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Analogues of Glycosphingolipids and Glycerolipids Suitable for Conjugation to Gold- and Amino-Functionalised Surfaces

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Dedicated to the memory of Professor Göran Magnusson

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Abstract—A general synthesis of analogues of natural lipids, (i.e. lactosylceramide, globotriasylceramide, and phosphatidylcholine) where one of the alkyl chains carries a terminal thiol- or carboxyl functionality, is described. The lipids were prepared by *N*- or *O*-acylation of sphingosine or monoacylglycerol derivatives. These lipids are suitable for anchoring to gold- or amino-functionalised surfaces, thus creating mimics of a cell membrane for use in the study of protein–carbohydrate interaction.

Introduction

Carbohydrates presented as glycolipids in cell membranes serve as receptors for proteins, antibodies and other biomolecules, for example, for pathogens such as bacteria and viruses during the initial phase of infection.[1] The study of these phenomena has traditionally been performed with natural or synthetic glycolipids presented on TLC plates, microtiter plates, glass or plastic particles, or in liposomes. However, these procedures are not always reliable; the mode of presentation could greatly influence the binding[2] and many of the methods used only give an answer to whether there is a binding or not.

One improvement could be to synthesise analogues of the naturally occurring glycosphingolipids and phoshoglycerolipids. If these analogues are equipped with a functionality that allows covalent conjugation to surfaces, mimics of cell membranes could be generated. Anchoring mixtures of functionalised lipids to surfaces should result in a surface where the carbohydrate will be presented in a way that closely resemble natural cell membranes, thereby minimising undesirable non-specific protein binding. The anchoring of long-chain alkyl-thiols to gold is a well-known phenomena,[2,3] and in the adsorption process they form self-assembled monolayers (SAM:s). Glycosides carrying various single-chain alkyl-thiol linker arms have been used in amperometric biosensors[4] and surface plasmon resonance measurements.[5,6] A recent report[7] describes an investigation of SAM:s of thiolterminated polyethylene-glycol chains (PEG) and thioacetyl GM1 glycolipid for biosensor applications. The PEG chain was reported to cause some problem with non-specific protein adsorption and phase separation in forming the SAM:s.[7]

We herein introduce a general synthesis of two series of lipid analogues, where one of the alkyl chains carries a terminal thiol or carboxyl group (Fig. 1). The first series is based on ω-mercapto terminated lipids[8] prepared from acylation of glycosylsphingosines (compounds **1** and **3**) and acylation of monoacylated *sn*-glycerol (compound **5**) with modified fatty acids. The second series of lipid analogues are ω-carboxyterminated analogues of lactosylceramide and globotriasylceramide (**2** and **4**). The corresponding phosphatidylcholine analogue has been reported earlier.[9] Anchoring mixtures of these lipids to gold respectively amino-functionalised surfaces is a possible route towards mimics of cell membranes.

The problems with non-specific protein adsorption and phase separation in forming the SAM:s using PEG chains[7] might be circumvented by substituting the PEG chain for natural lipids described in this paper. Additional advantages of the present work are that analogues of the carbohydrate part could be introduced and that the concentration of the glycolipid could be varied.

Results and Discussion

Synthesis of modified fatty acid

The hydroxyl acid **6** was transformed into the corresponding bromide **7** by refluxing in aqueous HBr and acetic acid for three days (Scheme 1). The product crystallised upon

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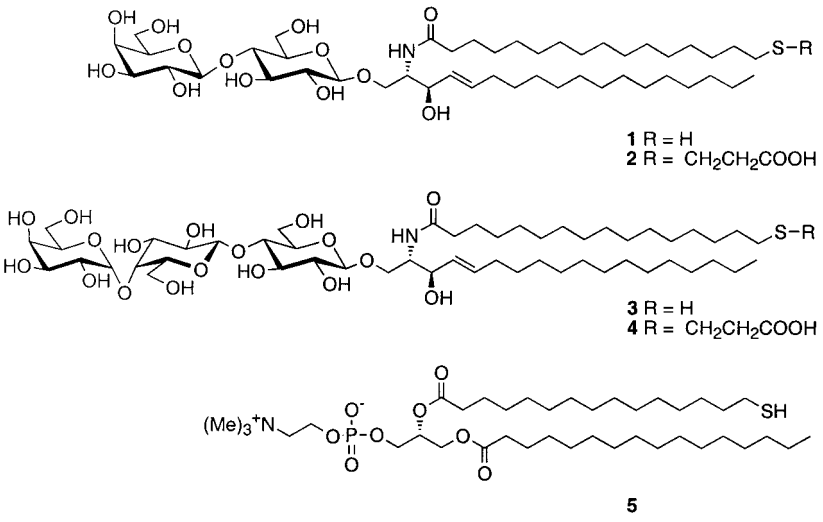
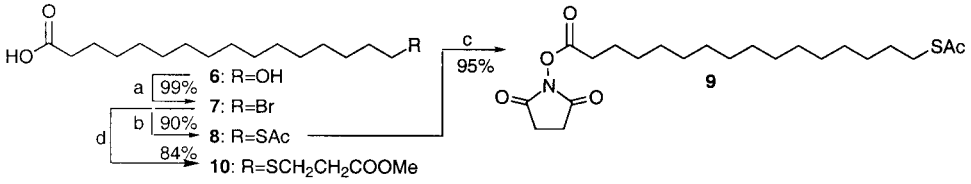


Figure 1.

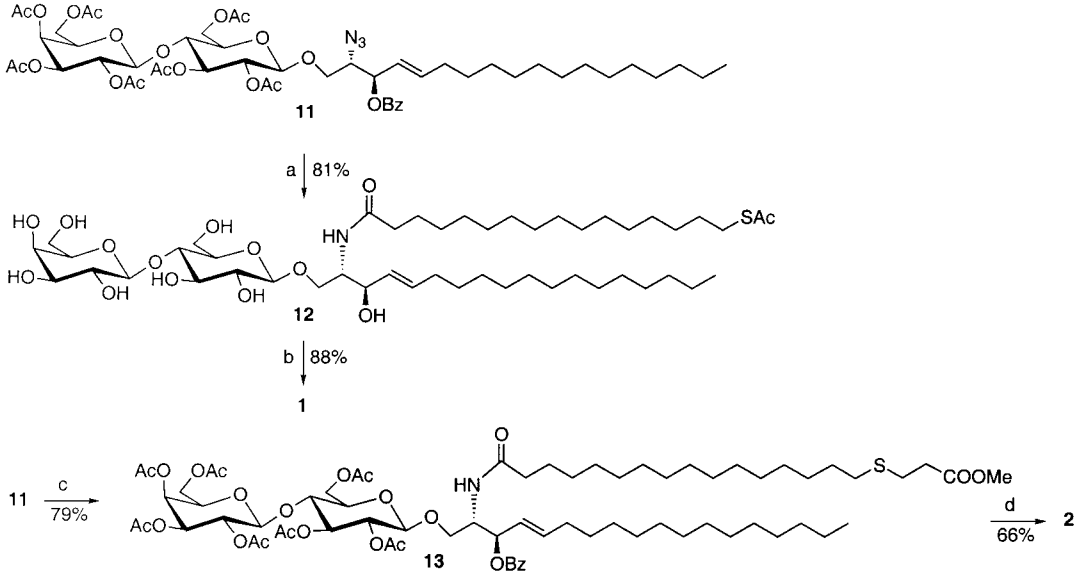


Scheme 1. (a) HBr, AcOH, reflux, 3 days. (b) AcSK, DMF, 50°C, 8 h. (c) *N*-hydroxysuccinimide, EDC, CH_2Cl_2, 12 h. (d) $HSCH_2CH_2COOMe$, Cs_2CO_3, DMF, 15 h.

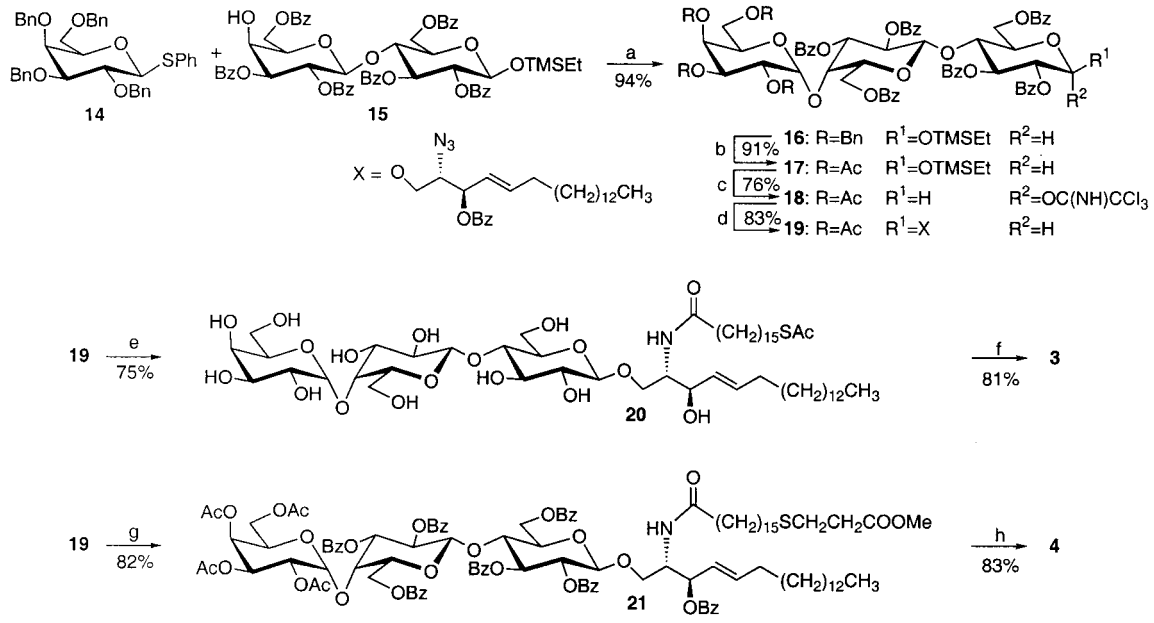
cooling and could be filtered off yielding the crude ω-bromo palmitic acid **7** as a white solid. This could be converted into either the thioacetate **8** in 90% yield by treatment with KSAc in DMF at 50°C or the methyl ester **10** in 84% yield by treatment with methyl 3-mercaptopropionate and Cs_2CO_3 in DMF. Treatment of **8** with *N*-hydroxysuccinimide(NHS) and ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) furnished the activated acid derivative **9**.

Synthesis of modified glycolipids

The known lactosyl azidosphingosine[10] derivative **11** was converted into **12** in 81% yield via deacetylation in methanolic NaOMe, azide reduction with H_2S, and acylation overnight with the NHS-ester **9** (Scheme 2). Removal of the protection group by treatment with methanolic NaOMe furnished the thiol and a small amount of disulfide.



Scheme 2. (a) (i) NaOMe, MeOH. (ii) H_2S, pyridine, Et_3N, MeOH, (iii) **9**, DMF, Et_3N. (b) (i) NaOMe, MeOH, (ii) DTE, iPrNEt, DMF. (c) (i) H_2S, pyridine/H_2O, 6:1, (ii) **10**, EDC, CH_2Cl_2. (d) (i) NaOMe, MeOH, (ii) NaOH, H_2O, MeOH.



Scheme 3. (a) NIS, TMSOTf, CH_2Cl_2/Et_2O, 1:2, −50°C. (b) (i) H_2, Pd/C, AcOH, (ii) Ac_2O, pyridine. (c) (i) CF_3COOH, CH_2Cl_2, (ii) Cl_3CCN, DBU, CH_2Cl_2. (d) (2*S*,3*R*,4*E*)-2-azido-3-benzoyloxy-octadec-4-ene-1-ol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, MS 300 AW. (e) (i) NaOMe, MeOH, (ii) H_2S, pyridine, Et_3N, MeOH, (iii) **9**, DMF, Et_3N. (f) (i) NaOMe, MeOH, (ii) DTE, iPr_2NEt, DMF. (g) (i) H_2S, pyridine/H_2O, 6:1, (ii) **10**, EDC, CH_2Cl_2. (h) (i) NaOMe, MeOH, (ii) NaOH, CH_2Cl_2, MeOH, H_2O.

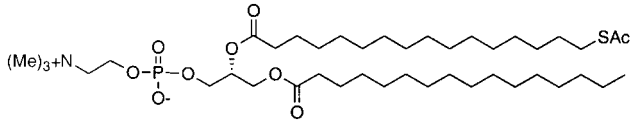
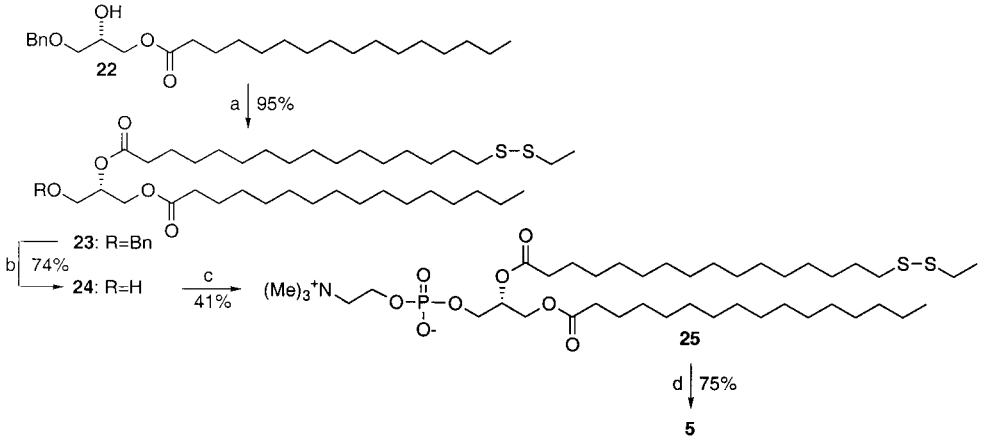


Figure 2.

In order to reverse the disulfide formation the mixture was routinely treated with dithioerythritol and Hünig's base in DMF[6] to give the lactosyl ceramide mimic **1** in 88% yield. The carboxyl-terminated lactosyl ceramide mimic **2** was prepared from **11** by reduction with H_2S in a mixture of pyridine and water to give the amine **13**. Under these less basic conditions base promoted acylmigration is prevented, although the reduction is somewhat slower than the conditions used in the preparation of **12**. Subsequent treatment with the fatty acid derivative **10** and EDC in CH_2Cl_2 gave the protected lactosyl ceramide mimic **13** in 79% yield from **11**. Compound **13** was deprotected in two steps to give the mimic **2** in 66% yield.

The synthesis of globotriasylceramide analogues **3** and **4** (Scheme 3) started with the preparation of globotriose **16**. The galactose donor **14**[11,12] was glycosylated with lactose acceptor **15**[13] using *N*-iodosuccinimide and TMS-triflate[14,15] in CH_2Cl_2/Et_2O at −50°C. By using electron withdrawing benzoyl protecting groups on the acceptor, less than 3% β-anomer is obtained still giving a 94% yield of the globotriose derivative **16**. This selectivity may be explained by the low nucleophilicity of the 4′-OH induced by the surrounding electron withdrawing benzoates.[13,16] Debenzylation of **16** with catalytic hydrogenation, followed by acetylation gave **17** in 91% yield.



Scheme 4. (a) (i) CH_2Cl_2, $CH_3CH_2SS(CH_2)_{15}COOH$, DMAP, DIC, 0°C, 0.5 h, (ii) 22°C, 4.5 h. (b) BCl_3/hexane, EtS–SEt, CH_2Cl_2, −78°C, 1 h. (c) (i) PCl_3, immidazole, Et_3N, toluene, (ii) cholin tosylate, NPCl, pyridine, (iii) I_2, pyridine/H_2O (49:1). (d) *n*-Bu_3P, EtOH/H_2O.

Conversion of the TMSEt-group of **17** into the corresponding trichloroacetimidate **18** was accomplished by treating **17** with CF_3COOH in CH_2Cl_2,[17] followed by Cl_3CCN and DBU in CH_2Cl_2.[18] Glycosylation of 3-*O*-benzoyl azidosphigosine[19–21] with **18** using $BF_3{\cdot}Et_2O$ as promoter in CH_2Cl_2 furnished **19** in 83% yield.

The thiol-terminated globotriasylceramide mimic **3** was prepared from **19**, in a manner similar to that described for the corresponding lactosylceramide mimic **1**, via the protected analogue **20** and finally 81% yield of **3** along with 5% of the corresponding disulfide after deprotection of the thioacetate followed by reduction. The carboxyl-terminated globotriasylceramide mimic **4** was prepared from **19** as described in the preparation of lactosylceramide analogue **2**, giving 82% of the protected intermediate **21** and then 83% yield of **4** after deprotection.

Synthesis of modified phosphatidylcholine

Initial attempts using the *S*-acetyl protected fatty acid **8** turned out to give disappointingly low yield in the final de-*S*-acetylation of the corresponding phospholipid analogue (shown in Fig. 2, prepared from **22**). Selective de-*S*-acylation was not accomplished in the presence of the fatty acid esters under all conditions tried (for example, methanolic NaOMe, methanolic NaSMe,[22] and pyrrolidine in CH_2Cl_2).[23]

As an alternative approach 16-(*S*-dithioethyl)hexadecanoic acid[24] was thus investigated (Scheme 4). The palmitoyl derivative **22** was prepared as described[8] from *sn*-3-*O*-benzylglycerol and palmitic acid. Acylation of **22** with 16-(*S*-dithioethyl)hexadecanoic acid promoted by diisopropylcarbodiimide (DIC) in CH_2Cl_2/DMAP-solution, gave the benzylprotected bis-acylglycerolderivative **23**. Debenzylation of **23** was performed with BCl_3 in CH_2Cl_2 at $-78°C$[25] yielding **24** in only 30%. One major side reaction was disproportionation of the disulfide which gave dimers via disulfide formation between the lipids. This large molecule turned out to be difficult to handle due to its poor solubility. In a first attempt to circumvent disulfide disproportion, changing the benzyl protection group to *p*-methoxybenzyl, was expected to allow the use of a milder Lewis' acid in the deprotection of **23**. Unfortunately the use of milder acids, such as $BF_3{\cdot}Et_2O$, $SnCl_4$, or 1–5% CF_3COOH, resulted in acyl migrations leading to inseparable mixtures of regioisomers. The disproportionation was finally solved by addition of diethyl disulfide to the reaction mixture in the debenzylation of **23** under the original conditions with BCl_3, which gave **24** in 74% yield.

Phosphorylation under dry conditions with PCl_3/Et_3N/imidazole in freshly distilled toluene,[26] coupling with choline tosylate[27] using 5,5-dimethyl-2-oxo-2-chloro-1,3,2-dioxaphosphorinan (NPCl)[28] as coupling agent, and mild oxidation of the phosphatide with iodine, furnished the phosphatidyl choline analogue **25**. Compound **25** was deprotected under mild reducing conditions using n-Bu_3P in $EtOH/H_2O$[24] yielding the phosphatidyl choline analogue **5**.

Conclusion

We have described the synthesis of thiol- and carboxy analogues of naturally occurring lipids suitable for conjugation to gold- or amino-functionalised surfaces. Such surfaces are expected to present the glycolipid in a more natural way. The synthesis (Schemes 1–4) is general, i.e. it allows the introduction of different carbohydrates, including chemically modified analogues.

Experimental

General

NMR spectra were recorded with a Bruker DRX-400 instrument using residual $CHCl_3$ as reference. ^1H NMR spectral assignments were made by COSY experiments. Concentrations were made using rotary evaporation with a bath temperature at or below 40°C. Flash chromatography was performed on Grace Amicon Silica gel 60 (0.035–0.070 mm) and TLC was performed on Kieselgel 60 F_{254} plates (Merck). All non-aqueous reactions were run in septum-capped, oven-dried flasks under Ar (1 atm). CH_2Cl_2, toluene, and pyridine was distilled from CaH_2. Et_2O was distilled from Na.

***S*-Acetyl-16-mercaptohexadecanoic acid (8).** To a solution of 16-hydroxyhexadecanoic acid (0.55 g, 2.0 mmol) in AcOH (9.4 mL) was added aqueous HBr (48%, 9.4 mL) and the solution was refluxed for 3 days. The product crystallised upon cooling of the reaction mixture to room temperature. The crystals were filtered off and washed with ice-cold water. Drying gave the desired 16-bromohexadecanoic acid **7** which was used in the next step without further purification.

To a solution of 16-bromohexadecanoic acid in freshly destilled DMF (13 mL) was added AcSK (0.34 g, 3.0 mmol) and the mixture was stirred at 50°C for 15 h, then poured into Et_2O/H_2O. 1 M aqueous HCl was added to the aqueous phase until pH 5–6 (moist pH-paper), which was then extracted with Et_2O (3×20 mL). The organic phases were combined, dried ($MgSO_4$), concentrated, and flash chromatographed (SiO_2, 10:1→2:1 heptane/EtOAc gradient) to give **8** (0.60 g, 91%) as a pale yellow solid; ν (film) 2920, 2870, 1700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.87 (t, 2H, J=7.3 Hz, CH_2SAc), 2.36 (t, 2H, J=7.4 Hz, CH_2COOH), 2.33 (s, 3H, SAc), 1.63 (m, 4H, CH_2CH_2SAc, CH_2CH_2COOH), 1.44–1.25 (m, 22H, CH_2); δ_C (100.6 MHz, $CDCl_3$) 196.7, 179.9, 34.4, 31.1, 30.06, 30.04, 30.00, 29.92, 29.90, 29.85, 29.7, 29.60, 29.55, 29.5, 29.3, 25.1; HRMS (FAB): $(M+H)^+$, found 331.2310. $C_{18}H_{35}O_3S$ requires 331.2307.

***N*-(*S*-Acetyl-16-mercaptohexadecanoyloxy)-succinimide (9).** To a solution of **8** (300 mg, 0.91 mmol) in CH_2Cl_2 (8 mL) was added *N*-hydroxysuccinimide (418 mg, 3.63 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (725 mg, 3.63 mmol) and the mixture was stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with H_2O (2×25 mL), dried (Na_2SO_4), concentrated, and flash chromatographed (SiO_2, 4:1→2:1

heptane/EtOAc gradient) to give **9** (370 mg, 95%) as a white solid; ν (film) 2920, 2870, 1740, 1700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.87 (m, 6H, CH_2SAc, $COCH_2CH_2CO$), 2.61 (t, 2H, J=7.4 Hz, CH_2COON), 2.34 (s, 3H, SAc), 1.75 (dt, 2H, J=7.2, 7.9 Hz, CH_2CH_2COON), 1.59 (dt, 2H, J=5.9, 7.5 Hz, CH_2CH_2SAc), 1.30–1.25 (m, 22H, CH_2); δ_C (100.6 MHz, $CDCl_3$) 196.6, 169.6, 169.1, 31.4, 31.1, 30.04, 30.03, 29.99, 29.97, 29.92, 29.91, 29.8, 29.59, 29.55, 29.5, 29.3, 29.2, 26.0, 25.0; HRMS (FAB): $(M+H)^+$, found 428.2468. $C_{22}H_{38}O_3NS$ requires 428.2471.

16-(2-Methoxycarbonylethylthio)-hexadecanoic acid (10). To a solution of crude 16-bromohexadecanoic acid **7** (200 mg), prepared as described for **8** in dry and deoxygenated DMF (10 mL) was added Cs_2CO_3 (290 mg, 0.90 mmol) and methyl 3-mercaptopropionate (0.13 mL, 1.20 mmol) and the mixture was stirred at room temperature for 15 h, then poured into Et_2O/H_2O. Aqueous HCl (1 M) was added to the aqueous phase until pH 5–6 (moist pH-paper). The aqueous phase was extracted with Et_2O (3×10 mL), the organic phases were combined, dried ($MgSO_4$), concentrated, and flash chromatographed (SiO_2, 4:1→3:1 heptane/EtOAc gradient) to give **10** (190 mg, 85%) as a white solid; ν (film) 2920, 2870, 1750, 1700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.71 (s, 3H, CH_3), 2.79 (t, 2H, J=7.4 Hz, CH_2COOMe), 2.62 (t, 2H, J=7.3 Hz, SCH_2CH_2COOMe), 2.54 (t, 2H, J=7.3 Hz, CH_2S), 2.36 (t, 2H J=7.5 Hz, CH_2COOH), 1.66–1.55 (m, 4H, CH_2CH_2COOH, CH_2CH_2S), 1.35–1.25 (m, 22H, CH_2); δ_C (100.6 MHz, $CDCl_3$) 180.2, 172.9, 52.1, 35.1, 34.4, 32.5, 30.0, 29.91, 29.85, 29.8, 29.6, 29.4, 29.2, 27.3, 25.0; HRMS (FAB): M^+, found 374.2498. $C_{20}H_{38}O_4S$ requires 374.2491.

(2*S*,3*R*,4*E*)-3-Hydroxy-2-(*S*-acetyl-16-mercaptohexadecanamido)octadec-4-enyl (β-D-galactopyranosyl)-(1→4)-β-D-glucopyranoside (12). Compound **11**[10] (210 mg, 0.197 mmol) was dissolved in MeOH (15 mL), NaOMe (0.080 mL, 1 M) was added, and the mixture was stirred at room temperature overnight, then neutralised with Amberlite IR-120 (H^+) resin, filtered, concentrated, flash chromatographed (SiO_2, 20:10, CH_2Cl_2/MeOH), and concentrated. The residue (118 mg, 0.186 mmol) was dissolved in pyridine (5.5 mL), Et_3N (2.8 mL), and MeOH (2.8 mL). The solution was saturated with H_2S by bubbling for 1 h at 0°C. The mixture was kept under H_2S at ambient temperature for 15 h, N_2 was bubbled through the mixture for 1 h, and the mixture was concentrated and co-concentrated with toluene. The residue was dissolved in DMF (10 mL) and compound **9** (119 mg, 0.28 mmol) and Et_3N (0.053 mL, 0.37 mmol) were added. The mixture was stirred overnight, concentrated, and flash chromatographed (SiO_2, 30:10:1 CH_2Cl_2/MeOH/H_2O). In order to remove residual *N*-hydroxysuccinimide, the residue was further purified on a Bond–Elut C-18 column (1:9→1:0 MeOH/H_2O gradient), which gave pure **12** (145 mg, 85%) as a white solid; $[\alpha]_D^{23}$=+1 (*c* 1.0, $CHCl_3/CH_3OH/H_2O$, 65:35:10); ν (film) 3850, 2920, 2870 cm^{-1}; δ_H (400 MHz, $CDCl_3/CD_3OD/D_2O$, 65:35:10) 7.33 (d, 1H, J=9.2 Hz, NH), 5.46 (m, 1H, =C*H*–CH_2), 5.22 (dd, 1H, J=7.6, 15.4 Hz, =C*H*–CH(OH), 5.13 (d, 1H, J=7.5 Hz, H-1′), 5.08 (d, 1H, J=7.8 Hz, H-1), 3.96 (dd, 1H, J=4.3, 7.6 Hz, OCH_aH_b), 3.84 (t, 1H, J=8.2 Hz, C*H*(OH)), 3.74 (m, 1H, C*H*(NH)), 3.98–3.30 (m, 11H), 3.20 (m, 1H), 3.10 (m, 1H, H-2), 2.65 (t, 2H, J=7.3 Hz, CH_2SAc), 2.08 (s, 3H, SAc), 1.95 (t, 2H, J=7.7 Hz, $NCOCH_2$), 1.80 (m, 2H, =CH–CH_2), 1.35 (m, 4H, $NCOCH_2CH_2$, CH_2CH_2SAc), 1.14–1.04 (m, 44H, CH_2), 0.68 (t, 3H, J=6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3/CD_3OD/D_2O$ 65:35:10) 197.2, 174.5, 134.3, 129.2, 103.5, 102.7, 79.2, 75.4, 74.5, 73.2, 73.0, 71.7, 71.0, 68.8, 61.2, 60.4, 36.3, 32.2, 31.7, 30.2, 29.6, 29.53, 29.51, 29.49, 29.42, 29.35, 29.31, 29.25, 29.22, 29.19, 29.1, 28.99, 28.95, 28.6, 25.8, 22.5, 13.8; HRMS (FAB): $(M+Na)^+$, found 958.5925. $C_{48}H_{89}O_{14}NSNa$ requires 958.5901.

(2*S*,3*R*,4*E*)-3-Hydroxy-2-(16-mercaptohexadecanamido)-octadec-4-enyl (β-D-galactopyranosyl)-(1→4)-β-D-glucopyranoside (1). To a solution of **12** (40 mg, 0.044 mmol) in MeOH (1.0 mL) and CH_2Cl_2 (1.0 mL) was added NaOMe (0.150 mL, 1 M in MeOH). After 2 h, methanolic acetic acid (20%) was added until neutral reaction on pH-paper and the solution was evaporated. The residue was dissolved in DMF (9.0 mL) followed by addition of dithioerythritol (41 mg, 0.26 mmol) and diisopropylethylamine (0.023 mL, 0.13 mmol). After 5 h, the mixture was filtered through a short SiO_2-column (CH_2Cl_2/MeOH/H_2O, 66:33:4), concentrated, and flash chromatographed (SiO_2, 7:1:0.2→7:3:0.2, CH_2Cl_2/MeOH/H_2O gradient) to give **1** (34 mg, 88%) as a white solid; $[\alpha]_D^{23}$=+2 (*c* 1.0, $CHCl_3$/MeOH/H_2O, 65:35:10); δ_H (400 MHz, $CDCl_3/CD_3OD/D_2O$, 65:35:10) 7.33 (d, 1H, J=9.2 Hz, NH), 5.46 (m, 1H, =C*H*–CH_2), 5.22 (dd, 1H, J=7.6 Hz, 15.4, =C*H*–CH(OH), 4.13 (d, 1H, J=7.5 Hz, H-1′), 4.08 (d, 1H, J=7.8 Hz, H-1), 3.96 (dd, 1H, J=4.3, 7.6 Hz, OCH_aH_b), 3.84 (t, 1H, J=8.2 Hz, C*H*(OH)), 3.74 (m, 1H, C*H*(NH)), 3.98–3.30 (m, 11H), 3.20 (m, 1H), 3.10 (m, 1H, H-2), 2.31 (t, 2H, J=7.3 Hz, CH_2SH), 1.96 (t, 2H, J=7.4 Hz, $NCOCH_2$), 1.82 (m, 2H, =CH–CH_2), 1.45–1.36 (m, 4H, $NCOCH_2CH_2$, CH_2CH_2SH), 1.14–1.06 (m, 44H, CH_2), 0.68 (t, 3H, J=6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3/CD_3OD/D_2O$ 65:35:10) 174.6, 134.6, 129.1, 103.3, 102.7, 78.8, 75.4, 74.8, 74.5, 73.03, 72.97, 71.6, 71.0, 68.7, 61.1, 60.2, 36.3, 33.9, 32.3, 31.8, 29.59, 29.56, 29.51, 29.47, 29.46, 29.42, 29.38, 29.32, 29.30. 29.21, 29.16, 28.9, 28.2, 25.9, 24.2, 22.5, 13.8; HRMS (FAB): $(M+Na)^+$, found 916.5784. $C_{46}H_{87}O_{13}NSNa$ requires 916.5796.

(2*S*,3*R*,4*E*)-3-*O*-Benzoyl-2-(16-(2-methoxycarbonylethylthio)hexadecanamido)octadec-4-enyl (2,3,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (13). H_2S was bubbled through a mixture of **11**[10] (50 mg, 0.047 mmol) in pyridine/H_2O (14 mL, 6:1) at 0°C for 1 h. The mixture was kept under H_2S at ambient temperature for 72 h, N_2 was bubbled through the mixture for 1 h, and the mixture was concentrated and co-concentrated with toluene. The residue was dissolved in CH_2Cl_2 (5 mL) and compound **10** (53 mg, 0.14 mmol) and EDC (27 mg, 0.14 mmol) were added. The mixture was stirred for 3 h, concentrated, and flash chromatographed (SiO_2, 3:1→1:1, heptane/EtOAc gradient) to give **13** (54 mg, 82%) as a white solid; $[\alpha]_D^{23}$=−1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.01 (m, 2H, Ar-H), 7.55 (m, 1H, Ar-H), 7.43 (m, 2H, Ar-H), 5.88 (m, 1H, =C*H*–CH_2), 5.53–5.45 (m, 2H, =C*H*–C*H*OBz), 5.33 (d, 1H, J=2.6 Hz, H-4′), 5.17 (t, 1H, J=9.5 Hz, H-3), 5.08 (dd, 1H, J=7.9, 10.4 Hz, H-2′), 4.94 (dd, 1H, J=3.4, 10.4 Hz,

H-3′), 4.87 (dd, 1H, *J*=7.8, 9.6 Hz, H-2), 4.49 (m, 3H, H-1, H-1′, C*H*NH), 4.35 (d, 1H, *J*=9.6 Hz, H-6), 4.15–4.01 (m, 2H, H-6′), 4.02–3.93 (m, 2H, H-6, CH_2O), 3.87 (t, 1H, *J*=9.6 Hz, H-4), 3.69 (s, 3H, Me), 3.62 (dd, 1H, *J*=4.6, 10.3 Hz, CH_2O), 3.55 (m, 1H, H-5), 2.78 (t, 2H, *J*=7.5 Hz, CH_2COOMe), 2.60 (t, 2H, *J*=7.4 Hz, CH_2CH$_2$COOMe), 2.51 (t, 2H, *J*=7.7 Hz, CH_2SCH$_2$CH$_2$COOMe), 2.14, 2.07, 2.05, 2.02, 2.01, 1.96, 1.95 (7 s, 3H each, OAc), 2.03 (m, 2H, =CH–CH_2), 1.57 (m, 4H, NCOCH_2, CH_2CH$_2$SCH$_2$CH$_2$-COOMe), 1.35–1.20 (m, 44H, CH_2), 0.87 (t, 3H, *J*=6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 173.1, 172.9, 170.8, 170.7, 170.6, 170.5, 170.2, 170.1, 169.5, 165.6, 138.0, 133.5, 130.6, 130.0, 128.8, 125.0, 101.5, 100.7, 76.5, 74.5, 73.1, 73.0, 72.2, 71.4, 71.1, 69.4, 67.9, 67.0, 62.3, 61.2, 52.2, 51.0, 37.3, 35.1, 32.8, 32.6, 32.3, 30.1, 30.04, 29.97, 29.91, 29.87, 29.8, 29.7, 29.4, 29.3, 27.4, 26.2, 23.1, 21.2, 21.09, 21.07, 21.0, 20.9, 14.6; HRMS (FAB): $(M+Na)^+$, found 1400.7142. $C_{71}H_{111}O_{25}NSNa$ requires 1400.7165.

(2*S*,3*R*,4*E*)-3-Hydroxy-2-(16-(1-thio)propionylhexadecanamido)octadec-4-enyl (β-D-galactopyranosyl)-(1→4)-β-D-glucopyranoside (2). To a solution of **13** (54 mg, 0.039 mmol) in MeOH (5.0 mL) and CH_2Cl_2 (4.0 mL) was added NaOMe (0.05 mL, 1 M in MeOH). After 16 h, methanolic acetic acid (20%) was added until neutral reaction (moist pH-paper) and the solution was filtered, concentrated and flash chromatographed (SiO_2, 5:1→2:1, CH_2Cl_2/EtOH gradient) to give the corresponding ester. To a solution of the ester in CH_2Cl_2 (1.5 mL), MeOH (2.5 mL) and H_2O (1.0 mL) was added 1 M aqueous NaOH (0.10 mL) and the resulting mixture was stirred for 24 h. Methanolic acetic acid (20%) was added until neutral reaction on pH-paper and the solution was concentrated. Flash chromatography of the residue (SiO_2, 70:20:2→66:33:4, $CHCl_3$/MeOH/H_2O gradient) gave **2** (24 mg, 64%) as a white solid; $[\alpha]_D^{23}$=+1 (*c* 1.0, $CHCl_3$/MeOH/H_2O, 65:35:10); δ_H (400 MHz, $CDCl_3CD_3OD/D_2O$, 65:35:10) 7.33 (d, 1H, *J*=9.2 Hz, NH), 5.42 (m, 1H, =C*H*–CH_2), 5.22 (dd, 1H, *J*=7.6, 15.4 Hz, =C*H*–CH(OH)), 4.08 (d, 1H, *J*=7.5 Hz, H-1′), 4.03 (d, 1H, *J*=7.8 Hz, H-1), 3.96 (dd, 1H, *J*=4.3, 7.6 Hz, OCH_aH_b), 3.84 (t, 1H, *J*=8.2 Hz, C*H*(OH)), 3.74 (m, 1H, C*H*(NH)), 3.98–3.30 (m, 11H), 3.20 (m, 1H), 3.10 (m, 1H, H-2), 2.49 (t, 2H, *J*=7.5 Hz, CH_2COOH), 2.29 (m, 4H, CH_2SCH_2), 1.88 (t, 2H, *J*=7.4 Hz, NCOCH_2), 1.74 (m, 2H, =CH–CH_2), 1.45–1.36 (m, 4H, NCOCH$_2$CH_2, CH_2CH$_2$SCH$_2$-CH$_2$COOH), 1.14–0.94 (m, 44H, CH_2), 0.61 (t, 3H, *J*=6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3/CD_3OD/D_2O$ 65:35:10) 174.5, 134.2, 129.1, 103.4, 102.7, 79.1, 77.4, 75.4, 74.8, 74.5, 73.1, 73.0, 71.6, 70.9, 68.7, 68.4, 67.6, 61.1, 60.2, 53.0, 36.2, 35.1, 33.9, 32.1, 31.7, 31.6, 29.4, 29.3, 29.2, 29.10, 29.06, 29.0, 28.9, 28.6, 26.9, 25.7, 25.2, 22.4, 13.6; HRMS (FAB): $(M+Na)^+$, found 958.5925. $C_{48}H_{89}O_{14}NSNa$ requires 958.5901.

2-(Trimethylsilyl)ethyl (2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (16). To a mixture of 2-(trimethylsilyl)ethyl (2,3,6-tri-*O*-benzoyl β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside[13] (400 mg, 0.368 mmol), phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside[11,12] (330 mg, 0.515 mmol), and *N*-iodosuccinimide (210 mg, 0.92 mmol) were added CH_2Cl_2 (12 mL) and Et_2O (24 mL) and the solution was cooled down to −50°C. Trimethylsilyl trifluoromethanesulfonate (0.020 mL, 0.110 mmol) was added and the mixture was stirred for 2.5 h. Triethylamine (2 mL) was added and the mixture was stirred for another 1 h at −50°C. The mixture was allowed to obtain room temperature, diluted with CH_2Cl_2 (20 mL), washed with 10% aqueous $Na_2S_2O_3$-solution (5 mL) and saturated aqueous $NaHCO_3$-solution (10 mL), dried ($MgSO_4$), and concentrated. The residue was flash chromatographed (SiO_2, 5:1→3:1, heptane/EtOAc gradient) to give **16** (560 mg, 94%) as a colourless oil; $[\alpha]_D^{23}$=+55 (*c* 1.0, $CHCl_3$); ν (film) 1740, 1260 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.06–7.09 (m, 50H, Ar-H), 5.85–5.75 (m, 2H, H-3″, H-2′), 5.39 (dd, 1H, *J*=7.9, 9.5 Hz, H-2″), 5.06 (dd, 1H, *J*=2.7, 10.7 Hz, H-3′), 4.91 (d, 1H, *J*=7.8 Hz, H-1′), 4.84 (d, 1H, *J*=11.1 Hz, H-1), 4.79–4.50 (m, 10H, H-1″, H-6′), 4.48 (d, 1H, *J*=2.3 Hz, H-4′), 4.33 (d, 1H, *J*=2.3 Hz, H-4′), 4.31–4.18 (m, 5H, H-4, H-6′), 4.11 (m, 1H), 4.00–3.88 (m, 4H), 3.71 (t, 1H, *J*=6.4 Hz, H-5′), 3.53 (dt, 1H, *J*=6.6, 10.1 Hz, OCH_2CH$_2$Si), 3.38 (t, 1H, *J*=8.8 Hz, H-6), 3.02 (dd, 1H, *J*=4.9, 8.5 Hz, H-6), 0.85 (m, 2H, CH_2Si), −0.10 (s, 9H, $SiMe_3$); δ_C (100.6 MHz, $CDCl_3$) 166.9, 166.3, 166.1, 165.8, 165.5, 139.4, 139.3, 138.7, 133.7, 133.54, 133.45, 130.31, 130.29, 130.25, 130.21, 130.16, 130.1, 130.0, 129.0, 128.84, 128.76, 128.73, 128.70, 128.6, 128.48, 128.45, 128.1, 127.9, 127.8, 127.74, 127.71, 101.7, 101.6, 100.7, 79.6, 77.0, 76.3, 75.4, 75.2, 74.9, 73.8, 73.7, 73.6, 73.5, 73.4, 73.1, 72.9, 70.3, 70.2, 67.9, 67.8, 63.1, 62.5, 18.3, −1.1; HRMS (FAB): $(M+Na)^+$, found 1611.5756. $C_{93}H_{92}O_{22}SiNa$ requires 1611.5747.

2-(Trimethylsilyl)ethyl (2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (17). Compound **16** (0.50 g, 0.31 mmol) was dissolved in AcOH (13 mL) and hydrogenated (H_2, 1 atm, 10% Pd/C, 0.20 g) for 5 h. The mixture was filtered through Celite and concentrated. The residue was dissolved in pyridine (15 mL), Ac_2O (12 mL) was added, and the mixture was stirred overnight, then concentrated and flash chromatographed (SiO_2, 2:1→1:1, heptane/EtOAc gradient) to give **17** (0.40 g, 91%) as a colourless oil; $[\alpha]_D^{23}$=+82 (*c* 1.0, $CHCl_3$); ν (film) 2920, 1730, 1250 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.06–7.21 (m, 30H, Ar-H), 5.80 (t, 1H, *J*=9.2 Hz, H-3), 5.69 (dd, 1H, *J*=7.8, 10.8 Hz, H-2′), 5.48 (d, 1H, *J*=2.2 Hz, H-4″), 5.40 (dd, 1H, *J*=7.9, 9.5 Hz, H-2), 5.34 (dd, 1H, *J*=3.3, 11.0 Hz, H-3″), 5.14 (m, 2H, H-3′, H-2″), 5.06 (d, 1H, *J*=3.7 Hz, H-1″), 4.81 (d, 1H, *J*=7.8 Hz, H-1′), 4.70 (d, 1H, *J*=7.9 Hz, H-1), 4.59 (dd, 1H, *J*=1.9, 11.9 Hz, H-6), 4.48 (m, 2H, H-6, H-5″), 4.26 (d, 1H, *J*=2.5 Hz, H-4′), 4.21 (t, 1H, *J*=9.5 Hz, H-4), 4.03–3.86 (m, 4H, H-5, H-6′, OCH_aH_bCH$_2$Si), 3.79 (d, 1H, *J*=8.0 Hz, H-6″), 3.77 (m, 2H, H-5′, H-6″), 3.53 (dt, 1H, *J*=6.6, 10.1 Hz, OCH$_a$$H_bCH_2$Si), 2.06, 2.02, 1.96, 1.93 (4 s, 3H each, OAc), 0.85 (m, 2H, CH_2Si), −0.10 (s, 9H, $SiMe_3$); δ_C (100.6 MHz, $CDCl_3$) 170.9, 170.8, 170.5, 170.0, 166.6, 166.2, 165.9, 165.7, 165.5, 165.4, 134.1, 134.0, 133.7, 133.54, 133.50, 130.2, 130.10, 130.08, 130.05, 130.0, 129.9, 129.7, 129.09, 129.06, 129.0, 128.9, 128.8, 128.7, 101.7, 100.6, 100.7, 79.6, 74.0, 73.8, 73.3, 73.0, 72.6, 70.0, 68.7, 68.2, 67.9, 67.6, 61.2, 21.12, 21.07, 21.0, 18.3,

−1.1; HRMS (FAB): $(M+Na)^+$, found 1419.4272. $C_{73}H_{76}O_{26}SiNa$ requires 1419.4291.

(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate (18). To a solution of **17** (281 mg, 0.198 mmol) in dry CH_2Cl_2 (1.33 mL) was added trifluoroacetic acid (2.70 mL) and the mixture was stirred at ambient temperature. After 1.5 h *n*-propylacetat (11 mL) and toluene (11 mL) were added and the mixture was concentrated and co-concentrated with toluene to give the corresponding hemiacetal. The crude hemiacetal was dissolved in dry CH_2Cl_2 (2.5 mL), and trichloroacetonitrile (0.75 mL) was added. The mixture was cooled down to 0°C, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.045 mL, 0.30 mmol) was added, the reaction mixture was stirred for 1.5 h, diluted with CH_2Cl_2 (10 mL), washed with ice-cold saturated aqueous $NaHCO_3$ (5 mL), dried (Na_2SO_4), and concentrated. The residue was flash chromatographed (SiO_2, 2:1:0.01→1:1:0.01, heptane/EtOAc/Et_3N gradient) to give **18** (220 mg, 76%) as a white solid; $[\alpha]_D^{23}=+82$ (*c* 1.0, $CHCl_3$); ν (film) 3090, 2950, 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.55 (s, 1H, NH), 8.10–7.20 (m, 30H, Ar-H), 6.69 (d, 1H, *J*=3.7 Hz, H-1), 6.18 (dd, 1H, *J*=8.6, 10.0 Hz, H-3), 5.74 (dd, 1H, *J*=7.9, 10.8 Hz, H-2′), 5.47 (m, 2H, H-2, H-1″), 5.35 (dd, 1H, *J*=3.3, 11.0 Hz, H-2″), 5.15 (m, 2H, H-3′, H-3″), 5.08 (d, 1H, *J*=3.6 Hz, H-4″), 4.93 (d, 1H, *J*=7.8 Hz, H-1′), 4.56 (m, 2H, H-6), 4.46 (t, 1H, *J*=7.2 Hz, H-5′), 4.31 (m, 3H, H-4, H-5, H-4′), 3.96 (m, 2H, H-6′), 3.75 (dd, 1H, *J*=8.1, 11.0 Hz, H-6″), 3.65 (m, 2H, H-5′, H-6″), 2.06, 2.02, 1.95, 1.91 (4 s, 3H each, OAc); δ_C (100.6 MHz, $CDCl_3$) 170.9, 170.8, 170.6, 170.0, 166.6, 166.1, 166.0, 165.8, 165.5, 165.3, 161.1, 134.1, 134.0, 133.8, 133.7, 133.6, 130.4, 130.2, 130.07, 130.05, 130.03, 130.00, 129.95, 129.6, 129.1, 129.02, 129.01, 128.97, 128.95, 128.91, 128.88, 128.86, 128.8, 102.4, 98.7, 93.4, 91.1, 75.4, 74.1, 72.9, 71.6, 71.2, 71.0, 70.1, 68.6, 68.2, 67.9, 67.5, 62.3, 61.3, 61.1, 21.12, 21.09, 21.0; HRMS (FAB): $(M+Na)^+$, found 1462.2655. $C_{70}H_{64}O_{25}NCl_3Na$ requires 1462.2680.

(2*S*,3*R*,4*E*)-2-Azido-3-benzoyloxyoctadec-4-enyl (2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (19). To a solution of **18** (220 mg, 0.15 mmol) and (2*S*,3*R*,4*E*)-2-azido-3-benzoyloxy-octadec-4-ene-1-ol[19–21] (97 mg, 0.23 mmol) in CH_2Cl_2 (8.0 mL) was added MS 300 AW (780 mg) and the resulting suspension was stirred for 1 h whereafter $BF_3{\cdot}Et_2O$ (0.028 mL, 0.23 mmol) was added. After 2.5 h, Et_3N (0.30 mL) was added, the mixture was filtered through Celite, concentrated, and flash chromatographed (SiO_2, heptane/EtOAc gradient, 2:1→1:1) to give **19** (219 mg, 83%) as a white solid; $[\alpha]_D^{23}=+54$ (*c* 1.0, $CHCl_3$) ν (film) 2950, 2380, 2100, 1750 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.07–7.20 (m, 30H, Ar-H), 5.81 (t, 1H, *J*=8.9 Hz, H-3), 5.72–5.64 (m, 2H, H-2′, =C*H*–CH_2), 5.54–5.34 (m, 5H, H-2, H-3″, H-4″, =C*H*–C*H*OBz), 5.15 (m, 2H, H-3′, H-2″), 5.06 (d, 1H, *J*=3.6 Hz, H-1″), 4.89 (d, 1H, *J*=7.9 Hz, H-1′), 4.73 (d, 1H, *J*=7.4 Hz, H-1), 4.62 (m, 1H, H-6), 4.48 (m, 2H, H-6, H-5″), 4.27 (m, 2H, H-4, H-4′), 4.04–3.78 (m, 6H, H-5, H-5′, H-6′, H-6″, CHN_3, CH_2O), 3.68 (m, 2H, H-6″, CH_2O), 3.52 (dd, 1H, *J*=6.0, 10.0 Hz, H-6′), 2.06, 2.02, 1.96, 1.92 (4 s, 3H each, OAc), 1.88 (m, 2H, =CH–CH_2), 1.30–1.15 (m, 22H, CH_2), 0.88 (t, 3H, *J*=6.7 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 170.9, 170.8, 170.5, 170.0, 166.6, 166.2, 165.9, 165.5, 165.40, 165.36, 139.4, 134.1, 134.0, 133.7, 133.64, 133.55, 133.5, 130.31, 130.26, 130.2, 130.14, 130.07, 130.0, 129.94, 129.92, 129.7, 129.0, 128.9, 128.81, 128.79, 128.78, 122.8, 102.0, 100.9, 98.8, 75.7, 74.0, 73.7, 73.4, 73.1, 72.4, 70.0, 68.62, 68.55, 68.2, 67.9, 67.6, 63.8, 62.7, 61.7, 61.2, 32.7, 32.4, 30.12, 30.09, 30.06, 30.0, 29.79, 29.78, 29.5, 29.0, 23.1, 21.10, 21.07, 21.0, 14.6; HRMS (FAB): $(M+Na)^+$, found 1730.6440. $C_{93}H_{101}O_{28}N_3Na$ requires 1730.6469.

(2*S*,3*R*,4*E*)-3-Hydroxy-2-(*S*-acetyl-16-mercaptohexadecanamido)octadec-4-enyl (α-D-galactopyranosyl)-(1→4)-(β-D-galactopyranosyl)-(1→4)-β-D-glucopyranoside (20). To a solution of **19** (204 mg, 0.12 mmol) in MeOH (15 mL) was added NaOMe (0.050 mL, 1 M in MeOH) and the resulting solution was stirred overnight, then quenched by addition of methanolic acetic acid (10%) until neutral reaction to pH-paper. Concentration and flash chromatography (SiO_2, CH_2Cl_2/MeOH/H_2O, 66:33:4) gave the deprotected intermediate globotriasyl azidosphingosine (90 mg, 91%). H_2S was bubbled through a solution of the residue (50 mg, 0.059 mmol) in pyridine (3 mL), MeOH (1.5 mL), and Et_3N (1.5 mL) at 0°C for 1 h. The solution was allowed to reach room temperature and after 24 h, N_2 was bubbled through the solution for 1 h. The mixture was concentrated and co-concentrated with toluene. To the residue in DMF (3 mL) was added **9** (38 mg, 0.089 mmol) and Et_3N (0.017 mL, 0.12 mmol) and the mixture was stirred at room temperature overnight. The mixture was evaporated and the residue was flash chromatographed (SiO_2, CH_2Cl_2/MeOH/H_2O, 70:20:3) In order to remove residual *N*-hydroxysuccinimide the product was further purified on a Bond–Elut C-18 column (1:9→1:0 MeOH/H_2O gradient), which gave **20** (53 mg, 82%) as a white solid; $[\alpha]_D^{23}=+28$ (*c* 1.0, $CHCl_3$/MeOH/H_2O, 66:33:10); δ_H (400 MHz, $CDCl_3$/CD_3OD/D_2O, 65:35:10) 7.33 (d, 1H, *J*=9.1 Hz, NH), 5.47 (m, 1H, =C*H*–CH_2), 5.21 (dd, 1H, *J*=7.6, 15.4 Hz, =C*H*–CH(OH)), 4.71 (d, 1H, *J*=3.2 Hz, H-1″), 4.21 (d, 1H, *J*=7.4 Hz, H-1′), 4.10 (d, 1H, *J*=7.7 Hz, H-1), 4.01 (t, 1H, *J*=6.1 Hz, H-5″), 3.95 (dd, 1H, *J*=4.3, 10.2 Hz, OCH_aH_b), 3.83 (t, 1H, *J*=8.0 Hz, C*H*(OH)), 3.76–3.30 (m, 17H), 3.20 (m, 1H), 3.12 (m, 1H, H-2), 2.65 (t, 2H, *J*=7.3 Hz, CH_2SAc), 1.95 (t, 2H, *J*=7.7 Hz, $NCOCH_2$), 1.80 (m, 2H, =CH–CH_2), 1.35 (m, 4H, $NCOCH_2CH_2$, CH_2CH_2SAc), 1.14–1.04 (m, 44H, CH_2), 0.68 (t, 3H, *J*=6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$/CD_3OD/D_2O, 65:35:10) 197.3, 174.6, 134.6, 129.1, 103.6, 102.6, 100.9, 79.1, 78.4, 77.4, 75.0, 74.8, 73.0, 72.8, 72.6, 72.3, 71.0, 69.5, 69.3, 68.8, 61.1, 60.3, 36.3, 32.3, 31.8, 30.2, 29.60, 29.55, 29.50, 29.47, 29.45, 29.4, 29.3, 29.24, 29.19, 29.1, 29.01, 28.95, 28.6, 25.9, 22.5, 13.8; HRMS (FAB): $(M+Na)^+$, found 1120.6418. $C_{54}H_{99}O_{19}NSNa$ requires 1120.6430.

(2*S*,3*R*,4*E*)-3-Hydroxy-2-(16-mercaptohexadecanamido)-octadec-4-enyl (α-D-galactopyranosyl)-(1→4)-(β-D-galactopyranosyl)-(1→4)-β-D-glucopyranoside (3). To a solution of **20** (15 mg, 0.014 mmol) in MeOH (0.4 mL) and CH_2Cl_2 (0.2 mL) was added NaOMe (0.034 mL, 1 M in MeOH). After 2 h methanolic acetic acid (10%) was added until

neutral reaction on pH-paper and the solution was evaporated. The residue was dissolved in DMF (2.0 mL) followed by addition of dithioerythritol (13 mg, 0.082 mmol) and diisopropylethylamine (0.007 mL, 0.041 mmol). After 2.5 h, the mixture was filtered through a short column (SiO_2, CH_2Cl_2/MeOH/H_2O, 66:33:4), concentrated, and flash chromatographed (SiO_2, CH_2Cl_2/MeOH/H_2O, 70:20:3 to give **3** (12 mg, 81%) as a white solid; $[\alpha]_D^{23}$=+27 (*c* 1.0, $CHCl_3$/MeOH/H_2O, 66:33:10); δ_H (400 MHz, $CDCl_3$/CD_3OD/D_2O, 65:35:10) 7.33 (d, 1H, *J*=9.1 Hz, NH), 5.47 (m, 1H, =C*H*–CH_2), 5.21 (dd, 1H, *J*=7.6, 15.4 Hz, =C*H*–CH(OH)), 4.71 (d, 1H, *J*=3.2 Hz, H-1″), 4.21 (d, 1H, *J*=7.4 Hz, H-1′), 4.10 (d, 1H, *J*=7.7 Hz, H-1), 4.02 (t, 1H, *J*=6.2 Hz, H-5″), 3.95 (dd, 1H, *J*=4.3, 10.2 Hz, OCH_aH_b), 3.83 (t, 1H, *J*=8.0 Hz, C*H*(OH)), 3.76–3.30 (m, 17H), 3.20 (m, 1H), 3.12 (m, 1H, H-2), 2.31 (t, 2H, *J*=7.3 Hz, CH_2SH), 1.95 (t, 2H, *J*=7.6 Hz, NC(O)OCH_2), 1.79 (m, 2H, =CH–CH_2), 1.43–1.31 (m, 4H, NC(O)OCH_2CH_2, CH_2CH_2SH), 1.10–1.03 (m, 44H, CH_2), 0.67 (t, 3H, *J*=6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$/CD_3OD/D_2O, 65:35:10) 174.6, 134.5, 129.0, 103.6, 102.6, 101.0, 79.1, 78.5, 77.4, 75.3, 74.9, 74.8, 72.8, 71.6, 71.3, 71.0, 69.4, 69.3, 68.7, 61.1, 55.3, 36.3, 33.8, 32.2, 31.7, 29.7, 29.52, 29.50, 29.46, 29.45, 29.4, 29.3, 29.22, 29.19, 29.1, 29.01, 28.97, 28.1, 25.8, 22.4, 13.7; HRMS (FAB): $(M+Na)^+$, found 1078.6337. $C_{52}H_{97}O_{18}NSNa$ requires 1078.6324.

(2*S*,3*R*,4*E*)-3-Hydroxy-2-(16-(2-methoxycarbonylethylthio)hexadecanamido)octadec-4-enyl (2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (21). H_2S was bubbled through a solution of **19** (58 mg, 0.033 mmol) in pyridine/H_2O (14 mL, 6:1) at 0°C for 1 h. The solution was allowed to reach room temperature and after 72 h, N_2 was bubbled through the solution for 1 h. The mixture was concentrated and co-concentrated with toluene. To the residue in CH_2Cl_2 (3 mL) was added **10** (37 mg, 0.10 mmol) and EDC (19 mg, 0.10 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was concentrated and the residue was flash chromatographed (SiO_2, heptane/EtOAc gradient, 3:1→1:1) to give 21 (56 mg, 82%) as a white solid; $[\alpha]_D^{23}$=+60 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.08–7.21 (m, 35H, Ar-H), 5.82–5.72 (m, 2H, H-3, =C*H*–CH_2), 5.70–5.60 (m, 2H, H-2′, NH), 5.47 (m, 2H, H-4″, C*H*OBz), 5.42–5.30 (m, 3H, H-2, H-3″, =C*H*–CHOBz), 5.15–5.10 (m, 2H, H-3′, H-2″), 5.05 (d, 1H, *J*=3.7 Hz, H-1″), 4.82 (d, 1H, *J*=7.9 Hz, H-1′), 4.63 (d, 1H, *J*=7.7 Hz, H-1), 4.47–4.37 (m, 4H, H-6, H-5″, C*H*NH), 4.25 (d, 1H, *J*=2.5 Hz, H-4′), 4.17 (t, 1H, *J*=9.5 Hz, H-4), 4.07 (dd, 1H, *J*=3.1, 10.1 Hz, CH_2O), 3.96 (m, 2H, H-6′), 3.85–3.75 (m, 2H, H-5, H-6″), 3.70–3.65 (m, 5H, H-5′, H-6″, Me), 3.55 (dd, 1H, *J*=3.8, 9.9 Hz, CH_2O), 2.79 (t, 2H, *J*=7.5 Hz, CH_2COOMe), 2.62 (t, 2H, *J*=7.5 Hz, CH_2CH$_2$COOMe), 2.53 (t, 2H, *J*=7.3 Hz, CH_2SCH$_2$CH$_2$COOMe), 2.06, 2.01, 1.95, 1.93 (4 s, 3H each, OAc), 2.03 (m, 2H, =CH–CH_2), 1.78 (t, 2H *J*=7.0 Hz, NHCHOCH_2), 1.58 (m, 2H, CH_2CH$_2$SCH$_2$CH$_2$COOMe), 1.38–1.10 (m, 44H, CH_2), 0.88 (t, 3H, *J*=6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 173.0, 170.9, 170.8, 170.5, 170.0, 166.6, 166.1, 165.9, 165.8, 165.6, 165.4, 165.3, 137.7, 134.0, 133.7, 133.5, 133.3, 130.6, 130.2, 130.08, 130.05, 130.03, 129.95, 129.9, 129.7, 129.5, 129.1, 129.03, 128.99, 128.95, 128.9, 128.8, 128.7, 125.2, 101.8, 101.1, 98.7, 74.5, 74.0, 73.5, 73.3, 73.0, 72.8, 69.9, 68.7, 68.2, 67.9, 67.6, 61.2, 52.2, 50.8, 36.9, 35.2, 32.7, 32.6, 32.4, 30.13, 30.10, 30.07, 30.05, 29.99, 29.97, 29.9, 29.8, 29.68, 29.67, 29.6, 29.34, 29.32, 27.4, 25.9, 23.1, 21.09, 21.06, 21.0, 14.5; HRMS (FAB): $(M+Na)^+$, found 2060.8931. $C_{113}H_{139}O_{31}NSNa$ requires 2060.8949.

(2*S*,3*R*,4*E*)-3-Hydroxy-2-(16-(1-thio)propionylhexadecanamido)octadec-4-enyl (α-D-galactopyranosyl)-(1→4)-(β-D-galactopyranosyl)-(1→4)-β-D-glucopyranoside (4). To a solution of **21** (50 mg, 0.024 mmol) in MeOH (4.0 mL) and CH_2Cl_2 (1.0 mL) was added NaOMe (0.050 mL, 1 M in MeOH). After 16 h, methanolic acetic acid (10%) was added until neutral reaction on pH-paper and the solution was filtered, concentrated and flash chromatographed (SiO_2, $CHCl_3$/MeOH/H_2O, 66:33:4) to give the corresponding ester. To a solution of the ester in CH_2Cl_2 (2.0 mL), MeOH (3.0 mL), and H_2O (1.0 mL) was added 1 M aqueous NaOH (0.10 mL) and the resulting mixture was stirred overnight. Methanolic acetic acid (10%) was added until neutral reaction on pH-paper and the solution was concentrated. Flash chromatography of the residue (SiO_2, $CHCl_3$/MeOH/H_2O, 66:33:4→66:33:10) gave **4** (22 mg, 83%) as a white solid; $[\alpha]_D^{23}$=+27 (*c* 1.0, $CHCl_3$/MeOH/H_2O, 66:33:10); δ_H (400 MHz, $CDCl_3$/CD_3OD/D_2O, 65:35:10) 7.33 (d, 1H, *J*=9.1 Hz, NH), 5.47 (m, 1H, =C*H*–CH_2), 5.21 (dd, 1H, *J*=7.6, 15.4 Hz, =C*H*–CH(OH)), 4.71 (d, 1H, *J*=3.2 Hz, H-1″), 4.21 (d, 1H, *J*=7.4 Hz, H-1′), 4.10 (d, 1H, *J*=7.7 Hz, H-1), 4.02 (t, 1H, *J*=6.2 Hz, H-5″), 3.95 (dd, 1H, *J*=4.3, 10.2 Hz, OCH_aH_b), 3.83 (t, 1H, *J*=8.0 Hz, C*H*(OH)), 3.76–3.30 (m, 17H), 3.20 (m, 1H), 3.12 (m, 1H, H-2), 2.54 (t, 2H, *J*=7.5 Hz, CH_2COOH), 2.34 (m, 4H, CH_2SCH_2), 1.94 (t, 2H, *J*=7.6 Hz, NC(O)OCH_2), 1.79 (m, 2H, =CH–CH_2), 1.40–1.32 (m, 4H, NC(O)OCH_2CH_2, CH_2CH$_2$S), 1.15–1.03 (m, 44H, CH_2), 0.66 (t, 3H, *J*=6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$/CD_3OD/D_2O, 65:35:10) 174.6, 134.6, 129.1, 103.6, 102.6, 100.9, 77.5, 75.0, 74.8, 74.4, 73.0, 72.7, 71.6, 71.2, 71.0, 69.4, 69.3, 68.73, 68.69, 61.0, 60.2, 60.1, 53.0, 31.9, 31.7, 29.6, 29.53, 29.48, 29.44, 29.43, 29.39, 29.37, 29.33, 29.30, 29.25, 29.2, 29.1, 29.0, 28.7, 26.9, 22.5, 13.8; HRMS (FAB): $(M+Na)^+$, found 1150.6500. $C_{55}H_{101}O_{20}NSNa$ requires 1150.6535.

2-*O*-(16-(Ethyldithio)hexadecanoyl)-1-*O*-hexadecanoyl-3-*O*-benzyl-*sn*-glycerol (23). To a solution of 1-*O*-hexadecanoyl-3-*O*-benzyl-*sn*-glycerol (**22**)[8] (118 mg, 0.28 mmol) and 16-(ethyldithio)hexadecanoic acid[24] (108 mg, 0.31 mmol) in CH_2Cl_2 (3.0 mL) at 0°C was added *N*,*N*-dimethylamino-4-pyridine (DMAP, 25 mg). A solution of diisopropylcarbodiimide (DIC, 0.052 mL, 0.34 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise over 10 min, and the mixture was stirred at room temperature for 5 h. The reaction mixture was filtered through Celite, the filtrate was concentrated, and flash chromatographed (SiO_2, heptane/EtOAc 5:1) to give **23** (200 mg, 96%) as a white solid; ν (film) 2950, 2870, 1750 cm^{-1}; $[\alpha]_D^{23}$=+5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.37–7.29 (m, 5H, Ar-H), 5.25 (m, 1H, H-*sn*2), 4.57/4.53 (ABq, 2H, *J*=12.1, 18.0 Hz, OCH_2Ph), 4.20 (dd, 1H, *J*=3.9, 12.0 Hz, H-*sn*1), 4.35 (dd, 1H, *J*=6.4, 11.9 Hz, H-*sn*1), 3.60 (dd, 2H, *J*=4.3, 5.2 Hz,

H-*sn*3), 2.68 (m, 4H, CH_2SSCH_2), 2.35–2.24 (m, 4H, $OCOCH_2$), 1.70–1.55 (m, 6H, $OCOCH_2CH_2$, CH_2CH_2S), 1.35–1.23 (m, 49H, CH_2, SCH_2CH_3), 0.89 (t, 3H, J=6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 173.6, 173.3, 137.9, 128.6, 128.0, 127.8, 73.5, 70.2, 68.5, 62.9, 39.5, 34.6, 33.0, 32.2, 29.9, 29.7, 29.6, 29.51, 29.48, 29.34, 29.31, 28.8, 25.2, 25.1, 24.8, 22.9, 14.6, 14.4; HRMS (FAB): $(M+H)^+$, found 751.5377. $C_{44}H_{79}O_5S_2$ requires 751.5369.

2-*O*-(16-(Etyldithio)hexadecanoyl)-1-*O*-hexadecanoyl-*sn*-glycerol (24). To a solution of **23** (100 mg, 0.127 mmol) and diethyl disulfid (0.078 mL, 0.064 mmol) in CH_2Cl_2 (5.0 mL) at −78°C was added dropwise over 10 min a 1 M solution of BCl_3 in hexane (0.57 mL, 0.57 mmol). The mixture was stirred at −78°C for 30 min. More BCl_3 (0.57 mL) was added and the resulting mixture was stirred for another 30 min. The reaction mixture was poured into ice-water (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The organic phases were combined, dried (Na_2SO_4), concentrated, and flash chromatographed (SiO_2, heptane/EtOAc 3:1) to give **24** (66 mg, 74%) as a white solid; $[\alpha]_D^{23}$=+2 (*c* 1.0, $CHCl_3$); ν (film) 3500, 2920, 2870, 1750, 1410 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.09 (m, 1H, H-*sn*2), 4.33 (dd, 1H, J=4.4, 11.9 Hz, H-*sn*1), 4.24 (dd, 1H, J=6.3, 11.8 Hz, H-*sn*1), 3.74 (s, 2H, H-*sn*3), 2.69 (m, 4H, CH_2SSCH_2), 2.35–2.24 (m, 4H, $OCOCH_2$), 2.05 (t, 1H, J=6.2 Hz, OH), 1.70–1.60 (m, 6H, $OCOCH_2CH_2$, CH_2CH_2S), 1.35–1.23 (m, 49H, CH_2, SCH_2CH_3), 0.89 (t, 3H, J=6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 174.0, 173.7, 72.3, 62.2, 61.7, 39.5, 34.5, 34.3, 33.0, 32.1, 29.90, 29.87, 29.85, 29.83, 29.80, 29.72, 29.68, 29.6, 29.48, 29.45, 29.32, 29.29, 28.7, 25.13, 25.08, 22.9, 14.7, 14.3; HRMS (FAB): M^+, found 660.4815. $C_{37}H_{72}O_5S_2$ requires 660.4821.

2-*O*-(16-(Etyldithio)hexadecanoyl)-1-*O*-hexadecanoyl-*sn*-glyceryl-3-phosphocholine (25). To a stirred solution of imidazole (45 mg, 0.67 mmol, co-concentrated once with freshly distilled toluene) in toluene (0.6 mL) at 0°C was added dropwise freshly distilled PCl_3 (0.013 mL, 0.146 mmol) in toluene (0.14 mL) followed by freshly distilled triethylamine (0.054 mL, 0.38 mmol) in toluene (0.14 mL). Stirring was continued for 10 min, the temperature was lowered to −10°C and **24** (34 mg, 0.049 mmol, dried over P_2O_5 overnight) in toluene (0.7 mL), was added dropwise over 1 h. After stirring for another 20 min at −10°C, the reaction was quenched by addition of water/pyridine (3 mL, 1:4) and the mixture was allowed to reach room temperature. CH_2Cl_2 (20 mL) was added and the organic layer was washed with water (1×7 mL), dried (Na_2SO_4), concentrated and dried (over P_2O_5 over night). The residue was dissolved in freshly distilled pyridine (1.0 mL) and cholintosylate[27] (27 mg, 0.098 mmol, dried over P_2O_5 over night) and 5,5-dimethyl-2-oxo-2-chloro-1,3,2-dioxaphosphorinan[28] (NPCl, 27 mg, 0.147 mmol) was added. The resulting mixture was stirred for 15 min. I_2 (25 mg, 0.098 mmol) dissolved in pyridine/water (1.0 mL, 98:2) was added and the mixture was stirred for 10 min. CH_2Cl_2 (35 mL) was added and the organic phase was washed with 5% (w/v) aqueous solution of sodium bisulfite (7 mL). The aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were concentrated and co-concentrated with toluene. Flash chromatography of the residue (SiO_2, $CHCl_3$/MeOH/H_2O 66:33:4) gave a crude product that was dissolved in THF/H_2O (10:1) and eluted through an ion-exchange column (TMD-8, conditioned in the same solvents) to give **25** (16 mg, 41%) as a white solid; $[\alpha]_D^{23}$=+4 (*c* 1.6, $CHCl_3$/CH_3OH/H_2O, 65:35:10); δ_H (400 MHz, $CDCl_3$/CD_3OD/D_2O, 65:35:10) 4.99 (m, 1H, H-*sn2*), 4.18 (dd, 1H, J=3.1, 12.1 Hz, H-*sn*1), 4.01 (m, 2H, β-CH_2), 3.92 (dd, 1H, J=7.1, 12.0 Hz, H-*sn1*), 3.75 (dt, 2H, J=5.8, 6.4 Hz, H-*sn*3), 3.38 (m, 2H, α-CH_2), 2.98 (s, 9H, $N(Me)_3$), 2.40 (m, 4H, CH_2SSCH_2), 2.12–2.04 (m, 4H, $OCOCH_2$), 1.40–1.25 (m, 6H, $OCOCH_2CH_2$, SCH_2CH_2), 1.10–1.00 (m, 49H, CH_2, SCH_2CH_3), 0.64 (t, 3H, J=6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$/CD_3OD/D_2O, 65:35:10) 174.1, 173.7, 70.3 (J=7.9 Hz), 66.2, 63.5 (J=5.4 Hz), 62.7, 59.0, 53.9, (J=3.6 Hz), 39.1, 34.1, 34.0, 32.6, 31.8, 29.6, 29.51, 29.45, 29.42, 29.39, 29.36, 29.21, 29.17, 29.1, 29.01, 28.98, 28.4, 24.8, 24.7, 22.5, 14.2, 13.8; HRMS (FAB): $(M+H)^+$, found 826.5466. $C_{42}H_{85}O_8NPS_2$ requires 826.5454.

2-*O*-(16-Mercaptohexadecanoyl)-1-*O*-hexadecanoyl-*sn*-glyceryl-3-phosphocholine (5). To a solution of **25** (15 mg, 0.019 mmol) in ethanol (1.0 mL) and water (0.5 mL) was added tri-*n*-butylphosphine (0.008 mL, 0.039 mmol) and the resulting mixture was stirred at room temperature in the dark for 7 h, after which the solvent was evaporated under reduced pressure. Flash chromatography of the residue (SiO_2, $CHCl_3$/MeOH/H_2O 66:33:4) gave **5** (10 mg, 75%) as a white solid; $[\alpha]_D^{23}$=+4 (*c* 1.0, $CHCl_3$/MeOH/H_2O, 65:35:10); δ_H (400 MHz, $CDCl_3$/CD_3OD/D_2O, 65:35:10) 5.03 (m, 1H, H-*sn*2), 4.21 (dd, 1H, J=3.1, 12.1 Hz, H-*sn*1), 3.96 (m, 2H, β-CH_2), 3.88 (dd, 1H, J=7.1, 12.0 Hz, H-*sn*1), 3.75 (dt, 2H, J=5.8, 6.4 Hz, H-*sn*3), 3.38 (m, 2H, α-CH_2), 2.98 (s, 9H, $N(Me)_3$), 2.31 (dt, 2H, J=6.2, 7.3 Hz, CH_2SH), 2.15–2.09 (m, 4H, $OCOCH_2$), 1.45–1.30 (m, 6H, $OCOCH_2CH_2$, SCH_2CH_2), 1.10–1.00 (m, 46H, CH_2), 0.68 (t, 3H, J=6.6 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$/CD_3OD/D_2O, 65:35:10) 174.1, 173.7, 70.3 (J=7.9 Hz), 66.2, 63.4 (J=5.4 Hz), 62.6, 59.0, 53.9, 34.1, 33.9, 33.8, 32.6, 31.7, 29.6, 29.51, 29.45, 29.42, 29.39, 29.36, 29.21, 29.17, 29.1, 29.01, 28.9 24.8, 24.7, 24.2, 22.5, 22.3, 13.8; HRMS (FAB): $(M+H)^+$, found 766.5407. $C_{40}H_{81}O_8SNP$ requires 766.5421.

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