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Synthesis of novel amphiphilic conjugates with a biological recognition function for developing targeted triggered liposomal delivery systems

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ABSTRACT

Several novel amphiphilic lipid derivatives were synthesized consisting of a lipid anchor connected to the hydrophilic moiety via a disulfide or glycoside bond and biotin linked to the hydrophilic part. Disulfide bonds were established by the help of 4-phenyltriazol-3,5-dione. Dansyl or fluorescein was covalently linked as fluorescent marker to some of the conjugates, allowing spectroscopic and microscopic detection. The conjugates represent first amphiphilic lipids carrying all four functions, i.e., lipophilic, hydrophilic, recognition, and disulfide cleavage group in one molecule, which are necessary for targeted, triggered drug delivery from phospholipid liposomes on demand.

1. Introduction

Targeted and triggered delivery of drugs in nano- and micro-containers is in the focus of contemporary medical and biomedical research.[1,2] It allows increasing stability of drugs in vivo by encapsulation in the carrier thus reducing systemic and local adverse drugs reactions. Furthermore, multiple drugs can be delivered in one carrier, the solubility in body fluids can be improved, and drugs can be efficiently shielded from multidrug resistance transporters in cancer cells. Amongst the various nano- and micro-containers applied, liposomes have attracted great interest because they are formed from biocompatible materials, namely essentially from phospho-, glycolipids, and sterols.[3,4] Also modified lipids were used for this purpose.[5–8]

Release of cargo from liposomes can be spontaneous or can be triggered by external factors, e.g., hyperthermia, irradiation, or by internal, i.e. (intra)cellular factors, e.g., by disassembly of the supramolecular carriers due to enzymatic cleavage of conjugates and pH changes.[5,8,9] These factors can cause instabilities or structural changes, for example, phospholipases are hydrolyzing phospholipids of liposomes to lipophilic chains and hydrophilic groups. While the latter redistributes into the aqueous environment, lipophilic chains remain in the membrane disturbing the supramolecular arrangement, e.g., by inducing hexagonal phase formation.[4,10] This rearrangement leads to cargo release, e.g., drug delivery, from the liposomes.

In continuation of our research activities in anchoring of nucleolipids in biocompatible phospholipid membranes,[11–16] we have approached amphiphilic lipids with the potential of triggering drug release from liposomes by reductive disulfide and enzymatic glucose cleavage.[17] Unlike previously known redox-cleavable disulfide systems,[9] these conjugates bear an additional biological targeting function linked to the hydrophilic moiety. The latter is connected to the lipophilic entity by a disulfide moiety and, hence, can be disconnected on demand by chemical means (Fig. 1). For fluorescence spectroscopy and microscopy imaging, the hydrophilic moieties can additionally be labeled with a fluorescence dye.

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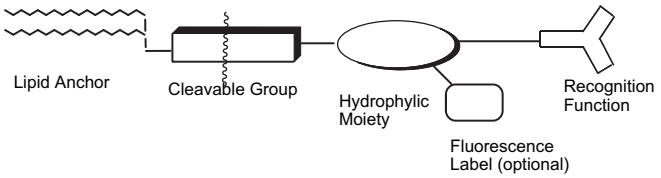


Fig. 1. Amphiphilic lipids with biological recognition function, a cleavable linker group and an optional fluorescence label useful for incorporation into liposomes.

2. Results and discussion

There is a variety of components, which can be used to establish amphiphilic lipid conjugates. We report here on the synthesis of conjugates wherein a disulfide or glucose moiety serves as a cleavable group and biotin as the recognition function. As a hydrophilic moiety we used either an oligoethylenglycol-thiocholine skeleton or a glucose unit, the latter acting as the cleavable group at the same time. Since two lipid chains are optimal for stable anchoring in phospholipid membranes, we chose a glycerol or thioglycerol unit with two octadecyl ether groups as lipid anchors. Although several compounds with disulfide or glucose moieties as cleavable groups have been already studied for drug delivery from liposomes, nevertheless, a targeting recognition function was missing in those cases.[18] For this purpose, we have introduced a biotin moiety. This allows a flexible attachment of receptors/ligands, e.g., antibodies, via streptavidin, and, hence, adaptation to the specific target cell.

It was our strategy to establish the disulfide unit early in the synthetic scheme because this reaction often gives low yields. Numerous methods for disulfide formation from two thiols are known.[19] Many of them, however, are not suitable for establishing unsymmetrical disulfides at all or are leading to the formation of symmetric and unsymmetrical disulfides mixtures. After checking several methods, we decided to apply phenyltriazolin-3,5-dione (PTAD) for establishing the disulfide moiety. Using this reagent it was possible to synthesize the unsymmetrical disulfides **4**, **8**, **11**, and **32** in yields higher than 60%. Although symmetric disulfides were also formed, they could be completely removed by column chromatography.

The conjugate **5** with a diethylenglycol-thiocholine moiety as hydrophilic group was obtained in only three steps starting from the known triethylenglycol tosylate **1** (Scheme 1). The thiocholine-derived disulfide **4** was quaternized by the biotinylated triethylenglycol tosylate **2** leading directly to the conjugate **5** in 39% yield in the final step.

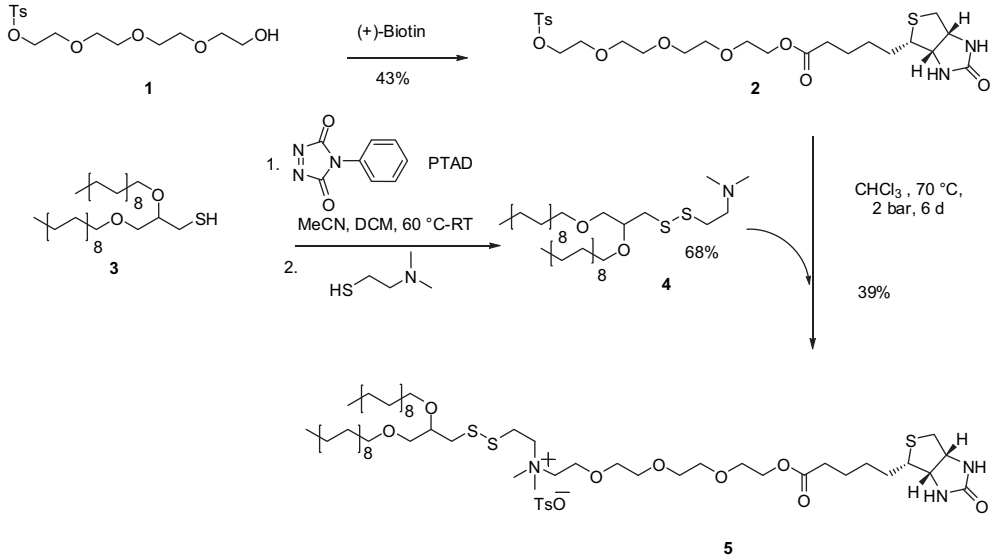
A different strategy was used for the ammonium conjugate **9** (Scheme 2). Here, a quaternary ammonium unit was built up by alkylation of *N*′-biotinylated *N*,*N*-dimethyl-1,2-diaminoethane **6** with bromoacetic acid in an earlier step. The resulting glycine derivative **7** was connected with the disulfide **8** by final amide formation to give pure conjugate **9** in 22% yield after column chromatography.

Linkage of a quaternary ammonium unit to the disulfide by amide formation was also used to synthesize conjugate **14** (Scheme 3). In this product the lipophilic part, quaternary ammonium group and the biotin as recognition function were not arranged in linear, but in a branched structure. The disulfide **11** derived from 2-amino-3-mercaptopropan-1-ol **10** was acylated by the known succinate **12**. Esterification of the untouched hydroxy group of the resulting amide **13** by biotin gave the conjugate **14**, which was isolated in 35% yield using column chromatography.

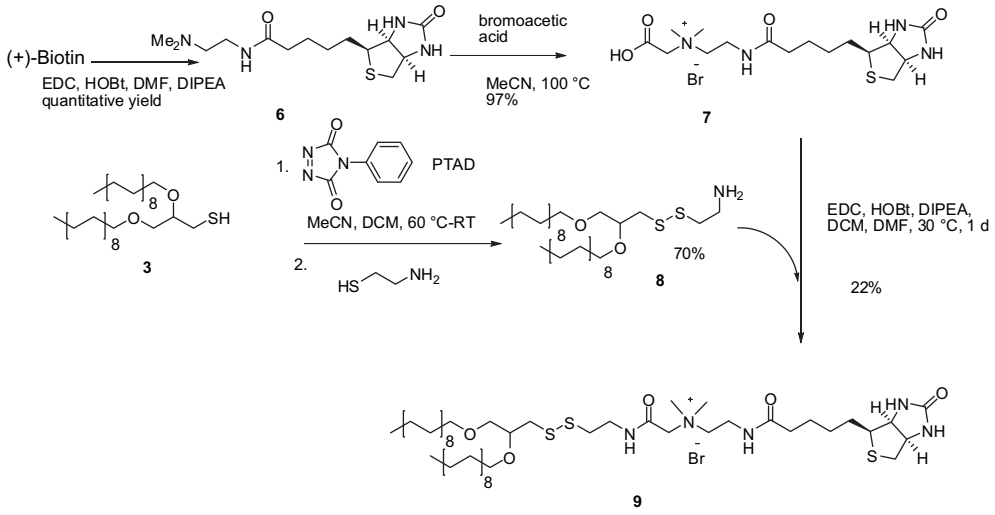
Approaching the synthesis of amphiphilic biotin conjugates containing an additional fluorescent label, the serine derivative **16** was biotinylated at the hydroxy group affording **17**. Selective cleavage of the methyl ester without touching the biotin ester was possible in good yields by trimethylstannanol. The resulting acid **18** was esterified with triethylene glycol monotosylate **1** in the presence of *N*,*N*-dicyclohexylcarbodiimide leading to the tosylate **19** in 33% yield. The latter was used as an alkylating reagent for the thiocholine-derived disulfide **4** to provide the dansyl-labeled amphiphilic biotin conjugate **20** in 50% yield after chromatography.

Further we sought to synthesize a dansyl-labeled conjugate, wherein biotin is situated not at the end of the linker but more in the middle. Here we started with *S*,*O*-diprotected 2-amino-3-mercaptopropan-1-ol derivative **23**, which was obtained from the corresponding hydroxy compound **21** by Mitsunobu reaction in two steps. Biotinylation gave quantitative yields of the amide **24**, which was then *S*-deprotected by treatment with sodium in liquid ammonia to give the thiol **25** in 55% yield. The mixed disulfide **26** with 2,3-dioctadecyloxypropan-1-thiol **3** was again obtained with PTAD in 38% yield. After deprotection the resulting alcohol **27** was esterified with the succinate **29** containing the hydrophilic choline unit and the dansyl group to give the final product **30** in comparatively high yield (55%).

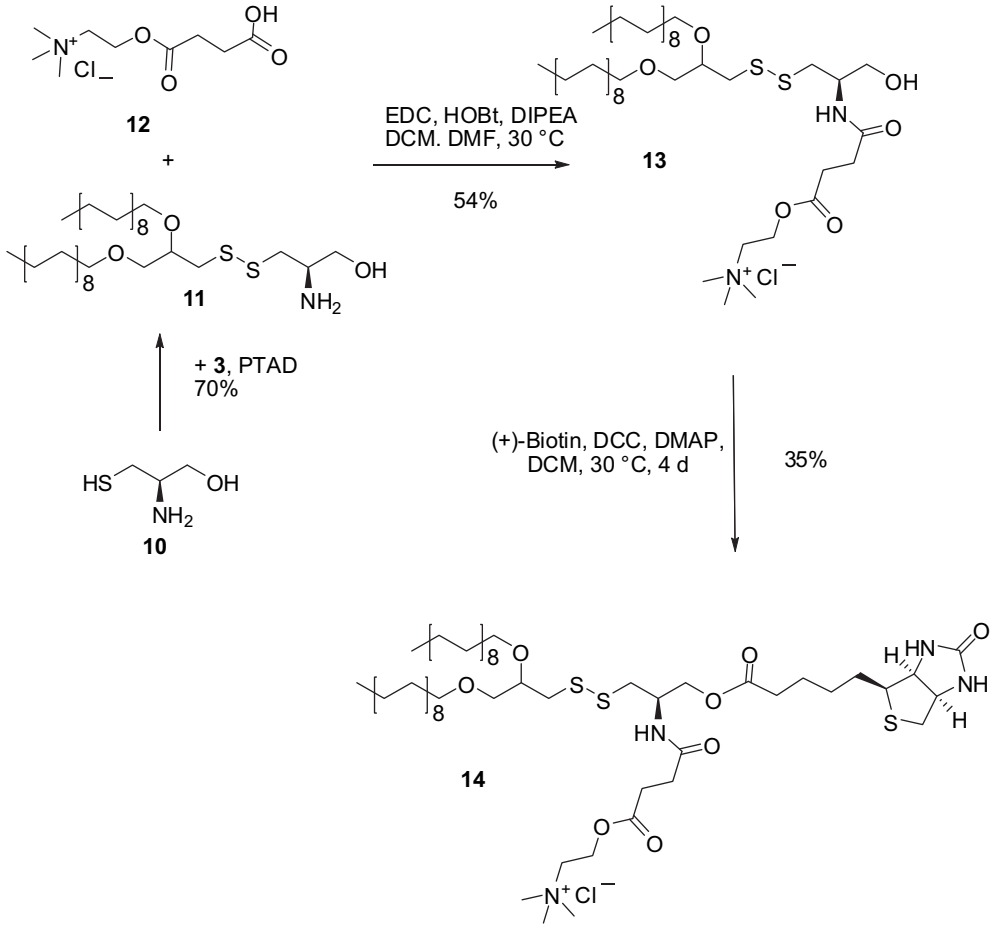
In a similar strategy, the synthesis of the fluorescein-labeled amphiphilic biotin conjugate **35** was followed up. As compared with the previous dansyl derivative **30** the hydrophilic character



Scheme 1. Synthesis of oligoethylene glycol conjugate **5**.



Scheme 2. Synthesis of glycine amide conjugate **9**.

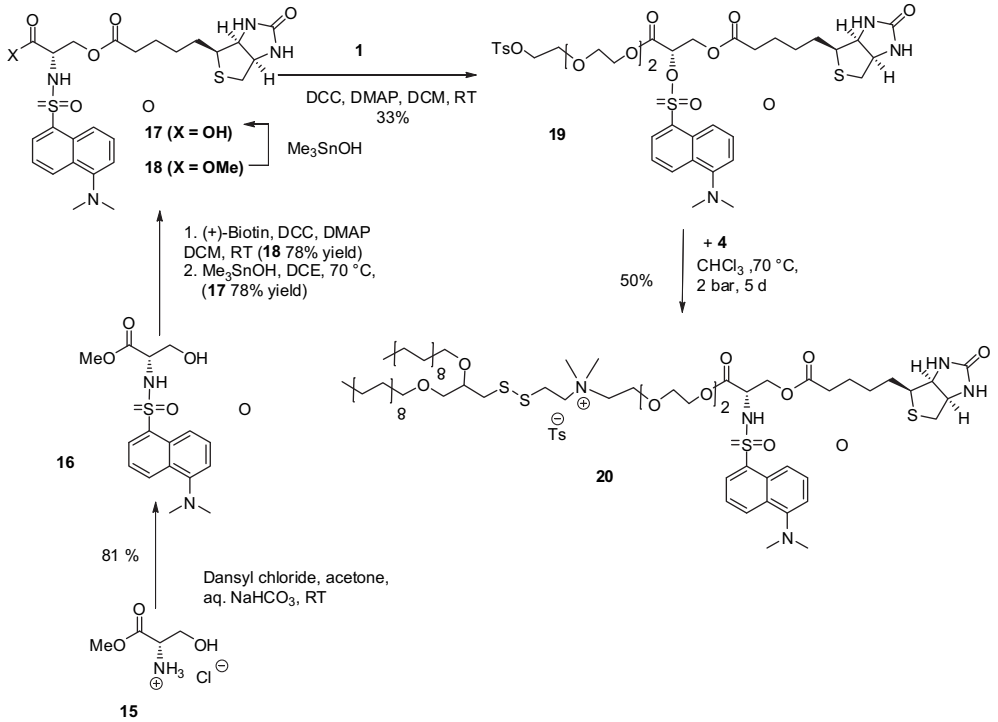


Scheme 3. Synthesis of conjugate **14** (hydrophilic group in the side chain).

was reduced in this target molecule because of the missing ammonium moiety. The thioglycerol-derived disulfide **31** was selectively biotinylated at the terminal hydroxy group in the presence of DCC providing 43% yield of the pure product **32** after 3 days reaction time. Esterification of the remaining hydroxy group with the succinated fluorescein **34** provided 52% of the final product **35**.

Finally, we designed a biotin conjugate **42** with a carbohydrate serving as the hydrophilic part and the cleavable group again by using the dioctadecylglyceryl unit as a lipid anchor. This synthesis (Scheme 7) started with peracetylated 2-bromoglucose, which was transformed into the amphiphilic glucoside **38** by Königs–Knorr method. After deprotection with sodium methoxide in methanol, the resulting glucose derivative **39** was transformed into the 6-aminoglucose derivative **41** by selective 6-tosylation (formation of **40**) and amination with liquid ammonia. The 6-aminogroup was biotinylated under EDC-activation providing the final product **42** in 61% yield.

If not otherwise mentioned, all compounds reported in Schemes 1–7 are new. Their structures were confirmed by NMR spectroscopy and HRMS. As it is typical for amphiphilic compounds, their purification was often not trivial and required repeated column chromatography.



Scheme 4. Synthesis of dansyl-labeled conjugate **20**.

3. Conclusion

Seven novel amphiphilic biotin conjugates were developed consisting of a dioctadecylglycerol-derived unit as a lipophilic part and different hydrophilic moieties by either disulfide or glycoside linkage. Three of them contain in addition a fluorescence marker linked to the hydrophilic site. The conjugates represent the first examples, in which all four functions (lipophilic, hydrophilic, recognition, disulfide or glucose cleavable group) are combined. Examples reported so far lack either a recognition function or a cleavable group. Our novel conjugates are designed for building liposomes filled with cargo and directing these liposomes to a biological/pharmacological target where the disulfide or glycoside would be cleaved. The cleavage will result in the separation of the hydrophilic part of the conjugates into the surrounding. As the remaining lipophilic structure adopts an inverted cone shape perturbing the stable bilayer arrangement of the membrane, defects in and/or reorganization of the liposomes are induced, leading to a release of the entrapped drug. The results of these investigations will be published elsewhere.

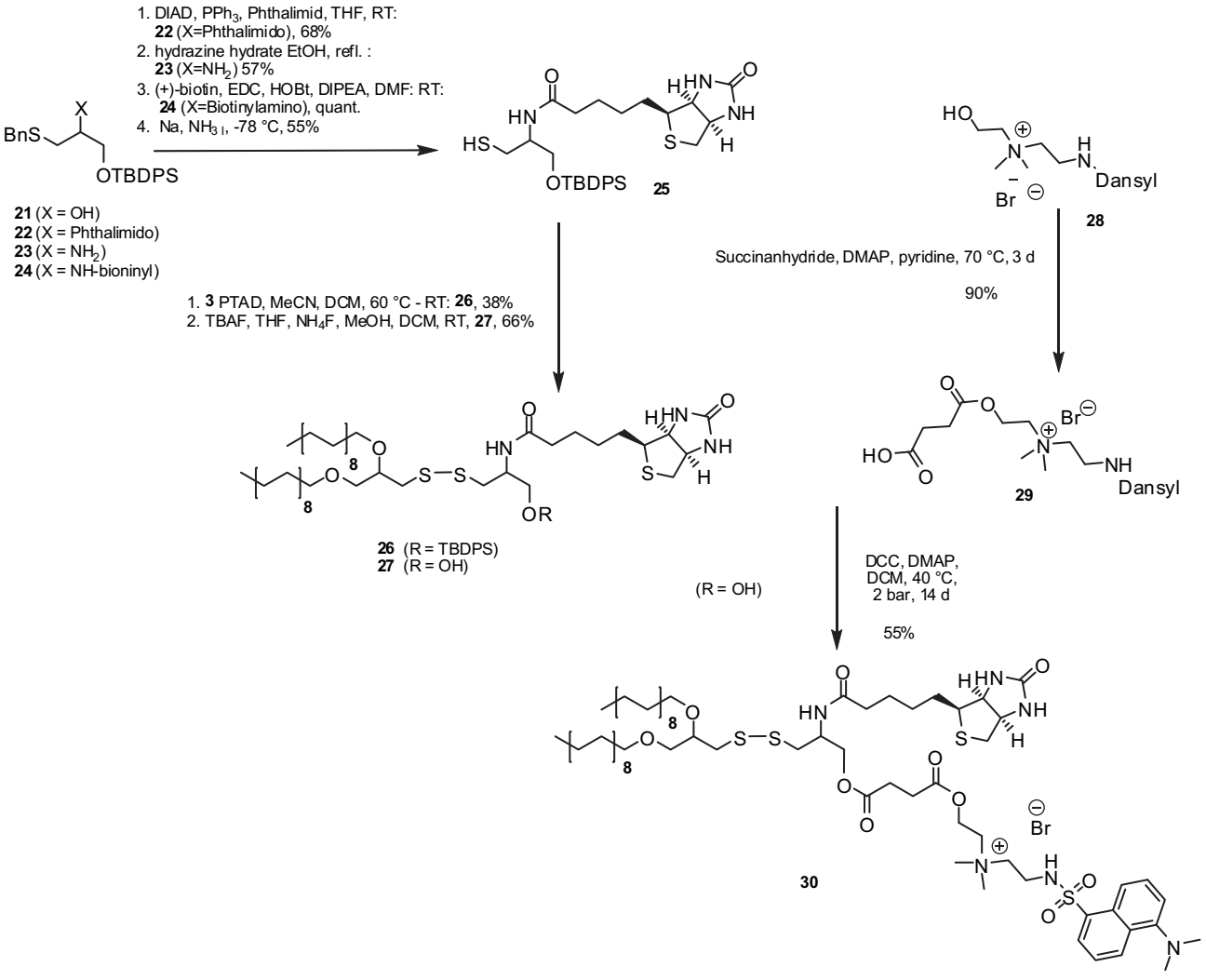
4. Experimental section

4.1. General remarks

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, with a Bruker AC 300 in $CDCl_3$ with TMS as internal standard. Silica gel (0.04–0.063 mm, Merck) was used for preparative column chromatography. Starting materials **1**,[20] **3**,[21] **8** (see also preparation of **4**),[22] **12**,[23,24] **28**,[25] **34**,[26] **37**[27] were synthesized according to literature procedures. All the other starting materials and reagents were purchased from commercial suppliers.

*4.1.1. 1-O-Tosyl-2-O-biotinyl-tetraethylenglycol (**2**).* (+)-Biotin (1.00 g, 4.1 mmol), 1-*O*-tosyl-tetraethylenglycol **1** (1.04 g, 4.1 mmol), *N*,*N*́-dicyclohexylcarbondimide (DCCI) (1.01 g, 4.9 mmol), and 4-dimethylaminopyridine (DMAP) (70 mg, 0.57 mmol) were combined in dichloromethane (DCM) (30 ml). The was stirred at rt for 96 h. The solvent was removed under vacuum and the remainder purified by column chromatography (silica, DCM/MeOH 10:1; R_f=0.3) to give product **2** (1.03 g, 1.7 mmol, 43%) as colorless solid. Mp 130–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.30–1.46 (m, 2H, $-CH_2-$), 1.51–1.73 (m, 4H, $-CH_2-$), 2.31 (t, J=7.55 Hz, 2H, $-CH_2-(C=O)-O-$), 2.39 (s, 3H, $C_{ar}-CH_3$), 2.63–2.90 (m, 2H, $-CH_2-S-CH-$), 3.03–3.14 (m, 1H, $-CH_2-S-CH-$), 3.50–3.54 (m, 4H, $-CH_2-O-$), 3.54–3.59 (m, 4H, $-CH_2-O-$), 3.59–3.67 (m, 4H, $-CH_2-O-$), 4.07–4.12 (m, 2H, $-CH_2-O-$), 4.15 (dd, J=5.76, 3.68 Hz, 2H, $-CH_2-O-$), 4.24 (dd, J=7.84, 4.82 Hz, 1H, $-CH-CH-$), 4.44 (dd, J=7.65, 4.82 Hz, 1H, $-CH-CH-$), 5.84 (br s, 1H, $-NH-(C=O)-NH-$), 6.32 (s, 1H, $-NH-(C=O)-NH-$), 7.30 (d, J=8.50 Hz, 2H, CH_{ar}), 7.73 (d, J=8.31 Hz, 2H, CH_{ar}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=21.4 ($C_{ar}-CH_3$), 24.5 (CH_2), 27.9 (CH_2), 28.1 (CH_2), 33.5 ($-CH_2-(C=O)-O-$), 40.3 ($-CH_2-S-CH-$), 55.4 ($-CH_2-S-CH-$), 59.9 ($-CH-CH-$), 61.7 ($-CH-CH-$), 63.1 ($-CH_2-O-$), 68.4 ($-CH_2-O-$), 68.8 ($-CH_2-O-$), 69.1 ($-CH_2-O-$), 70.2 ($-CH_2-O-$), 70.3 ($-CH_2-O-$), 70.4 ($-CH_2-O-$), 127.7 (CH_{ar}), 129.6 (CH_{ar}), 132.6 (C_{ar}), 144.6 (C_{ar}), 163.7 ($-NH-(C=O)-NH-$), 173.4 ($-CH_2-(C=O)-O-$) ppm. HRMS (ESI): calcd for $C_{25}H_{39}N_2O_9S_2$ $[M+H]^+$ 575.2116; found 575.2091.

*4.1.2. 2-((2,3-Bis(octadecyloxy)propyl)disulfanyl)-N,N-dimethylethanamine **4**.* PTAD (114 mg, 0.66 mmol) was added to a solution of thiol **3** (400 mg, 0.66 mmol) in dry dichloromethane (DCM, 14 ml) and MeCN (5.4 ml) under stirring in an argon atmosphere. After stirring at rt for 30 min the temperature was elevated to 50–55 °C.

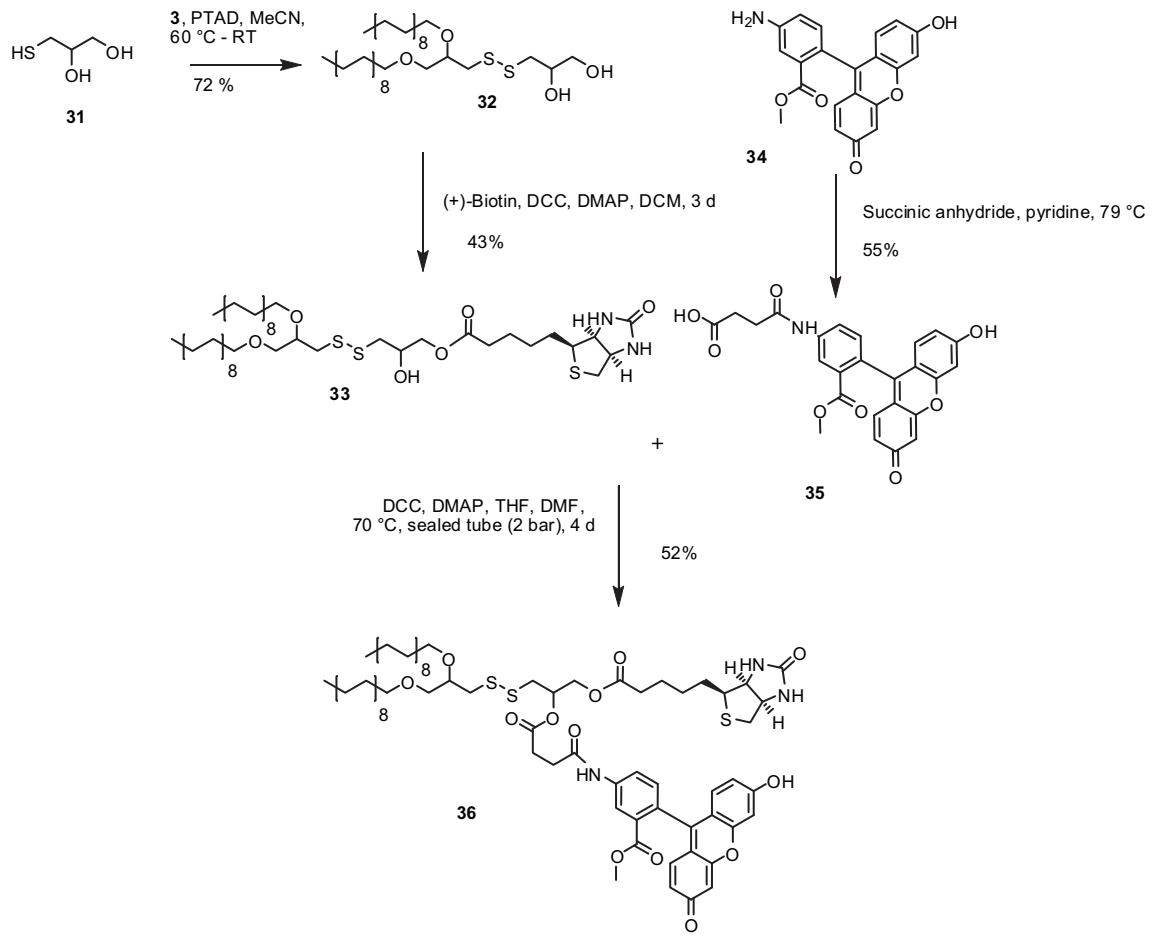


Scheme 5. Synthesis of conjugate **30** with a dansyl label in the side chain.

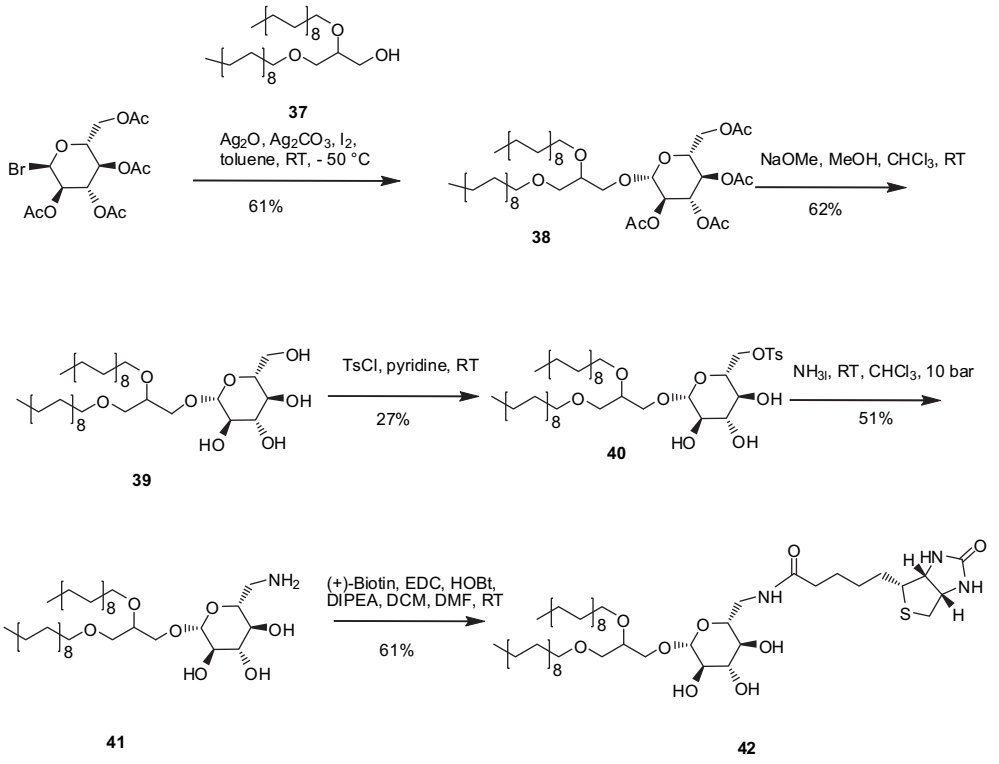
After the color of the mixture had faded (about 2 h) *N,N*-dimethylaminoethanthiol·HCl (243 mg, 1.72 mmol) was added and the mixture was stirred at rt for 20 h. The solvent was distilled off and the remainder was purified by column chromatography (silica; DCM/MeOH, 12:1; R_f=0.6) giving product **4** (322 mg, 0.45 mmol, 68%) as colorless solid. Mp 42–44 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.77–0.87 (m, 6H, $-CH_2-CH_3$), 1.10–1.34 (m, 60H, $-CH_2-$), 1.42–1.59 (m, 4H, $-CH_2-CH_2-O-$), 2.25 (s, 6H, $-CH_2-N-(CH_3)_2$), 2.61 (t, J=7.18 Hz, 2H, $-S-CH_2-CH_2-$), 2.72–2.94 (m, 4H, $-S-CH_2-CH_2-$, $-S-CH_2-CH-$), 3.31–3.54 (m, 6H,$-O-CH_2-$), 3.55–3.65 (m, 1H, $-S-CH_2-CH-$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0 ($-CH_2-CH_3$), 22.6 ($-CH_2-CH_3$), 26.0 (CH_2), 26.0 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 31.8 (CH_2), 36.2 ($-SCH_2-CH_2-$), 41.2 ($-S-CH_2-CH-$), 45.0 ($-CH_2-N(CH_3)_2$), 58.4 ($-S-CH_2-CH_2-$), 70.3 ($-O-CH_2-$), 71.3 ($-O-CH_2-$), 71.5 ($-O-CH_2-$), 77.4 ($-CH_2-CH-CH_2-$) ppm.

*4.1.3. 2-((2,3-Bis(octadecyloxy)propyl)disulfanyl)-N,N-dimethyl-N-(2-O-biotinyl-tetraethylenglykol-1-yl)-ethanammonium tosylate **5**.* A suspension of disulfide **4** (161 mg, 0.23 mmol) and tosylate **2** in trichloromethane (1.7 ml) was put into a pressure vessel under argon and stirred at 70 °C (pressure around 2 bar) for 7 days. After cooling to rt the solvent was stripped off and the residue was purified by column chromatography (silica; dichloromethane/MeOH, 5:1; R_f=0.2) giving the product (115 mg, 0.09 mmol, 39%) as yellow solid. Mp >190 °C (decomposition). $C_{68}H_{127}N_3O_{11}S_4$. HRMS: calcd for $C_{61}H_{121}N_3O_8S_2^{2+}$ 559.9152; found 559.9158.

*4.1.4. 2-N-Biotinyl-N,N-dimethylethan-1,2-diamine **6**.* *N,N*-Dimethylethylendiamine (195 µl, 1.8 mmol) and (+)-Biotin (437 mg, 1.8 mmol) were dissolved in dry DMF (17 ml). After the addition of EDC (380 µl, 2.1 mmol), HOBt (380 mg, 2.5 mmol) and DIPEA (310 µl, 1.8 mmol) the mixture was stirred for 24 h. After the addition of toluene (5 ml) all solvent was distilled off. The remainder was kept under vacuum (5 mbar, 40 °C) for several hours and was then purified by column chromatography (silica; DCM/MeOH/Et_3N, 7:1:0.5; R_f=0.4) giving the product **6** (566 mg) as colorless wax in quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.19–1.33 (m, 2H, $-S-CH-CH_2-$), 1.38–1.62 (m, 4H, $-SCH-CH_2-CH_2-CH_2-$), 2.05 (s, 6H, $-CH_2-N(CH_3)_2$), 2.27 (t, J=5.85 Hz, 2H, $-CH_2-N(CH_3)_2$), 2.48–2.79 (m, 2H, $-S-CH_2-CH-$), 2.92–3.05 (m, 1H, $-S-CH-CH_2-$), 3.10–3.19 (m, 2H, $-NHCH_2-$), 4.13 (dd, J=7.55, 4.91 Hz, 1H, $-CH-CH-$), 4.34 (dd, J=7.55, 4.91 Hz, 1H, $-CH-CH-$), 6.72 (s, 1H, $-NH-(C=O)-NH-$), 6.86 (s, 1H, $-NH-(C=O)-NH-$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=25.3 (CH_2), 27.5 (CH_2), 28.1 (CH_2), 36.5 ($-CH_2-(C=O)$), 44.8 ($-CH_2-N(CH_3)_2$), 55.6 ($-S-CH-CH_2-$), 57.8 ($-CH_2-N(CH_3)_2$),



Scheme 6. Synthesis of fluorescein-labeled conjugate **36**.



Scheme 7. Conjugate of glucose containing conjugate **42**.

59.9 (−CH−CH−), 61.6 (−CH−CH−), 164.3 (−NH−(C=O)−NH), 173.3 (−NH−(C=O)−CH_2−) ppm.

4.1.5. 2-N-Biotinyl-2-amino-N-(carboxymethyl)-N,N-dimethylethanammonium bromide ***7***. Bromoacetic acid (323 mg, 2.3 mmol) was added to a solution of the biotin amide **6** (566 mg, 1.8 mmol) in dry MeCN (3 ml). After heating the mixture to 100 °C for 30 h the solvent was removed by a rotary evaporator and the remainder was recrystallized from MeOH/Et_2O (1:3) providing the product **7** (808 mg, 1.78 mmol, 97%) as colorless semicrystalline solid. TLC R_f=0.0 (dichloromethane/MeOH/Et_3N, 7:1:0.5). HRMS: calcd for $C_{16}H_{29}N_4O_4S^+$ 373.1904; found 373.1908.

4.1.6. 2-(2-((2,3-Bis(octadecyloxy)propyl)disulfanyl)ethylamino)-N,N-dimethyl-2-oxo-N-(biotinylethyl)ethanammonium bromide ***9***. EDC (97 μl, 0.55 mmol), HOBt (98 mg, 0.64 mmol), and DIPEA (76 μl, 0.46 mmol) were added to a suspension of the disulfide **8** (158 mg, 0.23 mmol) and the carboxylic acid **7** (208 mg, 0.46 mmol) in dry DCM/DMF (1:1, 8 ml). The yellowish solution was stirred at 30 °C for 3 h. After distilling off the solvent the remainder was purified by column chromatography (ALOX, Typ-T, neutral; dichloromethane/MeOH, 10:1; R_f=0.5) giving product **9** (56 mg, 0.05 mmol, 22%) as a colorless solid. The diastereomers were not separated. Mp 68–70 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.81–0.94 (m, 6H, −CH_2−CH_3), 1.16–1.36 (m, 60H, −CH_2−), 1.40–1.87 (m, 10H, −CH_2−CH_2−O, −CH_2−), 2.25–2.47 (m, 2H, −CH_2−(C=O)−O−), 2.77–2.98 (m, 4H, −CH_2−S−S−CH_2−), 3.15 (td, J=7.36, 4.91 Hz, 1H, −CH_2−S−CH−), 3.34–3.67 (m, 15H, −CH_2−N(CH_3)$_2$−, −CH_2−O−, −(C=O)−NH−CH_2−, −CH_2−CH−CH_2−), 3.69–3.98 (m, 4H, −(C=O)−NH−CH_2−CH_2−), 4.33–4.61 (m, 4H, −CH−CH−, −(C=O)−CH_2−N(CH_3)$_2$−), 5.88–6.15 (m, 1H, NH−(C=O)−NH), 6.67–6.87 (m, 1H, −NH−(C=O)−CH_2−) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (−CH_2−CH_3), 22.7 (−CH_2−CH_2), 26.1 (CH_2), 27.9(CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 30.1 (CH_2), 31.9 (CH_2), 33.9 (−CH_2−(C=O)−O−), 36.8 (−NH−CH_2−), 38.4 (−CH_2−S−S−), 41.1 (−CH_2−S−S−), 41.3 (−CH_2−S−CH−), 46.0 (−NH−CH_2−), 50.8 (−N(CH_3)$_2$−), 52.8 (−CH−), 56.0 (−CH−), 62.0 (−CH−), 70.5 (CH_2), 71.5 (CH_2), 71.7 (CH_2), 71.8 (CH_2), 77.5 (−CH−O−CH_2−), 164.1 (−NH−(C=O)−NH−), 173.5 (−CH_2−(C=O)−NH−), 174.6 (−CH_2−(C=O)−NH−) ppm. HRMS: calcd for $C_{57}H_{112}N_5O_5S_3$+1042.7820; found 1042.7837.

4.1.7. (2R)-2-Amino-3-((2,3-bis(octadecyloxy)propyl)disulfanyl) propan-1-ol ***11***. PTAD (114 mg, 0.66 mmol) was added to a solution of the octadecyl ether **3** (400 mg, 0.66 mmol) in dry DCM (14 ml), and dry MeCN (5.4 ml) under stirring in an argon atmosphere. The mixture was stirred for 30 min at rt and was then heated to 50–55 °C until the color had faded (about 2 h). (*R*)-cysteinol (180 mg, 1.68 mmol) and MeOH (4 ml) were added and the resulting mixture was stirred at rt for 20 h. After the solvent was stripped off the remainder was purified by column chromatography (silica gel; $CHCl_3$/MeOH, 10:1; R_f=0.4). The colorless waxy product **11** was obtained as a diastereomeric mixture (332 mg, 0.46 mmol, 70%). Mp 206–207 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.82–0.92 (m, 6H, −CH_2−CH_3), 1.00–1.40 (m, 60H, −CH_2−), 1.45–1.69 (m, 4H, −CH_2−CH_2−O), 2.24 (br s, 2H, −CH−NH_2), 2.50–3.03 (m, 4H, −CH_2−S−S−CH_2−), 3.12–3.25 (m, 1H, −CH−NH_2), 3.35–3.75 (m, 9H, −O−CH_2−CH−, −CH−CH_2−OH, −CH_2−, −O−CH_2−CH−) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (−CH_2−CH_3), 22.7 (−CH_2−CH_3), 26.1 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 31.9 (CH_2), 41.3 (−CH−CH_2−S−), 43.1 (NH_2−CH−CH_2−S−), 51.5 (−CH−NH_2), 65.4 (−CH_2−OH), 70.5 (O−CH_2−CH_2), 71.3 (CH−CH_2−O), 71.7 (O−CH_2−CH_2), 77.4 (−O−CH−CH_2−O) ppm. HRMS: calcd for $C_{42}H_{88}NO_3S_2$ $[M+H]^+$ 718.6200; found 718.6192.

4.1.8. (2R)-2-Amino-2-N-(2-O-succinyl-choline)-3-((2,3-bis(octadecyloxy)propyl)disulfanyl) propan-1-ol chloride ***13***. The disulfide **11** (141 mg, 0.20 mmol) and the acid **12** (47 mg, 0.20 mmol) were suspended in dry DCM/DMF (1:1, 4 ml). After the addition of EDC (37 μl, 0.23 mmol), HOBt (42 mg, 0.27 mmol) and DIPEA (34 μl, 0.20 mmol) the mixture was stirred at 30 °C for 20 h. The solvent was distilled off and the remainder purified by column chromatography affording a diastereomeric mixture of the product **13** (100 mg, 0.11 mmol, 54%) as colorless foam. Mp 63–65 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.78–0.89 (m, 6H, −CH_2−CH_3), 0.94–1.33 (m, 60H, −CH_2−), 1.42–1.52 (m, 4H, −CH_2−CH_2−O), 2.40–2.73 (m, 4H, −(C=O)−CH_2−CH_2−(C=O)−), 2.75–2.92 (m, 4H, −CH_2−S−S−, −CH−CH_2−S−S−), 3.23–3.52 (m, 15H, −CH_2−N(CH_3)$_3$, −CH_2−O−), 3.58 (dt, J=9.82, 4.91 Hz, 1H, −CH−O−CH_2−), 3.64–3.75 (m, 2H, −CH_2−OH), 3.82–4.03 (m, 2H, −CH_2−O−(C=O)−), 4.06–4.17 (m, 1H, −CH−NH), 4.40–4.67 (m, 2H, −CH_2−N(CH_3)$_3$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0 (−CH_2−CH_3), 22.6 (−CH_2−CH_3), 26.0 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 30.0 (CH_2), 30.6 (CH_2), 31.8 (CH_2), 39.5 (−CH_2−S−S−), 40.8 (−CH_2−S−S−), 51.2 (−CH−NH−), 54.3 (−CH_2−N(CH_3)$_3$), 58.1 (−CH_2−N(CH_3)$_3$), 62.6 (−CH_2−OH), 64.8 (−(C=O)−O−CH_2−), 70.4 (−O−CH_2−), 71.5 (−O−CH_2−), 71.6 (−O−CH_2−), 77.3 (−CH−O−CH_2−), 171.8 (−(C=O)−O−), 172.1 (−(C=O)−O−) ppm. HRMS: calcd for $C_{51}H_{103}N_2O_6S_2$ $[M-Cl]^+$ 903.7252; found 903.7240.

4.1.9. 1-O-Biotinyl-(2R)-2-amino-2-N-(2-O-succinyl-choline)-3-((2,3-bis(octadecyloxy) propyl)disulfanyl)propan-1-ol chloride ***14***. A suspension of (+)-biotin (104 mg, 0.42 mmol) and the alcohol **13** (58.88 mg, 0.42 mmol) in dichloromethane (3.5 ml) and DMAP (19 mg, 0.15 mmol) was stirred at 30 °C for 4 days. The mixture was concentrated with a rotary evaporator and the remainder was purified by column chromatography (ALOX, Type-T, neutral; $CHCl_3$/MeOH, 10:1; R_f=0.3) affording a diastereomeric mixture of the product **14** (45 mg, 0.04 mmol, 35%) as colorless solid. Mp 51–53 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.81–0.91 (m, 6H, −CH_2−CH_3), 1.00–1.34 (m, 60H, −CH_2−), 1.36–1.78 (m, 10H, −CH_2−CH2−O, −CH_2−), 2.24–2.43 (m, 2H, −CH_2−(C=O)−O−), 2.44–2.80 (m, 4H, −(C=O)−CH_2−CH_2−(C=O)−), 2.80–2.96 (m, 4H, −CH_2−S−S−, −CH_2−S−CH−), 3.07–3.20 (m, 2H, −CH_2−S−S−), 3.33–3.56 (m, 15H, −CH_2−N(CH_3)$_3$, −CH_2−O−), 3.57–3.67 (m, 1H, −CH−OCH_2−), 3.96–4.60 (m, 9H, −CH_2−OH, −CH_2−O−(C=O)−, −CH−NH, −CH_2−N(CH_3)$_3$, −CH−CH−), 5.52.5.75 (m, 1H, NH−(C=O)−NH), 6.03–6.18 (m, 1H, NH−(C=O)−NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (−CH_2−CH_3), 22.6 (−CH_2−CH_3), 24.7 (CH_2), 26.1 (CH_2), 28.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 30.0 (CH_2), 30.8 (CH_2), 31.9 (CH_2), 33.6 (−CH_2−(C=O)−O−), 39.8 (−CH_2−S−S−), 40.6 (−CH_2−S−S−), 41.2 (CH_2), 48.1 (−CH−NH−), 54.3 (−CH_2−N(CH_3)$_3$), 55.5 (−CH−), 58.2 (−CH_2−N(CH_3)$_3$), 60.1 (−CH−), 61.8 (−CH−), 64.3 (CH_2), 64.7 (−(C=O)−O−CH_2−), 70.5 (−O−CH_2−), 71.5 (−O−CH_2−), 71.7 (−O−CH_2−), 77.3 (−CH−O−CH_2−), 163.9 (−NH−(C=O)−NH−), 171.4 (−(C=O)−O−), 172.2 (−(C=O)−O−), 173.8 (−CH_2−(C=O)−NH−) ppm. HRMS: calcd for $C_{61}H_{117}N_4O_8S_3$ $[M-Cl]^+$ 1129.8028; found 1129.8017.

4.1.10. 2-N-Dansyl-serine methyl ester ***16***. A solution of serine methyl ester·HCl (311 mg, 2 mmol) in satd aqueous $NaHCO_3$ (6 ml) was added drop wise into a mixture of dansyl chloride (540 mg, 2 mmol) and acetone/water (2:1, 24 ml) in a brown colored flask. After the mixture was stirred at rt for 20 h the solvent was stripped off under vacuum. The remainder was put into a mixture of water (100 ml) and EtOAc (140 ml). The organic layer was separated, dried over $MgSO_4$ and concentrated with a rotary evaporator. The remainder was put under vacuum for a view hours (4 mbar, 40 °C) giving the yellow solid (568 mg, 1.6 mmol, 81%), which was used in the next step without further purification.

4.1.11. 3-O-Biotinyl-2-N-dansyl-serine ***17***. Me_3SnOH (1 g, 5.5 mmol) was added to a suspension of the methyl ester **18** (725 mg, 1.3 mmol) in 1,2-dichloroethane (10 ml) under stirring and argon

atmosphere in a brown colored flask. After stirring at 70 °C for 1.5 h the solvent was removed by a rotary evaporator. The remainder was combined with EtOAc (150 ml) and the organic layer was washed with (0.01 N) $KHSO_4$ (three times 150 ml). After drying over $MgSO_4$ the solvent was removed and the remainder was put under vacuum (3 mbar, 40 °C) for a few hours providing the product **17** (558 mg, 0.99 mmol, 79%) as yellow solid. TLC (DCM/MeOH, 10:1); R_f=0.4. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.97–1.32 (m, 2H, −C*H*$_2$−), 1.38–1.62 (m, 4H, −C*H*$_2$−), 2.02–2.17 (m, 2H, −C*H*$_2$−(C=O)−O−), 2.53–2.66 (m, 1H, −C*H*$_2$−S−CH−), 2.71–2.92 (m, 7H, −C*H*$_2$−S−CH−, −N(C*H*$_3$)$_2$), 2.98–3.14 (m, 1H, −CH$_2$−S−C*H*−), 4.06–4.36 (m, 4H, −C*H*−C*H*$_2$−O−, −C*H*−CH−), 4.37–4.47 (m, 1H, −C*H*−CH−), 7.12 (d, *J*=7.74 Hz, 1H, C*H*$_{ar}$), 7.37–7.58 (m, 2H, C*H*$_{ar}$), 8.20 (d, *J*=7.18 Hz, 1H, C*H*$_{ar}$), 8.28 (d, *J*=8.50 Hz, 1H, C*H*$_{ar}$), 8.47 (d, *J*=8.31 Hz, 1H, C*H*$_{ar}$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=24.7 (*C*H$_2$), 27.7 (*C*H$_2$), 33.4 (−*C*H$_2$−(C=O)−O−), 40.1 (−*C*H$_2$−S−CH−), 45.3 (−N(*C*H$_3$)$_2$), 55.0 (−*C*H−NH−SO$_2$−), 57.8 (−CH$_2$−S−*C*H−), 60.3 (−*C*H$_2$−O−(C=O)−), 60.4 (−*C*H−CH−), 62.0 (−*C*H−CH−), 115.2 (*C*H$_{ar}$), 119.1 (*C*H$_{ar}$), 123.1 (*C*H$_{ar}$), 128.2 (*C*H$_{ar}$), 129.1 (*C*H$_{ar}$), 129.6 (*C*$_{ar}$), 129.6 (*C*H$_{ar}$), 130.5 (*C*$_{ar}$), 135.0 (*C*$_{ar}$), 151.4 (*C*$_{ar}$), 164.8 (−NH−(*C*=O)−NH−), 172.2 (−CH−(*C*=O)−O−), 172.9 (−CH2−(*C*=O)−O−) ppm.

4.1.12. 3-O-Biotinyl-2-N-dansyl-serine methyl ester ***18***. (+)-Biotin (394 mg, 1.6 mmol), DCCI (399 mg, 1.9 mmol), and DMAP (28 mg, 0.23 mmol) were added to a solution of *N*-dansylserine **16** (568 mg, 1.6 mmol) in dry dichloromethane (12 ml) under stirring in a brown colored flask. The suspension was stirred at rt for 9 days. After distilling off the solvent the remainder was purified by column chromatography (silica gel; dichloromethane/MeOH, 20:1; R_f=0.5) affording product **18** (725 mg, 78% yield) as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.22–1.46 (m, 2H, −C*H*$_2$−), 1.44–1.78 (m, 4H, −C*H*$_2$−), 2.06–2.31 (m, 2H, −C*H*$_2$−(C=O)−O−), 2.57–2.79 (m, 2H, −C*H*$_2$−S−CH−), 2.82 (s, 6H, −N(C*H*$_3$)$_2$), 3.02–3.12 (m, 1H, −CH$_2$−S−C*H*−), 3.36 (s, 3H, −(C=O)−O−C*H*$_3$), 4.13–4.33 (m, 4H, −C*H*−C*H*$_2$−O−, −C*H*−CH−), 4.39–4.48 (m, 1H, −C*H*−CH−), 6.58 (s, 1H, C=O−N*H*), 7.13 (d, *J*=7.55 Hz, 1H, C*H*$_{ar}$), 7.19 (s, 1H, C=O−N*H*), 7.44 (dd, *J*=8.40, 7.46 Hz, 1H, C*H*$_{ar}$), 7.48–7.57 (m, 1H, C*H*$_{ar}$), 7.91–8.05 (m, 1H, C=O−N*H*), 8.21 (dd, *J*=7.36, 0.94 Hz, 1H, C*H*$_{ar}$), 8.34 (d, *J*=8.69 Hz, 1H, C*H*$_{ar}$), 8.47 (d, *J*=8.50 Hz, 1H, C*H*$_{ar}$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=24.4 (*C*H$_2$), 27.8 (*C*H$_2$), 28.1 (*C*H$_2$), 33.0 (−*C*H$_2$−(C=O)−O−), 40.4 (−*C*H$_2$−S−CH−), 45.2 (−N(*C*H$_3$)$_2$), 52.3 (−(C=O)−O−*C*H$_3$), 54.8 (−*C*H−NH−SO$_2$−), 56.1 (−CH$_2$−S−*C*H−), 60.2 (−*C*H−CH−), 61.5 (−*C*H−CH−), 64.2 (−*C*H$_2$−O−(C=O)−), 115.0 (*C*H$_{ar}$), 119.1 (*C*H$_{ar}$), 122.9 (*C*H$_{ar}$), 128.0 (*C*H$_{ar}$), 128.8 (*C*H$_{ar}$), 129.5 (*C*$_{ar}$), 129.5 (*C*H$_{ar}$), 130.2 (*C*$_{ar}$), 135.3 (*C*$_{ar}$), 151.5 (*C*$_{ar}$), 164.6 (−NH−(*C*=O)−NH−), 169.2 (−CH−(*C*=O)−O−), 173.0 (−CH$_2$−(*C*=O)−O−) ppm.

4.1.13. 3-O-Biotinyl-2-N-dansyl-serin-(1-O-tosyl-tetraethylenglykol) ester ***19***. Tosylate **1** (345 mg, 0.99 mmol), DCCI (245 mg, 1.2 mmol), and DMAP 20 mg (0.16 mmol) were added to a solution of the acid **17** (558 mg, 0.99 mmol) in dry dichloromethane (8 ml) under stirring in a brown colored flask. The mixture was stirred at rt for 72 h. Then the solvent was removed by a rotary evaporator and the remainder purified by column chromatography (Silica gel; dichloromethane/MeOH, 13:1; R_f=0.4) affording product **19** (292 mg, 0.33 mmol, 33% yield) as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.26–1.76 (m, 6H, −C*H*$_2$−), 2.03–2.31 (m, 2H, −C*H*$_2$−(C=O)−O−), 2.40 (s, 3H, C$_{ar}$−C*H*$_3$), 2.56–2.81 (m, 2H, −C*H*$_2$−S−CH−), 2.83 (s, 6H, −N(C*H*$_3$)$_2$), 3.00–3.15 (m, 1H, −CH$_2$−S−C*H*−), 3.42 (t, *J*=4.82 Hz, 2H, −C*H*$_2$−O−), 3.45–3.60 (m, 8H, −C*H*$_2$−O−), 3.61–3.66 (m, 2H, −C*H*$_2$−O−), 3.91–4.05 (m, 2H, −C*H*$_2$−O−SO$_2$−), 4.09–4.15 (m, 2H, −C*H*$_2$−O−(C=O)−), 4.18–4.34 (m, 4H, −C*H*−CH−, −C*H*$_2$−C*H*−(C=O)−O−), 4.38–4.48 (m, 1H, −C*H*−CH−), 6.28 (s, 1H, −N*H*−SO$_2$−), 7.08–7.17 (m, 2H, C*H*$_{ar}$), 7.27–7.34 (m, 2H, C*H*$_{ar}$), 7.39–7.60 (m, 2H, C*H*$_{ar}$), 7.73–7.80 (m, 1H, C*H*$_{ar}$), 8.19–8.24 (m, 1H, C*H*$_{ar}$), 8.34 (d, *J*=8.69 Hz, 1H, C*H*$_{ar}$), 8.48 (d, *J*=8.50 Hz, 1H, C*H*$_{ar}$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=21.5 (C$_{ar}$−*C*H$_3$), 24.4 (*C*H$_2$), 27.9 (*C*H$_2$), 28.1 (*C*H$_2$), 33.1 (−*C*H$_2$−(C=O)−O−), 40.4 (−*C*H$_2$−S−CH−), 45.3 (−N(*C*H$_3$)$_2$), 55.0 (−*C*H−NH−SO$_2$−), 56.1 (−CH$_2$−S−*C*H−), 60.3 (−*C*H−CH−), 61.6 (−*C*H−CH−), 64.3 (−*C*H$_2$−O−(C=O)−), 64.6 (−*C*H$_2$−O−), 68.3 (−*C*H$_2$−O−), 68.5 (−*C*H$_2$−O−), 69.2 (−*C*H$_2$−O−), 70.3 (−*C*H$_2$−O−), 70.6 (−*C*H$_2$−O−), 115.1 (*C*H$_{ar}$), 119.3 (*C*H$_{ar}$), 123.1 (*C*H$_{ar}$), 127.8 (*C*H$_{ar}$), 128.1 (*C*H$_{ar}$), 128.8 (*C*H$_{ar}$), 129.5 (*C*$_{ar}$), 129.6 (*C*$_{ar}$), 129.7 (*C*H$_{ar}$), 130.3 (*C*H$_{ar}$), 132.8 (*C*$_{ar}$), 135.5 (*C*$_{ar}$), 144.7 (*C*$_{ar}$), 151.5 (*C*$_{ar}$), 164.5 (−NH−(*C*=O)−NH−), 168.8 (−CH−(*C*=O)−O−), 173.0 (−CH$_2$−(*C*=O)−O−) ppm.

4.1.14. 2-((2,3-Bis(octadecyloxy)propyl)disulfanyl)-N,N-dimethyl-N-(2-O-(3-O-biotinyl-2-N-dansyl-serin-1-yl)-tetraethylenglykol-1-yl)-ethanammonium tosylate ***20***. A solution of the tosylate **19** (292 mg, 0.33 mmol) and disulfide **4** (80 mg, 0.11 mmol) in $CHCl_3$ (1 ml) was stirred under argon in a sealed flask to 70 °C (2 bar) for 5 days. The solvent was stripped of by a rotary evaporator and the remainder was purified by column chromatography (silica, dichloromethane/MeOH, 5:1; R_f=0.2). The product was obtained as diastereomeric mixture in 50% yield (88 mg) as yellow solid. Mp 55–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$/CD_3COD, 7:2): δ=0.66–0.71 (m, 6H, −CH$_2$−C*H*$_3$), 0.81–1.17 (m, 60H, −C*H*$_2$−), 1.17–1.53 (m, 10H, −C*H*$_2$−CH$_2$−O, −C*H*$_2$−), 1.76 (t, *J*=7.28 Hz, 2H, −C*H*$_2$−(C=O)−O−), 2.17 (s, 3H, C$_{ar}$−C*H*$_3$), 2.49–2.59 (m, 1H, −C*H*$_2$−S−CH−), 2.67–2.76 (m, 7H, −C*H*$_2$−S−CH−, −N(C*H*$_3$)$_2$), 3.20–3.55 (m, 27H, −C*H*$_2$−S−S−C*H*$_2$−, −C*H*$_2$−O−, −CH$_2$−S−C*H*−, −N(C*H*$_3$)$_2$), 3.70–3.77 (m, 2H, −C*H*$_2$−), 3.78–3.85 (m, 1H, −C*H*−O−CH$_2$−), 3.87–4.11 (m, 10H, −C*H*−C*H*$_2$−O−, −C*H*−CH−, −C*H*$_2$−), 4.24–4.33 (m, 1H, −C*H*−CH−), 7.00 (d, *J*=8.03 Hz, 2H, C*H*$_{ar}$), 7.05 (d, *J*=7.53 Hz, 1H, C*H*$_{ar}$), 7.31–7.45 (m, 2H, C*H*$_{ar}$), 7.53 (d, *J*=8.03 Hz, 2H, C*H*$_{ar}$), 8.04 (dd, *J*=7.28, 1.25 Hz, 1H, C*H*$_{ar}$), 8.12 (d, *J*=8.53 Hz, 1H, C*H*$_{ar}$), 8.36 (d, *J*=8.53 Hz, 1H, C*H*$_{ar}$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$/CD_3COD, 7:2): δ=13.6 (−CH$_2$−*C*H$_3$), 20.7 (C$_{ar}$−*C*H$_3$), 22.3 (−*C*H$_2$−CH$_3$), 25.7 (*C*H$_2$), 27.8 (*C*H$_2$), 27.9 (*C*H$_2$), 28.9 (*C*H$_2$), 29.1 (*C*H$_2$), 29.2 (*C*H$_2$), 29.2 (*C*H$_2$), 29.3 (*C*H$_2$), 29.5 (*C*H$_2$), 29.6 (*C*H$_2$), 31.5 (*C*H$_2$), 32.7 (−CH$_2$−(C=O)−O−), 39.9 (−*C*H$_2$−S−S−), 40.8 (−CH$_2$−S−CH−), 45.0 (−N(*C*H$_3$)$_2$), 51.6 (−N(*C*H$_3$)$_2$), 54.7 (−CH−NH−SO$_2$−), 55.2 (−CH$_2$−S−*C*H−), 59.8 (−*C*H−CH−), 61.7 (−CH−*C*H−), 62.9 (*C*H$_2$), 63.2 (*C*H$_2$), 64.3 (*C*H$_2$), 64.6 (*C*H$_2$), 68.2 (*C*H$_2$), 69.8 (*C*H$_2$), 69.9 (*C*H$_2$), 69.9 (*C*H$_2$), 70.1 (*C*H$_2$), 70.2 (*C*H$_2$), 70.9 (*C*H$_2$), 71.4 (*C*H$_2$), 76.9 (−CH$_2$−O−*C*H−), 115.0 (*C*H$_{ar}$), 119.0 (*C*H$_{ar}$), 123.0 (*C*H$_{ar}$), 125.4 (*C*H$_{ar}$), 127.9 (*C*H$_{ar}$), 128.5 (*C*H$_{ar}$), 128.9 (*C*H$_{ar}$), 129.2 (*C*$_{ar}$), 129.3 (*C*$_{ar}$), 130.1 (*C*H$_{ar}$), 135.0 (*C*$_{ar}$), 140.2 (*C*$_{ar}$), 141.2 (*C*$_{ar}$), 151.0 (*C*$_{ar}$), 168.7 (−CH$_2$−(*C*=O)−O−), 172.8 (−CH$_2$−(*C*=O)−O−) ppm. HRMS: calcd for $C_{76}H_{136}N_5O_{12}S_4$ (M−tosylate)$^+$ 1438.9063; found 1438.9057.

4.1.15. 1-(Benzylthio)-3-(tert-butyldiphenylsilyloxy)propan-2-ol ***21***. Imidazole (2.55 g, 37.8 mmol) and TDPS chloride (8.5 g, 31 mmol) were added to a solution of 1-benzylthio propan 2,3-diol (5.75 g, 29 mmol) in dry DMF (140 ml). The mixture was stirred at rt for 72 h. Ethanol (30 ml) was added and all solvents were distilled off. The remainder was dissolved in $CHCl_3$ (200 ml) and washed with water (2×100 ml). The organic layer was dried over $MgSO_4$ and concentrated by a rotary evaporator. The remainder was purified by column chromatography (silica gel; $CHCl_3$/MeOH, 30:1; R_f=0.8) providing the product **21** (12.37 g, 96% yield) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *d*=1.16 (s, 9H, Cq−CH$_3$), 2.66–2.77 (m, 2H, S−CH$_2$−CH), 3.70–3.82 (m, 4H, CH−CH$_2$−O, S−CH$_2$−Ph), 3.88 (dd, *J*=7.27, 5.00 Hz, 1H, CH$_2$−CH−CH$_2$), 7.24–7.39 (m, 5H, CH$_{ar}$), 7.42–7.57 (m, 6H, CH$_{ar}$), 7.69–7.82 (m, 4H, CH$_{ar}$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): *d*=19.1 (Cq), 26.8 (−Cq−CH$_3$), 34.5 (S−CH$_2$−CH), 36.4 (SCH$_2$−Ph), 66.4 (CH−CH$_2$−O), 70.4 (CH−CH$_2$−O), 127.0 (CH$_{ar}$), 127.7 (CH$_{ar}$), 128.4 (CH$_{ar}$), 128.8 (CH$_{ar}$), 129.7 (CH$_{ar}$), 132.9 (C$_{ar}$), 135.4 (CH$_{ar}$), 138.0 (C$_{ar}$) ppm.

4.1.16. 2-(1-(Benzylthio)-3-(tert-butyldiphenylsilyloxy)propan-2-yl) isoindoline-1,3-dione ***22***. Diisopropyl azodicarboxylate (DIAD)

(2.09 g, 10.3 mmol) was slowly added to a solution of the alcohol **21** (3.72 g, 8.5 mmol), triphenylphosphane (2.41 g, 9.2 mmol), and phthalimid (1.39 g, 9.4 mmol) in dry THF (68 ml) under stirring at rt under argon within 30 min. After stirring for 24 h the solvent was distilled off and the remainder purified by column chromatography (silica gel; dichloromethane/cyclohexane, 1:2; R_f=0.4) affording product **22** (3.26 g, 68% yield) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.12 (s, 9H, $C_q(CH_3)_3$), 3.15–3.28 (m, 1H, $-CH_2-CH-CH_2-$), 3.49–3.74 (m, 2H, $-CH-CH_2-S-$), 3.75–3.98 (m, 3H, $-S-CH_2-C_{ar}$, $-O-CH_2-$), 4.07–4.20 (m, 1H, $-O-CH_2-$), 7.09–7.21 (m, 5H, CH_{ar}), 7.36–7.50 (m, 6H, CH_{ar}), 7.64–7.79 (m, 6H, CH_{ar}), 7.79–7.89 (m, 2H, CH_{ar}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=19.0 ($C_q(CH_3)_3$), 26.6 ($C_q(CH_3)_3$), 35.5 ($C_{ar}-CH_2-S-$), 39.2 ($-S-CH_2-$), 45.8 ($-CH_2-CH-CH_2-$), 65.7 ($-CH_2-O-$), 123.1 (CH_{ar}), 126.7 (CH_{ar}), 127.6 (CH_{ar}), 128.1 (CH_{ar}), 128.6 (CH_{ar}), 129.6 (CH_{ar}), 131.9 (C_{ar}), 133.0 (C_{ar}), 133.6 (CH_{ar}), 135.5 (CH_{ar}), 135.6 (CH_{ar}), 138.2 (C_{ar}), 167.9 ($-(C=O)-NH-$) ppm.

*4.1.17. 1-(Benzylthio)-3-(tert-butyldiphenylsilyloxy)propan-2-amine **23**.* Hydrazine hydrate (51%, 0.4 ml, 6.6 mol) was added to a solution of the phthalimid **22** (3.2 g, 5.66 mmol) in 96% EtOH (48 ml) under stirring. After refluxing for 2.5 h the mixture was stirred at rt for 3 days. After distilling off the solvent the remainder was purified by column chromatography (silica gel; dichloromethane/MeOH, 25:1; R_f=0.3) affording the product **23** (1.40 g, 57% yield) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.04–1.16 (m, 9H, $C_q(CH_3)_3$), 2.64–2.76 (m, 1H, $-CH_2-CH-CH_2-$), 2.80–3.14 (m, 2H, $-CH-CH_2-S-$), 3.63–3.88 (m, 4H, $-S-CH_2-C_{ar}$, $-O-CH_2-$), 7.21–7.36 (m, 5H, CH_{ar}), 7.37–7.54 (m, 6H, CH_{ar}), 7.65–7.77 (m, 4H, CH_{ar}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=19.1 ($C_q(CH_3)_3$), 26.8 ($C_q(CH_3)_3$), 35.6 ($C_{ar}-CH_2-S-$), 42.8 ($-S-CH_2-$), 50.8 ($-CH_2-CH-CH_2-$), 64.9 ($-CH_2-O-$), 126.9 (CH_{ar}), 127.7 (CH_{ar}), 128.4(CH_{ar}), 128.7 (CH_{ar}), 129.7 (CH_{ar}), 133.2 (C_{ar}), 133.3 (C_{ar}), 135.5 (CH_{ar}), 138.5 (C_{ar}) ppm.

*4.1.18. 1-Mercapto-3-(tert-butyldicyclohexa-2,5-dienylsilyloxy) propan-2-biotinylamide **25**.* EDC (38 ml, 0.21 mmol), HOBt (38 mg, 0.25 mmol), and DIPEA (31 ml, 0.18 mmol) were added to a solution of the amine **23** (77 mg, 0.18 mmol) and (+)-biotin (40 mg, 0.16 mmol) in dry DMF. After stirring at rt for 24 h toluene (5 ml) was added and all solvents removed by distillation. The remainder was kept under vacuum (5 mbar, 40 °C) and then dissolved in $CHCl_3$ (20 ml). The organic layer was washed with water (3×20 ml) and dried over $MgSO_4$. The solvent was removed by a rotary evaporator leaving behind 1-(benzylthio)-3-(*tert*-butyldiphenylsilyloxy) propan-2-biotinylamide **24** (124 mg, quantitative yield). Liquid ammonia is condensed into a solution of the benzylthioether **24** (200 mg, 0.3 mmol) in a dry-ice bath (−78 °C) under argon. Sodium (100 mg, 4.3 mol) was added in small pieces under a current of argon and stirring. The dark blue solution was stirred at (−78 °C) for 2.5 h NH_4Cl (500 mg) were added and ammonia was removed from the colorless suspension by a continuous stream of argon. Water (40 ml) was added to the residue and the suspension was adjusted to pH 3 by adding 2 N aqueous HCl. The mixture was extracted with trichloromethane (100 ml). The organic layer was separated and concentrated with a rotary evaporator. The reminder was purified by column chromatography (silica gel; dichloromethane/MeOH, 10:1; R_f=0.3) affording a diastereomeric mixture of product **26** (95 mg, 55% yield) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.89–1.10 (m, 9H, $C_q(CH_3)_3$), 1.34–1.50 (m, 2H, $-CH_2-$), 1.55–1.85 (m, 4H, $-CH_2-$), 2.20 (t, J=7.36 Hz, 2H, $-CH_2-(C=O)-O-$), 2.61–2.91 (m, 6H, $-CH_2-S-CH-$, $-CH=CH-CH_2-$), 3.02–3.29 (m, 3H, $HS-CH_2-CH-$, $-CH_2-S-CH-$), 3.60–3.76 (m, 1H, $HS-CH_2-CH-$), 3.80–4.09 (m, 2H, $-CH_2-O-$), 4.19–4.32 (m, 1H, $-CH-CH-$), 4.41–4.53 (m, 1H, $-CH-CH-$), 5.48–5.59 (m, 4H, $-CH=CH-$), 5.73–5.83 (m, 4H, $-CH=CH-$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=20.0 (C_q), 21.7 ($-CH=CH-CH_2-$), 25.6 ($-CH_2-$), 26.0 ($-CH_2-$), 27.6 ($C_q(CH_3)_3$), 28.1 ($-CH_2-$), 28.2 ($-CH_2-$), 28.7 ($-CH-CH=CH-$), 36.0 ($-CH_2-(C=O)-O-$), 40.4 ($-CH_2-S-CH-$), 42.2 ($-CH_2-CH-CH_2-$), 43.8 ($-CH_2-SH$), 55.6 ($-CH_2-S-CH-$), 60.2 ($-CH-CH-$), 61.7 ($-CH-CH-$), 67.6 ($-CH_2-O-$), 122.1 ($-CH=CH-$), 122.2 ($-CH=CH-$), 125.4 ($-CH=CH-$), 125.5 ($-CH=CH-$), 164.2 ($-NH-(C=O)-NH-$), 173.4 ($-CH_2-(C=O)-NH-$) ppm.

*4.1.19. 1-(tert-Butyl(cyclohexa-2,5-dienyl)phenylsilyloxy)-2-N-biotinyl-3-((2,3-bis(octadecyloxy)propyl)disulfanyl)-2-aminopropane **26**.* PTAD (26 mg, 0.15 mmol) was added to a solution of the thiol **3** (91 mg, 0.15 mmol) in dry dichloromethane (3.4 ml) DCM and dry MeCN under argon and stirring. After stirring at rt for 1.5 h the temperature was elevated to 60 °C. After the solution had become colorless the biotin derivative **25** (95 mg, 0.17 mmol) was added and stirring continued at rt for 24 h. The solvent was removed by distillation and the residue purified by column chromatography (silica gel; gradient: dichloromethane≥dichloromethane/MeOH, 10:1; R_f=0.5). The product **26** (76 mg, 38% yield) was obtained as diastereomeric mixture of a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.83–0.92 (m, 6H, $-CH_2-CH_3$), 0.92–1.11 (m, 9H, $C_q(CH_3)_3$), 1.11–1.36 (m, 60H, $-CH_2-$), 1.36–1.78 (m, 10H, $-CH_2-$, $-CH_2-CH_2-O-$), 1.98–2.32 (m, 2H, $-CH_2-(C=O)-O-$), 2.65–2.99 (m, 6H, $-CH_2-CH=CH$, $-CH-CH=CH$, $-CH_2-S-CH-$), 3.02–3.18 (m, 2H, $-CH_2-S-$), 3.33–3.66 (m, 9H, $-CH_2-S-$, $-CH_2-O-$, $-CH_2-CH-CH_2-$), 3.71–4.17 (m, 2H, $-CH_2-O-$), 4.19–4.33 (m, 1H, $-CH-CH-$), 4.41–4.48 (m, 1H, $-CH-CH-$), 5.46–5.97 (m, 4H, $-CH=CH-$), 7.29–7.70 (m, 5H, CH_{ar}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 ($-CH_2-CH_3$), 19.3 (C_q), 22.6 ($-CH_2-$), 25.6 ($-CH_2-$), 26.1 ($-CH_2-$), 26.8 ($C_q(CH_3)_3$), 28.1 ($-CH_2-$), 29.3 ($-CH_2-$), 29.5 ($-CH_2-$), 29.6 ($-CH_2-$), 30.0 ($-CH_2-$), 31.9 ($-CH_2-$), 36.0 ($-CH_2-(C=O)-O-$), 40.4 ($-CH_2-S-$), 42.3 ($-CH_2-S-$), 42.5 ($-CH_2-S-$), 53.0 ($-NH-CH-$), 55.5 ($-CH_2-S-CH-$), 60.2 ($-CH-CH-$), 61.7 ($-CH-CH-$), 65.4 ($-CH_2-O-$), 70.5 ($-CH_2-O-$), 71.4 ($-CH_2-O-$), 71.7 ($-CH_2-O-$), 77.6 ($-CH-O-$), 122.2 ($-CH=CH-$), 125.7 ($-CH=CH-$), 127.8 (CH_{ar}), 129.9 (CH_{ar}), 132.9 (C_{ar}), 133.0 (C_{ar}), 135.6 (CH_{ar}), 169.2 ($-NH-(C=O)-NH-$), 173.2 ($-CH2-(C=O)-NH-$) ppm.

*4.1.20. 2-N-Biotinyl-3-((2,3-bis(octadecyloxy)propyl)disulfanyl)-2-aminopropanol **27**.* Ammonium fluoride (50 mg, 1.35 mol) was added to a solution of the silyl ether **26** (76 mg, 0.064 mmol) in THF (2 ml) under stirring. 1 M solution of TBAF in THF (1 ml, 1 mmol) was added and this suspension was drop wise. After the mixture had been stirred at rt for 3 days, the solvent was distilled of under vacuum and the remainder purified by column chromatography (silica gel; gradient: dichloromethane≥dichloromethane/MeOH, 12:1; R_f=0.3). The colorless solid product **27** (40 mg) was obtained as diastereomeric mixture in 66% yield. Mp 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.82–0.92 (m, 6H, $-CH_2-CH_3$), 0.96–1.37 (m, 60H, $-CH_2-$), 1.38–1.76 (m, 10H, $-CH_2-$, $-CH_2-CH_2-O-$), 2.25 (t, J=7.46 Hz, 2H, $-CH_2-(C=O)-O-$), 2.67–2.96 (m, 4H, $-CH_2-S-CH-$, $-CH_2-S-$), 3.00–3.08 (m, 1H, $-CH-NH-$), 3.09–3.16 (m, 1H, $-CH_2-S-CH-$), 3.38–3.59 (m, 8H, $-CH_2-S-$, $-CH_2-O-$), 3.59–3.69 (m, 1H, $-CH_2-CH-CH_2-$), 3.69–3.81 (m, 2H, $-CH_2-O-$), 4.27–4.36 (m, 1H, $-CH-CH-$), 4.47–4.56 (m, 1H, $-CH-CH-$), 5.79 (d, J=7.93 Hz, 1H, $-(C=O)-NH-$), 6.81 (d, J=8.50 Hz, 1H, $-(C=O)-NH-$), 6.90–7.06 (m, 1H, $-(C=O)-NH-$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 ($-CH_2-CH_3$), 22.7 ($-CH_2-CH_3$), 25.8 (CH_2), 26.1 (CH_2), 28.0 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 31.9 (CH_2), 35.8 ($-CH_2-(C=O)-O-$), 39.2 ($-CH_2-S-$), 40.5 ($-CH_2-S-$), 42.1 ($-CH_2-S-$), 52.8 ($-NH-CH-$), 55.7 ($-CH_2-S-CH-$), 60.2 ($-CH-CH-$), 61.4 ($-CH_2-OH$), 61.8 ($-CH-CH-$), 70.5 ($-CH_2-O-$), 71.4 ($-CH_2-O-$), 71.8 ($-CH_2-O-$), 77.4 ($-CH-O-$), 164.3 ($-NH-(C=O)-NH-$), 174.9 ($-CH_2-(C=O)-$

NH–) ppm. HRMS: calcd for $C_{52}H_{102}N_3O_5S_3$ $[M+H]^+$ 944.6976; found 944.6985.

*4.1.21. 2-Dansylamido-N-(2-O-succinyl-ethyl)-N,N-dimethylethanammonium bromide **29**.* A suspension of the choline derivative **8** (1 g, 2.24 mmol), succinic anhydride (540 mg, 5.4 mmol), and DMAP (15 mg, 0.12 mmol) in dry pyridine (10 ml) was heated to 70 °C under argon in a brown flask for 3 days. After cooling to rt toluene (20 ml) was added and all solvents were distilled off under vacuum. The remainder was purified by column chromatography (silica gel; dichloromethane/MeOH/formic acid, 5:1:0.2; R_f=0.3) affording product **29** (1.1 g) in 90% yield as a yellowish green hygroscopic solid. ^{1}H NMR (300 MHz, CD_3OD): δ=2.47–2.56 (m, 4H, –(C=O)–CH_2–CH_2–(C=O)–), 2.78–2.89 (m, 6H, C_{ar}–N(CH_3)$_2$), 3.09–3.19 (m, 6H, –N(CH_3)$_2$), 3.24–3.33 (m, 2H, –CH_2–NH–), 3.53 (t, J=6.23 Hz, 2H, –(CH$_3$)$_2$N$^+$–CH_2–), 3.65–3.72 (m, 2H, –(CH$_3$)$_2$N$^+$–CH_2–), 4.39–4.54 (m, 2H, –CH_2–O–(C=O)–), 7.25 (d, J=7.36 Hz, 1H, CH_{ar}), 7.51–7.66 (m, 2H, CH_{ar}), 8.18–8.24 (m, 1H, CH_{ar}), 8.27 (d, J=8.50 Hz, 1H, CH_{ar}), 8.55 (d, J=8.50 Hz, 1H, CH_{ar}) ppm. ^{13}C NMR (75.5 MHz, CD_3OD): δ=30.7 (–(C=O)–CH_2–CH_2–(C=O)–), 38.2 (–CH_2–NH–), 45.9 (C_{ar}–N(CH_3)$_2$), 52.9 (–N(CH_3)$_2$), 58.8 (–CH_2–O–(C=O)–), 64.7 (–(CH$_3$)$_2$N$^+$–CH_2–), 65.1 (–(CH$_3$)$_2$–CH_2–), 116.8 (CH_{ar}), 120.2 (CH_{ar}), 124.6 (CH_{ar}), 129.7 (CH_{ar}), 130.8 (CH_{ar}), 130.9 (C_{ar}), 131.4 (C_{ar}), 131.9 (CH_{ar}), 135.8 (C_{ar}), 153.6 (C_{ar}), 173.9 (–CH$_2$–(C=O)–O–) ppm. HRMS: calcd for $C_{22}H_{32}N_3O_6S$ $[M-Br]^+$ 466.2006; found 466.2006.

*4.1.22. 1-O-(2-Dansylamido-N,N-dimethylethanammonium bromid-N-(ethyl-O-succinyl))-2-N-biotinyl-3-((2,3-bis(octadecyloxy)propyl) disulfanyl)-2-aminopropanol **30**.* DCC (181 mg, 0.88 mmol) and DMAP (37 mg, 0.30 mmol) were added to a solution of succinate **29** (46 mg, 0.084 mmol) and the biotin amide **27** (40 mg, 0.042 mmol) in dichloromethane (1.1 ml). The mixture was stirred in a sealed tube at 40 °C (2 bar) for 14 days. The solvent was distilled off and the remainder purified by column chromatography (silica gel; dichloromethane/MeOH, 5:1; R_f=0.2). The solid yellow product (34 mg) was obtained in 55% yield as diastereomeric mixture. Mp 42–44 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.81–0.92 (m, 6H, –CH$_2$–CH_3), 1.01–1.37 (m, 60H, –CH_2–), 1.44–1.73 (m, 10H, –CH_2–, –CH_2–CH$_2$–O–), 1.71–1.93 (m, 4H, –CH_2–(C=O)–O–), 2.45–2.59 (m, 2H, –CH_2–(C=O)–O–), 2.68–2.78 (m, 2H, –CH_2–S–CH–), 2.80–2.88 (m, 8H, C_{ar}–N(CH_3)$_2$, –CH_2–S–), 3.09–3.24 (m, 6H, –N(CH_3)$_2$), 3.28–3.53 (m, 10H, –CH_2–S–CH–, –CH$_2$–S–CH–, –SO$_2$–NH–CH_2–, –NH–CH–, –CH_2–O–(C=O)–), 3.53–3.63 (m, 2H, –CH_2–O–), 3.76–3.95 (m, 5H, –CH_2–O–, –CH–O–, –CH_2–N(CH$_3$)$_2$), 3.99–4.09 (m, 2H, –CH_2–O–), 4.47–4.59 (m, 2H, –CH–CH–), 7.13 (d, J=7.37 Hz, 1H, CH_{ar}), 7.41–7.64 (m, 2H, CH_{ar}), 8.07–8.20 (m, 1H, CH_{ar}), 8.25–8.36 (m, 1H, CH_{ar}), 8.48 (d, J=8.50 Hz, 1H, CH_{ar}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (–CH$_2$–CH_3), 22.6 (–CH_2–CH$_3$), 24.9 (CH_2), 25.3 (CH_2), 25.9 (CH_2), 26.0 (CH_2), 29.6 (CH_2), 30.7 (CH_2), 31.9 (CH_2), 32.2 (CH_2), 37.7 (CH_2), 40.0 (C_{ar}–N(CH_3)$_2$), 40.3 (–NH–CH–), 45.4 (–N(CH$_3$)$_2$), 50.4 (–CH–S–CH$_2$–), 52.5 (–CH–CH–), 54.6 (–CH–CH–), 57.8 (–CH_2–), 63.5 (–CH$_2$–), 64.0 (–CH_2–), 70.6 (–CH_2–), 71.7 (–CH_2–), 77.2 (–CH$_2$–CH–CH$_2$–), 115.4 (CH_{ar}), 119.2 (CH_{ar}), 123.2 (CH_{ar}), 128.6 (CH_{ar}), 128.9 (CH_{ar}), 129.4 (C_{ar}), 129.8 (C_{ar}), 130.5 (CH_{ar}), 134.2 (C_{ar}), 151.7 (C_{ar}), 170.0 (–CH$_2$–(C=O)–O–), 172.4 (–CH$_2$–(C=O)–NH–) ppm. HRMS: calcd for $C_{74}H_{129}N_6O_{10}S_4$ $[M-2H-Br]^-$ 1389.8653; found 1389.7842.

*4.1.23. 3-((2,3-Bis(octadecyloxy)propyl)disulfanyl)propan-1,2-diol **32**.* PTAD (64 mg, 0.36 mmol) was added to a solution of the diether **3** (220 mg, 0.36 mmol) in dry dichloromethane (6 ml) and dry MeCN (3 ml) under stirring at rt. The resulting red solution was stirred under argon for 1.5 h and afterward at 55 °C for about 2 h until the mixture became colorless. A solution of 1-thioglycerol (44 mg, 0.40 mmol) was added and the mixture was stirred at rt for 20 h. The solvent was distilled off and the remainder purified by column chromatography (silica gel; dichloromethane/MeOH, 10:1; R_f=0.5) affording the colorless solid product **32** (186 mg) as diastereomeric mixture in 72% yield. As a by-product the symmetric disulfide of **3** was isolated in 20% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.81–0.95 (m, 6H, –CH$_2$–CH_3), 1.14–1.48 (m, 60H, –CH_2–), 1.50–1.63 (m, 4H, –CH_2–), 2.70–3.02 (m, 4H, –CH_2–S–S–CH_2–), 3.38–3.82 (m, 9H, H–O–CH, –CH_2–O–CH_2, –CH_2–O–CH, CH–CH$_2$–OH), 3.90–4.08 (m, 1H, –CH$_2$–O–CH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (–CH$_2$–CH_3), 22.7 (–CH_2–CH$_3$), 26.0 (–CH_2–), 29.3 (–CH_2–), 29.4 (–CH_2–), 29.5 (–CH_2–), 29.6 (–CH_2–), 29.7 (–CH_2–), 30.0 (–CH_2–), 31.9 (–CH_2–), 41.1 (CH$_2$–S–S–), 42.0 (CH$_2$–S–S–), 65.1 (CH$_2$–O–CH_2–CH), 70.2 (CH–O–CH$_2$–), 70.5 (–CH$_2$–CH_2–O–), 71.2 (HO–CH$_2$–CH), 71.8 (–CH$_2$–CH_2–O–), 77.5 (CH–OH) ppm.

*4.1.24. 1-O-Biotinyl-3-((2,3-bis(octadecyloxy)propyl)disulfanyl) propan-1,2-diol **33**.* A suspension of (+)-biotin (135 mg, 0.56 mmol), disulfide **32** (264 mg, 0.37 mmol), DCC (152 mg, 0.74 mmol), and DMA (30 mg, 0.24 mmol) was stirred at rt for 3 days. The solvent was removed by a rotary evaporator and the remainder purified by column chromatography (silica gel; CHCl3/MeOH, 25:1; R_f=0.3) affording the colorless solid product **33** (150 mg) as diastereomeric mixture in 43% yield. Mp 62–64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.79–0.90 (m, 6H, –CH$_2$–CH_3), 0.99–1.34 (m, 60H, –CH_2–), 1.37–1.48 (m, 2H, –CH_2–), 1.49–1.60 (m, 4H, –CH_2–), 1.61–1.75 (m, 4H, –CH_2–), 2.37 (t, J=7.55 Hz, 2H, –CH$_2$–CH_2–(C=O)–O–), 2.67–2.98 (m, 6H, –CH–CH_2–S–S–, –CH_2–S–CH–), 3.04–3.16 (m, 1H, –CH–CH–CH$_2$–), 3.37–3.46 (m, 2H, –CH$_2$–CH_2–O–), 3.47–3.57 (m, 4H, –CH$_2$–CH_2–O–, –CH–CH_2–O–), 3.58–3.67 (m, 1H, –CH–CH$_2$–O–CH$_2$–), 3.98–4.23 (m, 3H, –CH–OH, –CH_2–O–(C=O)–), 4.24–4.33 (m, 1H, –CH–CH–), 4.43–4.54 (m, 1H, –CH–CH–), 5.91 (d, J=10.01 Hz, 1H, NH–(C=O)–NH), 6.72–6.83 (m, 1H, NH–(C=O)–NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0 (–CH$_2$–CH$_3$), 22.6 (CH$_2$–CH$_3$), 24.7 (CH$_2$), 26.0 (CH$_2$), 28.0 (CH$_2$), 28.2 (CH$_2$), 29.3 (CH$_2$), 29.4 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 30.0 (CH$_2$), 31.8 (CH$_2$), 33.6 (–CH$_2$–(C=O)–O–), 40.5 (–CH$_2$–S–S–), 41.1 (–CH$_2$–S–S–), 42.1 (–CH$_2$–S–CH–), 55.7 (–CH$_2$–S–CH–), 60.2 (–CH$_2$–CH–CH–), 61.7 (–CH$_2$–CH–CH–), 66.8 (–CH$_2$–O–), 68.0 (–CH–OH), 70.5 (–CH$_2$–O–), 71.3 (–CH$_2$–O–), 71.7 (–CH$_2$–O–), 77.4 (–CH–O–CH$_2$–), 164.2 (–NH–(C=O)–NH–), 173.7 (–(C=O)–O–) ppm. HRMS: calcd for $C_{52}H_{101}N_2O_6S_3$ $(M+H)^+$ 945.6826; found 945.6816.

*4.1.25. 5-N-Succinyl-5-aminofluorescein methyl ester **35**.* A suspension of 5-aminofluorescein-methyl ester (292 mg, 0.81 mmol) and succinic anhydride (350 mg, 3.5 mmol) in dry pyridine (9 ml) was stirred under argon for 26 h. After cooling to rt toluene (20 ml) was added and all solvents were distilled off under vacuum. The remainder was purified by column chromatography (silica gel; dichloromethane/MeOH, gradient: 10:1≥4:1; R_f=0.3) giving product **35** (205 mg) as yellow solid in 55% yield.

*4.1.26. 1-O-Biotinyl-2-O-(5-aminofluorescein methyl ester-5-N-succinyl)-3-((2,3-bis(octadecyloxy)propyl)disulfanyl)propan-1,2-diol **36**.* TMSCl (6 μl, 0.05) was added to a suspension of succinate **35** (23 mg, 0.05 mmol) and DMAP (6 mg, 0.05 mmol) in dry pyridine (1 ml). After stirring under argon at rt for 1 h DCC (26 mg, 0.13 mmol), DMAP (8 mg, 0.065 mmol), and THF (2 ml) were added. The mixture was heated in a sealed tube at 70 °C under argon for 4 days. After removing the solvent by a rotary evaporator the remainder was purified by column chromatography (silica gel; dichloromethane/MeOH, 10:1; R_f=0.5) affording a diastereomeric mixture of product **36** (36 mg) as yellow solid in 52% yield. Mp 152–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.86 (t, J=6.12 Hz, 6H, –CH$_2$–CH_3), 0.93–1.41 (m, 60H, –CH_2–), 1.39–1.72 (m, 10H, –CH_2–CH$_2$–O–, –CH_2–), 1.92–2.47 (m, 2H, –CH_2–(C=O)–O–), 2.57–3.17 (m, 14H, –CH_2–S–S–CH_2–, –CH_2–S–CH–, –(C=O)–

CH_2–CH_2–(C=O)–, –(C=O)–O–CH_3), 3.35–3.71 (m, 7H, –CH_2–O–, –CH_2–O–CH–), 4.14–4.61 (m, 4H, –CH–CH–, –CH_2–O–(C=O)–), 5.60–5.72 (m, 1H, –CH–O–(C=O)–), 6.65–7.01 (m, 7H, CH_{ar}), 7.36–7.48 (m, 1H, CH_{ar}), 7.73 (d, J=8.29 Hz, 1H, CH_{ar}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$/CD_3COD, 6:1): δ=13.8 (–CH_2–CH_3), 22.4 (–CH_2–CH_3), 25.8 (CH_2), 28.2 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 29.7 (CH_2), 31.7 (CH_2), 33.7 (–CH_2–(C=O)–O–), 40.1 (–CH_2–S–S–), 40.9 (–CH_2–S–S–), 46.0 (–CH_2–S–CH–), 52.4 (–(C=O)–O–CH_3), 55.3 (–CH_2–S–CH–), 59.9 (–CH–CH–), 61.8 (–CH–CH–), 63.3 (–CH_2–O–), 64.9 (–CH_2–O–), 70.3 (–CH_2–O–), 71.1 (–CH_2–O–), 71.6 (–CH_2–O–), 71.8 (–CH_2–O–), 77.2 (–CH_2–O–CH–), 103.6 (CH_{ar}), 114.9 (C_{ar}), 121.6 (CH_{ar}), 121.6 (CH_{ar}), 121.7 (CH_{ar}), 128.8 (CH_{ar}), 130.0 (CH_{ar}), 130.2 (CH_{ar}), 130.9 (C_{ar}), 131.1 (CH_{ar}), 133.2 (C_{ar}), 134.3 (C_{ar}), 152.4 (C_{ar}), 157.1 (C_{ar}), 163.8 (–NH–(C=O)–NH–), 163.9 (–NH–(C=O)–NH–), 164.4 (–CH_2–(C=O)–O–), 172.7 (–CH_2–(C=O)–O–), 172.9 (–CH_2–(C=O)–O–), 176.0 (–CH_2–(C=O)–O–) ppm. HRMS: calcd for $C_{77}H_{118}N_3O_{13}S_3$ $[M+H]^+$ 1388.7821; found 1388.7485.

*4.1.27. 2,3,4,6-O-Tetraacetyl-β-1-O-(2,3-bis(octadecyloxy)propyl)-glucose **38**.* Molecular sieve (4 Å) (3.3 g) was added to a solution of glycerol-1,2-dioctadecylether (**37**) (2.96 mg, 5.0 mmol) in dry toluene (60 ml). Ag_2O (2.55 g, 11.0 mmol), Ag_2CO_3 (1.38 g, 5.0 mmol), iodine (1.27 g, 5.0 mmol), and 1-bromo-tetraacetyl-D-glucose (4.11 g, 10.0 mmol) were added under stirring and the resulting violet mixture was heated to 50 °C for 24 h. The black precipitate was filtered off and the slightly yellow filtrate was concentrated by a rotary evaporator. The remainder was purified by column chromatography (silica gel; dichloromethane/EtOAc/cyclohexane, 8:1:7; R_f=0.4) giving rise to the colorless solid product (2.81 g) as 1:1 diastereomeric mixture in 61% yield. Mp 57–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): d=0.80–0.92 (m, 6H, –CH_2–CH_3), 1.12–1.37 (m, 60H, –CH_2–), 1.44–1.58 (m, 4H, –CH_2–CH_2–O–), 1.99 (s, 3H, CH_3–(C=O)–O–), 2.01 (s, 3H, CH_3–(C=O)–O–), 2.02 (s, 1.5H, CH_3–(C=O)–O–), 2.03 (s, 1H, CH_3–(C=O)–O–), 2.07 (s, 3H, CH_3–(C=O)–O–), 3.34–3.73 (m, 9H, –CH_2–O–, CH-5, –CH_2–CH–CH_2–, –O–CH_2–), 3.81–3.96 (m, 1H, –O–CH_2–), 4.06–4.31 (m, 2H, CH_2-6), 4.50–4.62 (m, 1H, CH-1), 4.93–5.25 (m, 3H, CH-2, CH-3, CH-4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): d=14.1 (–CH_2–CH_3), 20.5 (CH_3–(C=O)–O–), 20.6 (CH_3–(C=O)–O–), 20.6 (CH_3–(C=O)–O–), 20.7 (CH_3–(C=O)–O–), 22.6 (–CH_2–CH_3), 26.1 (CH_2), 26.1 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 30.1 (CH_2), 31.9 (CH_2), 61.9 (CH_2-6), 68.4 (CH-4), 69.0 (–CH_2–O–), 70.1 (–CH_2–O–), 70.3 (–CH_2–O–), 70.5 (–CH_2–O–), 70.9 (–CH_2–O–), 71.3 (CH-2), 71.3 (CH-2), 71.7 (CH-3), 71.7 (–CH_2–O–), 71.7 (CH-3), 72.8 (CH-5), 72.9 (CH-5), 77.4 (–CH_2–CH–CH_2–), 77.9 (–CH_2–CH–CH_2–), 101.0 (CH-1), 101.0 (CH-1), 169.2 (CH_3–(C=O)–O–), 169.2 (CH3–(C=O)–O–), 169.4 (CH_3–(C=O)–O–), 170.2 (CH_3–(C=O)–O–), 170.6 (CH_3–(C=O)–O–) ppm.

*4.1.28. β-1-O-(2,3-Bis(octadecyloxy)propyl)-glucose **39**.* NaOMe (0.5 N) in MeOH (2 ml, 1 mmol) was slowly added to a solution of the tetraacetyl derivative **38** (2.81 g, 3.0 mmol) in $CHCl_3$ (10 ml) and MeOH (10 ml) drop wise under stirring. After 24 h at rt the orange mixture was neutralized by ion exchange (DOWEX 50× 400). the solvent was removed by a rotary evaporator and the residue was dissolved in $CHCl_3$ (300 ml). After drying over $MgSO_4$ the solvent was removed by a rotary evaporator. The residue was recrystallized from affording product **39** (1.41 g, 1:1 diastereomeric mixture) as voluminous colorless solid in 62% yield; R_f=0.5 (dichloromethane/MeOH, 5:1). Mp 57–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, J=6.61 Hz, 6H, –CH_2–CH_3), 1.04–1.38 (m, 60H, –CH_2–), 1.46–1.68 (m, 4H, –CH_2–CH_2–O–), 3.09–3.35 (m, 2H, –CH_2–O–), 3.36–3.71 (m, 9H, CH–2, CH–3, CH–4, CH–5, –CH_2–CH–CH_2–), 3.76–3.88 (m, 2H, –CH_2–O–,), 3.89–4.22 (m, 2H, CH_2-6), 4.24–4.48 (m, 1H, CH-1) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$/CD_3OD, 4:3): δ=13.3 (–CH_2–CH_3), 22.1 (–CH_2–CH_3), 25.4 (CH_2), 25.5 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 31.4 (CH_2), 59.5 (CH_2-6), 61.2 (–CH_2–O–), 68.4 (–CH_2–O–), 68.5 (–CH_2–O–), 69.8 (CH-4), 70.2 (–CH_2–O–), 71.2 (–CH_2–O–), 71.9 (CH-2), 73.1 (CH-3), 75.8 (CH-5), 75.9 (CH-5), 77.4 (–CH_2–CH–CH_2–), 102.8 (CH-1) ppm.

*4.1.29. 6-O-Tosyl-β-1-O-(2,3-bis(octadecyloxy)propyl)-glucose **40**.* Tetrabutylammonium hydrosulfate (70 mg, 0.21 mmol) and 2 N aqueous NaOH (2 ml, 4 mmol) were added to a solution of glucose derivative **39** (652 mg, 0.86 mmol) in $CHCl_3$. After cooling to 13 °C tosyl chloride (210 mg, 1.12 mmol) was slowly added. After 24 h stirring at rt $CHCl_3$ (30 ml) and water (50 ml) were added. The organic layer was separated and washed with brine (2×50 ml). The solvent was removed by a rotary evaporator and the remainder purified by column chromatography (silica gel; dichloromethane/MeOH, 20:1; R_f=0.5). The product **40** (210 mg, 1:1 diastereomeric mixture) was obtained as colorless solid in 27% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.81–0.91 (m, 6H, –CH_2–CH_3), 1.14–1.36 (m, 60H, –CH_2–), 1.45–1.60 (m, 4H, –CH_2–CH_2–O–), 2.43 (s, 3H, C_{ar}–CH_3), 3.34–3.62 (m, 10H, CH–4, –CH_2–CH–CH_2–, –CH_2–O–), 3.72–3.92 (m, 2H, CH–2, CH–3), 4.11–4.22 (m, 3H, CH_2-6, CH-5), 4.37–4.46 (m, 1H, CH-1), 7.33 (d, J=7.93 Hz, 2H, CH_{ar}), 7.78 (d, J=8.31 Hz, 2H, CH_{ar}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0 (–CH_2–CH_3), 21.6 (C_{ar}–CH_3), 22.6 (–CH_2–CH_3), 25.9 (CH_2), 26.0 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 31.8 (CH_2), 66.2 (CH-5), 66.4 (CH-5), 68.4 (-CH_2–O–), 68.5 (CH-4), 68.7 (CH-2), 68.7 (–CH_2–O–), 69.4 (–CH_2–O–), 69.8 (–CH_2–O–), 70.2 (–CH_2–O–), 70.4 (–CH_2–O–), 70.5 (–CH_2–O–), 71.0 (CH-3), 71.1 (CH-3), 71.7 (–CH_2–O–), 77.4 (–CH_2–CH–CH_2–), 103.6 (CH-1), 127.9 (CH_{ar}), 129.9 (CH_{ar}), 132.4 (C_{ar}), 145.1 (C_{ar}) ppm.

*4.1.30. 6-Desoxy-6-amino-β-1-O-(2,3-bis(octadecyloxy)propyl)-glucose **41**.* Liquid ammonia (100 ml) and a solution of tosylate **40** (162 mg, 0.18 mmol) in $CHCl_3$ (10 ml) were stirred in an autoclave at 25 °C for 20 h. The ammonia was allowed to evaporate and the remainder was washed out of the autoclave by $CHCl_3$ (100 ml). After filtration the filtrate was dried over $MgSO_4$ and the solvent removed by a rotary evaporator. The remainder was purified by column chromatography (silica gel; dichloromethane/MeOH, 5:1; R_f=0.3) affording a diastereomeric mixture of product **41** (70 mg) as colorless wax in 51% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.84–0.95 (m, 6H, –CH_2–CH_3), 1.02–1.41 (m, 60H, –CH_2–), 1.51–1.67 (m, 4H, –CH_2–CH_2–O–), 2.69–2.90 (m, 2H, –CH_2–NH_2), 2.91–3.18 (m, 2H, –CH_2–NH_2), 3.29–3.37 (m, 1H, CH-4), 3.39–3.69 (m, 9H, –CH_2–O–, CH-2, CH-3, –CH_2–CH–CH_2–,), 3.80–4.08 (m, 2H, –CH_2–O–), 4.10–4.28 (m, 1H, CH-5), 4.43–4.54 (m, 1H, CH-1) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (–CH_2–CH_3), 22.7 (–CH_2–CH_3), 26.0 (CH_2), 26.1 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.9 (CH_2), 30.0 (CH_2), 31.9 (–CH_2–CH_2–CH_3), 44.3 (–CH_2–NH_2), 55.5 (CH), 55.5 (CH), 56.6 (CH), 69.5 (CH), 69.6 (CH), 69.8 (–CH_2–O–), 70.1 (–CH_2–O–), 70.3 (–CH_2–O–), 70.4 (–CH_2–O–), 70.5 (–CH_2–O–), 70.5 (–CH_2–O–), 71.8 (–CH_2–O–), 77.5 (–CH_2–CH–CH_2–), 100.9 (CH-1), 101.2 (CH-1)ppm.

*4.1.31. 6-Desoxy-6-N-biotinyl-β-1-O-(2,3-bis(octadecyloxy)propyl)-glucose **42**.* EDC (20 ml, 0.11 mmol), HOBt (20 mg, 0.13 mmol), and DIPEA (31 ml, 0.18 mmol) were added to a solution of the amine **41** (70 mg, 0.09 mmol) and (+)-biotin (20 mg, 0.08 mmol) in dry DMF (1 ml) and dry dichloromethane (1 ml). The mixture was stirred at rt for 24 h and then combined with toluene (5 ml). Solvents were distilled off, the remainder was kept under vacuum (5 mbar, 40 °C) and purified by column chromatography (silica gel; dichloromethane/MeOH, 7:1; R_f=0.6). The colorless waxy product **42** (52 mg) was obtained as diastereomeric mixture in 61% yield. Mp 50–52 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.83–0.91 (m, 6H, –CH_2–CH_3), 1.00–1.33 (m, 60H, –CH_2–), 1.36–1.80 (m, 10H, –CH_2–, –CH_2–CH_2–O–), 2.16–2.31 (m, 2H, –CH_2–(C=O)–NH–), 2.66–2.93 (m, 2H,

–C*H*$_2$–S–CH–), 3.09–3.16 (m, 1H, –CH$_2$–S–C*H*–), 3.32–3.72 (m, 12H, –C*H*$_2$–O–, –C*H*$_2$–C*H*–C*H*$_2$–, –C*H*–, C*H*$_2$-6), 3.76–3.81 (m, 1H, C*H*-3), 3.88–3.95 (m, 1H, C*H*-5), 4.08–4.13 (m, 1H, C*H*-2), 4.28–4.34 (m, 1H, –C*H*–CH–), 4.39–4.57 (m, 2H, -C*H*–CH–, C*H*-1) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (–CH$_2$–*C*H$_3$), 22.7 (–*C*H$_2$–CH$_3$), 25.7 (*C*H$_2$), 26.0 (*C*H$_2$), 26.1 (*C*H$_2$), 28.0 (*C*H$_2$), 28.2 (*C*H$_2$), 29.3 (*C*H$_2$), 29.5 (*C*H$_2$), 29.7 (*C*H$_2$), 29.8 (*C*H$_2$), 29.9 (*C*H$_2$), 29.9 (*C*H$_2$), 30.0 (*C*H$_2$), 31.9 (*C*H$_2$), 36.0 (–*C*H$_2$–(C=O)–O–), 40.5 (–*C*H$_2$–S–CH–), 41.1 (–*C*H$_2$–NH–(C=O)–), 55.6 (–CH$_2$–S–*C*H–), 60.2 (–*C*H–CH–), 61.7 (–*C*H–CH–), 69.4 (*C*H-5), 69.5 (–*C*H–), 70.0 (–*C*H$_2$–O–), 70.1 (–*C*H$_2$–O–), 70.4 (–*C*H$_2$–O–), 70.5 (–*C*H$_2$–O–), 70.5 (–*C*H$_2$–O–), 70.9 (–*C*H$_2$–O–), 71.8 (–*C*H$_2$–O–), 71.9 (–*C*H$_2$–O–), 73.3 (–*C*H–), 73.3 (–*C*H–), 77.4(–CH$_2$–*C*H–CH$_2$–), 101.1 (*C*H-1), 164.2 (–NH–(*C*=O)–NH–), 173.6 (–CH$_2$–(*C*=O)–NH–) ppm. HRMS: calcd for $C_{55}H_{106}N_3O_9S$ $[M+H]^+$ 984.7644; found 984.7646.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.07.089. These data include MOL files and InChIKeys of the most important compounds described in this article.

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