Ar), 131.7, 131.1, 129.8, 129.7, 129.5, 129.4 (CH, Ar), 100.9, 97.6 (C-1) , 77.7 (2C), 73.7, 72.9, 70.6, 69.6, 69.1, 67.9, 67.7 (C-2,3,4,5,7), 30.4, 29.5, 28.0, 19.6, 18.6 (C-8,9,10), 16.5 (2C, C-6). [Found: m/z (FAB) 361.1268 (M + Na). $C_{17}H_{22}O_7$ requires M + Na 361.1263].

7-[4-Hydroxy-1-butynyl]-1,2,3,4-tetrahydronaphthalen-1-one (12). The palladium coupling procedure described above was applied to aryl triflate **7**[13] (0.96 g, 3.3 mmol) and but-3-yn-1-ol (0.35 g, 5.0 mmol). The product was obtained after silica gel chromatography (EtOAc/petroleum ether, gradient) as an oil which solidified on

standing (**12**, 0.58 g, 82%, R_f=0.4, EtOAc/petroleum ether, 1/1): δ_H 8.05 (1H, d, *J* 1.9 Hz, Ar-H), 7.48 (1H, dd, *J* 1.9 and 8.0 Hz, Ar-H), 7.18 (1H, d, *J* 8.0 Hz, Ar-H), 3.82 (2H, t, *J* 6.0 Hz, CH_2), 2.94 (2H, t, *J* 6.0 Hz, CH_2), 2.68 and 2.64 (each H, each t, *J* 6.0 Hz, CH_2), 2.27 (1H, br s, OH), 2.12 (2H, q, *J* 6.0 Hz, CH_2): δ_C 197.8 (C=O), 144.0, 136.1, 122.0 (C, Ar), 136.1, 130.4, 128.9 (CH, Ar), 87.0, 81.4 (C=C) 61.2, 39.0, 29.5, 23.8 and 23.0 (CH_2). [Found: *m/z* (EI) 214.0990 (M). $C_{14}H_{14}O_2$ requires M 214.0993]. [Found: C, 78.2; H, 6.6%. $C_{14}H_{14}O_2$ requires C, 78.5; H, 6.5%]

7-[4-Hydroxybutyl]-1,2,3,4-tetrahydronaphthalene-1-one (13a). The acetylene **12** (0.30 g, 1.4 mmol) was dissolved in ethanol (5 mL) and the solution was stirred under an atmosphere of H_2 for 1 h in the presence of 10% Pd-C (30 mg). The mixture was then filtered through Celite and the solvent was removed; the product was obtained after chromatography of the reaction residue (silica gel, EtOAc/petroleum ether, 1/2) and was an oil (**13a**, 0.29 g, 96%, R_f=0.35, EtOAc/petroleum ether, 1/1); δ_H 7.85 (1H, d, *J* 1.8 Hz, Ar-H), 7.30 (1H, dd, *J* 1.8 and 7.8 Hz, Ar-H), 7.16 (1H, d, *J* 7.8 Hz, Ar-H), 3.65 (2H, t, *J* 6.4 Hz, CH_2), 2.93 (2H, t, *J* 6.0 Hz, CH_2), 2.66 and 2.63 (each 2H, each t, *J* 6.4, 6.0 Hz, CH_2), 2.27 (1H, br s, OH), 2.12 (2H, q, *J* 6.5 Hz, CH_2), 1.76–1.56 (5H, ms, CH_2 and OH),: δ_C 198.8 (C=O), 142.1, 140.8, 132.4 (C, Ar), 133.8, 128.8, 126.6 (CH, Ar), 62.7, 39.2, 35.1, 32.2, 29.3, 27.4 and 23.4 (CH_2). [Found: *m/z* (EI) 218.1310 (M). $C_{14}H_{18}O_2$ requires M 218.1307].

7-Carboxypropyl-1,2,3,4-tetrahydronaphthalene-1-one (13b). The Jones reagent was prepared by adding concd sulfuric acid (0.6 mL) to CrO_3 (0.67 g, 6.7 mmol) in water (1.4 mL). This reagent (1.6 mL) was added dropwise over 30 min to **13a** (0.52 g, 2.38 mmol) in acetone (10 mL). The mixture was left to stir for 2 h. Propan-2-ol (0.5 mL) was added to remove any unreacted dichromate and solid $NaHCO_3$ was added until the pH was ~4. The product was filtered washing thoroughly with acetone and the solvent was removed. The residue was taken up in ether and the organic layer was washed with 5% Na_2CO_3. The aqueous layer was separated and acidified to pH 1.0 with dilute 5% HCl. The aqueous layer was then washed with ether, the ether layer washed with water and dried over anhydrous $MgSO_4$. Filtration and removal of solvent gave the title compound as a dark brown oil which solidified on cooling (**13b**, 0.34 g, 61%); δ_H 9.50 (1H, br s, OH), 7.86 (1H, d, *J* 1.7 Hz, Ar-H), 7.16–7.32 (2H, ms, Ar-H), 2.93 (2H, t, *J* 6.1 Hz, CH_2), 2.69 and 2.65 (each 2H, each t, *J* 7.2 Hz, CH_2), 2.37 (2H, t, *J* 7.3 Hz, CH_2), 2.12 and 1.96 (each 2H, each quintet, *J* 7.2 Hz, CH_2): δ_C 198.9 (C=O, ketone), 179.3 (C=O, acid), 142.4, 139.8, 132.5 (C, Ar), 133.8, 129.0, 126.8 (CH, Ar), 39.1, 34.5, 33.2, 29.3, 26.0 and 23.3 (CH_2). [Found: *m/z* (EI) 232.1108. $C_{14}H_{16}O_3$ requires M 232.1099].

7-Benzyloxycarbonylpropyl-1,2,3,4-tetrahydronaphthalene-1-one (13c). The acid **13b** (0.39 g, 1.7 mmol), benzyl alcohol (0.40 g, 3.4 mmol), DCC (0.35 g, 1.9 mmol), and DMAP (20 mg, 0.19 mmol) were stirred in CH_2Cl_2 (10 mL) for 18 h. The product was filtered and the solvent removed. The resulting residue was chromatographed (silica gel, EtOAc/petroleum ether, gradient) and gave the title compound as an oil (0.48 g, 88%); δ_H 7.84 (1H, d, *J* 1.9 Hz, Ar-H), 7.14–7.36 (7H, ms, Ar-H), 5.11 (2H, s, CH_2Ph), 2.60 (2H, t, *J* 7.5 Hz, CH_2), 2.61–2.80 (2H, m, CH_2), 2.37 (2H, t, *J* 7.5 Hz, CH_2), 1.71–2.01 (7H, ms, CH_2 and OH): δ_C 140.2, 138.6, 134.4 (C, Ar), 128.9, 128.5, 127.8 (CH, Ar), 68.2 (CH), 62.7, 35.2, 32.4, 32.3, 30.9, 28.9, 27.6 and 18.9 (CH_2): [Found: *m/z* (EI) 322.1553 (M). $C_{21}H_{22}O_3$ requires M 322.1569].

7-Benzyloxycarbonylpropyl-1,2,3,4-tetrahydro-1-naphthol (14). Reduction of tetralone **13c** (0.49 g, 1.5 mmol) with sodium borohydride as described above gave the title compound (**14**, 0.39 g, 79%); δ_H 6.99–7.37 (8H, ms, Ar-H), 5.09 (2H, s, CH_2Ph), 4.72 (2H, t, *J* 4.5 Hz, CH) 2.92 (2H, t, *J* 6.2 Hz, CH_2), 2.66 and 2.64 (each 2H, each t, *J* 7.2 Hz, CH_2), 2.36 (2H, t, *J* 7.2 Hz, CH_2), 2.11 and 1.97 (each 2H, each quintet, *J* 6.2, 7.2 Hz, CH_2): δ_C 173.3 (C=O), 139.1, 138.8, 136.0, 134.7 (C, Ar), 129.0, 128.9, 128.7, 128.4, 128.2, 127.8 (CH, Ar), 68.1 (CH), 66.2, 34.7, 33.7, 32.3, 28.9, 26.5 and 18.9 (CH_2). [Found: *m/z* (CI) 342.2077 ($M+NH_4$). $C_{21}H_{24}O_3$ requires $M+NH_4$ 342.2070].

1-[7-Benzyloxycarbonylpropyl-1,2,3,4-tetrahydro-1(*R*,*S*)-naphthyl]-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (15). Glycosylation was carried out as described above using **9** (1.73 g, 3.6 mmol) and **14** (0.39 g, 1.2 mmol). The residue, which was obtained, was chromatographed (silica gel, EtOAc/petroleum ether gradient). The fraction with R_f=0.4–0.5 (EtOAc/petroleum ether, 1/4) was concentrated. Further purification was necessary and this fraction was subjected to chromatography (silica gel; toluene/EtOAc gradient). The mid fraction was the title compound (**15**, 0.37 g, 42%, R_f=0.4–0.5, EtOAc/petroleum ether, 1/4): δ_H 6.97–7.33 (62H, ms, Ar-H), 5.20 and 5.12 (each 1H, each d, *J* 3.6 Hz, H-1) 5.07 and 5.06 (each 2H, each s, CH_2Ph), 4.57–5.00, (14H, ms, CH_2Ph and C-7), 3.92–4.06 (6H, ms, H-2,3,5) 3.67 (2H, br s, H-4), 2.60–2.76 (4H, m, H-10 and CH_2), 2.57 (4H, *J* 7.5 Hz, CH_2), 2.34–2.45 (8H, ms, CH_2), 2.25 (4H, apparent, *J* 7.5 Hz, CH_2), 1.65–2.02 (16H, ms, H-8,9, CH_2), 1.18 (3H, d, *J* 6.9 Hz, H-6), 1.15 (3H, d, *J* 6.9 Hz, H-6): δ_C 173.2, 173.1 (C=O), 139.0, 138.9, 138.7, 138.4, 136.6, 136.4, 136.0 (2C), 135.5, 135.0 (C, Ar), 129.7, 128.9, 128.8, 128.6, 128.5 (2C), 128.4 (2C), 128.3, 128.2, 128.1, 127.7 (2C), 127.6, 127.4 (2C), 127.3 (CH, Ar), 98.2, 95.8 (C-1), 79.5, 79.4, 77.2, 76.8, 76.3, 76.2, 72.7, 66.1, 66.0 (C-2,3,4,5,7), 74.8, 73.0 (2C) 72.7, 66.6 (CH_2Ph), 34.7, 34.6, 33.6, 30.5, 28.7, 28.5, 27.9, 26.4, 19.6, 18.3 (C-8,9,10,

CH_2), 16.7 (C-6). [Found: *m/z* (CI) 758.4061 (M + NH_4). $C_{48}H_{52}O_7$ requires M + NH_4 758.4068].

1-[7-Carboxypropyl-1,2,3,4-tetrahydro-1(*R*,*S*)-naphthyl]-α-L-fucopyranose (2a). The benzyl groups were removed from **15** (100 mg, 0.14 mmol) as described above and the product purified by chromatography (silica gel, MeOH/EtOAc, gradient) to give the product as a gum (**2a**, 35 mg, 71%): δ_H (Acetone-d_6/D_2O) 7.46 (1H, br s, Ar-H), 7.17–7.22 (5H, ms, Ar-H), 5.33 (1H, d, *J* 1.0 Hz, H-1), 5.25 (1H, d, *J* 3.5 Hz, H-1), 4.80 (2H, overlapping with HOD, H-7), 4.23 and 4.25 (each 1H, each q, *J* 6.5 Hz, H-5), 3.84–4.00 (6H, m, H-2,3,4), 2.71–2.87 (4H, m, H-10), 2.73 (4H, t, *J* 7.4 Hz, CH_2), 2.41 (4H, t, *J* 7.5 Hz, CH_2), 1.86–2.10 (12H, ms, H-8,9, CH_2), 1.44 (3H, d, *J* 6.5 Hz, H-6), 1.38 (3H, d, *J* 6.5 Hz, H-6): δ_C 180.0, 179.5 (C=O), 140.3, 140.2, 137.0, 136.7, 136.4, 135.7 (C, Ar), 130.6, 130.2, 130.1, 129.9, 129.1, 129.0 (CH, Ar), 100.8, 98.1 (C-1) , 77.7 (2C), 74.2, 72.9, 70.8, 69.6, 69.1, 67.7, 67.6 (C-2,3,4,5,7), 34.6, 30.4, 28.5, 28.4, 27.7, 27.2, 27.1, 19.1, 18.0 (C-8,9,10, CH_2), 15.9, 15.8 (C-6). [Found: *m/z* (FAB) 403.1736 (M + Na). $C_{20}H_{24}O_7$ requires M + Na 403.1733].

2,2-Dimethyl-3-butynoic acid, benzyl ester (17). 2,2-Dimethyl-3-butynoic acid[20] (**16**, 0.25 g, 2.2 mmol), DCC (0.55 g, 2.7 mmol), DMAP (32 mg, 0.26 mmol) and benzyl alcohol (0.29 g, 2.7 mmol) were stirred in dichloromethane (5 mL) overnight. The mixture was filtered and the solvent was removed. Chromatography of the residue (silica gel; ether/petroleum ether) gave the product as an oil (**17**, 0.33 g, 74%); δ_H 7.22–7.28 (5H, ms, Ar-H), 5.09 (2H, s, CH_2), 2.19 (1H, s, CH), 1.43 (6H, s, $(CH_3)_2C$): δ_C 173.1 (C=O), 135.7 (C, Ar), 128.4, 128.1, 127.6 (CH, Ar), 86.0, 70.0 (C=C), 67.0 (CH_2), 38.1 ($(CH_3)_2C$), 26.9 (CH_3). [Found: C, 77.2; H, 6.9%. $C_{13}H_{14}O_2$ requires C, 77.0; H, 7.0%]

7-[3-(Benzyloxycarbonyl)-2,2-dimethyl-1-propynyl]-1,2,3,4-tetrahydronaphthalen-1-one (18). Palladium coupling of the triflate **7** (0.87 g, 3.0 mmol) and the acetylene **17** (0.90 g, 4.5 mmol) as described above gave the title compound (**18**, 0.58 g, 57%); δ_H 8.08 (1H, d, *J* 1.9 Hz, Ar-H), 7.44 (1H, dd, *J* 8.0 Hz, 1.9 Hz, Ar-H), 7.31–7.38 (5H, ms, Ar-H), 7.17 (1H, *J* 8.0 Hz, Ar-H), 5.20 (2H, s, CH_2Ph), 2.94 (2H, t, *J* 7.0 Hz, CH_2), 2.66 (2H, t, *J* 7.0 Hz, CH_2), 2.12 (2H, quintet, *J* 7.0 Hz, CH_2), 1.58 (6H, s, $(CH_3)_2C$): δ_C 197.5 (C=O, ketone), 173.2 (C=O, ester), 144.1, 135.9, 132.3, 121.7 (C, Ar), 135.9, 130.4, 128.7, 128.5, 128.0, 127.5 (CH, Ar), 92.0, 82.9 (C=C), 68.9 (CH_2Ph), 38.9 (CH2), 38.7 ($(CH_3)_2C$), 29.4 (CH_2), 27.0 (CH_3), 23.0 (CH_2). [Found: C, 79.7; H, 6.4%. $C_{13}H_{14}O_2$ requires C, 79.7; H, 6.1%]

7-[3-(Benzyloxycarbonyl)-2,2-dimethyl-1-propynyl]-1,2,3,4-tetrahydro-1(*R*,*S*)-naphthol (19). Treatment of **18** (0.50 g, 1.4 mmol) with sodium borohydride as described above gave the product as an oil (0.36 g, 72%); δ_H 7.48 (1H, d, *J* 1.8 Hz, Ar-H), 7.24–7.40 (5H, ms, Ar-H), 7.19 (2H, dd, *J* 8.0 Hz, 1.8 Hz, Ar-H), 6.99 (1H, d, *J* 8.0 Hz, Ar-H), 5.20 (2H, s, CH_2Ph), 4.68 (1H, br s, CH), 2.63–2.81 (2H, m, CH_2), 1.61–2.00 (5H, ms, CH_2 and OH), 1.57 (6H, s, $((CH_3)_2C)$: δ_C 173.6 (C=O), 138.8, 137.2, 136.0, 120.8 (C, Ar), 131.9, 130.5, 128.8, 128.5, 128.0, 127.6 (CH, Ar), 91.0, 81.8 (C=C), 67.8 (CH), 66.9 (CH_2Ph), 38.8 ($(CH_3)_2C$), 32.1, 29.1 (CH_2), 27.1 (CH_3), 18.7 (CH_2). [Found: *m/z* (CI) 366.2066 (M + NH_4). $C_{23}H_{24}O_3$ requires M + NH_4 366.2069]. [Found: C, 78.9; H, 7.0%. $C_{13}H_{14}O_2$ requires C, 79.3; H, 6.9%].

1-[7-[3-(Benzyloxycarbonyl)-2,2-dimethyl-1-propynyl]-1,2,3,4-tetrahydro-1(*R*,*S*)-naphthyl]-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (20). Glycosylation as described above for **9** (0.50 g, 1.0 mmol) and **19** (0.19 g, 0.55 mmol) gave the title compound (**20**, 0.11 g, 26%, R_f = 0.25, EtOAc/petroleum ether, 1/10) after chromatography (silica gel, EtOAc/petroleum ether, gradient); δ_H 7.59 (2H, apparent d, *J* 1.8 Hz, Ar-H), 7.19–7.34 (58H, ms, Ar-H), 7.03 (2H, apparent dd, *J* 8.0, 1.8 Hz, Ar-H), 5.18, 5.16 (each 2H, each s, CH_2Ph), 5.08, 5.09 (each 1H, each d, *J* 3.8 Hz, H-1), 4.57–5.00 (14H, ms, CH_2Ph and H-7), 3.88–4.08 (6H, ms, H-2,3,5), 3.66 and 3.64 (each 1H, each br s, H-4), 2.60–2.84 (4H, m, H-10), 1.60–2.15 (8H, ms, H-8,9), 1.55 and 1.53 (each 6H, each s, CH_3), 1.16 (3H, d, *J* 6.5 Hz, H-6), 1.15 (3H, d, *J* 6.5 Hz, H-6): δ_C 173.5 (C=O), 139.0, 138.9, 138.8, 138.7, 138.6, 138.1, 136.4, 136.3, 136.0, 120.4, 120.3 (C, Ar), 133.5, 132.5, 131.0, 130.5, 128.9, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.5, 127.4, 127.3, 127.1, 127.0 (CH, Ar), 97.2, 96.5 (C-1), 90.8 (2C), 82.1, 82.0 (C=C), 79.5, 79.4, 77.7, 76.3, 76.2 74.1 66.6, 66.5 (C-2,3,4,5,7), 74.8, 73.0 (2C), 72.6, 66.8 (CH_2Ph), 38.8 ($(CH_3)_2C$) 30.0, 29.0, 28.6, 28.1 (CH_2), 18.8, 18.0 (C-8,9,10), 27.2 (CH_3), 16.7, 16.4 (C-6). [Found: *m/z* (CI) 782.4052 (M + NH_4). $C_{50}H_{52}O_7$ requires M + NH_4 782.4057].

1-[7-[3-Carboxy-2,2-dimethylpropyl]-1,2,3,4-tetrahydro-1(*R*,*S*)-naphthyl]-α-L-fucopyranose (2e). The acetylene **20** (110 mg, 0.14 mmol) was dissolved in EtOH (5 mL) and 5% Pd-C (100 mg) was added. The mixture was stirred in an atmosphere of H_2 until TLC analysis indicated a product with R_f = 0.2–0.3 (EtOAc/MeOH, 4/1) had formed (40 h, catalyst replenished every 12 h). The product was filtered through Celite and the solvent removed to give **2e** (42 mg, 73%) as a gum; δ_H (Acetone-d_6/D_2O) 7.31 (1H, br s, Ar-H), 6.98–7.12 (5H, ms, Ar-H), 5.20 (1H, br s, H-1), 5.13 (1H, d, *J* 3.6 Hz, H-1), 4.64 (2H, br s, H-7), 4.09 and 4.12 (each 1H, each q, *J* 6.5 Hz, H-5), 3.71–3.84 (6H, m, H-2,3,4), 2.49–2.73 (8H, m, H-10 and CH_2), 1.73–2.04 (12H, ms, H-8,9 and CH_2), 1.33 (3H, d, *J* 6.5 Hz, H-6), 1.26 (3H, d, *J* 6.5 Hz, H-6), 1.20 (12H, s, CH_3): δ_C 183.9, 183.4 (C=O), 140.8, 140.6,

136.8, 136.4, 136.2, 135.5 (C, Ar), 130.2, 129.9, 129.7, 128.7, 128.6, (CH, Ar), 100.5, 98.2 (C-1), 77.2, 74.4, 73.8, 71.5, 70.5, 70.4, 69.3, 68.8, 67.5 (C-2,3,4,5,7), 43.1, 42.9 ($(CH_3)_2C$), 43.5, 31.5, 31.4, 30.7, 28.8, 28.7, 27.2, 19.4, 18.3 (C-8,9,10 and CH_2), 24.1, 24.0 (CH_3), 16.3, 16.2 (C-6). [Found: *m/z* (FAB) 426.2498 (M + NH_4). $C_{22}H_{32}O_7$ requires M + NH_4 426.2492].

7-*tert*-Butyldimethylsilyloxy-1,2,3,4-tetrahydronaphthalen-1-one (21). 7-Hydroxytetralone (0.20 g, 1.23 mmol), *t*-butyldimethylsilylchloride (0.19 g, 1.25 mmol) and imidazole (0.20 g, 3.1 mmol) were added to DMF (10 mL) and the product was stirred overnight at ambient temperature. The mixture was partitioned between EtOAc and water. The aqueous layer was further washed with EtOAc and the combined organic washings were washed with water and dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography (silica gel; ether/petroleum ether, 1/10) to give the title compound as an oil (**21**, 0.33 g, 92%); δ_H 7.47 (1H, d, *J* 2.7 Hz, Ar-H), 7.10 (1H, d, *J* 8.0 Hz, Ar-H), 6.95 (1H, dd, *J* 2.7, 8.0 Hz, Ar-H), 2.86 (2H, t, *J* 6.5 Hz, CH_2), 2.60 (2H, t, *J* 6.5 Hz, CH_2), 2.08 (2H, quintet, *J* 6.5 Hz), 0.98 (9H, s, *t*-butyl), 0.19 (6H, s, $(CH_3)_2$Si): δ_C 198.4 (C=O), 154.3, 137.5, 135.0 (C, Ar), 129.9, 126.0, 117.2 (CH, Ar), 39.1, 28.9, 23.4 (CH_2), 25.6 ($(CH_3)_3C$), 18.1 ($(CH_3)_3C$), −4.5 ($(CH_3)_2$Si). [Found: *m/z* (CI) 277.1622 (M + H). $C_{16}H_{24}O_2Si$ requires M + H 277.1624].

7-*tert*-Butyldimethylsilyloxy-1,2,3,4-tetrahydro-1-naphthol (22). Treatment of **21** (0.30 g, 1.1 mmol) with sodium borohydride as described above gave the title compound after bulb to bulb distillation (**22**, 0.24 g, 77%, bp 200 °C, 0.1 mm Hg): δ_H 6.93 (1H, d, *J* 8.0 Hz, Ar-H), 6.90 (1H, d, *J* 2.7, Ar-H), 6.68 (1H, dd, *J* 2.7, 8.0 Hz, Ar-H), 4.67 (1H, t, *J* 4.5 Hz, CHOH), 2.58–2.78 (2H, m, CH_2), 1.66–2.14 (5H, ms, CH_2 and OH), 0.98 (9H, s, *t*-butyl), 0.19 (6H, s, $(CH_3)_2$Si): δ_C 153.8, 139.8, 129.7 (C, Ar), 129.8, 119.6, 119.5 (CH, Ar), 68.3 (CH), 33.3, 28.5, 19.1 (CH_2), 25.7 ($(CH_3)_3C$), 18.2 ($(CH_3)_3C$), −4.4 ($(CH_3)_2$Si). [Found: *m/z* (EI) 278.1708 (M). $C_{16}H_{26}O_2Si$ requires M 278.1702]. [Found: C, 69.0; H, 9.5%. $C_{16}H_{26}O_2Si$ requires C, 69.1; H, 9.4%].

1-[7-(*tert*-Butyldimethylsilyloxy)-1,2,3,4-tetrahydro-1(*R,S*)-naphthyl]-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (23). Glycosylation of **22** (0.50 g, 1.8 mmol) and **9** (2.58 g, 5.4 mmol) as described above gave the title compound (**23**, 0.91 g, 73%, R_f = 0.6, EtOAc/petroleum ether, 1/4) which was purified by chromatography (silica gel, EtOAc/petroleum ether, gradient); δ_H 7.15–7.34 (44H, ms, Ar-H), 6.93 (2H, d, *J* 8.0 Hz, Ar-H), 6.66–6.73 (2H, m, Ar-H), 5.10 and 5.08 (each 1H, each d, *J* 4.0 Hz, H-1), 4.58–4.87 (14H, ms, CH_2Ph and H-7), 3.94–4.11 (6H, ms, H-2,3,5), 3.68 and 3.64 (each 1H, each br s, C-4), 2.55–2.75 (4H, m, H-10), 1.62–2.10 (8H, ms, H-8,9), 1.20 (3H, d, *J* 6.5 Hz, H-6), 1.14 (3H, d, *J* 6.5 Hz, H-6), 0.97, 0.95 (each 9H, each s, *t*-butyl), 0.15 (12H, s, $(CH_3)_2$)Si): δ_C 153.4, 153.2, 139.1, 139.0, 138.8, 137.7, 137.4, 130.7 129.5 (C, Ar), 129.9, 129.7, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.5 (2C), 127.4, 127.3, 120.1, 120.0, 119.6 (2C, CH, Ar), 98.1, 95.4 (C-1), 79.6, 79.5, 78.0, 76.7, 76.3 72.3, 66.6 (C-2,3,4,5,7), 74.9, 74.7, 73.3, 73.1, 72.7 (CH_2Ph), 30.3, 28.4, 28.1, 27.5, 19.6, 18.5 (C-8,9,10), 25.7 ($(CH_3)_3C$), 18.2 ($(CH_3)_3C$), −4.5 (2C, $(CH_3)_2$Si). [Found: *m/z* (CI) 712.4050 (M + NH_4). $C_{43}H_{54}O_6Si$ requires M + NH_4 712.4033].

1-[7-(*tert*-Butyldimethylsilyloxy)-1,2,3,4-tetrahydro-1(*R,S*)-naphthyl]-2,3,4-tri-*O*-acetyl-α-L-fucopyranose (24). The benzyl groups were removed from **23** as described above. The residue was treated with Ac_2O/Py (10 mL, 1/1) and DMAP (10 mg). The mixture was left to stand for 24 h and then water was added. This was followed by extraction with EtOAc and the organic layer was subsequently washed with $KHSO_4$ (10%), $NaHCO_3$ (satd), water, and dried over anhydrous $MgSO_4$. Chromatography of the residue (silica gel; EtOAc/petroleum ether, 1/1) which was obtained after filtration and removal of solvent gave **24** (0.72 g, 91%); δ_H 6.97 and 6.94 (each 1H, each d, *J* 8.0 Hz, Ar-H), 6.78 and 6.74 (each 1H, each d, *J* 2.7 Hz, Ar-H), 6.69 (2H, apparent dd, *J* 2.7, 8.0 Hz, Ar-H), 5.38–5.26 (6H, H-1,2,4), 5.13 and 5.09, (each 1H, each dd, *J* 3.9 and 10.4, 3.9 and 10.0 Hz, H-3), 4.59 and 4.54 (each 1H, each t, *J* 4.5 Hz, H-7), 4.12 (2H, apparent q, *J* 6.5 Hz, H-5), 2.62–2.75 (4H, m, H-10), 2.18, 2.17, 2.07, 2.04, 1.97, 1.96 (each 3H, each s, OAc), 1.70–2.14 (8H, ms, H-8,9), 1.20 and 1.16 (each 3H, each d, *J* 6.5 Hz, H-6), 0.99 and 0.98 (each 9H, each s, *t*-butyl), 0.19 and 0.18 (each 6H, each s, $(CH_3)_2$)Si): δ_C 170.7, 170.6, 170.5, 170.0 (C=O, OAc), 153.5, 153.4, 136.9, 136.3, 130.4, 130.0 (C, Ar), 130.0, 129.7, 120.9, 120.1, 120.0, 119.6 (CH, Ar), 98.9, 94.5 (C-1), 77.1, 73.6, 71.3, 68.5, 68.3, 68.1, 64.7 (2C, C-2,3,4,5,7), 30.2, 28.2, 28.0 (2C) 28.5, 19.3, 17.9 (C-8,9,10), 25.7 (2C, $(CH_3)_3C$), 20.7 (OAc), 18.2 ($(CH_3)_3C$), 15.9 (2C, C-6), −4.4 ($(CH_3)_2$Si). [Found: *m/z* (CI) 568.2946 (M + NH4). $C_{28}H_{42}O_9Si$ requires M + NH_4 568.2941].

1-[7-(Trifluoromethanesulfonyloxy)-1,2,3,4-tetrahydro-1(*R,S*)-naphthyl]-2,3,4-tri-*O*-acetyl-α-L-fucopyranose (25). The silyl derivative **24** (0.72 g, 1.3 mmol) was dissolved in THF (25 mL) and the mixture was stirred at 0 °C. TBAF (1.0 M, 3 mL) was then added and stirring was continued for 30 min. The reaction mixture was concentrated in vacuo and the residue was dissolved in dichloromethane and was cooled to −20 °C. 2,6-Lutidine (0.22 g, 2.0 mmol), DMAP (27 mg, 0.22 mmol), and trifluoromethanesulfonic anhydride (0.60 g, 2.1 mmol) were added and the mixture was stirred at −20 °C to rt (24 h). Water was added and mixture extracted with

EtOAc. The organic portion was washed successively with $KHSO_4$, $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (silica gel, EtOAc/petroleum ether, 1/1) gave the title compound (**25**, 0.54 g, 79%); δ_H 7.08–7.30, 6H, ms, Ar-H), 5.19–5.36 (6H, H-1,2,4), 5.09 (2H, dd, *J* 3.9 and 10.5 Hz, H-3), 4.60 and 4.65 (each 1H, each t, *J* 4.5 Hz, H-7), 4.12–4.33 (2H, ms, H-5), 2.71–2.85 (4H, m, H-10), 2.18, 2.17, 2.10, 2.07, 1.99, 1.97 (each 3H, each s, OAc), 1.68–2.10 (8H, ms, H-8,9), 1.19 and 1.16 (each 3H, each d, *J* 7.0 Hz, H-6): δ_C 170.6, 170.4, 170.0 (C=O, OAc), 147.4, 138.8, 138.2, 137.7, (C, Ar), 121.4, 116.3 (CF_3), 131.0, 130.7, 121.1, 120.8, 120.6, 120.3, (CH, Ar), 97.8, 95.1 (C-1), 77.1, 73.5, 71.1, 68.4, 68.2, 67.9, 65.0 (C-2,3,4,5,7), 29.9, 29.6, 28.4, 27.8, 19.2, 17.4 (C-8,9,10), 20.6 (OAc), 15.8 (2C, C-6). [Found: *m/z* (CI) 586.1566 ($M+NH_4$). $C_{23}H_{27}F_3O_{11}S$ requires $M+NH_4$ 586.1570].

1-[7-[3-(Benzyloxycarbonyl)-2,2-dimethyl-1-propynyl]-1,2,3,4-tetrahydro-1(*R*,*S*)-naphthyl]-2,3,4-tri-*O*-acetyl-α-L-fucopyranose (26). The triflate **25** (0.15 g, 0.26 mmol) and 2,2-dimethyl-3-butynoic acid, benzyl ester (**17**, 0.16 g, 0.8 mmol), triethylamine (0.5 mL) and DMF (0.5 mL) were added to a 5 mL flask and were purged with N_2 for 30 min. Catalytic $Pd(II)Cl_2(PPh_3)_2$ (18 mg, 0.025 mmol) was added and the mixture was stirred at 80 °C under N_2 for 5 h. EtOAc was then added and the product washed with water. The aqueous layer was further washed with EtOAc, and the combined organic layers were washed with water, dried ($MgSO_4$), filtered and the solvent evaporated. Chromatography (silica gel, EtOAc/petroleum ether, gradient) gave the title compound (91 mg, 56%); δ_H 7.00–7.98 (16H, m, Ar-H), 4.96–5.38 (ms, 12H, H-1,2,3,4, CH_2Ph), 4.57 (2H, br s, H-7), 4.10–4.33 (2H, ms, H-5), 2.71–2.85 (4H, m, H-10), 2.17, 2.16, 2.07, 2.05, 1.97, 1.96 (each 3H, each s, OAc), 1.71–2.10 (8H, ms, H-8,9), 1.57, 1.56 (each 6H, each s, CH_3) 1.17 and 1.14 (each 3H, each d, *J* 6.5 Hz, H-6): δ_C 173.4 (2C, C=O, ester), 170.6 (2C), 170.5, 170.1 (C=O, OAc), 137.9, 137.6, 136.2, 136.0, 135.4, 133.5 (C, Ar), 131.6, 131.0, 130.9, 129.1, 128.9, 128.8, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 127.6, 120.6, 120.5 (CH, Ar), 97.6, 95.4 (C-1), 91.1, 90.9, 81.9, 81.7 (C≡C), 77.1, 74.3, 71.3, 71.2, 68.5, 68.3 (2C), 68.1, 64.7 (2C) (C-2,3,4,5,7) 66.9 (2C, CH_2Ph), 38.8, 38.7 ($(CH_3)_2C$), 30.4, 28.8, 28.6, 19.2, 17.5 (C-8,9,10), 27.1 ($(CH_3)_2C$), 20.8, 20.7 (2C, OAc), 15.9, 15.6 (C-6). [Found: *m/z* (CI) 638.2956 ($M+NH_4$). $C_{35}H_{40}O_{10}$ requires $M+NH_4$ 638.2965].

1-[7-(3-Carboxy-2,2-dimethyl-1-propynyl)-1,2,3,4-tetrahydro-1(*R*,*S*)-naphthyl]-α-L-fucopyranose (2f). The intermediate **26** (0.120 g, 0.19 mmol) was stirred in methanol and freshly prepared sodium methoxide solution in methanol was added (2 mL of a 0.6 g Na/100 mL MeOH). Stirring was continued until by TLC analysis a product with R_f = 0.1–0.20 (EtOAc) was formed and no further addition of methoxide caused a change to the TLC (1 h). Water (1 mL) was added followed by LiOH (0.10 g, 4.3 mmol) and stirring was continued overnight. TLC analysis indicated a product with R_f 0.0 (EtOAc) and R_f 0.0–0.1 (EtOAc/MeOH, 5/1). Water (5 mL) was added and KH_2PO_4 was added until the pH was 7. The water was removed in vacuo and the residue was adsorbed on silica gel. Chromatography (silica gel, EtOAc/MeOH, gradient) gave the title compound (**2f**, 38 mg, 50%); δ_H (Acetone-d_6/D_2O) 7.59 (1H, br s, Ar-H), 7.38 (1H, br s, Ar-H), 7.36 and 7.30 (each 1H, each d, *J* 7.6, 6.0 Hz, Ar-H), 7.13 and 7.10 (each 1H, each d, *J* 7.6, 6.0 Hz, Ar-H), 5.23 (1H, br s, H-1), 5.19 (1H, d, *J* 4.0 Hz, H-1), 4.68 (2H, br s, H-7), 4.16 and 4.07 (each 1H, each q, *J* 6.6 Hz, H-5), 3.76–3.87 (6H, m, H-2,3,4), 2.61–2.85 (4H, m, H-10), 1.70–2.10 (8H, ms, H-8,9), 1.51 (6H, s, CH_3), 1.35 (3H, d, *J* 6.6 Hz, H-6), 1.29 (3H, d, *J* 6.6 Hz, H-6): δ_C 181.6, 181.5 (C=O), 139.0, 138.5, 137.2, 136.8, 121.6, 121.7 (C, Ar), 133.8, 133.1, 131.4, 131.3, 130.1, 130.0 (CH, Ar), 100.7, 98.4 (C-1), 96.6, 96.4, 81.6, 81.4 (C≡C), 77.1, 74.4, 72.8, 70.7, 69.4, 69.0, 67.8, 67.7 (C-2,3,4,5,7), 41.7 ($(CH_3)_2C$), 30.7, 28.5, 24.3, 19.6, 18.5 (C-8,9,10), 24.3 (CH_3), 16.4 (C-6). [Found: *m/z* (FAB) 427.1730 (M + Na). $C_{22}H_{28}O_7$ requires M + Na 427.1732].

7-*tert*-Butyldimethylsilyloxy-1-naphthol (27). 7-*tert*-Butyldimethylsilyloxy-1,2,3,4-tetrahydronaphthalen-1-one (**21**, 1.20 g, 4.3 mmol) and 5% Pd-C (1.20 g) were stirred in cumene and heated at reflux for 48 h under N_2 (fresh catalyst was added after 18 h). The product mixture was filtered through Celite, the solvent was removed and the residue chromatographed (silica gel, ether/petroleum ether, 1/20) to give the title compound as an oil (**27**, 0.61 g, 50%); δ_H 7.43 (1H, d, *J* 9.0 Hz, Ar-H), 7.34 (1H, d, *J* 2.4 Hz, Ar-H), 7.09 (1H, d, *J* 7.5 Hz, Ar-H), 6.79–6.94 (2H, m, Ar-H), 6.44 (1H, d, *J* 7.5 Hz), 5.63 (1H, br s, OH), 0.81 (9H, s, *t*-butyl), 0.01 (6H, s, Me_2Si): δ_C 153.0, 150.4, 130.5, 125.5 (C, Ar), 129.7, 123.6, 122.5, 120.3, 109.3, 108.8 (CH, Ar), 25.9 ($(CH_3)_3C$), 18.4 ($(CH_3)_3C$), −4.3 (Me_2Si): [Found: *m/z* (EI) 274.1381 (M). $C_{16}H_{22}O_2Si$ requires M 274.1390].

1[7-(*tert*-Butyldimethylsilyloxy)-1-naphthyl]-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (28). Glycosylation was carried out with the thiofucoside **9** (2.60 g, 5.5 mmol) and the naphthalene (**27**, 0.30 g, 1.1 mmol) as described above and gave title compound (**28**, 0.51 g, 71%) after chromatography (silica gel, EtOAc/petroleum ether, 1/10); $[\alpha]_D$ −62° (*c*, 0.24, $CHCl_3$); δ_H 7.79 (1H, d, *J* 2.4 Hz, Ar-H), 7.68 (1H, d, *J* 8.6 Hz, Ar-H), 7.07–7.47 (25H, ms, Ar-H), 5.63 (1H, br s, H-1) 4.65–5.04 (6H, ms, CH_2Ph), 4.28 (2H, br s, H-2,3) 4.06 (1H, q, *J* 6.5 Hz, H-5), 3.72 (1H, br s, H-4), 1.12 (3H, d, *J* 6.5 Hz, H-6), 0.81 (9H, s, *t*-butyl), 0.24 and 0.21 (each 3H, each s, Me_2Si):

δ_C 153.4, 152.3, 139.0, 138.5, 138.4, 130.1, 127.2 (C, Ar), 129.0, 128.7, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6 (2C), 127.5, 127.4, 127.3, 123.7, 122.4, 121.3, 120.6, 109.3, 108.9 (CH, Ar), 97.0 (C-1), 79.7, 78.0, 76.6, 67.4 (C-2,3,4,5), 73.9, 73.3, 72.8 (CH_2Ph), 25.8 ($(CH_3)_3C$), 18.3 ($(CH_3)_3C$), 16.6 (C-6), −4.4 (Me_2Si). [Found: *m/z* (CI) 708.3723 (M + NH_4). $C_{43}H_{54}O_6Si$ requires M + NH_4 708.3720].

1-[7-(Trifluoromethanesulfonyloxy)-1-naphthyl]-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (29). The intermediate **28** (0.25 g, 0.38 mmol) was dissolved in THF (2 mL) and the mixture was stirred at 0 °C. TBAF (1.0 M, 1.9 mL) was added and stirring was continued for 30 min. The solvent was removed and residue chromatographed (silica gel, EtOAc/petroleum ether, 1/10) to give the phenol. The phenol was dissolved in dichloromethane (5 mL) and was cooled to −78 °C. 2,6-Lutidine (0.15 mL, excess), DMAP (5 mg, 0.04 mmol) and trifluoromethanesulphonic anhydride (0.1 mL, excess) were added and the mixture was stirred overnight (−78 to 20 °C). Ethyl acetate was added and the product was washed successively with 10% $KHSO_4$, satd $NaHCO_3$, and water and dried over anhydrous magnesium sulfate. Removal of solvent followed by chromatography of the residue (EtOAc/petroleum ether, 1/4) gave the title compound as a syrup (0.11 g, 44%, R_f = 0.6, EtOAc/petroleum ether, 1/4); $[\alpha]_D$ −48° (*c*, 0.23, $CHCl_3$): δ 8.27 (1H, d, *J* 2.5 Hz, Ar-H), 7.86 (1H, d, *J* 9.0 Hz, Ar-H), 7.14–7.52 (25H, ms, Ar-H), 5.58 (1H, d, *J* 3.0 Hz, H-1), 4.65–5.09 (6H, ms, CH_2Ph), 4.29 (1H, dd, *J* 3.0, 10.0 Hz, H-2), 4.23 (1H, dd, *J* 2.5, 10.0 Hz, H-3), 4.11 (1H, q, *J* 6.5 Hz, H-5), 3.73 (1H, br s, H-4), 1.12 (3H, d, *J* 6.5 Hz, H-6): δ_C 153.3, 147.1, 138.7, 138.5, 133.3, 130.2, 126.3 (C, Ar), 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.5, 121.4, 120.0, 114.4, 110.6 (CH, Ar and CF_3), 97.8 (C-1), 78.9, 77.7, 76.4, 67.8 (C-2,3,4,5), 75.0, 73.4, 73.2 (CH_2Ph), 16.6 (C-6): [Found: *m/z* (CI) 726.2351 (M + NH_4). $C_{38}H_{35}O_8SF_3$ requires M + NH_4 726.2385].

1-[7-Carboxymethyl-1-naphthyl]-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (30). The triflate **29** (0.11 g, 0.14 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), dppp (15 mg, 0.35 mmol), Et_3N (0.05 mL, excess), MeOH (1 mL) and DMF (1 mL) were added to a dry flask at rt. Carbon monoxide was bubbled through this mixture for 30 min and the mixture was heated at reflux for 1 h. EtOAc was added and the product was washed with satd NH_4Cl and water and the organic portion was dried over anhydrous magnesium sulfate. The solvent was removed and chromatography of the residue (silica gel, EtOAc/petroleum ether, gradient) gave the title compound as a heavy syrup (**30**, 61 mg, 65%); $[\alpha]_D$ −56° (*c*, 0.36, $CHCl_3$): δ_H 9.16 (1H, s, Ar-H), 8.08 (1H, dd, *J* 1.5, 8.5 Hz, Ar-H), 7.84 (1H, d, *J* 8.5 Hz, Ar-H), 7.15–7.52 (24H, ms, Ar-H), 5.65 (1H, d, *J* 3.0 Hz, H-1), 4.69–5.08 (6H, ms, CH_2Ph), 4.36 (1H, dd, *J* 3.0, 10.0 Hz, H-2), 4.23 (1H, dd, *J* 3.0, 10.0 Hz, H-3), 4.06 (1H, q, *J* 6.5 Hz, H-5), 3.94 (3H, s, CO_2Me), 3.72 (1H, br s, H-4), 1.15 (3H, d, *J* 6.5 Hz, H-6): δ_C 167.3 (C=O), 154.3, 138.9, 138.6, 136.5, 126.9, 125.8, 125.5 (C, Ar), 128.7, 128.5, 128.2 (2C), 127.8, 127.7, 127.6, 127.4 (2C), 125.5, 121.5, 110.0 (CH, Ar), 97.5 (C-1), 78.9, 77.9, 76.6, 67.8 (C-2,3,4,5), 75.0, 73.6, 72.0 (CH_2Ph), 16.6 (C-6): [Found: *m/z* (CI) 636.2958 (M + NH_4). $C_{39}H_{38}O_7$ requires M + NH_4 636.2961].

1-[7-Carboxy-1-naphthyl]-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (31). The ester **30** (0.20 g, 0.34 mmol) and LiOH (78 mg, 3.4 mmol) were heated at reflux for 18 h in THF/water (5 mL, 4/1). The solvent was removed, water added, the aqueous solution was neutralized with KH_2PO_4, and the product extracted into EtOAc. The organic layer was dried over anhydrous magnesium sulfate and chromatography (silica gel, EtOAc/petroleum ether, 1/1) gave the title compound (**31**, 0.137 g, 74%, R_f = 0.5, EtOAc/petroleum ether, 1/1): $[\alpha]_D$ −45° (*c*, 0.40, $CHCl_3$); δ_H 9.27 (1H, d, *J* 1.7 Hz, Ar-H), 8.15 (1H, dd, *J* 1.7, 8.5 Hz, Ar-H), 7.85 (1H, d, *J* 8.5 Hz, Ar-H), 7.15–7.53 (24H, ms, Ar-H), 5.66 (1H, d, *J* 2.0 Hz, H-1), 4.67–5.07 (6H, ms, CH_2Ph), 4.30 (2H, br s, H-2,3), 4.03 (1H, q, *J* 6.5 Hz), 3.65 (1H, br s, H-4), 1.10 (3H, d, *J* 6.5 Hz): δ_C 172.4 (C=O), 154.4, 138.7, 138.6, 136.9, 126.1, 126.0 (C, Ar), 129.1, 128.5 (2C), 128.3, 128.2, 128.0, 127.7, 127.6, 127.4, 126.8, 125.4, 121.4, 109.8 (CH, Ar), 97.4 (C-1), 78.3, 77.8, 76.4, 67.8 (C-2,3,4,5), 75.0, 73.1, 73.0 (CH_2Ph), 16.6 (C-6): [Found: *m/z* (CI) 622.2804 (M + NH_4). $C_{38}H_{36}O_7$ requires M + NH_4 622.2805].

1-[7-Carboxy-1-naphthyl]-α-L-fucopyranose (3). The acid **31** (0.10 g, 0.17 mmol) in EtOH (10 mL) was stirred under an atmosphere of H_2 for 12 h. The mixture was filtered through Celite and the product was adsorbed on silica gel. Chromatography (silica gel, MeOH/EtOAc, gradient) gave the title compound (**3**, 18 mg, 33%): $[\alpha]_D$ −74° (*c*, 0.9, MeOH); δ_H 9.12 (1H, s, Ar-H), 8.20 (1H, dd, *J* 1.5, 8.5 Hz, Ar-H), 8.04 (1H, d, *J* 8.5 Hz, Ar-H), 7.72 and 7.67 (each 1H, each t, *J* 8.0 Hz, Ar-H), 7.41 (1H, dd, *J* 1.5, 8.5 Hz), 5.97 (1H, d, *J* 4.0 Hz, H-1), 4.54 (1H, dd, *J* 4.0, 10.5 Hz, H-2), 4.28 (1H, q *J* 6.5 Hz, H-5), 4.25 (1H, dd, *J* 4.0, 10.5 Hz, H-3), 4.08 (1H, br d, 4.0 Hz, H-4), 1.32 (3H, d, *J* 6.5 Hz): δ_C 173.2 (C=O), 153.9, 136.8, 133.0, 125.9 (C, Ar), 128.9, 128.4, 127.6, 124.9, 122.2, 109.6 (CH, Ar), 98.3 (C-1), 72.7, 70.7, 69.2, 68.6 (C-2,3,4,5), 16.6 (C-6): [Found: *m/z* (FAB) 357.0950 (M + Na). $C_{17}H_{18}O_7$ requires M + Na 357.0950].

[1,2,3,4-Tetrahydro-1-naphthyl]-2,3,4-tri-*O*-benzyl-α-L-fucopyranose (32). Glycosylation was carried out as described above for the thiofucoside **6** (1.63 g, 3.4 mmol) and 1,2,3,4-tetrahydro-1-naphthol (0.50 g, 3.4 mmol).

Chromatography of the reaction residue (silica gel, EtOAc/petroleum ether gradient) gave **32** (0.75 g, 39%); δ_H 7.56 and 7.53 (each 1H, each s, Ar-H), 7.04–7.33 (48H, ms, Ar-H), 5.17 and 5.13 (each 1H, each d, *J* 3.6 and 4.0 Hz, H-1) 4.56–5.01 (14H, ms, H-7 and CH_2Ph), 3.89–4.09 (6H, ms, H-2,3,5) 3.66 (2H, br s, H-4), 2.65–2.90 (4H, ms, H-10), 1.65–2.05 (8H, ms, CH_2), 1.15 and 1.16 (each 3H, each d, *J* 6.5 Hz, H-6): δ_C 139.0, 138.8 (2C), 138.6, 137.8, 137.2, 136.7, 136.4 (C, Ar), 129.6, 129.0, 128.9, 128.7, 128.6, 128.4, 128.2, 128.1, 127.7, 127.6, 127.5, 127.4, 127.3, 126.8, 125.6 (CH, Ar), 98.2, 95.4 (C-1), 79.5, 79.3, 77.7 (2C), 76.8, 76.4, 76.0, 66.5, 60.3 (2C) (C-2,3,4,5,7), 74.7, 73.0, 72.9, 72.8 (CH_2Ph), 30.4, 29.1, 28.8, 27.6, 19.5, 18.3 (CH_2), 16.7 and 16.6 (C-6) [Found: *m/z* 582.3219 ($M+NH_4$). $C_{37}H_{44}O_5$ requires $M+NH_4$ 582].

[1,2,3,4-Tetrahydro-1-naphthyl]-2,3,4-α-L-fucopyranose (2h). The benzyl groups were removed from **32** (0.30 g, 0.53 mmol) as described above and the title compound (**2h**, 0.12 g, 77%) was obtained after chromatography (silica gel, MeOH/EtOAc, gradient): δ_H 7.22–7.64 (6H, ms, Ar-H), 5.29 and 5.32 (each 1H, each d, *J* 2.9, 3.9 Hz, H-1), 4.84 (2H, br s, overlapping with HOD, CH), 4.22 and 4.21 (each 1H, each q *J* 6.5 Hz, H-5), 3.86–4.01 (6H, ms, H-2,3,4), 2.76–2.98 (4H, ms, H-10), 1.82–2.33 (8H, ms, H-8,9), 1.39 and 1.41 (each 3H, each d, *J* 6.5 Hz): δ_C 138.8, 138.2, 137.1, 136.9 (C, Ar), 130.6, 130.3, 130.0, 129.8, 128.7, 126.7 (CH, Ar), 100.8, 98.3 (C-1), 77.3, 73.8, 72.9, 70.9, 70.8, 69.6, 69.1, 67.6 (C-2,3,4,5,7), 31.0, 29.5 (2C), 28.2, 19.7, 18.7 (C-8,9,10), 19.7, 18.7 (C-6): [Found: *m/z* (CI) 312.1813 ($M+NH_4$). $C_{16}H_{26}O_5$ requires $M+NH_4$ 312.1820].

6-Carboxypropyl-1,2,3,4-tetrahydronaphthalene (4). Trifluoromethanesulfonic anhydride (3.0 g, 10.6 mmol) was added to a stirred solution of 6-hydroxy-1,2,3,4-tetrahydro-1-naphthalene (1.2 g, 8.0 mmol), 2,6-lutidine (1.3 g, 12 mmol) and DMAP (0.13 g, 0.12 mmol) at −78 °C in dichloromethane (50 mL) and the mixture was left to warm to rt overnight. The product was then washed with satd NH_4Cl, 10% $KHSO_4$, water, and dried over anhydrous magnesium sulfate. The residue which was obtained after the removal of solvent was added to a mixture of Et_3N (2.4 g, 24 mmol), $PdCl_2(PPh_3)_2$ (0.113 g, 5%) and 3 butyn-1-ol (1.0 g, 12 mmol) in DMF (10 mL). The mixture was purged with N_2 for 10 min and was then heated at 80 °C for 3 h. The product was partitioned between EtOAc and satd NH_4Cl and the organic layer was then washed with water. The residue which was obtained after drying ($MgSO_4$) and removal of solvent was subjected to silica gel chromatography and the product with R_f 0.1 (EtOAc/petroleum ether, 1/4) was dissolved in EtOH, 5% Pd-C (0.05 g) was added and the mixture stirred under an atmosphere of H_2 for 1 h. The suspension was then filtered through a layer of Celite and the solvent was removed and the residue (0.32 g) was taken up in acetone (10 mL). Jones' reagent was added (1.5 mL of a solution prepared from 0.67 g CrO_3, 1.6 mL of H_2O and 0.6 mL of H_2SO_4) dropwise over 20 min and the mixture was left stirring for 1 h. 2-Propanol (1 mL) was then added and the mixture was filtered and the solvent removed. The product was partitioned between EtOAc and 5% aqueous Na_2CO_3. The aqueous layer was acidified with dilute HCl and washed with EtOAc. The organic layer was washed with water and was dried (anhyd $MgSO_4$) and the solvent was removed. The product (R_f 0.1, EtOAc/petroleum ether, 1/4) was chromatographed (silica gel, EtOAc/petroleum ether, 1/1) and gave the title compound as a white solid (**4**, 0.22 g, 12% over 4 steps); δ_H 11.03 (1H, br s, CO_2H), 6.87–6.98 (3H, ms, Ar-H), 2.72 (4H, br s, CH_2), 2.58 (2H, t, *J* 7.3 Hz, CH_2), 2.36 (2H, t, *J* 7.3 Hz, CH_2), 1.92 (2H, quintet, *J* 7.3 Hz, CH_2), 1.76 (4H, br s, CH_2): δ_C 180.4 (CO_2H), 138.2, 137.0, 134.7 (C, Ar), 129.1 (2C), 125.6 (CH, Ar), 34.6, 33.5, 29.4, 29.0, 26.3, 23.3, 23.2 (CH_2): [Found: *m/z* (EI) 218.1296 (M). $C_{14}H_{18}O_2$ requires M 218.1307].

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