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Synthesis of Benzaldehyde-Functionalized Glycans: A Novel Approach Towards Glyco-SAMs as a Tool for Surface Plasmon Resonance Studies

Sebastian Kopitzki,[a] Knud J. Jensen,[b] and Joachim Thiem*[a]

Abstract: In recent years the interest in tools for investigating carbohydrate–protein (CPI) and carbohydrate-carbohydrate interactions (CCI) has increased significantly. For the investigation of CPI and CCI, several techniques employing different linking methods are available. Surface plasmon resonance (SPR) imaging is a most appropriate tool for analyzing the formation of self-assembled monolayers (SAM) of carbohydrate derivatives, which can mimic the glycocalyx. In contrast to the SPR imaging methods used previously to analyze CPI and CCI, the novel approach reported herein allows a facile and rapid synthesis of linker spacers and carbohydrate derivatives and enhances the binding event by controlling the amount and orientation of ligand. For immobilization on biorepulsive amino-functionalized SPR chips by reductive amination, diverse aldehyde-functionalized glycan structures (glucose, galactose, mannose, glucosamine, cellobiose, lactose, and lactosamine) have been synthesized in several facile steps that include olefin metathesis. Effective immobilization and the first binding studies are presented for the lectin concanavalin A.

Keywords: amination · carbohydrates · metathesis · monolayers · surface plasmon resonance

Introduction

Carbohydrates conjugated to proteins or lipids are structural constituents of all eukaryotic cell surfaces. This layer, which is composed of glycoproteins, glycolipids, complex oligosaccharides as well as proteoglycans and other glycoconjugates, is called the "glycocalyx" and has a thickness of up to 100 nm.[1] The molecular interactions of these glycoconjugates play a crucial role in various cellular processes, including bacterial and viral infection, cancer metastasis, modulation and activation of the immune system, tissue differentiation and development, and many other intercellular recognition events.[2–4] In addition, carbohydrate-associated cellular recognition events can be classified into carbohydrate–protein-interactions (CPI), especially between sugars and lectins[5] and also selectins,[6] and carbohydrate–carbohydrate interactions (CCI).[7]

Both types of interactions are typically weak in in vitro testing (K_D values in the millimolar or high micromolar range) compared with antigen–antibody interactions ($K_D \approx 10^{-8}$ to 10^{-12} M).[8–10] However, a multivalent presentation of carbohydrate recognition units can increase the binding affinity dramatically.[11,12] Although the elucidation and biological assignment of the glycocalyx has been well advanced by glycobiology, the development of a general mechanistic concept for carbohydrate recognition is still hampered by difficulties in studying these interactions.

Thus, novel analytical and synthetic approaches such as chemoenzymatic and automated solid-phase synthesis of oligosaccharides and glycomimics as well as chemical tools, microarrays, glyconanoparticle technology, and molecular modeling could facilitate the study of carbohydrate-based recognition events.[13–20] The phenomenon of self-assembly of thiol-functionalized molecules on gold surfaces, first developed by Bain and Whitesides in 1988,[21] is quite advantageous for mimicking the glycocalyx. In particular, the concept of glyco-self-assembled monolayers (glyco-SAMs) is well suited to the investigation of the molecular interactions of carbohydrates: It allows the density and orientation of carbohydrate ligands to be controlled, and there are several

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methods for their characterization.[22] Furthermore, glyco-SAMs on gold can be advantageously studied by spectroscopic techniques such as surface plasmon resonance (SPR), ellipsometry, atomic force microscopy (AFM), and X-ray photoelectron spectroscopy.[23,24]

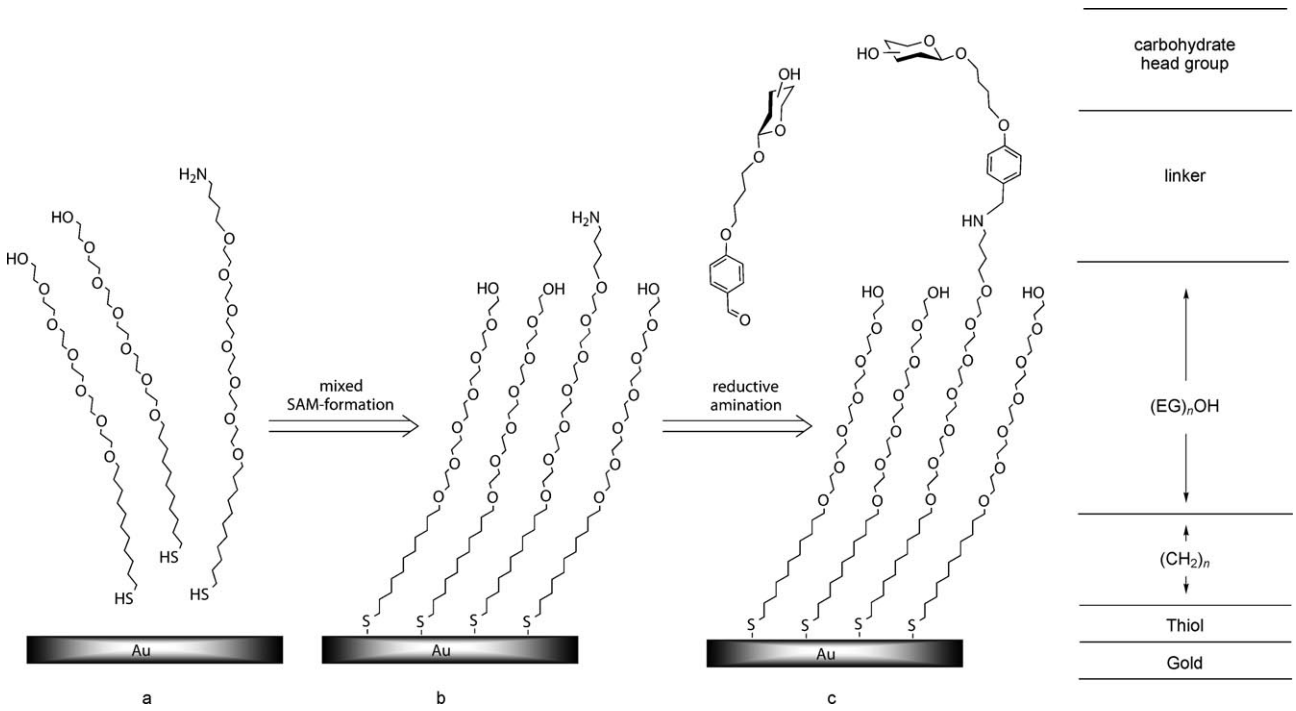
The novel systematic approach to the immobilization of synthetic glycosides reported herein is based on 1) the control of the orientation by well-defined tethers, 2) the control of the binding event by calculable tether length and provision of functionalization by the preparation of mixed SAMs in different ratios, 3) a facile in situ immobilization through thioalkanes on gold as SAMs, and 4) a facile in situ attachment of glycoderivatives by reductive amination (Scheme 1).

To achieve these aims benzaldehyde-functionalized glycostructures were chosen to attach carbohydrate head groups to amine-bearing SAMs diluted with biorepulsive spacers to control the ligand interdistance. The two essential requirements for these biorepulsive compounds synthesized for self-assembly are a long alkane chain and a terminal oligoethylene glycol moiety. The first is needed to form strong van der Waals interactions between spacers, which promotes accurate SAM formation.[25] The oligoethylene glycol moiety was introduced to prevent the nonspecific adhesion of biomaterial to the SAM[26] and an anchor group is provided by the insertion of the amino function. The approach used to obtain the aldehyde-linking partner for covalent immobilization by reductive amination does not depend on conventional glycosylation, which usually leads to α/β mixtures and requires tedious chromatographic purification. Instead, the aldehyde function is introduced into anomerically pure allyl glycosides by cross metathesis. Olefin metathesis has become a mainstay in organic synthesis.[27,28] Cross-metathesis (CM), however, is less developed, especially in carbohydrate chemistry, than ring-closing metathesis (RCM) and ring-opening metathesis polymerization (ROMP).[29] Encouraged by recent reports, which solved the problems of self-metathesis and accepted the challenges of aqueous CM,[30,31] olefin metathesis was applied to modify the carbohydrate derivatives. Glyco-SAMs could successfully be prepared by the incubation of plain gold sensor surfaces with amino-functionalized and biorepulsive spacers and subsequent attachment of the glycoderivates by reductive amination. The evidence for effective immobilization of carbohydrates was supplied by initial binding experiments of the lectin concanavalin A to modified SAMs carrying α-mannopyranoside structures.

Results and Discussion

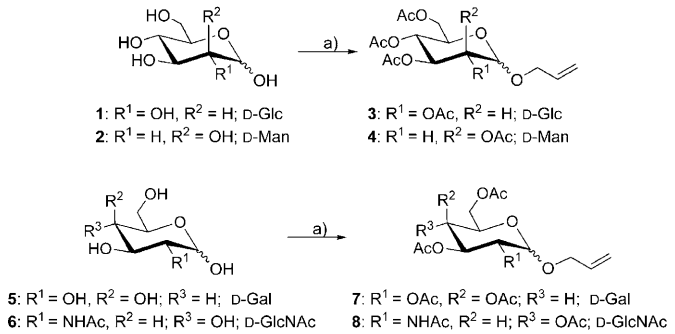
The use of reductive amination as a coupling procedure for glyco-SAM formation requires the amino functionalization of spacers and aldehyde derivatization of anomerically pure glycosides. Thus, the target compounds were synthesized by a convergent building block approach. Following the preparation of a series of allyl mono- and disaccharides, the next step was benzaldehyde functionalization by cross metathesis.

Synthesis of monosaccharide allyl glycosides: Sugars were suspended in commercially available allyl alcohol and by



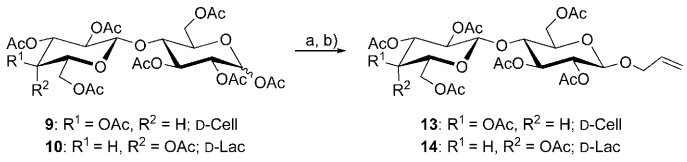
Scheme 1. Schematic depiction of glyco-SAMs for surface plasmon resonance studies: a) cleaned SPR sensor chips are incubated with different thiofunctionalized spacers **44** and **49** in a ratio of 9:1; b) preformed SAMs with amino-functionalized head groups allows the presentation of bioactive compounds in a well-defined manner; c) covalent immobilization of carbohydrates by imine formation and subsequent reductive amination.

simple Fischer glycosylation the corresponding allyl glycosides of monosaccharides **1**, **2**, **5**, and **6** were obtained, interestingly in both anomeric forms.[32,33] Subsequent acetylation allowed the isolation of anomerically pure glycosides **3**, **4**, **7**, and **8** in good yields by column chromatography (Scheme 2). Thus, a fairly large repertoire of monomeric building blocks can be obtained in only two steps (see the Supporting Information for experimental procedures).



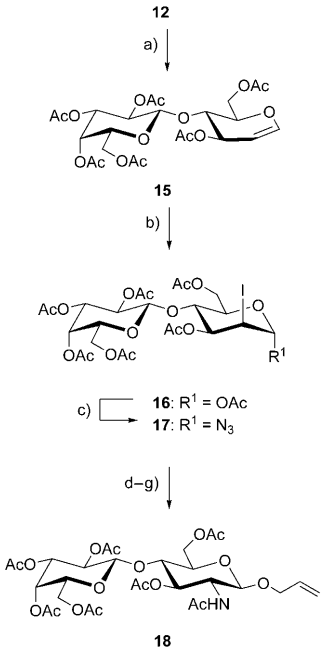
Scheme 2. Synthesis of peracetylated monosaccharide allyl glycosides. Reagents and conditions: a) 1. Allyl alcohol, conc. H_2SO_4, 80 °C, 3–4 h; 2. Ac_2O, Py, RT, 16–18 h; 2 steps. Yields: **3**α: 36 %; **3**β: 25 %; **4**α:34 %; **4**β: 21 %; **7**α: 41 %; **7**β: 21 %; **8**α: 34 %; **8**β: 15 %.

Synthesis of disaccharide allyl glycosides: In the case of disaccharides, allylation has to be carried out by following the Koenigs–Knorr procedure.[34] Thus, the peracetates of cellobiose **9** and lactose **10** were converted into the glycosyl bromides **11** and **12** by treatment with hydrogen bromide in glacial acetic acid. The bromides **11** and **12** were then treated with allyl alcohol in the presence of silver carbonate to afford only the β-configured compounds **13** and **14** (Scheme 3; see the Supporting Information for experimental procedures).



Scheme 3. Synthesis of peracetylated allyl glycosides of cellobiose **9** and lactose **10**. Reagents and conditions: a) Ac_2O, AcOH, HBr, 0 °C, 4 h; **11**: 85 %; **12**: 92 %; b) allyl alcohol, Ag_2CO_3, CH_2Cl_2, RT, 12 h; **13**: 75 %; **14**: 71 %.

Because *N*-acetyllactosamine is rather expensive, precursor **18** was synthesized by following the procedure of Lafont et al. (Scheme 4).[35] Thus, the bromide **12** was converted into the lactal **15** by reductive elimination using zinc and 1-methylimidazole in ethyl acetate at reflux. *trans* iodoacetoxylation can be achieved by using either iodine and a metal acetate in acetic acid or *N*-iodosuccinimide, most often in acetic acid to prepare 2-deoxy-2-iodo sugars from



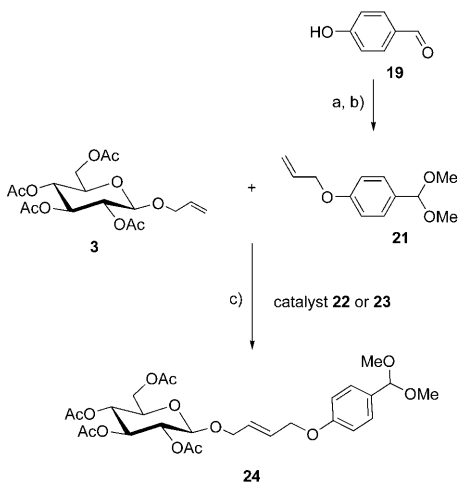
Scheme 4. Synthesis of peracetylated allyl *N*-acetyllactosaminide **18**. Reagents and conditions: a) 1-methylimidazole, Zn, ethyl acetate, reflux, 3 h; **15**: 87 %; b) $Cu(OAc)_2$, I_2, AcOH, 80 °C, 6 h; **16**: 96 %; c) TMS-N_3, TMS-OTf, dichloromethane, RT, 16 h; **17**: 94 %; d) allyl alcohol, PPh_3, dichloromethane, 0 °C to RT, 4 h; e) DOWEX (OH^-), EtOH, column filtration; f) NaOMe, MeOH, RT, 12 h; g) Ac_2O, Py, 12 h; **18**: three steps 82 %.

glycals.[36] The 1-*O*-acetyl-2-iodo derivative **16** was obtained by the addition of a slight excess of iodine in the presence of cupric acetate in acetic acid at 80 °C. Complete *trans* stereoselectivity led to the manno-configured derivative, as determined by ^1H and ^{13}C NMR spectroscopy and by comparison with the literature data.[37] Treatment of **16** with trimethylsilyl azide and trifluoromethanesulfonate afforded the corresponding mannopyranosyl azide **17** in nearly quantitative yield with conservation of the α-anomeric configuration. The ^1H and ^{13}C NMR data were in agreement with those previously reported.[38] The azide **17** was treated with triphenylphosphine and allyl alcohol to generate an (allyl 2-aminophosphonium β-glucopyranosyl) iodide, which was subjected to anion exchange with DOWEX 2X8 (OH^-). Remaining acetyl groups were removed with NaOMe in dry methanol. Reacetylation under classic conditions with acetic anhydride and dry pyridine afforded the desired product **18** (see the Supporting Information for experimental procedures). In this way, the target compound **18** was isolated in a yield of 82 % over four steps without separation of intermediates

Synthesis of benzaldehyde-functionalized carbohydrates by cross metathesis: To attach the glycoderivatives to the amino-functionalized SAMs, readily accessible allylic saccharides were chosen. This approach is not limited to attachment just through the anomeric position of the carbohy-

drates. The aldehyde linker was introduced by olefin metathesis.[39] This approach was used to take advantage of the high diversity of potential coupling partners to form larger libraries of tethered glycans. Another advantage of this transformation is the tolerance towards various protecting groups. Furthermore, recent developments in the field of aqueous olefin metathesis has led to novel possible applications for the use of unprotected carbohydrates.[40]

The required simple aldehyde linker **21** was obtained by nucleophilic substitution of allyl bromide with 4-hydroxybenzaldehyde (**19**) and acetalization with trimethyl orthoformate (TM*o*F) in nearly quantitative yield (Scheme 5).[41,42]



Scheme 5. Synthesis of benzaldehyde-functionalized glucoderivative **24**. Reagents and conditions: a) Allyl bromide, K_2CO_3, acetone, reflux, 17 h; **20**: 94%; b) pTSA, TM*o*F, RT, 6 h; **21**: 98%; c) for reaction conditions, see Table 1.

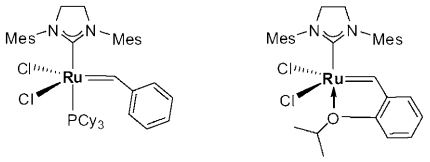
Unlike the widely used ring-closing metathesis procedure, cross metathesis gives the desired compounds along with several byproducts.[43] Cross metathesis has only recently attracted more attention in carbohydrate chemistry because novel and more active catalysts have only just become available.[44] The desired cross-products, which are usually obtained as mixtures of *E* and *Z* isomers, compete with the formation of the two self-metathesis products, each one being a mixture of *E* and *Z* isomers. To be useful in synthesis, a method had to be developed to obtain a well-defined product without any byproducts. Thus, the reaction conditions were optimized by using the allyl glucopyranoside **3β** and compound **21** (Table 1). As mentioned above, in every case of cross metathesis, only products with the *E* configuration were observed. To explore the efficiency of the reaction, the two ruthenium catalysts **22** and **23** were studied (Scheme 6).

The initial cross-metathesis experiments performed under conditions described by Wong and co-workers to construct a glycolipid library yielded the desired cross-product **24**.[45] No dimerization of **3β** was observed, however, self-metathesis of the corresponding coupling partner **21** was detected and a significant amount of starting material was reisolated. It was

Table 1. Optimization of the cross metathesis reaction conditions for the synthesis of the benzaldehyde-linked glycoderivatives.[a]

Entry	*T* [°C]	*t* [h]	Yield [%][b]
1	25	3	36
2	40	3	55
3	40	6	92
4	40	12	89
5[c]	40	6	54

[a] Unless otherwise noted, the reactions were carried out in degassed anhydrous dichloromethane with coupling partner **21** and catalyst **23**. [b] Only the *E* configuration was observed by ^{1}H NMR spectroscopy. [c] With catalyst **22**.



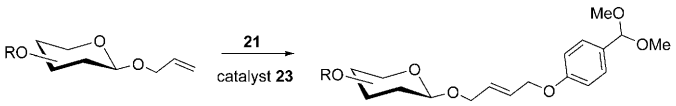
Scheme 6. Ruthenium catalysts applied in cross metathesis: Grubbs second-generation catalyst **22** and Grubbs–Hoveyda second-generation catalyst **23**.

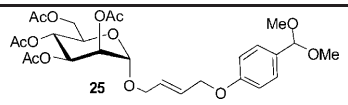
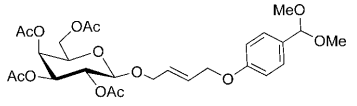
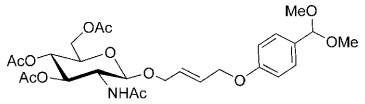
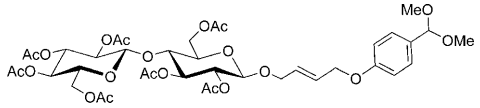
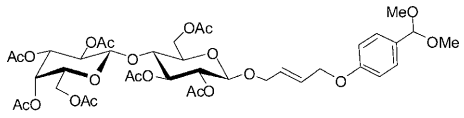
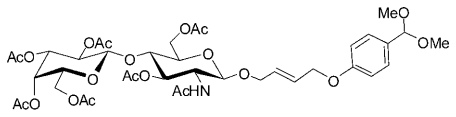
assumed that catalyst activity was lost by self-metathesis. Thus, the Grubbs catalyst **22** was replaced by the Grubbs–Hoveyda catalyst **23** in the hope of increased activity and stability. However, a substantial improvement in the yields was not observed, and this also applies to studies with increased amounts of catalyst (results not shown). Hence, the conditions applied by Meinke and Thiem in the synthesis of potential sialyltransferase inhibitors[46] with less self-metathesis under dilution were considered. The best results were obtained when the more active and stable catalyst **23** was used in cross metathesis under reflux conditions in dry dichloromethane for 6 hours (Table 1, entry 3).

The optimized conditions were accordingly applied to link allyl glycosides **4**, **7**, and **8** to obtain the corresponding benzaldehyde-functionalized derivatives **25**, **26**, and **27** (Table 2). With disaccharides, decreased yields were observed and thus further optimization of the reaction conditions was needed for oligosaccharides. In contrast to the observations of Roy and Das, homodimerization of the carbohydrate moieties was never detected.[47]

The glycoderivatives **31**–**37** required for surface plasmon resonance studies were obtained by deacetalization of benzaldehyde dimethyl acetal followed by hydrogenolysis catalyzed by palladium on charcoal poisoned with diphenyl sulfite and subsequent classical Zemplén deprotection (Table 3). In this way, the desired target products were obtained and purified by column chromatography and characterized by NMR spectroscopy and high-resolution mass spectrometry. To remove the dimethyl acetal the tethered glycoderivatives were dissolved in aqueous THF containing 0.1% trifluoroacetic acid.[42] After stirring for 1 hour the reaction was stopped by dilution with CH_2Cl_2 and the addition of triethylamine. The reaction mixture was then concentrat-

Table 2. Formation of benzaldehyde-linked glycoderivatives by olefin metathesis.[a]

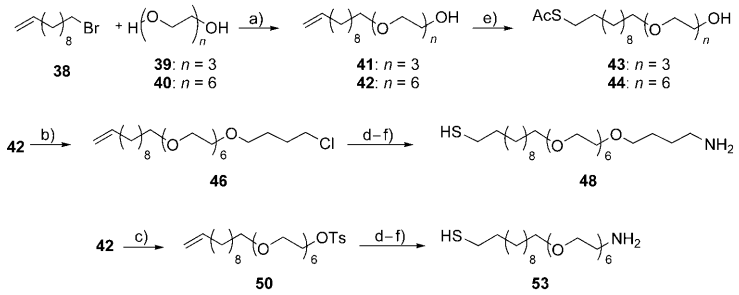


	Product	Yield [%][b]
4	 25	87
7	 26	75
8	 27	81
13	 28	46
14	 29	52
18	 30	12

[a] Unless otherwise noted, reactions were carried out in degassed anhydrous dichloromethane with coupling partner **21** and catalyst **23**. [b] Only *E*-configured products were observed by ^{1}H NMR spectroscopy.

ed. To convert the double bond into an alkane motif the palladium catalyst was poisoned with diphenyl sulfite and dry ethyl acetate was used as the solvent otherwise the benzaldehyde function could be transformed into an undesired methylene group.[48] After filtration and evaporation the acetyl groups were removed by the addition of a methanolic sodium methoxylate solution (0.1 M) under Zemplén conditions.[49] Subsequent treatment with Amberlite IR 120 (H^+ form) and evaporation of the solvent gave a syrupy residue. Removal of salts and further purification followed by lyophilization conclude this advantageous, facile, and rapid work-up protocol.

Synthesis of amino-functionalized spacers: For glyco-SAM formation two types of spacers, dilution and attachment molecules, are needed. To avoid nonspecific adhesion of biomolecules in biological investigations using SAMs both types of spacers have to carry a terminal oligoethylene glycol (OEG) unit. Thus, initially, dilution molecules **43** and **44** carrying thioacetyl functions to allow SAM formation on gold were synthesized by nucleophilic substitution of the bromide in commercially available ω-bromoundecene (**38**) with tri- or hexaethylene glycol (**39** or **40**; Scheme 7). To prevent disubstitution the glycoderivatives were used in



Scheme 7. Synthesis of amino-functionalized spacers. Reagents and conditions: a) NaH, DMF, 0 °C to RT, 12 h; **39**: 95 %; **40**: 96 %; b) **45**, NaH, DMF, 0 °C for 2 h then 0 °C to RT, 15 h; **46**: 78 %; c) TsCl, Py, 0 °C to RT, 15 h; **50**: 92 %; d) NaN_3, TBAI, DMF, 70 °C, 2 h; **47**: 82 %; **51**: 85 %; e) AcSH, AIBN, THF, *hν*, 3 h; **43**: quant.; **44**: quant.; **48**: 95 %; **52**: 96 %; f) LAH, Et_2O, 0 °C to RT, 2–3 h; **49**: 64 %; **53**: 66 %.

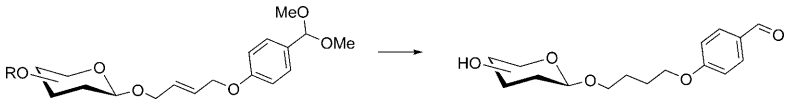
two-fold excess.[26] The oligoethylene glycol capped alkenes **41** and **42** were obtained in almost quantitative yields after flash chromatographic purification. Both dilution molecules were thioacetylated by photoreaction with thioacetic acid in THF using AIBN as radical initiator.[50] After irradiation with a standard UV mercury pressure lamp over a short period the required dilution molecules **43** and **44** were obtained in nearly quantitative yields in only two steps.

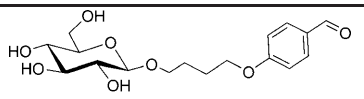
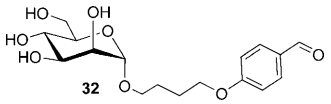
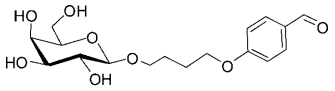
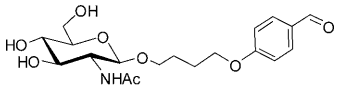
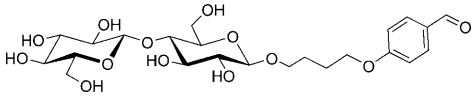
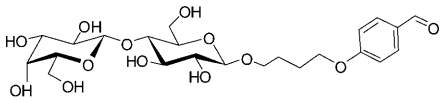
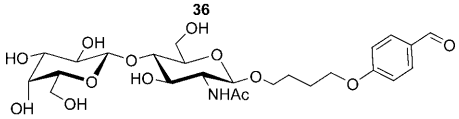
In addition, an amino function is required for attachment of the benzaldehyde-functionalized glycoderivatives to SPR sensor chips by reductive amination. Thus, alkene-terminated hexaethylene glycol **42** served as the starting material for the synthesis of attachment spacers **49** and **53**. In one case an additional tether was introduced into the alcohol **42** by employing a slightly modified procedure developed for tethering sugars to cisplatin as antitumor agents.[51] The halogen derivative **46** was obtained by nucleophilic monosubstitution of 1-bromo-4-chlorobutane (**45**) with glycol **42** and sodium hydride in DMF in a yield of 78 %. Then the chloride was substituted by azide in DMF at 70 °C to give compound **47** in a yield of 82 %. After photochemical thioacetylation and reduction of the azide by lithium aluminum hydride in diethyl ether at 0 °C, the amino-functionalized spacer **49** was isolated in a nonoptimized yield of 64 %.

These conditions were also applied to the synthesis of the attachment molecule **53**, except for the first step, in which the azide function was introduced by nucleophilic substitution of tosylate **50**, which in turn was obtained by reaction of alcohol **42** with tosyl chloride in pyridine in a yield of 92 %. Following the procedure used to elaborate compound **49**, the second nontethered attachment molecule **53** was obtained in a yield of 66 %.

SPR experiments: Cell surface glycans play a crucial role in many different recognition events and thus various efficient

Table 3. Deprotection of aldehyde-functionalized glycoderivatives.[a]



	Product	Yield [%][b]
24	 **31**	91
25	 **32**	92
26	 **33**	89
27	 **34**	80
28	 **35**	82
29	 **36**	89
30	 **37**	79

[a] Reagents and conditions: 1) THF, TFA, H_2O, RT, 1 h; 2) Pd/C, H_2, DPS, EtOAc, RT, 24–48 h; 3) NaOMe, MeOH, RT, 24 h. [b] Overall yields.

tools for analyzing these processes are required. Surface plasmon resonance is one of the most important techniques used in this area and a number of groups have developed different approaches for the immobilization of carbohydrates on sensor chips.[52–55] In many cases SAMs are formed by the covalent binding of thiols to gold.[56–59] For example, Zhi et al. reported a concept that could be applied to synthetic glycosides and glycans from natural sources.[57] However, the approach reported herein focused on well-defined synthetic saccharides. Recently, Penades and co-workers used long-chain alkenyl *N*-acetylglucosaminopyranosides and 11-mercapto-1-undecanol as a reference for the formation of SAMs.[60] A disadvantage of this approach is the lack of any biorepulsive spacer unit. A building block system was established by Kleinert and co-workers; both azide- and alkyne-derivatized glycol and biorepulsive OEG spacer structures were synthesized and the construction and modification of the glyco-SAMs were carried out by copper-catalyzed "click" chemistry before SAM formation occurred directly on sensor chips.[61,62] Owing to its cytotoxicity, the use of copper could be a drawback in SPR assays in the study of cell systems. Houseman and Mrksich formed SAMs with OEG-capped and benzoquinone-functionalized spacers prior to immobilizing carbohydrate–cyclopentadiene conjugates by Diels–Alder reactions. However, in their work, nonfunctionalized chips showed unspecific protein binding.[63]

The approach presented herein anticipates nonspecific binding and uses on-chip immobilization of carbohydrates to ensure accurate SAM formation and avoid the use of heavy metals by attachment by reductive amination. Furthermore, to the best of our knowledge, this is the first example of the online observation of SAM formation and carbohydrate attachment.

Online SAM formation: In the preparation of glyco-SAMs the first step was to form accurate monolayers containing attachment and dilution molecules at a well-defined distance. Thus, a 100 μM solution of compounds **44** and **49** (25:1 ratio) in phosphate-buffered saline (pH 7.4) was prepared. Prior to use, the plain gold sensor chips were cleaned by treatment with piranha solution. These blank chips were incubated with the thiol solution inside the SPR instrument by injecting the thiol over a minimum period of 45 min (Figure 1). SAM formation was observed online. After an initial washing procedure in which buffer solution was passed over the gold chips for 10 min, the premixed thiols were injected at a flow rate of 5 $\mu L\,min^{-1}$. SAM formation was observed by the increase in the response unit (RU). After injection, the RU increased rapidly as a result of a quick adsorption of thiols on the gold surface. Then reorganization of the SAM is shown by a slight growth of the RU. After saturation and accurate SAM formation, as indicated by a horizontal line (zero gradient), injection was interrupted. No significant decrease in the RU was observed. This indicates that the SAM formed by in-system incubation with thiols is well arranged.

The biorepulsive nature of the coated sensor chips carrying amino functions was proven by adhesion experiments with the proteins bovine serum albumin (BSA) and concanavalin A (ConA). Neither BSA nor ConA were adsorbed at the surface (data not shown). Also, comparison of the online-coated surface with surfaces resulting from standard

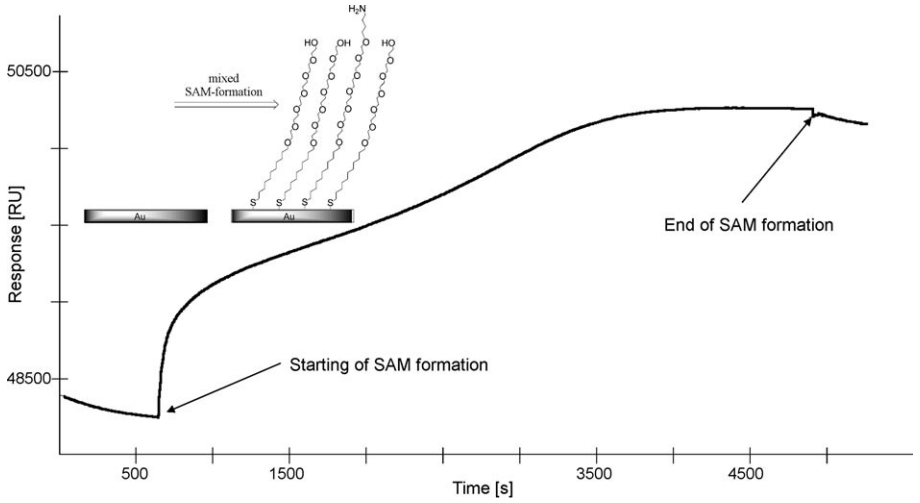


Figure 1. Online SAM formation observed by an increase in the response unit (RU) after injection of 100 μM solution of **44** and **49** (ratio 25:1), with SAM formation completed after saturation.

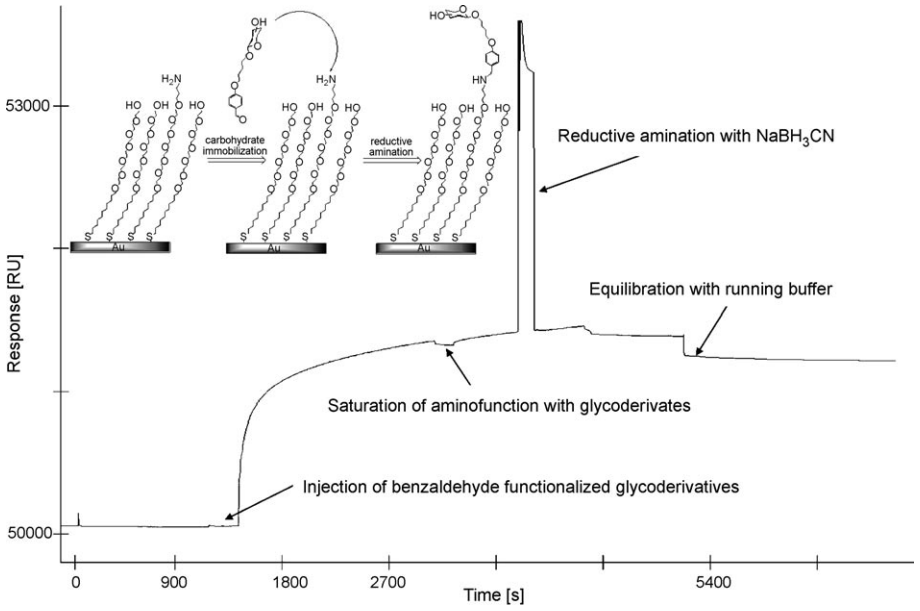


Figure 2. Online glycol-SAM formation and attachment of mannopyranoside **25**.

SAM formation with ethanolic solutions of thiols showed the advantage of this approach.

Online carbohydrate attachment and lectin binding studies: After the SAMs had been successfully formed the following attachment procedure was applied to immobilize benzaldehyde-functionalized mannopyranoside **25** to the sensor surface. The glycoside was dissolved in PBS buffer and injected at a flow rate of 10 μL min^{-1}. After no further imine formation was observed, as indicated by a horizontal RU curve, injection of the carbohydrate conjugate was interrupted and the irreversible linkage was established by reductive amination with sodium cyanoborohydride. Hence, a 0.1 M solution of $NaBH_3CN$ was injected, which resulted in a sharp peak in the sensorgram (Figure 2). The flow rate in this process was 10 μL min^{-1} and the contact time required for the reaction to form a stable amino function was 4 min. Afterwards the flow cell was thoroughly washed with PBS buffer to remove unreacted residues. Then the eluent was changed to HEPES buffer for lectin binding studies. The stabile base line indicated the success of immobilization of mannopyranoside **25**.

The immobilization of mannopyranoside **25** was proven by a lectin binding assay employing ConA (Figure 3). Thus, solutions of ConA and BSA at various concentrations (6.25–100 μM) were eluted over the glyco-SAM. Only in the case of ConA was a binding event observed, as shown in Figure 3. The adsorption coefficient (K_{ads}) of ConA with the mannose-functionalized surface was determined to be $(5.2\pm1.5)\times10^6$ M^{-1} and this is similar to previously observed data ($K_{ads}=(5.6\pm1.7)\times10^6$ and $(3.1\pm1.4)\times10^6$ M^{-1}).[23,64] The data for BSA are not shown. From the sensorgram in Figure 3, the first qualitative results have been unequivocally demonstrated for the binding ConA to mannopyranoside-functionalized SPR

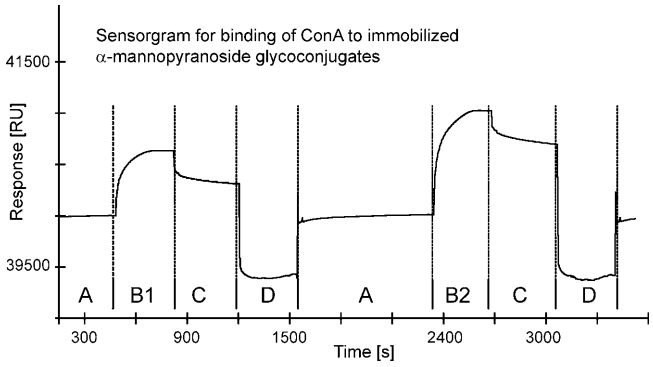


Figure 3. Binding studies of ConA to mannopyranoside-functionalized SPR sensorchips. A: Equilibration phase; B1: association (50 μM ConA); B2: association (100 μM ConA); C: dissociation; D: regeneration (0.1% SDS solution).

sensor chips (see the Supporting Information for details and the difference sensorgram).

Conclusion

Benzaldehyde-functionalized glycoderivatives and amino-functionalized spacers for glyco-SAM formation have been synthesized. The successful use of CM for the modification of sugars has enhanced the opportunities of this reaction type in carbohydrate chemistry and especially in the construction of larger libraries of tethered glycans. The immobilization of carbohydrates on sensor chips by reductive amination has circumvented the disadvantages of previously reported attachment procedures. In a preliminary experiment, proof-of-concept evidence for the attachment of mannose was provided by binding studies with the well-known lectin ConA.

This novel and advantageous immobilization method is presently being employed in various biomimetic studies of carbohydrates and in the development of a carbohydrate-based array for diagnostics and screening. We are currently exploring the scope of this approach with other biologically important systems as well as extending it to other applications such as glyconanoparticles.

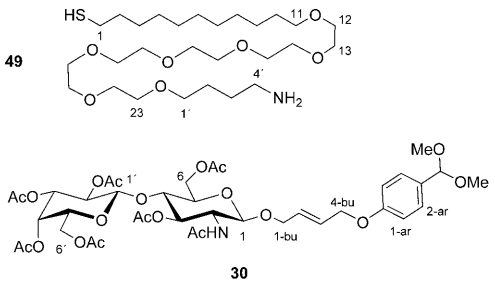
Experimental Section

General: Reagents of commercial quality were purchased from Aldrich, Sigma, or Merck and were used without further purification. Solvents were dried according to standard methods. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on precoated aluminum plates (silica gel 60 F254, Merck5554) and compound spots were visualized by UV light (254 nm) and by staining with a yellow solution containing $Ce(NH_4)_2(NO_3)_6$ (0.5 g) and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (24.0 g) in 6% H_2SO_4 (500 mL) or with 10% H_2SO_4 in ethanol followed by heat treatment. For column chromatography, silica gel 60 (230–400 mesh, 40–63 μm) (Merck) was used.

^1H and ^{13}C NMR spectra were recorded on Bruker AMX-400 (400 MHz for ^1H, 100.6 MHz for ^{13}C) and DRX-500 (500 MHz for ^1H, 125.8 MHz for ^{13}C) spectrometers at 300 K. Chemical shifts were calibrated against solvent residual peaks ($CDCl_3$: $\delta = 7.24$ and 77.0 ppm for ^1H and ^{13}C, respectively; [D_4]methanol: $\delta = 3.35$ and 49.30 ppm for ^1H and ^{13}C, respectively). The signals were assigned by ^1H–^1H COSY, HSQC, HMBC, and, if necessary, NOESY experiments. Hydrogen and carbon atoms are indexed as follows: The sugar residue is numbered as usual from 1 to 6 with the anomeric position being number 1. The atoms of the anomeric spacer moiety then receive numbers with the index "bu" for butyl and "ar" for aromatic with the numbering starting from the glycosidic bond. This is shown for compound **30** in Scheme 8. In the sugar-free spacer molecules, the thiol function is defined as the terminus of the molecule, as exemplified for **49** (Scheme 8).

Optical rotations were measured by using a Krüss Optronic P8000 (589 nm) instrument at 20 °C. MALDI-TOF MS was performed on a BrukerBiflex III spectrometer with dihydroxybenzoic acid or trihydroxyanthracene as the matrix in positive reflector mode. FAB HRMS was performed on a Thermo Finnigan MAT95 XL mass spectrometer.

SPR measurements: The BIACORE T100 SPR imaging instrument was used in the study of the carbohydrate arrays described herein. Uncoated gold surfaces (BIACORE SIA kit Au) were used as sensor chips. Before use they were cleaned by treatment with piranha solution (conc. H_2SO_4/30% H_2O_2, 1:1) for 10 min. After rinsing with twice-distilled water and ethanol the plain gold chips were dried in a flow of nitrogen. The SAM formation was effected immediately after cleaning by elution (flow 5 μL min^{-1}) with 100 μM solutions of **44**/**49** (ratio 25:1) for a minimum of 45 min. The following general procedure was used for immobilizing carbohydrate conjugates on to amino-functionalized SPR sensor chips by reductive amination: 100 μM solutions of **25** in PBS buffer were injected (flow rate 10 μL min^{-1}) over a period of 30 min. When a sensorgram exhibited saturation, the injection was stopped and the reduction was initiated by adding a $NaCNBH_3$-solution (4 min at 10 μL min^{-1}). For the binding studies, the lectin concanavalin A (ConA/mannose positive) was used. The measurements were carried out in HEPES-buffered saline (150 mM NaCl, 10 mM NaHEPES, 0.005% Tween 20/pH 7.4) containing Ca^{2+} (1 mM $CaCl_2{\cdot}2H_2O$) and Mn^{2+} (1 mM $MnCl_2{\cdot}4H_2O$) ions for ConA activation. ConA was dialyzed for 2 d in HEPES buffer to remove any remaining mannose. Solutions of ConA as well as BSA in HEPES buffer (6.25, 12.5, 25, 50, and 100 μM) were injected over 3 min at a flow rate of 20 μL min^{-1}. The injection of 60 μL of 0.1% SDS solution was appropriate to regenerate the sensor surface.



Scheme 8. Numbering of hydrogen and carbon atoms for the assignment of NMR data.

General procedure A—Cross metathesis with allyl glycosides: Peracetylated allyl glycoside (1 mmol) and a five- to eight-fold excess of the corresponding coupling partner **37** (5–8 mmol) were dissolved in dry and degassed dichloromethane (49 mL) and placed in a flame-dried flask containing activated molecular sieves (4 Å) using standard Schlenk techniques. Grubbs catalyst **23** (0.10 mmol) dissolved in dry and degassed dichloromethane (1 mL) was added through a syringe or as a solid to attain a 0.02 M solution. The reaction mixture was heated at reflux for 6 h. Conversion of the starting material was detected by TLC. The solution was concentrated under reduced pressure and the crude product was directly purified by column chromatography by using silica and a petroleum ether/ethyl acetate gradient (4:1→2:1/1:1 for disaccharides).

General procedure B—Deprotection and hydrogenolysis of benzaldehyde-functionalized glycosides: The CM products (90–870 μmol) were dissolved in a mixture of THF, water, and TFA (90:9.9:0.1, v/v; solvent A) to obtain a 0.2 M solution. After stirring for 1 h the reaction mixture was diluted with CH_2Cl_2 (100 mL) and the reaction was stopped by the addition of triethylamine (2 mL) and then water (100 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was used in the next transformation step without further purification. For hydrogenolysis, the aldehyde was dissolved in anhydrous EtOAc and placed in a flame-dried flask containing palladium (10%) on charcoal and diphenyl sulfide (0.01 equiv). The suspension was degassed and after purging with hydrogen the mixture was stirred for 12 h. Then the suspension was filtered and thoroughly dried before the residue was redissolved in a methanolic sodium methoxide solution (20 mL, 0.1 M). The solution was stirred for 6 h at room temperature and the mixture was then neutralized with Amberlite IR 120 (H^+) resin. After filtration and evaporation of the solvent the crude products were purified by flash chromatography using silica and dichloromethane/methanol (5:1) as eluent.

(*E*)-4-(4-Dimethoxymethylphenoxy)but-2-enyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (24): The reaction was carried out according to general

procedure A using compound **3β** (388 mg, 1.00 mmol) and compound **21** (1.04 g, 5.00 mmol) with catalyst **23** (63 mg, 0.10 mmol). The product **24** was obtained as a colorless syrup (523 mg, 92%). R_f=0.36 (petroleum/EtOAc, 1:1); $[\alpha]_D^{20}$=−15.3 (c=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=7.32 (d, $^3J_{Ar}$=8.4 Hz, 2H; 1-H_{arom}), 6.86 (d, $^3J_{Ar}$= 8.4 Hz, 2H; 2-H_{arom}), 5.96–5.80 (m, 2H; 2-$H_{bu,}$ 3-H_{bu}), 5.32 (s, 1H; H_{acetal}), 5.18 (dd, $^3J_{2,3}$=9.4, $^3J_{3,4}$=9.6 Hz, 1H; 3-H), 5.06 (dd, $^3J_{3,4}$=9.6, $^3J_{4,5}$= 9.9 Hz, 1H; 4-H), 4.99 (dd, $^3J_{1,2}$=7.9, $^3J_{2,3}$=9.4 Hz, 1H; 2-H), 4.53 (d, $^3J_{1,2}$=7.9 Hz, 1H; 1-H), 4.50–4.48 (m, 2H; 4-H_{bu}), 4.38–4.32 (m, 1H; 1a-H_{bu}), 4.23 (dd, $^3J_{5,6b}$=4.7, $^2J_{6a,6b}$=12.3 Hz, 1H; 6b-H), 4.15–4.03 (m, 2H; 1b-H_{bu} ,6a-H), 3.65 (ddd, $^3J_{4,5}$=9.9, $^3J_{5,6a}$=2.4, $^3J_{5,6b}$=4.7 Hz, 1H; 5-H), 3.28 (s, 6H; OCH_3), 2.06 (s, 3H; H_{ac}), 2.01 (s, 3H; H_{ac}), 2.00 (s, 3H; H_{ac}), 1.98 ppm (s, 3H; H_{ac}); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=170.5 (CH_3CO), 170.1 (CH_3CO), 169.3 (CH_3CO), 169.2 (CH_3CO), 130.6 (C_{arom}), 128.4 (C_{arom}), 128.2 (C_{arom}), 127.9 (C_{arom}), 114.2 (C-2_{bu}), 114.1 (C-3_{bu}), 102.9 (C_{acetal}), 99.6 (C-1), 72.8 (C-3), 71.7 (C-5), 71.2 (C-2), 68.8 (C-4_{bu}), 68.3 (C-4), 67.5 (C-1_{bu}), 61.8 (C-6), 52.5 (OCH_3), 20.7 (CH_3CO), 20.6 (CH_3CO), 20.5 (CH_3CO), 20.4 ppm (CH_3CO); HRMS (FAB): m/z: calcd. for $C_{27}H_{37}O_{13}^+$: 569.2229 $[M+H]^+$; found: 569.2157.

(*E*)-4-(4-Dimethoxymethylphenoxy)but-2-enyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (25): The reaction was carried out according to the general procedure A using compound **4α** (388 mg, 1.00 mmol) and compound **21** (1.04 g, 5.00 mmol) with catalyst **23** (63 mg, 0.10 mmol). The product **25** was obtained as a colorless syrup (495 mg, 87%). R_f=0.30 (petroleum/EtOAc, 1:1); $[\alpha]_D^{20}$=+32.6 (c=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=7.29 (d, $^3J_{Ar}$=8.4 Hz, 2H; 1-H_{arom}), 6.95 (d, $^3J_{Ar}$=8.4 Hz, 2H; 2-H_{arom}), 5.95–5.82 (m, 2H; 2-$H_{bu,}$ 3-H_{bu}), 5.30 (dd, $^3J_{3,4}$=9.8, $^3J_{4,5}$=10.0 Hz, 1H; 4-H), 5.28 (s, 1H; H_{acetal}), 5.24 (dd, $^3J_{2,3}$= 2.7, $^3J_{3,4}$=9.8 Hz, 1H; 3-H), 5.28 (s, 1H), 5.19 (dd, $^3J_{1,2}$=1.4, $^3J_{2,3}$=2.7 Hz, 1H; 2-H), 4.80 (d, $^3J_{1,2}$=1.4 Hz, 1H; 1-H), 4.54–4.50 (m, 1H; 1a-H_{bu}), 4.28–4.18 (m, 2H; 1b-H_{bu}, 6-H_a), 4.08–3.98 (m, 3H; 4-H_{bu}, 6-H_a), 3.94 (ddd, $^3J_{4,5}$=10.0, $^3J_{5,6a}$=3.1, $^3J_{5,6b}$=5.6 Hz, 1H; 5-H), 3.24 (s, 6H; OCH_3), 2.09 (s, 3H; H_{ac}), 2.03 (s, 3H; H_{ac}), 1.98 (s, 3H; H_{ac}), 1.93 ppm (s, 3H; H_{ac}); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=170.6 (CH_3CO), 170.0 (CH_3CO), 169.8 (CH_3CO), 169.6 (CH_3CO), 131.9 (C_{arom}), 130.7 (C_{arom}), 129.1 (C_{arom}), 127.9 (C_{arom}), 114.9 (C-2_{bu}), 114.2 (C-3_{bu}), 103.0 (C_{acetal}), 96.7 (C-1), 69.5 (C-2), 69.0 (C-4), 68.6 (C-5), 68.6 (C-1_{bu}), 67.5 (C-4_{bu}), 66.1 (C-3), 62.4 (C-6), 52.6 (OCH_3), 20.8 (CH_3CO), 20.7 (CH_3CO), 20.6 ppm (CH_3CO); HRMS (FAB): calcd. for $C_{27}H_{37}O_{13}^+$: 569.2229 $[M+H]^+$; found: 569.2258.

(*E*)-4-(4-Dimethoxymethylphenoxy)but-2-enyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (26): The reaction was carried out according to general procedure A using compound **5β** (395 mg, 1.02 mmol) and compound **21** (1.18 g, 5.65 mmol) with catalyst **23** (63 mg, 0.10 mmol). The product **26** was obtained as a colorless syrup (435 mg, 75%). R_f=0.32 (petroleum/EtOAc, 1:1); $[\alpha]_D^{20}$=+9.8 (c=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=7.35 (d, $^3J_{Ar}$=8.5 Hz, 2H; 1-H_{arom}), 6.88 (d, $^3J_{Ar}$=8.5 Hz, 2H; 2-H_{arom}), 5.99–5.85 (m, 2H; 2-$H_{bu,}$ 3-H_{bu}), 5.38 (dd, $^3J_{3,4}$=3.9, $^3J_{4,5}$= 0.9 Hz, 1H; 4-H), 5.28 (s, 1H; H_{acetal}), 5.24 (dd, $^3J_{1,2}$=7.9, $^3J_{2,3}$=10.5 Hz, 1H; 2-H), 5.01 (dd, $^3J_{2,3}$=10.5, $^3J_{3,4}$=3.9 Hz, 1H; 3-H), 4.58–4.54 (m, 1H; 1a-H_{bu}), 4.51 (d, $^3J_{1,2}$=7.9 Hz, 1H; 1-H), 4.44–4.36 (m, 1H; 1b-H_{bu}), 4.20–4.08 (m, 4H; 4-H_{bu}, 6-$H_{a,b}$), 3.89 (ddd, $^3J_{4,5}$=0.9, $^3J_{5,6a}$=6.7, $^3J_{5,6b}$=6.8 Hz, 1H; 5-H), 3.30 (s, 6H; OCH_3), 2.09 (s, 3H; H_{ac}), 2.03 (s, 3H; H_{ac}), 1.98 (s, 3H; H_{ac}), 1.93 ppm (s, 3H; H_{ac}); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=170.3 (CH_3CO), 132.0 (C_{arom}), 129.3 (C_{arom}), 128.0 (C_{arom}), 126.9 (C_{arom}), 114.9 (C-2_{bu}), 114.3 (C-3_{bu}), 103.1 (C_{acetal}), 100.4 (C-1), 70.9 (C-3), 70.7 (C-5), 68.8 (C-2), 68.7 (C-1_{bu}), 67.9 (C-4_{bu}), 67.0 (C-4), 61.2 (C-6), 52.7 (OCH_3), 20.8 (CH_3CO), 20.7 (CH_3CO), 20.6 ppm (CH_3CO); HRMS (FAB): calcd. for $C_{27}H_{37}O_{13}^+$: 569.2229 $[M+H]^+$; found: 569.2230.

(*E*)-4-(4-Dimethoxymethylphenoxy)but-2-enyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranoside (27): The reaction was carried out according to general procedure A using compound **6β** (387 mg, 1.00 mmol) and compound **21** (1.04 g, 5.00 mmol) with catalyst **23** (63 mg, 0.10 mmol). The product **27** was obtained as a colorless syrup (494 mg, 81%). R_f=0.10 (petroleum/EtOAc, 1:1); $[\alpha]_D^{20}$=−14.7 (c=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=7.34 (d, $^3J_{Ar}$=8.5 Hz, 2H; 1-H_{arom}), 6.87 (d, $^3J_{Ar}$=8.5 Hz, 2H; 2-H_{arom}), 5.92–5.85 (m, 2H; 2-$H_{bu,}$ 3-H_{bu}), 5.29–5.21 (m, 2H; H_{acetal}, 3-H), 4.97 (dd, $^3J_{3,4}$=10.5, $^3J_{4,5}$=10.5 Hz, 1H; 4-H), 4.80 (d, $^3J_{1,2}$=8.5 Hz, 1H; 1-H), 4.52–4.50 (m, 1H; 1a-H_{bu}), 4.40–4.36 (m, 1H; 1b-H_{bu}), 4.27 (m, 3H; 4-H_{bu}, 6b-H), 4.09 (dd, $^3J_{5,6b}$= 2.4, $^3J_{6a,6b}$=12.2 Hz, 1H; 6a-H), 3.82 (dd, $^3J_{1,2}$=8.5, $^3J_{2,3}$=10.5 Hz, 1H; 2-H), 3.80 (ddd, $^3J_{5,6a}$=5.0, $^3J_{5,6b}$=2.5, $^3J_{6a,6b}$=12.2 Hz, 1H; 5-H), 3.29 (s, 6H; OCH_3), 2.05 (s, 3H; H_{ac}),1.99 (s, 3H; H_{ac}), 1.97 (s, 3H; H_{ac}), 1.88 ppm (s, 3H; H_{ac}); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=170.6 (CH_3CO), 170.3 (CH_3CO), 170.2 (CH_3CO), 169.1 (CH_3CON), 132.0 (C_{arom}), 129.3 (C_{arom}), 128.0 (C_{arom}), 126.9 (C_{arom}), 114.7 (C-2_{bu}), 114.1 (C-3_{bu}), 102.9 (C_{acetal}), 99.4 (C-1), 71.8 (C-3), 71.0 (C-5), 68.8 (C-4), 68.7 (C-1_{bu}), 67.7 (C-4_{bu}), 61.9 (C-6), 53.9 (C-5), 52.6 (OCH_3), 22.7 (CH_3CON), 20.8 (CH_3CO), 20.7 (CH_3CO), 20.6 ppm (CH_3CO); HRMS (FAB): calcd. for $C_{27}H_{38}NO_{12}^+$: 568.2389 $[M+H]^+$; found: 568.2370.

(*E*)-4-(4-Dimethoxymethylphenoxy)but-2-enyl 2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-β-cellobioside (28): The reaction was carried out according to general procedure A using compound **13** (677 mg, 1.00 mmol) and compound **21** (1.67 g, 8.00 mmol) with catalyst **23** (63 mg, 0.10 mmol). The product **28** was obtained as a colorless syrup (394 mg, 46%). R_f=0.25 (petroleum/EtOAc, 1:1); $[\alpha]_D^{20}$=−21.1 (c=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=7.34 (d, $^3J_{Ar}$=8.5 Hz, 2H; 1-H_{arom}), 6.86 (d, $^3J_{Ar}$= 8.5 Hz, 2H; 2-H_{arom}), 5.95–5.85 (m, 2H; 2-H_{bu}, 3-H_{bu}), 5.32 (s, 1H; H_{acetal}), 5.20–5.10 (m, 2H; 3-H, 3′-H), 5.04 (dd, $^3J_{3',4'}$=9.6, $^3J_{4',5'}$=9.8 Hz, 1H; 4′-H), 4.94–4.86 (m, 2H; 2-H, 2′-H), 4.52–4.46 (m, $^3J_{1,2}$=7.6, $^3J_{1',2'}$=7.6 Hz, 5H; 1-H, 1′-H, 6a-H, 4-H_{bu}), 4.35 (dd, $^3J_{5,6a}$=4.3, $^3J_{6a,6b}$=12.3 Hz, 1H; 6b-H), 3.78–3.74 (m, 3H;4-H, 1-HBu), 3.64 (ddd, $^3J_{4',5'}$=9.8 Hz, $^3J_{5',6'a}$=4.2, $^3J_{5',6'b}$=2.2 Hz, 1H; 5′-H), 3.55 (ddd, $^3J_{4,5}$=9.9, $^3J_{5,6a}$=4.3, $^3J_{5,6b}$=1.9 Hz, 1H; 5-H), 3.29 (s, 6H; OCH_3), 2.11 (s, 3H; H_{ac}), 2.07 (s, 3H; H_{ac}), 2.01 (s, 3H; H_{ac}), 2.00 (s, 3H; H_{ac}), 1.99 (s, 3H; H_{ac}), 1.96 ppm (s, 3H; H_{ac}); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=170.4 (CH_3CO), 170.3 (CH_3CO), 170.2 (CH_3CO), 169.8 (CH_3CO), 169.5 (CH_3CO), 169.2 (CH_3CO), 169.0 (CH_3CO), 132.0 (C_{arom}), 129.3 (C_{arom}), 128.0 (C_{arom}), 126.9 (C_{arom}), 114.7 (C-2_{bu}), 114.1 (C-3_{bu}), 103.5 (C_{acetal}), 100.7 (C-1′), 99.3 (C-1′), 76.4 (C-4), 72.9 (C-5), 72.6 (C-3′), 72.5 (C-3), 71.94 (C-5′), 71.6 (C-2′), 71.5 (C-2), 68.3 (C-1_{bu}), 67.7 (C-4′), 67.5 (C-4_{bu}), 61.8 (C-6), 61.5 (C-6′), 20.8 (CH_3CO), 20.7 (CH_3CO), 20.6 (CH_3CO), 20.5 ppm (CH_3CO); HRMS (FAB): calcd. for $C_{39}H_{53}O_{21}^+$: 857.3074 $[M+H]^+$; found: 857.3000.

(*E*)-4-(4-Dimethoxymethylphenoxy)but-2-enyl 2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-β-lactoside (29): The reaction was carried out according to general procedure A using compound **14** (677 mg, 1.00 mmol) and compound **21** (1.67 g, 8.00 mmol) with catalyst **23** (63 mg, 0.10 mmol). The product **29** was obtained as a colorless syrup (446 mg, 52%). R_f=0.27 (petroleum/EtOAc, 1:1); $[\alpha]_D^{20}$=+33.1 (c=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=7.35 (d, $^3J_{Ar}$=8.5 Hz, 2H; 1-H_{arom}), 6.88 (d, $^3J_{Ar}$= 8.5 Hz, 2H; 2-H_{arom}), 5.95–5.80 (m, 2H; 2-$H_{bu,}$ 3-H_{bu}), 5.36–5.33 (m, 2H; 4′-H, H_{acetal}), 5.19 (dd, $^3J_{2,3}$=10.5, $^3J_{3,4}$=9.8 Hz, 1H; 3-H), 4.94–4.86 (m, 2H; 2-H, 2′-H), 5.10 (dd, $^3J_{1',2'}$=7.9, $^3J_{2',3'}$=10.4 Hz, 1H; 2′-H), 4.94–4.86 (m, 2H; 2-H, 3′-H), 4.52–4.46 (m, $^3J_{1,2}$=7.6, $^3J_{1',2'}$=7.6 Hz, 5H; 1-H, 1′-H, 6a-H, 4-H_{bu}), 4.35–4.33 (m, 1H; 1a-H_{bu}), 4.15–4.00 (m, 4H; 1b-H_{bu}, 6b-H, 6′ab-H), 3.87 (ddd, $^3J_{4',5'}$=0.8, $^3J_{5',6'a}$=6.4, $^3J_{5',6'b}$=6.5 Hz, 1H; 5′-H), 3.80 (dd, $^3J_{3,4}$=9.4, $^3J_{4,5}$=9.5 Hz, 1H; 4-H), 3.58 (ddd, $^3J_{5,6a}$=1.9, $^3J_{5,6b}$=4.9, $^3J_{4,5}$=9.5 Hz, 1H; 5-H), 3.31 (s, 6H; OCH_3), 2.16 (s, 3H; H_{ac}), 2.15 (s, 3H; H_{ac}), 2.11 (s, 3H; H_{ac}), 2.05 (s, 3H; H_{ac}), 2.04 (s, 3H; H_{ac}), 2.03 (s, 3H; H_{ac}), 1.96 ppm (s, 3H; H_{ac}); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ= 170.4 (CH_3CO), 170.3 (CH_3CO), 170.2 (CH_3CO), 169.8 (CH_3CO), 169.5 (CH_3CO), 169.2 (CH_3CO), 169.0 (CH_3CO), 132.0 (C_{arom}), 129.3 (C_{arom}), 128.0 (C_{arom}), 126.9 (C_{arom}), 114.7 (C-2_{bu}), 114.1 (C-3_{bu}), 103.0 (C_{acetal}), 101.0 (C-1′), 99.4 (C-1), 76.23 (C-4), 72.8 (C-3), 72.6 (C-5′), 71.6 (C-2), 70.9 (C-3′), 70.6 (C-5″), 69.1 (C-2′), 68.88 (C-1_{bu}), 67.62 (C-4_{bu}), 66.61 (C-4′), 61.9 (C-6), 60.7 (C-6′), 52.6 (OCH_3), 20.8 (CH_3CO), 20.7 (CH_3CO), 20.6 (CH_3CO), 20.5 ppm (CH_3CO); HRMS (FAB): calcd. for $C_{39}H_{53}O_{21}^+$: 857.3074 $[M+H]^+$; found: 857.3052.

(*E*)-4-(4-Dimethoxymethylphenoxy)but-2-enyl 2-acetamido-3,6-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-β-D-glucopyranoside (30): The reaction was carried out according to general procedure A using compound **18** (720 mg, 1.07 mmol) and compound **21** (1.67 g, 8.00 mmol) with catalyst **23** (63 mg, 0.10 mmol). The product **30** was obtained as a colorless solid (110 mg, 12%). R_f=0.21 (EtOAc); m.p. 87°C; $[\alpha]_D^{20}$=−9.4 (c=0.5 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=7.36 (d, $^3J_{Ar}$=8.5 Hz, 2H; 1-H_{arom}), 6.92 (d, $^3J_{Ar}$=8.5 Hz, 2H; 2-H_{arom}),

5.92–5.85 (m, 2H; 2-H_{bu}, 3-H_{bu}), 5.68 (d, $^3J_{NH,2}$ = 6.4 Hz, 1H; NH), 5.31 (s, 1H; H_{acetal}), 5.29–5.20 (m, 2H; 4-H, 3-H), 5.07 (dd, $^3J_{2',3'}$ = 7.6 Hz, 1H; 2′-H), 4.90 (dd, $^3J_{2',3'}$ = 7.6, $^3J_{3',4'}$ = 3.6 Hz, 1H; 3′-H), 4.50–4.40 (m, 3H; 1′-H, 1-H_{bu}), 4.42 (d, $^3J_{1,2}$ = 8.1 Hz, 1H; 1-H), 4.39 (dd, $^3J_{5,6a}$ = 5.7, $^3J_{6a',b}$ = 12.3 Hz, 1H; 6a-H), 4.28–4.12 (m, 3H; 2-H, 4-H_{bu}), 4.05–3.99 (m, 3H; 6b-H, 6a′b′-H), 3.83–3.78 (m, 2H; 5-H, 5′-H), 3.70 (dd, $^3J_{3,5}$ = 9.9, $^3J_{4,54}$ = 9.9 Hz, 1H; 4-H), 2.15 (s, 3H; H_{ac}), 2.14 (s, 3H; H_{ac}), 2.13 (s, 3H; H_{ac}), 2.06 (s, 3H; H_{ac}), 2.05 (s, 3H; H_{ac}), 1.88 ppm (s, 3H; H_{NHAc}); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 170.4 (CH_3CO), 170.3 (CH_3CO), 170.2 (CH_3CO), 169.8 (CH_3CON), 169.5 (CH_3CO), 169.2 (CH_3CO), 169.0 (CH_3CO), 132.0 (C_{arom}), 129.3 (C_{arom}), 128.0 (C_{arom}), 126.9 (C_{arom}), 114.7 (C-2$_{bu}$), 114.1 (C-3$_{bu}$), 103.5 (C_{acetal}), 100.2 (C-1′), 95.2 (C-1), 75.3 (C-4), 70.6 (C-3), 70.00 (C-3′), 69.5 (C-5), 68.3 (C-4$_{bu}$), 68.2 (C-2′), 67.5 (C-4$_{bu}$), 67.2 (C-5′), 65.5 (C-4′), 60.9 (C-6), 59.7 (C-6′), 52.7 (OCH_3), 51.0 (C-2), 20.8 (CH_3CO), 22.8 (CH_3CON), 20.6 (CH_3CO), 20.5 ppm (CH_3CO); HRMS (FAB): calcd. for $C_{39}H_{54}NO_{20}^+$: 856.3234 [M+H]$^+$; found: 856.3239.

4-(4-Formylphenoxy)butyl β-D-glucopyranoside (31): The reaction was carried out according to the general procedure B using compound **24** (500 mg, 879 μmol). The product **31** was obtained as a colorless syrup (285 mg, 91 %). R_f = 0.45 (CH_2Cl_2/MeOH, 5:1); $[\alpha]_D^{20}$ = +42.5 (c = 1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.81 (s, 1H; H_{ald}), 7.84 (d, $^3J_{Ar}$ = 8.8 Hz, 1H; 1-H_{arom}), 7.07 (d, $^3J_{Ar}$ = 8.8 Hz, 1H; 2-H_{arom}), 4.27 (d, $^3J_{1,2}$ = 7.9 Hz, 1H; 1-H), 4.12 (t, $^3J_{3bu,4bu}$ = 6.7 Hz, 2H; 4-H_{bu}), 4.05–3.95 (m, 1H; 1a-H_{bu}), 3.90–3.83 (m, 1H; 1b-H_{bu}), 3.66 (dd, $^3J_{5,6a}$ = 5.03, $^2J_{6a,6b}$ = 12.17 Hz, 1H; 6a-H), 3.40–3.23 (m, 3H; 3-H, 4-H, 6b-H), 3.17 (dd, $^3J_{1,2}$ = 7.9, $^3J_{2,3}$ = 8.9 Hz, 1H; 2-H), 1.96–1.87 (m, 2H; 3-H_{bu}), 1.85–1.75 ppm (m, 2H; 2-H_{bu}); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 192.9 (C_{ald}), 133.1 (C_{arom}), 116.0 (C_{arom}), 104.4 (C-1), 78.1 (C-4), 77.9 (C-5), 75.1 (C-2), 71.7 (C-1$_{bu}$), 70.31 (C-4$_{bu}$), 69.39 (C-3), 62.85 (C-6), 27.2 (C-3$_{bu}$), 26.9 ppm (C-2$_{bu}$); HRMS (FAB): calcd. for $C_{17}H_{25}O_8^+$: 357.1544 [M+H]$^+$; found: 357.1548.

4-(4-Formylphenoxy)butyl α-D-mannopyranoside (32): The reaction was carried out according to general procedure B using compound **25** (400 mg, 704 μmol). The product **32** was obtained as a colorless oil. (230 mg, 92 %). R_f = 0.44 (CH_2Cl_2/MeOH, 5:1); $[\alpha]_D^{20}$ = +10.2 (c = 1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.83 (s, 1H; H_{ald}), 7.86 (d, $^3J_{Ar}$ = 8.7 Hz, 1H; 1-H_{arom}), 7.08 (d, $^3J_{Ar}$ = 8.8 Hz, 1H; 2-H_{arom}), 4.77 (d, $^3J_{1,2}$ = 1.3 Hz, 1H; 1-H), 4.13 (t, $^3J_{3bu,4bu}$ = 6.7 Hz, 2H; 4-H_{bu}), 3.93–3.65 (m, 4H; 6ab-H, 1-H), 3.55–3.46 (m, 4H; 2-H, 3-H, 4-H, 5-H), 1.92–1.85 (m, 2H; 3-H_{bu}), 1.84–1.76 ppm (m, 2H; 2-H_{bu}); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 192.9 (C_{ald}), 129.0 (C_{arom}), 115.1 (C_{arom}), 101.6 (C-1), 74.6 (C-5), 72.7 (C-4), 72.3 (C-2), 68.81 (C-1$_{bu}$), 68.7 (C-3), 68.3 (C-4$_{bu}$), 62.9 (C-6), 27.3 (C-3$_{bu}$), 27.2 ppm (C-2$_{bu}$); HRMS (FAB): calcd. for $C_{17}H_{25}O_8^+$: 357.1544 [M+H]$^+$; found: 357.1539.

4-(4-Formylphenoxy)butyl β-D-galactopyranoside (33): The reaction was carried out according to general procedure B using compound **26** (400 mg, 704 μmol). The product **33** was obtained as a colorless oil (223 mg, 89 %). R_f = 0.45 (CH_2Cl_2/MeOH, 5:1); $[\alpha]_D^{20}$ = - 4.5 (c = 1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.80 (s, 1H; H_{ald}), 7.83 (d, $^3J_{Ar}$ = 8.8 Hz, 1H; 1-H_{arom}), 7.06 (d, $^3J_{Ar}$ = 8.8 Hz, 1H; 2-H_{arom}), 4.22 (d, $^3J_{1,2}$ = 7.4 Hz, 1H; 1-H), 4.11 (t, $^3J_{3bu,4bu}$ = 6.4 Hz, 2H; 4-H_{bu}), 4.02–3.93 (m, 1H; 1a-H_{bu}), 3.82 (dd, $^3J_{3,4}$ = 3.1, $^3J_{4,5}$ = 0.5 Hz, 1H; 4-H), 3.74–3.70 (m, 2H; 6ab-H), 3.65–3.57 (m, 1H; 1a-H_{bu}), 3.53–3.42 (m, 3H; 2-H, 3-H, 5-H), 1.95–1.85 (m, 2H; 3-H_{bu}), 1.82–1.75 ppm (m, 2H; 2-H_{bu}); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 193.0 (C_{ald}), 133.1 (C_{arom}), 116.0 (C_{arom}), 105.0 (C-1), 76.6 (C-3), 75.0 (C-5), 72.6 (C-2), 70.3 (C-4), 70.2 (C-1$_{bu}$), 69.3 (C-4$_{bu}$), 62.5 (C-6), 27.3 (C-3$_{bu}$), 26.9 ppm (C-2$_{bu}$); HRMS (FAB): calcd. for $C_{17}H_{25}O_8^+$: 357.1544 [M+H]$^+$; found: 357.1551.

4-(4-Formylphenoxy)butyl 2-acetamido-2-deoxy-β-D-glucopyranoside (34): The reaction was carried out according to general procedure B using compound **27** (450 mg, 793 μmol). The product **34** was obtained as a colorless syrup (252 mg, 80 %). R_f = 0.21 (CH_2Cl_2/MeOH, 5:1); $[\alpha]_D^{20}$ = −4.5 (c = 1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.80 (s, 1H; H_{ald}), 7.84 (d, $^3J_{Ar}$ = 8.7 Hz, 1H; 1-H_{arom}), 7.10 (d, $^3J_{Ar}$ = 8.8 Hz, 1H; 2-H_{arom}), 4.42 (d, $^3J_{1,2}$ = 8.5 Hz, 1H; 1-H), 4.10 (t, $^3J_{3bu,4bu}$ = 6.7 Hz, 2H; 4-H_{bu}), 3.86 (dd, $^3J_{5,6b}$ = 2.5, $^2J_{6a,6b}$ = 12.3 Hz, 1H; 6a-H), 3.65–3.50 (m, 3H; 6b-H, 1-H_{bu}), 3.32 (dd, $^3J_{1,2}$ = 8.5, $^3J_{2,3}$ = 12.3 Hz, 1H; 2-H), 3.26–3.21 (m, 2H; 3-H, 4-H), 3.23 (ddd, 3$J_{5,6a}$ = 2.5, $^3J_{5,6b}$ = 5.0, $^3J_{4,5}$ = 10.5 Hz, 1H; 5-H), 1.96 (s, 3H; H_{NHAc}), 1.92–1.85 (m, 2H; 3-H_{bu}), 1.84–1.76 ppm (m, 2H; 2-H_{bu}); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 192.9 (C_{ald}), 129.0 (C_{arom}), 115.1 (C_{arom}), 98.5 (C-1), 73.6 (C-4), 73.1 (C-5), 68.2 (C-1$_{bu}$), 68.7 (C-3), 67.3 (C-4$_{bu}$), 62.5 (C-6), 55.3 (C-2), 27.3 (C-3$_{bu}$), 27.2 (C-3$_{bu}$), 22.8 ppm (CH_3CON); HRMS (FAB): calcd. for $C_{19}H_{28}NO_8^+$: 398.1809 [M+H]$^+$; found: 398.1812.

4-(4-Formylphenoxy)butyl β-cellobioside (35): The reaction was carried out according to general procedure B using compound **28** (300 mg, 350 μmol). The product **35** was obtained as a colorless solid (149 mg, 82%). R_f = 0.16 (CH_2Cl_2/MeOH, 5:1); m.p. 120 °C; $[\alpha]_D^{20}$ = +20.4 (c = 1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.80 (s, 1H; H_{ald}), 7.84 (d, $^3J_{Ar}$ = 8.7 Hz, 1H; 1-H_{arom}), 7.10 (d, $^3J_{Ar}$ = 8.8 Hz, 1H; 2-H_{arom}), 4.52 (d, $^3J_{1,2}$ = 7.9 Hz, 1H; 1-H), 4.43 (d, $^3J_{1,2}$ = 7.9 Hz, 1H; 1′-H), 4.20 (t, $^3J_{3bu,4bu}$ = 6.7 Hz, 2H; 4-H_{bu}), 3.86–3.57 (m, 6H; 6-H, 6′-H, 1-H_{bu}), 3.50–3.30 (m, 8H; 2-H, 3-H, 4-H, 5-H, 2′-H, 3′-H, 4′-H, 5′-H), 1.92–1.85 (m, 2H; 3-H_{bu}), 1.84–1.76 ppm (m, 2H; 2-H_{bu}); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 192.9 (C_{ald}), 129.0 (C_{arom}), 115.1 (C_{arom}), 103.4 (C-1′), 102.2 (C-1), 80.7 (C-4), 77.1 (C-3′), 77.0 (C-5′), 75.3 (C-3′), 74.9 (C-5), 73.8 (C-2′), 73.5 (C-2), 70.7 (C-4′), 68.8 (C-1$_{bu}$), 67.6 (C-4$_{bu}$), 66.6 (C-4′), 63.9 (C-6′), 63.0 (C-6), 27.3 (C-2$_{bu}$), 27.2 ppm (C-3$_{bu}$); HRMS (FAB): calcd. for $C_{23}H_{35}O_{13}^+$: 519.2072 [M+H]$^+$; found: 519.2066.

4-(4-Formylphenoxy)butyl β-lactoside (36): The reaction was carried out according to general procedure B using compound **29** (400 mg, 446 μmol). The product **36** was obtained as a colorless solid (206 mg, 85 %). R_f = 0.15 (CH_2Cl_2/MeOH, 5:1); m.p. 114 °C; $[\alpha]_D^{20}$ = +20.4 (c = 1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.81 (s, 1H; H_{ald}), 7.84 (d, $^3J_{Ar}$ = 8.8 Hz, 1H; 1-H_{arom}), 7.11 (d, $^3J_{Ar}$ = 8.8 Hz, 1H; 2-H_{arom}), 4.50 (d, $^3J_{1,2}$ = 8.0 Hz, 1H; 1′-H), 4.42 (d, $^3J_{1,2}$ = 7.7 Hz, 1H; 1-H), 4.17 (t, $^3J_{3bu,4bu}$ = 6.6 Hz, 2H; 4-H_{bu}), 3.95 (dd, $^3J_{5,6a}$ = 1.7, $^2J_{6a,6b}$ = 12.2 Hz, 1H; 6a-H), 3.89 (dd, $^3J_{3',4'}$ = 3.1, $^3J_{4',5'}$ = 0.7 Hz, 1H; 4′-H), 3.78–3.65 (m, 5H; 6-H, 6′ab-H, 1-H_{bu}), 3.52 (dd, $^3J_{3,,4}$ = 8.9, $^3J_{4,5}$ = 9.8 Hz, 4-H), 3.50–3.30 (m, 6H; 2-H, 3-H, 5-H, 2′-H, 3′-H, 5′-H), 1.95–1.86 (m, 2H; 3-H_{bu}), 1.83–1.77 ppm (m, 2H; 2-H_{bu}); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 192.9 (C_{ald}), 129.0 (C_{arom}), 115.1 (C_{arom}), 105.8 (C-1′), 103.9 (C-1), 81.3 (C-4), 78.3 (C-5′), 77.6 (C-5), 77.3 (C-3), 75.9 (C-2), 74.8 (C-3′), 73.6 (C-2′), 70.7 (C-4′), 68.8 (C-1$_{bu}$), 67.6 (C-4$_{bu}$), 66.6 (C-4′), 63.9 (C-6′), 63.0 (C-6), 27.3 (C-2$_{bu}$), 27.2 ppm (C-3$_{bu}$); HRMS (FAB): calcd. for $C_{23}H_{35}O_{13}^+$: 519.2072 [M+H]$^+$; found: 519.2063.

4-(4-Formylphenoxy)butyl 2-acetamido-4-*O*-β-D-galactopyranosyl)-2-deoxy-β-D-glucopyranoside (37): The reaction was carried out according to general procedure B using compound **30** (80 mg, 93 μmol). The product **37** was obtained as a colorless solid (41 mg, 79 %). R_f = 0.25 (CH_2Cl_2/MeOH, 3:1); m.p. 150 °C; $[\alpha]_D^{20}$ = +20.4 (c = 1.0 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.85 (s, 1H; H_{ald}), 7.80 (d, $^3J_{Ar}$ = 8.8 Hz, 1H; 1-H_{arom}), 7.08 (d, $^3J_{Ar}$ = 8.8 Hz, 1H; 2-H_{arom}), 4.60 (d, $^3J_{1',2'}$ = 7.8 Hz, 1H; 1′-H), 4.49 (d, $^3J_{1,,2}$ = 7.8 Hz, 1H; 1-H), 4.12 (t, $^3J_{3bu,4bu}$ = 6.6 Hz, 2H; 4-H_{bu}), 4.02–3.93 (m, 2H; 6a-H, 1a-H_{bu}), 3.94 (dd, $^3J_{3',4'}$ = 3.1, $^3J_{4'5'}$ = 0.6 Hz, 1H; 4′-H), 3.85 (dd, $^3J_{5,6b}$ = 5.5, $^2J_{6a,6b}$ = 12.3 Hz, 1H; 6b-H), 3.80–3.65 (m, 7H; 3-H, 4-H, 2′-H, 3′-H, 5′-H, 6′-H), 3.62–3.60 (m, 2H; 5-H, 1b-H_{bu}), 3.55 (d, $^3J_{1,,2}$ = 7.8, $^3J_{2,,3}$ = 9.9 Hz, 1H; 2-H), 2.05 (s, 3H; H_{NHAc}), 1.95–1.86 (m, 2H; 3-H_{bu}), 1.83–1.77 ppm (m, 2H; 2-H_{bu}); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 193.0 (C_{ald}), 174.5 (CH_3CON), 133.1 (C_{arom}), 116.0 (C_{arom}), 102.8 (C-1′), 100.0 (C-1), 78.4 (C-4), 75.3, 74.7, 72.4, 70.9 (C-3, C-2′, C-3′, C-5′), 70.4 (C-4′), 68.8 (C-1$_{bu}$), 68.5 (C-5), 67.6 (C-4$_{bu}$), 61.0 (C-6), 60.0 (C-6′), 55.0 (C-2), 27.3 (C-2$_{bu}$), 26.9 (C-2$_{bu}$), 22.1 ppm (CH_3CON); HRMS (FAB): calcd. for $C_{25}H_{33}NO_{13}^+$: 560.2338 [M+H]$^+$; found: 560.2330.

Undec-10-enyl triethylene glycol (41): Sodium hydride (217 mg, 9.02 mmol) was added slowly to a solution of triethylene glycol (**39**; 1.33 g, 8.81 mmol) in dry DMF (8 mL). After stirring for 30 min at room temperature the suspension was cooled to 0 °C and a solution of 11-bromoundec-2-ene (**38**; 1.03 g, 4.41 mmol) in dry DMF (4 mL) was added slowly. After warming to room temperature, the mixture was stirred for 12 h. The reaction was quenched with a sat. NH_4Cl solution (10 mL) and then diluted with ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic layers were washed with a sat. NaCl solution and dried over Na_2SO_4. After filtration

the solvents were evaporated and the crude product was purified by column chromatography using silica and dichloromethane/methanol (20:1) as eluent to yield the title compound **39** as a yellowish oil (1.27 g, 4.19 mmol, 95%). R_f=0.43 (CH_2Cl_2/MeOH, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=5.73 (ddt, $^3J_{2,3}$=6.8, $^3J_{cis}$=10.3, $^3J_{trans}$=16.9 Hz, 1H; 2-H); 4.89 (dq, $^4J_{1,3}$=2.0 Hz, $^3J_{trans}$=16.9 Hz, 2H; 1-H), 3.61–3.50 (m, 12H; 12-H, 13-H, 14-H, 15-H, 16-H, 17-H), 3.38 (t, $^3J_{10,11}$=7.1 Hz, 2H; 11-H), 2.60 (brs, 1H; OH), 1.96 (q, $^3J_{2,3}$=6.8 Hz, 2H; 3-H), 1.51 (t, $^3J_{10,11}$=7.1 Hz, 2H; 10-H), 1.28–1.21 ppm (m, 12H; 4-H, 5-H, 6-H, 7-H, 8-H, 9-H); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=139.2 (C-2), 114.1 (C-1), 72.5 (C-16), 71.5 (C-11), 70.6–70.0 (C-12–C-16), 61.7 (C-17), 36.4 (C-3), 33.8–26.0 ppm (C-4–C-10).

Undec-10-enyl hexaethylene glycol (42): Following the procedure used for the synthesis of compound **41**, hexaethylene glycol (**40**; 2.50 g, 8.85 mmol) and sodium hydride (218 mg, 9.10 mmol) were suspended in dry DMF (8 mL) and then 11-bromoundec-2-ene (**38**; 1.05 g, 4.50 mmol) in dry DMF (4 mL) was added. After washing and purification, compound **42** was obtained as a yellowish oil (1.88 g, 4.32 mmol, 96%). R_f= 0.56 (CH_2Cl_2/MeOH, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=5.80 (ddt, $^3J_{2,3}$=6.8, $^3J_{cis}$=10.3, $^3J_{trans}$=16.9 Hz, 1H; 2-H), 4.95 (dq, $^4J_{1,3}$= 2.0 Hz, $^3J_{trans}$=16.9 Hz, 2H; 1-H), 3.68–3.56 (m, 24H; 12-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H, 20-H, 21-H, 22-H, 23-H), 3.44 (t, $^3J_{10,11}$= 6.8 Hz, 2H; 11-H), 2.60 (brs, 1H; OH), 2.02 (m, 2H; 3-H), 1.56 (t, $^3J_{10,11}$=6.8 Hz, 2H; 10-H), 1.33–1.22 ppm (m, 12H; 4-H, 5-H, 6-H, 7-H, 8-H, 9-H); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=139.2 (C-2), 114.9 (C-1), 72.5 (C-22), 71.5 (C-11), 71.5–70.0 (C-3, C-12–C-20), 61.7 (C-23), 36.4 (C-10), 33.8–26.0 9 (C-3–C-11).

11-Thioacetylundecyl triethylene glycol (43): Thioacetic acid (740 μL, 10.4 mmol) and AIBN (450 mg, 2.74 mmol) were added to a stirred solution of alkene **41** (1.05 g, 3.47 mmol) in abs. THF (20 mL) and the mixture was irradiated with UV light for 3 h at room temperature. The solvents were evaporated and the yellow crude product was purified by chromatography with a CH_2Cl_2/methanol gradient (20:1 → 18:1) to yield a colorless oil (1.31 g, quant.). R_f=0.40 (CH_2Cl_2/MeOH, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=3.66 (m, 2H; 17-H), 3.61–3.51 (m, 10H; 12-H, 13-H, 14-H, 15-H, 16-H), 3.38 (t, $^3J_{10,11}$=6.8 Hz, 2H; 11-H), 2.79 (t, $^3J_{1,2}$=7.3 Hz, 2H; 1-H), 2.45 (m, 2H; 16-H), 2.25 (s, 3H; OSCCH$_3$), 1.49 (m, 2H; 8-H), 1.25–1.16 ppm (m, 12H; 9-H, 10-H, 11-H, 12-H, 13-H, 14-H); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=196.1 (OS*C*CH$_3$), 70.0- 72.5 (C-11, C-12, C-13, C-14, C-15, C-16), 61.8 (C-17), 30.6 (C-1), 26.0–29.5 ppm (C-2, C-3, C-4, C-5, C-6, C-7, C-8, C-9, C-10).

11-Thioacetylundecyl hexaethylene glycol (44): Following the procedure used for the synthesis of compound **43**, alkene **42** (1.56 g, 3.59 mmol), thioacetic acid (770 μL, 10.8 mmol), and AIBN (470 mg, 2.87 mmol) were allowed to react in THF (20 mL) to yield a colorless oil (1.83 g, quant.). R_f=0.35 (CH_2Cl_2/MeOH, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ= 3.71–3.69 (m, 2H; 23-H), 3.66–3.52 (m, 22H; 12-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H, 20-H, 21-H, 22-H), 3.42 (t, ^3J=6.8 Hz, 1H; 11-H), 2.83 (t, $^3J_{1,2}$=7.4 Hz, 2H; 1-H), 2.30 (s, 3H; OSCCH$_3$), 1.53 (m, 4H; 2-H, 10-H), 1.33–1.23 ppm (m, 14H; 3-H, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=196.1 (OS*C*CH$_3$), 70.0–72.5 (C-11, C-12, C-13, C-14, C-15, C-16, C-17, C-18, C-19, C-20, C-21, C-22), 61.8 (C-23), 30.6 (CH$_3$), 29.5–26.5 ppm (C-1, C-2, C-3, C-4, C-5, C-6, C-7, C-8, C-9, C-10).

***O*-(4′-Chlorobutyl)-(ω-undec-10-enyl) hexaethylene glycol (46)**: Alcohol **42** (632 mg, 1.45 mmol) was dissolved in dry DMF (15 mL) and cooled to 0°C. A suspension of sodium hydride (68 mg, 1.68 mmol) in DMF (5 mL) was added slowly to the solution. After stirring for 30 min a solution of 1-bromo-4-chlorobutane (**45**; 1.75 mL, 15.2 mmol) in dry DMF (15 mL) was added dropwise. The reaction mixture was maintained at 0°C for 2 h, then allowed to warm to room temperature, and stirred for 15 h. After quenching the reaction with a sat. NH_4Cl solution (5 mL) the mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica using CH_2Cl_2/methanol (30:1) as eluent to yield a colorless oil (594 mg, 78%). R_f=0.68 (CH_2Cl_2/MeOH, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=5.80 (ddt, $^3J_{2,3}$=6.8, $^3J_{cis\ 2}$=10.2, $^3J_{,trans}$= 16.9 Hz, 1H; 2-H), 5.00–4.91 (m, 2H; 1-H), 3.64–3.42 (m, 26H; 12-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H, 20-H, 21-H, 22-H, 23-H, 4′-H), 2.03–2.00 (m, 2H; 3-H), 1.84–1.80 (m, 1H; 3′-H), 1.73–1.71 (m, 2H; 2′-H), 1.58–1.55 (m, 2H; 10-H), 1.36–1.27 ppm (m, 16H; 4-H, 5-H, 6-H, 7-H, 8-H, 9-H, 11-H, 1′-H); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=139.5 (C-2), 114.4 (C-1), 77.3–69.2 (C-11, C-12, C-13, C-14, C-15, C-16, C-17, C-18, C-19, C-20, C-21, C-22, C-23, C-1′), 45.2 (C-4′), 34.1–26.4 ppm (C-3, C-4, C-5, C-6, C-7, C-8, C-9, C-10, C-2′, C-3′).

***O*-(4′-Azidobutyl)-(ω-undec-10-enyl) hexaethylene glycol (47)**: The chloride **46** (500 mg, 952 μmol), sodium azide (250 mg, 3.80 mmol), and tetrabutylammonium iodide (175 mg, 476 μmol) were dissolved in abs. DMF (20 mL) and were heated at 70°C for 2 h with stirring. Then the solvents were removed under reduced pressure and the crude material was purified by flash chromatography on silica using petroleum/ethyl acetate (1:1). The title compound **47** was obtained as a colorless oil (415 mg, 82%). R_f=0.68 (CH_2Cl_2/MeOH, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=5.80 (ddt, $^3J_{2,3}$=6.8, $^3J_{cis\ 2}$=10.2, $^3J_{,trans}$=16.9 Hz, 1H; 2-H), 5.01–4.92 (m, 2H; 1-H), 3.64–3.42 (m, 26H; 12-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H, 20-H, 21-H, 22-H, 23-H, 1′-H), 3.39 (t, $^3J_{1,2}$=5.8 Hz, 2H; 4′-H), 2.03–2.00 (m, 2H; 3-H), 1.73–1.71 (m, 2H; 2′-H),1.62–1.60 (m, 2H; 3′-H), 1.58–1.55 (m, 2H; 10-H), 1.36–1.27 ppm (m, 12H; 4-H, 5-H, 6-H, 7-H, 8-H, 9-H); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=139.9 (C-2), 114.0 (C-1), 77.3–69.2 (C-11, C-12, C-13, C-14, C-15, C-16, C-17, C-18, C-19, C-20, C-21, C-22, C-23, C-1′), 51.2 (C-4′), 34.1–26.4 ppm (C-3, C-4, C-5, C-6, C-7, C-8, C-9, C-10, C-2′, C-3′).

***O*-(4′-Azidobutyl)-(ω-11-thioacetylundecyl) hexaethylene glycol (48)**: Following the procedure used for the synthesis of compound **43**, compound **47** (400 mg, 752 μmol), thioacetic acid (160 μL, 2.26 mmol), and AIBN (100 mg, 600 μmol) were allowed to react in THF (15 mL) to yield a colorless oil (434 mg, 95%). R_f=0.52 (CH_2Cl_2/MeOH, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=3.64–3.45 (m, 26H; 12-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H, 20-H, 21-H, 22-H, 23-H, 1′-H), 3.40 (t, $^3J_{1,2}$= 7.4 Hz, 2H; 11-H), 3.39 (t, $^3J_{1,2}$=5.8 Hz, 2H; 4′-H), 2.85 (t, $^3J_{1,2}$=7.4 Hz, 2H; 1-H), 2.67–2.65 (m, 2H; 2-H), 1.73–1.70 (m, 2H; 2′-H), 1.62–1.60 (m, 2H; 3′-H), 1.58–1.55 (m, 2H; 10-H), 1.36–1.27 ppm (m, 14H; 3-H, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=77.3–69.2 (C-11, C-12, C-13, C-14, C-15, C-16, C-17, C-18, C-19, C-20, C-21, C-22, C-23, C-1′), 51.2 (C-4′), 34.1–26.4 ppm (C-1, C-2, C-3, C-4, C-5, C-6, C-7, C-8, C-9, C-10, C-2′, C-3′, CH$_3$); MS (MALDI-TOF): *m*/*z*: calcd for $C_{29}H_{57}N_3O_8S$: 607.39 $[M+Na]^+$; found: 630.9.

***O*-(4′-Aminobutyl)-(ω-11-mercaptoundecyl) hexaethylene glycol (49)**: A suspension of lithium aluminum hydride (105 mg, 2.76 mmol) in dry THF (10 mL) was cooled to 0°C. Then a solution of compound **47** (420 mg, 691 μmol) in dry THF (5 mL) was added slowly. The reaction was allowed to warm to room temperature and stirred for 3 h and then quenched by adding water (5 mL). The suspension was filtered and the residue extracted by THF (100 mL). The combined organic layers were evaporated under reduced pressure and the crude product was purified by chromatography with a CH_2Cl_2/methanol gradient (20:1 → 18:1) to yield a pale-yellow oil (239 mg, 64%). R_f=0.33 (CH_2Cl_2/MeOH, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=3.64–3.45 (m, 26H; 12-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H, 20-H, 21-H, 22-H, 23-H, 1′-H), 3.40 (t, $^3J_{1,2}$=7.4 Hz, 2H; 11-H), 3.39 (t, $^3J_{1,2}$=5.8 Hz, 2H; 4′-H), 2.85 (t, $^3J_{1,2}$= 7.4 Hz, 2H; 1-H), 2.66–2.63 (m, 2H; 2-H), 1.73–1.70 (m, 2H; 2′-H), 1.62–1.60 (m, 4H; 2-H, 3′-H), 1.58–1.55 (m, 2H; 10-H), 1.36–1.27 ppm (m, 14H; 3-H, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ=77.3–69.2 (C-11, C-12, C-13, C-14, C-15, C-16, C-17, C-18, C-19, C-20, C-21, C-22, C-23, C-1′), 42.3 (C-4′), 39.4 (C-1), 34.1–26.4 ppm (C-2, C-3, C-4, C-5, C-6, C-7, C-8, C-9, C-10, C-2′, C-3′); HRMS (FAB): *m*/*z*: calcd. for $C_{27}H_{57}NO_7S$: 539.3856 $[M-Na]^+$; found: 562.3802.

***O*-Tosyl-(ω-undec-10-enyl) hexaethylene glycol (50)**: A stirred solution of the alcohol **42** (2.01 g, 4.62 mmol) in dry pyridine (20 mL) was cooled to 0°C and then tosyl chloride (1.76 g, 9.24 mmol) was added portionwise. The mixture was warmed to room temperature, stirred for 15 h, and then concentrated. The crude product was purified by column chromatography using silica and a petroleum/ethyl acetate gradient (1:1 → 1:2). The product **51** was obtained as a pale-yellow oil (2.50 g, 92%). R_f=0.60 (CH_2Cl_2/MeOH, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ=7.79 (d, $^3J_{Ar}$=8.4 Hz, 2H; 1-H$_{arom}$), 7.39 (d, $^3J_{Ar}$=8.4 Hz, 2H; 2-H$_{arom}$), 5.80 (ddt, $^3J_{2,3}$=6.8, $^3J_{cis}$=10.0, $^3J_{trans}$=16.8, 1H; 2-H), 5.00–4.91 (m, 2H; 1-H), 4.15

(t, $^3J_{H22,23}$ = 4.8 Hz, 2H; 23-H), 3.69–3.56 (m, 22H; 12-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H, 20-H, 21-H, 22-H), 3.44 (t, $^3J_{H11,10}$ = 6.8 Hz, 2H; 11-H), 2.44 (s, 3H; Ar-CH_3), 2.03 (q, 2H; 3-H), 1.58–1.53 (m, 2H; 10-H), 1.36–1.27 ppm (m, 12H; 4-H, 5-H, 6-H, 7-H, 8-H, 9-H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 144.7 (C-1$_{arom}$), 139.2 (C-2), 132.9 (C-2$_{arom}$), 129.8 (C-2$_{arom}$), 127.9 (C-2$_{arom}$), 114.1 (C-1), 71.5 (C-22), 70.5–70.0 (C-13, C-14, C-15, C-16, C-17, C-18, C-19, C-20, C-21), 69.7 (C-23), 69.2 (C-12), 68.6 (C-11), 33.7 (C-3), 29.1–26.0 (C-4, C-5, C-6, C-7, C-8, C-9, C-10), 21.6 ppm (CH_3); MS (MALDI-TOF): *m*/*z*: calcd for $C_{30}H_{52}O_9S$: 588.33 $[M+Na]^+$; found: 611.5.

Azido-(ω-undec-10-enyl) hexaethylene glycol (51): The tosylate **50** (2.05 g, 3.48 mmol), sodium azide (905 mg, 13.9 mmol), and tetrabutylammonium iodide (642 mg, 1.74 mmol) were dissolved in abs. DMF (40 mL) and the mixture was heated at 70 °C for 2 h with stirring. Then the solvents were removed under reduced pressure and the crude material was purified by flash chromatography on silica using petroleum/ ethyl acetate (1:1) as eluent. The title compound **51** was obtained as a colorless oil (1.36 g, 85 %). R_f = 0.41 (CH_2Cl_2/MeOH, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.80 (ddt, $^3J_{2,3}$ = 6.8, $^3J_{cis}$ = 10.3, $^3J_{trans}$ = 17.1, 1H; 2-H), 4.98 (ddt, $^4J_{1,3a}$ = 1.6, $^4J_{1,3b}$ = 2.2, $^3J_{trans}$ = 17.1 Hz, 1H; 1a-H), 4.98 (ddt, $^4J_{1,3a}$ = 1.1, $^4J_{1,3b}$ = 2.0, $^3J_{trans}$ = 10.3 Hz, 1H; 1a-H), 3.69–3.62 (m, 22H; 12-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H, 20-H, 21-H, 22-H), 3.44 (t, $^3J_{H11,10}$ = 6.8 Hz, 2H; 11-H), 3.38 (t, $^3J_{22,\ 23}$ = 5.1 Hz, 2H; 23-H), 2.05–2.05 (m, 2H; 3-H), 1.58–1.53 (m, 2H; 10-H), 1.36–1.27 ppm (m, 12H; 4-H, 5-H, 6-H, 7-H, 8-H, 9-H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 139.3 (C-2), 114.0 (C-1), 71.5 (C-11), 70.5–70.0 (C-13, C-14, C-15, C-16, C-17, C-18, C-19, C-20, C-21, C-22), 50.6 (C-23), 33.7 (C-3), 29.1–26.0 ppm (C-4, C-5, C-6, C-7, C-8, C-9, C-10); MS (MALDI-TOF): *m*/*z*: calcd for $C_{23}H_{45}N_3O_6$: 459.33 $[M+Na]^+$; found: 482.6.

Azido-(ω-11-thioacetylundecyl) hexaethylene glycol (52): Following the procedure used for the synthesis of compound **43**, compound **51** (1.10 g, 2.39 mmol), thioacetic acid (510 μL, 7.17 mmol), and AIBN (314 mg, 1.91 mmol) were allowed to react in THF (15 mL) to yield a colorless oil (1.22 g, 96 %). R_f = 0.38 (CH_2Cl_2/MeOH, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.69–3.66 (m, 20H; 12-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H, 20-H, 21-H), 3.57–3.55 (m, 2H; 22-H), 3.43 (t, $^3J_{10,11}$ = 6.8 Hz, 2H; 11-H), 3.38 (t, $^3J_{22,23}$ = 5.0 Hz, 2H; 23-H), 2.85 (t, $^3J_{1,2}$ = 7.4 Hz, 2H; 1-H), 2.31 (s, 3H; OSCCH_3), 1.53–1.51 (m, 4H; 2-H, 10-H), 1.33–1.23 ppm (m, 14H; 3-H, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 196.0 (OS*C*CH$_3$), 72.5–70.1 (C-11, C-12, C-13, C-14, C-15, C-16, C-17, C-18, C-19, C-20, C-21, C-22), 50.6 (C-23), 30.6 (CH_3), 29.5–26.5 ppm (C-1, C-2, C-3, C-4, C-5, C-6, C-7, C-8, C-9, C-10); MS (MALDI-TOF): *m*/*z*: calcd for $C_{25}H_{49}N_3O_7S$: 535.33 $[M+Na]^+$; found: 558.9.

Amino-(ω-11-mercaptoundecyl) hexaethylene glycol (53): Following the procedure used for the synthesis of compound **49**, compound **52** (850 mg, 1.59 mmol) and lithium aluminum hydride (241 mg, 6.36 mmol) were allowed to react in THF (30 mL) to yield a colorless oil (491 mg, 66 %). R_f = 0.32 (CH_2Cl_2/MeOH, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.69–3.66 (m, 20H; 12-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H, 20-H, 21-H), 3.57–3.55 (m, 2H; 22-H), 3.40 (t, $^3J_{10,11}$ = 6.8 Hz, 2H; 11-H), 2.80 (t, $^3J_{22,23}$ = 6.2 Hz, 2H; 23-H), 2.65 (t, $^3J_{1,2}$ = 7.4 Hz, 2H; 1-H), 1.51–1.49 (m, 2H; 10-H), 1.33–1.23 ppm (m, 16H; 2-H, 3-H, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 72.5–70.1 (C-11, C-12, C-13, C-14, C-15, C-16, C-17, C-18, C-19, C-20, C-21, C-22), 41.8 (C-23), 29.5–26.5 ppm (C-1, C-2, C-3, C-4, C-5, C-6, C-7, C-8, C-9, C-10); HRMS (FAB): *m*/*z*: calcd. for $C_{23}H_{49}NO_6S$: 467.3281 $[M-Na]^+$; found: 490.3155.

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