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Synthesis and biological evaluation of lipophilic Ca_1a_2L analogues as potential bisubstrate inhibitors of protein:geranylgeranyl transferase-1

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Abstract—Ca_1a_2L analogues, having the central dipeptide a_1a_2 replaced by a sugar amino acid, were provided at the N-terminal end directly or via a spacer with a lipid. The inhibitory potency toward PGGT-1 of the set of lipophilic Ca_1a_2L analogues was improved in comparison with the original analogues, **1** and **2**. The most potent inhibitors, **39** and **40**, were found to inhibit PGGT-1 with an IC_{50}-value of 12.7 and 12.3 μM, respectively, which is a 6-fold improvement over the corresponding analogue **1**.

1. Introduction

The involvement of mutated Ras proteins in the growth and development of about 30% of all human tumors is an incentive to continue the search after compounds that have the ability to interfere with processes that influence Ras activity.[1] A series of post-translational modifications that result in embedding of Ras proteins in the inner cell membrane are essential for their functioning. The first and most important event comprises isoprenylation of a specific cysteine residue near the *C*-terminus in pro-Ras proteins. Two enzymatic activities may execute this transformation, being protein:farnesyl transferase (PFT),[2] which catalyzes the transfer of a farnesyl group from farnesylpyrophosphate to the cysteine thiol, and protein:geranylgeranyltransferase 1 (PGGT-1)[3] that performs the same reaction but with geranylgeranylpyrophosphate as a substrate (Fig. 1).[4] Both enzymes recognize and isoprenylate cysteine residues that are part of a well-conserved C-terminal tetrapeptide motif, the so-called Ca_1a_2X box, that is, present in (the proform of) a number of plasma membrane proteins.[5] With C encoding for cysteine and a_1a_2 representing hydrophobic dipeptide residues, it is the nature of the X residue, which determines substrate specificity of PFT and PGGT-1.[6] PFT preferably targets substrates where X is Met, Ser, Gln, or Ala, while PGGT-1 prefers substrates with X is Leu or Phe.[6,7] Most native Ras proteins, including their oncogenic counterparts, feature either a methionine or a serine residue at the *C*-terminus, and, as a consequence, are normally farnesylated through the action of PFT. It is therefore not surprising that PFT is widely considered as the main target in pharmacological research programs aimed at disabling oncogenic Ras functioning.[8] However, the recent finding that, upon inhibition of PFT, the most abundant human oncogenic Ras protein, Ras K-4B is geranylgeranylated through the action of PGGT-1 (with functional onco-Ras as a result) has led to the awareness that the successful development of an effective therapeutic strategy may well hinge upon the ability to block the action of both.

In general, the reported strategies aimed at the development of PFT and PGGT-1 inhibitors are based on either of the two substrates, that is, the isoprenylpyrophosphate entity or the Ca_1a_2X tetrapeptide, as a lead structure.[9] A relatively unexplored area of research entails the design of bisubstrate analogue inhibitors,[10] containing elements from both tetrapeptide and isoprenyl moieties. The viability of this approach is underscored by

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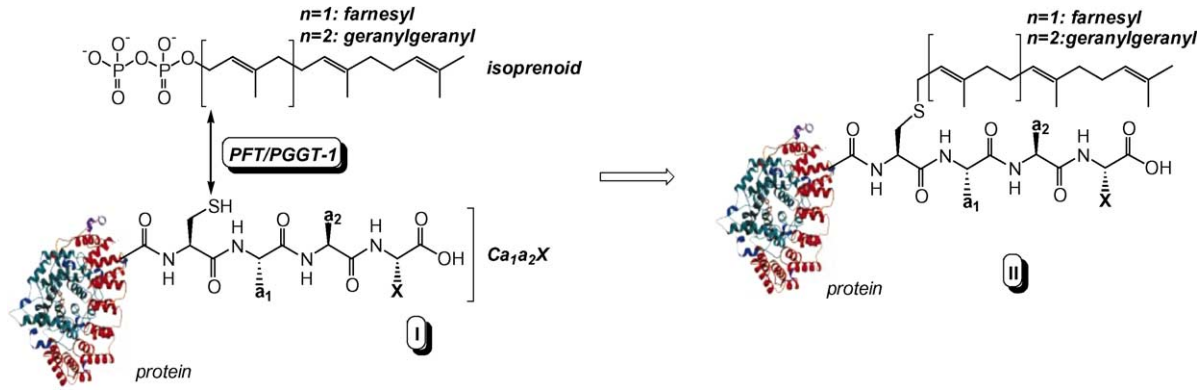


Figure 1. Isoprenylation of proteins (**I**→**II**).

the finding that prenyl transferases exhibit an unusual high affinity for their two substrates and especially for the turnover product. Prenylated proteins are removed from the active site only when a new isoprenyl pyrophosphate enters the active site.[2,3] Based on these considerations, several research groups have reported on the development of bisubstrate inhibitors against PFT.[11] In line with these studies, we here present our results in the generation of lipophilic Ca_1a_2L analogues as potential bisubstrate inhibitors of PGGT-1.

With the objective to develop new PGGT-1 inhibitors[12] we recently reported a series of Ca_1a_2L analogues featuring sugar amino acid (SAA) based dipeptide isosters as replacement of the central a_1a_2 dipeptide.[13] From these, Ca_1a_2L analogue **1** (Fig. 2), with the amino acid derivatives arranged in a 2,6-*trans* fashion on the pyranoid SAA core, was found to be the most active compound, inhibiting PGGT-1 with an IC_{50}-value of 68 ± 16 μM. In contrast, the corresponding 2,6-*cis* analogue (**2**), with the stereochemistry at C-6 inverted, was found to be much less active against PGGT-1, with an IC_{50}-value of ~1000 μM. Using Ca_1a_2X mimetics **1** and **2** as a basis, we set out to the preparation of a set of lipophilic Ca_1a_2L analogues with general structure **III** (Fig. 2). The potential bisubstrate inhibitors are composed of Ca_1a_2L analogues **1** or **2**, which are connected, either directly or via a linker (C_2: glycine or C_4: 4-aminobutyric acid), to lauric (C_{12}), or palmitic acid (C_{16}). It should be noted that saturated fatty acids are known to be well tolerated by PFT and PGGT-1 as isoprenyl analogues.[11d,14]

2. Results and discussion

The synthesis of the partially protected precursors of the projected inhibitors, having a 2,6-*trans* or 2,6-*cis* relationship in the central SAA residue, is shown in Schemes 1a and b, respectively. TFA/DCM mediated removal of the Boc group in compounds **3** and **13**, the syntheses of which are previously reported,[13]and condensation of the free amine with Boc–Cys(S*t*Bu)–OH (BOP, HOBt, DiPEA) furnished suitably protected Ca_1a_2L analogues **4** and **14**, respectively, both in 72% overall yield. Next, unmasking the amine in **4** and **14** followed by condensation with either lauric ($CH_3(CH_2)_{10}CO_2H$) or palmitic acid ($CH_3(CH_2)_{14}CO_2H$) with BOP/HOBt gave the 2,6-*trans* compounds **7**, **8** and 2,6-*cis* compounds **17**, **18**, respectively (84% to >99%, two steps). The synthesis of lipophilic Ca_1a_2L analogues provided with a linker started with condensation of Boc–Gly–OH or Boc-4-aminobutyric acid with the ammonium salt of **4** or **14** to give the desired 2,6-*trans* intermediates **5** and **6** and the 2,6-*cis* isomers **15** and **16**, respectively (70–75%, two steps). Finally, these intermediates were elongated with lauric or palmitic acid according to the same procedure as described for **7** and **8** to give the desired 2,6-*trans* moieties **9**–**12** (64–95%, two steps)and 2,6-*cis* compounds **19**–**22** (78% to >99%, two steps).

The partially protected precursors **7**–**12** and **17**–**22** were converted to the target analogues (**35**–**40** and **41**–**46**, respectively), by a two step deprotection procedure

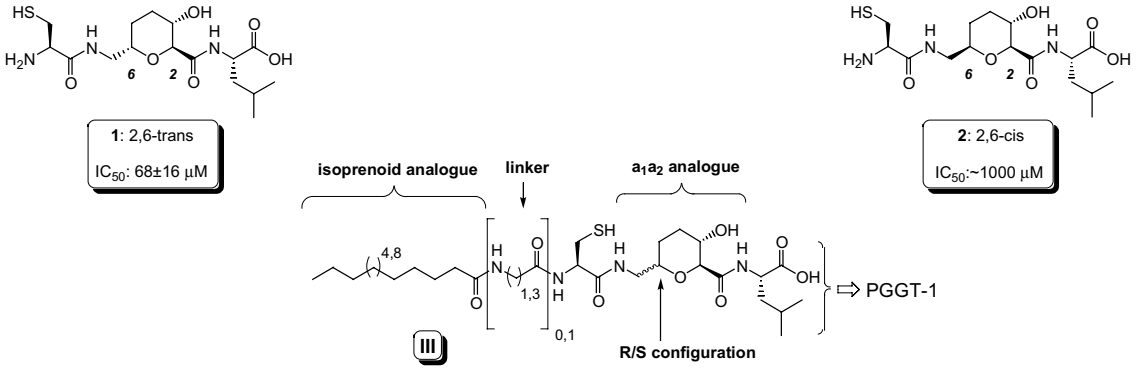
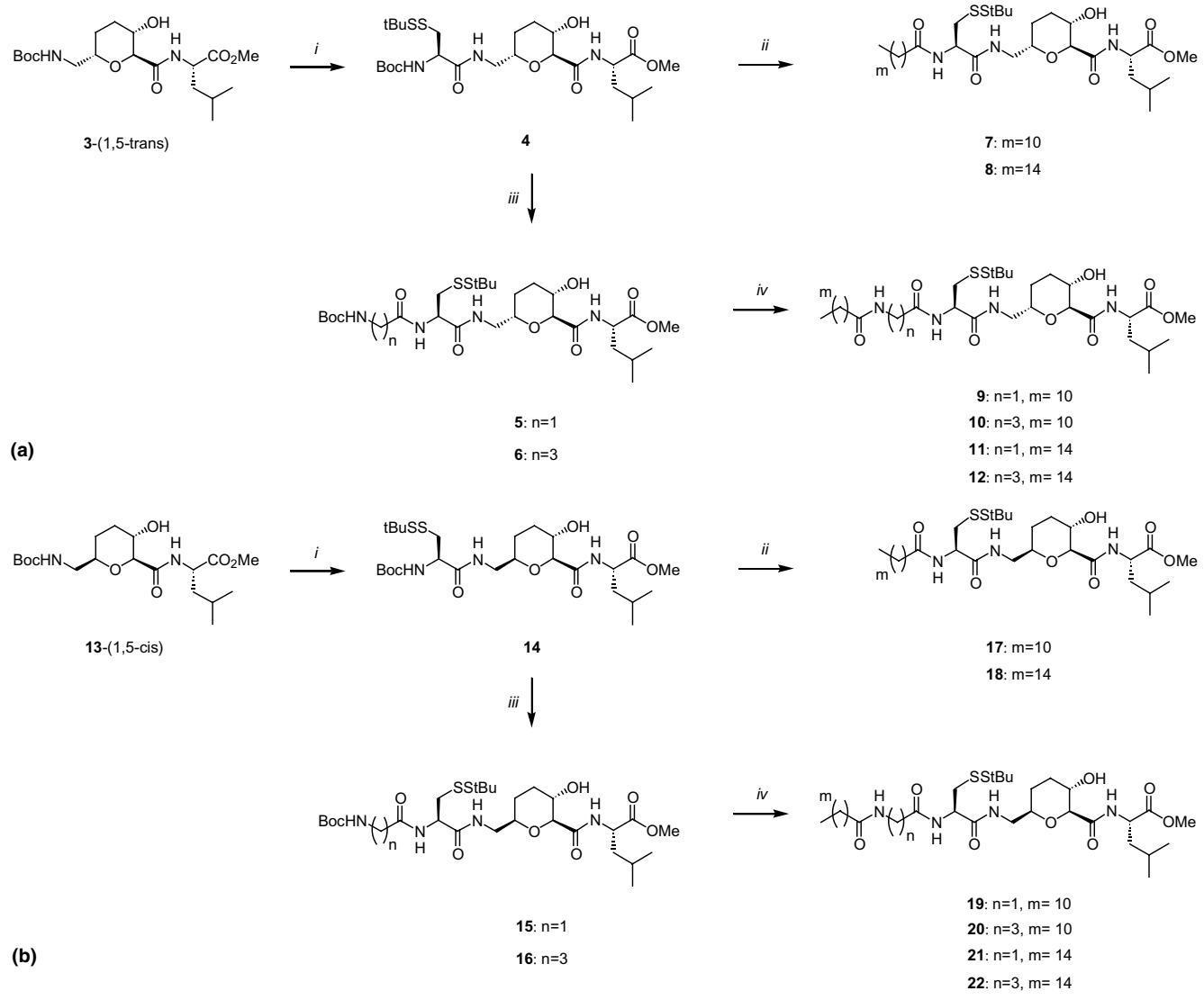


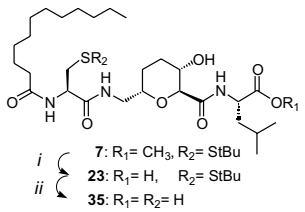
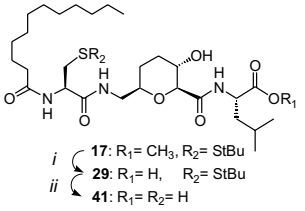
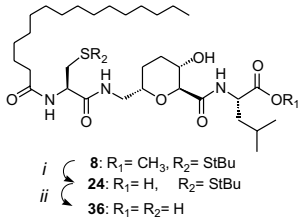
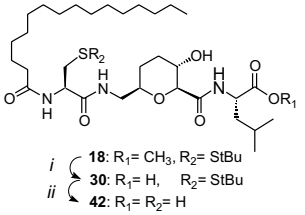
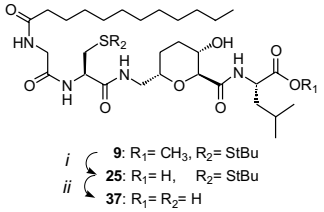
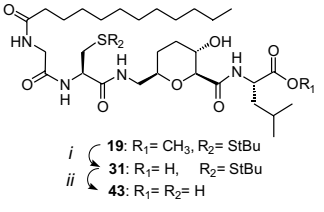
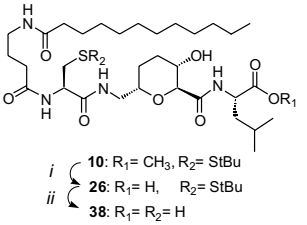
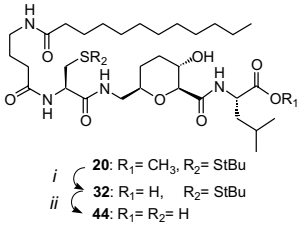
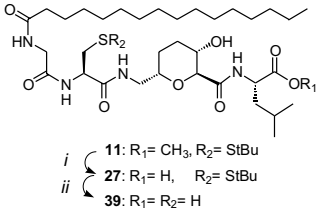
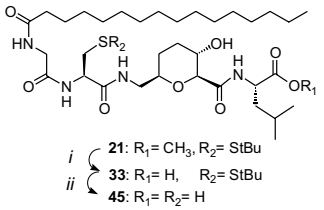
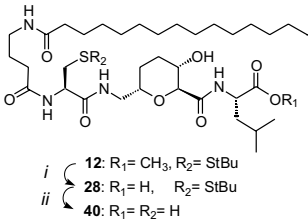
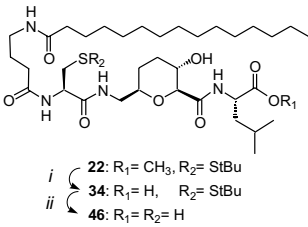
Figure 2. Ca_1a_2L analogues **1** and **2** and general structure of potential bisubstrate inhibitors (**III**).



Scheme 1. Synthesis of 2,6-*trans* SAA substituted lipophilic Ca_1a_2L analogues: (a) **7**–**12** and (b) **17**–**22**. Reagents and conditions. (i) (a) TFA/DCM, *i*Pr_3SiH; (b) Boc–Cys(S*t*Bu)–OH, BOP, DiPEA, HOBt, DMF/DCM (**4**: 72%, **14**: 72%, over two steps); (ii) (a) TFA/DCM, *i*Pr_3SiH; (b) for **7** and **17**: $CH_3(CH_2)_{10}CO_2H$, for **8** and **18**: $CH_3(CH_2)_{14}CO_2H$, BOP, DiPEA, HOBt, DMF/DCM (**7**: >99%, **8**: 87%, **17**: 91%, **18**: 84%, over two steps); (iii) (a) TFA/DCM, *i*Pr_3SiH; (b) for **5** and **15**: Boc–Gly–OH, for **6** and **16**: Boc-4-aminobutyric acid, BOP, DiPEA, HOBt, DMF/DCM (**5**: 75%, **6**: 75%, **15**: 72%, **16**: 70%, over two steps); (iv) (a) TFA/DCM, *i*Pr_3SiH; (b) for **9**, **10**, **19**, and **20**: $CH_3(CH_2)_{10}CO_2H$, for **11**, **12**, **21**, and **22**: $CH_3(CH_2)_{14}CO_2H$, BOP, DiPEA, HOBt, DMF/DCM (**9**: 95%, **10**:64%, **11**: 90%, **12**: 85%, **19**: >99%, **20**: 92%, **21**: 98%, **22**: 78%, over two steps).

(Scheme 2): aq LiOH mediated hydrolysis of the methyl ester released the acid (**23**–**34**) and treatment with dithiotreitol (DTT) resulted in cleavage of the thio-*tert*-butyl group. The crude products were purified by RP-HPLC and characterized by LC/MS analysis. All compounds (**35**–**46**) were subsequently evaluated for their inhibitory potency against PGGT-1 (Scheme 2) by determining the residual enzyme activity in vitro at two different concentrations (10 and 100 μM) according to the procedure previously described by us.[12d] The results of the biological evaluation are presented in Scheme 2. Similar to the monosubstrate analogues (**1** and **2**, Fig. 2), the most potent compounds **39** and **40** feature a 2,6-*trans* substitution pattern. Determination of the IC_{50}-values revealed that **39** ($IC_{50} = 12.7 \pm 1.3$ μM) and **40**, differing in the nature of the linker ($IC_{50} = 12.3 \pm 1.0$ μM), inhibit PGGT-1 with equal efficacy, representing a ~6-fold improvement in potency compared to the corresponding monosubstrate **1** ($IC_{50} = 68 \pm 16$ μM).

Whereas monosubstrate **2** shows little activity below 1000 μM, compounds **41**–**46**, featuring an isoprenyl analogue, all appear to exhibit an enhanced activity. The most potent member of this series was found to be compound **42**, in which the C_{16} palmitic acid is directly connected to the cysteine. In contrast to the 2,6-*trans* series (**35**–**40**) where the introduction of a longer alkyl chain and linker gradually increases the inhibitory potency, introduction of a linker or increasing the length of the alkyl chain in the 2,6-*cis* series (**41**–**46**) seems to have no additional effect on the potency.

	Activity (%)[a]		IC_{50} (μM)[b]		Activity (%)[a]	
	10 μM	100 μM			10 μM	100 μM
 i, ii: **7**: R_1= CH_3, R_2= StBu; **23**: R_1= H, R_2= StBu; **35**: R_1= R_2= H	96	32	-[c]	 i, ii: **17**: R_1= CH_3, R_2= StBu; **29**: R_1= H, R_2= StBu; **41**: R_1= R_2= H	>100	44
 i, ii: **8**: R_1= CH_3, R_2= StBu; **24**: R_1= H, R_2= StBu; **36**: R_1= R_2= H	82	21	-[c]	 i, ii: **18**: R_1= CH_3, R_2= StBu; **30**: R_1= H, R_2= StBu; **42**: R_1= R_2= H	57	31
 i, ii: **9**: R_1= CH_3, R_2= StBu; **25**: R_1= H, R_2= StBu; **37**: R_1= R_2= H	71	19	-[c]	 i, ii: **19**: R_1= CH_3, R_2= StBu; **31**: R_1= H, R_2= StBu; **43**: R_1= R_2= H	80	57
 i, ii: **10**: R_1= CH_3, R_2= StBu; **26**: R_1= H, R_2= StBu; **38**: R_1= R_2= H	>100	79	-[c]	 i, ii: **20**: R_1= CH_3, R_2= StBu; **32**: R_1= H, R_2= StBu; **44**: R_1= R_2= H	78	27
 i, ii: **11**: R_1= CH_3, R_2= StBu; **27**: R_1= H, R_2= StBu; **39**: R_1= R_2= H	57	15	12.7 ± 1.3	 i, ii: **21**: R_1= CH_3, R_2= StBu; **33**: R_1= H, R_2= StBu; **45**: R_1= R_2= H	89	43
 i, ii: **12**: R_1= CH_3, R_2= StBu; **28**: R_1= H, R_2= StBu; **40**: R_1= R_2= H	48	10	12.3 ± 1.0	 i, ii: **22**: R_1= CH_3, R_2= StBu; **34**: R_1= H, R_2= StBu; **46**: R_1= R_2= H	87	42

Scheme 2. Biological evaluation of target compounds **35**–**46**. (i) 1 M LiOH, H_2O/1,4-dioxane, 0 °C→rt; (ii) (a) DTT, Tris buffer pH 7.4, MeOH or EtOH; (b) RP-HPLC purification. [a]activity of enzyme at 10 or 100 μM of compound: expressed as percent of control activity (without test compound). Values for monosubstrate **1**: PGGT-1 activity at 10 μM = >100%; activity at 100 μM = 42%; **2**: PGGT-1 activity at 10 μM = >100%; activity at 100 μM = 80%. [b]IC_{50}: concentration of compound required to inhibit for 50% the PGGT-1 catalyzed incorporation of [^{3}H]-GGPP; IC_{50}-values are means of three determinations: one determination involves performing the assay at five concentrations (1, 3, 10, 30, and 100 μM) of compound in duplicate. By using a mathematical function fitting to the concentration/inhibition curve, the IC_{50}-value was determined. [c]Not determined.

3. Conclusions

In summary, we have shown that attachment of simple lipids (with or without a linker) to our previously reported Ca_1a_2L analogues **1** and **2** is a promising approach to increase their inhibition potency against PGGT-1. Compounds **39** and **40** were found to inhibit PGGT-1 with an IC_{50}-value of 12.7 and 12.3 μM,

respectively, which is a 6-fold improvement over the corresponding monosubstrate analogue (**1**). Although the inhibitors based on **2**, having a 2,6-*cis* SAA configuration, yielded (slightly) less potent inhibitors, the gain of inhibition potency is more pronounced in comparison with the 2,6-*trans* series. At the moment we do not have experimental prove that the here presented inhibitors actually act by occupying the peptide and prenylpyrophosphate pocket of the enzyme. Alternative binding modes are possible due to the presence of different hydrophobic pockets in the active site in which the introduced acyl residues could bind.[2b,3,6] As compounds **35**–**46** are provided with the zinc-binding thiol function, it is unlikely that they adopt a product-like conformation in the active site of the enzyme.[2b,3] Current research activities are aimed toward the elucidation of the binding mode of the here presented PGGT-1 inhibitors in order to develop more potent derivatives.

4. Experimental section

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AC-200 (200, 50.1 MHz), a Bruker DPX-300 (300, 75 MHz), a Bruker Avance-400 (400, 100 MHz), or a Bruker DMX-600 (600, 150 MHz). Chemical shifts are given in parts per million (δ) relative to tetramethylsilane as internal standard. Mass spectra were recorded with a Perkin Elmer/SCIEX API 165 mass instrument and HR-Mass spectra were recorded with a API QSTAR™ Pulsar (Applied Biosystems). LC/MS analysis was performed on a Jasco HPLC system (detection simultaneously at 214 and 254 nm) coupled to a Perkin Elmer/SCIEX API 165 mass instrument. RP-HPLC Purifications were performed on a BioCad Vision (AppliedBiosystem) HPLC system. Column chromatography was performed on silica gel 60 (0.04–0.063 mm, Fluka). DMF (Biosolve p.a.), 1,4-dioxane (Biosolve p.a.), DCM (Biosolve, p.a.), and toluene (Biosolve, p.a.) were stored over molecular sieves (4 Å). Ethylacetate and petroleum ether (40–60) were of technical grade and distilled before use. L-Leu–OMe·HCl (Nova Biochem), benzotriazol-l-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP, Nova Chemicals), *N*,*N*-diisopropylethylamine (DiPEA, Biosolve), triisopropylsilane (iPr$_3$SiH, Aldrich), trifluoroacetic acid (TFA, Biosolve), Boc–Cys(S*t*Bu)–OH (NovaBiochem), Boc–Gly–OH (Bissendorf Biochemicals), Boc-4-aminobutyric acid (NeoSystems), palmitic acid (Janssen Chimica), lauric acid (Acros), di-*tert*-butyl dicarbonate (Boc_2O, Fluka) were used as received. Reactions were followed by TLC analysis on silica gel (Schleicher & Schuell, F 1500 LS 254) or HPTLC aluminum sheets (Merck, silica gel 60, F254), with detection by UV-absorption (254 nm) where applicable and charring at 150 °C with 20% H_2SO_4 in EtOH (25 g/L), ninhydrin (3 g/L) in EtOH/AcOH (100/3, v/v), $NH_4(Mo)_7O_{24}{\cdot}4H_2O$ (25 g/L) and $NH_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% aq H_2SO_4 or $KMnO_4$ (2%) in 1% aq K_2CO_3.

4.2. General procedures

4.2.1. General procedure 1a—deprotection Boc. To a ~0.05 M soln of the dimer in CH_2Cl_2 were added iPr$_3$-SiH (1.3 equiv) and TFA (→TFA/DCM 1/1, v/v). After TLC analysis (PE/EtOAc 1/1, v/v) showed consumption of the starting material, the reaction mixture was coevaporated with toluene (5 × 10 mL). The free amine can be visualized with TLC analysis by employing Et_2O/EtOH/25% aq ammonia (6/3/1, v/v/v) and spraying with ninhydrin soln.

4.2.2. General procedure 1b—condensation with RCO_2H. To a ~0.1 M soln of the amine in DMF was added the appropriate acid (1.2 equiv), BOP (1.2 equiv), and DiPEA (4 equiv). After TLC analysis (DCM/MeOH: 9/1, v/v, $KMnO_4$) showed consumption of the starting material, DMF was removed in vacuo. The residue was dissolved in EtOAc and washed with water (2×), satd $NaHCO_3$ (2×), water (2×), 5% $KHSO_4$ (2×), and brine. The organic phase was dried ($MgSO_4$) and evaporated in vacuo.

4.2.3. General procedure 2—hydrolyses methyl ester. To a stirred solution of the methyl ester in 1,4-dioxane/H_2O (1/1, v/v) at 0 °C was added LiOH (1.0 M, 1.0 equiv) and the temperature was allowed to rise to room temperature. After TLC analysis (CH_2Cl_2/MeOH 9/1, v/v) showed consumption of the starting material (30–45 min) the reaction mixture was neutralized (pH 7) by addition of Amberlite-H^+. The Amberlite-H^+ was filtered off and the solvents were removed in vacuo by coevaporation with toluene. Dissolving the crude acid in a minimal amount of DCM allowed precipitation of the product in cold petroleum ether.

4.2.4. General procedure 3—DTT treatment. A solution of the disulfide in MeOH or EtOH (*c* 0.025–0.05 M, degassed by argon) is treated with Tris–HCl buffer (pH 7.4, 1 mL) and DTT (25–50 equiv). The reaction mixture is stirred for 24 h under argon, diluted with a solution of *t*BuOH/CH_3CN/H_2O (1/1/1, v/v/v, 2 mL), analyzed by LC/MS and purified by RP-HPLC.

4.3. *N*-(6-[(*N*-*tert*-Butyloxycarbonyl)-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine methyl ester (4)

Following general procedures 1a and 1b employing **3** (1.8 g, 4.6 mmol) and Boc-*S*-*tert*-butylmercapto-L-cysteine (1.7 g, 5.5 mmol) gave after purification by silica gel chromatography compound **4** (R_f = 0.5, EtOAc) in 72% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 and 7.40 (2m, 2H, 2 × N*H*-C$_\alpha$), 5.89 (br s, 1H, N*H*Boc), 4.60 (br s, 1H, H_α^{Leu}), 4.39 (br s, 1H, H_α^{Cys}), 4.06 (d, 1H, H_6, J = 7.2 Hz), 3.97 (br s, 1H, H_6), 3.87 (br s, 1H, H_3), 3.76 (s, 3H, C*H*$_3$CO), 3.43–3.38 (m, 2H, H_7), 3.10 (m, 2H, H_β^{Cys}), 1.90 and 1.73–1.68 (m, 7H, H_4, H_5 and $H_{\beta\&\gamma}^{Leu}$), 1.46 and 1.34 (2 × s, 2 × 9H, 2 × *t*Bu), 0.96 (m, 6H, 2 × CH_3^{Leu}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2–171.0 (C=O ester and amide), 154.7 (C=O Boc), 79.1 (C$_q$,

*t*Bu-Boc), 73.5, 71.6 and 66.2 (C_2, C_3, and C_6), 54.1, 51.7, and 49.6 (C_α^{Leu}, C_α^{Cys} and CO_2CH_3), 47.2 (C_7), 41.8 and 39.5 (C_q, *t*Bu, C_β^{Leu} and C_β^{Cys}), 29.0 and 27.4 ($2\times t$Bu), 26.1 and 23.2 (C_4 and C_5), 24.1 (C_γ^{Leu}), 22.1 and 20.8 ($2\times CH_3^{Leu}$). LR-MS: *m*/*z* 594.5 $(M+H)^+$, 616.4 $(M+Na)^+$. HR-MS: calculated for $[C_{26}H_{47}N_3O_8S_2–H]^+$ 594.28773, found 594.28674. $[\alpha]_D^{20}$ +2.0 ($CHCl_3$, *c* 0.5).

4.4. *N*-(6-[(*N*-*tert*-Butyloxycarbonyl)*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine methyl ester (14)

Following general procedures 1a and 1b using **13** (0.8 g, 2.1 mmol) and Boc–Cys(S*t*Bu)–OH (0.8 g, 2.5 mmol) gave after purification by silica gel chromatography compound **14** (R_f = 0.5, EtOAc) in 72% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, 1H, NH, J = 7.2 Hz), 6.80 (t, 1H, NH, J = 4.8 and 5.6 Hz), 5.53 (br s, 1H, N*H*Boc), 4.51 (m, 1H, H_α^{Leu}), 4.29 (dd, 1H, H_α^{Cys}, J = 6.6 and 6.9 Hz), 3.95 (d, 1H, H_2, J = 8.0 Hz), 3.88 (m, 1H, H_6), 3.71 (m, 1H, H_3), 3.67 (s, 3H, C*H*$_3$CO), 3.64 (m, 1H, H_{7a}), 3.17 (m, 1H, H_{7b}), 3.05 (m, 2H, H_β^{Cys}), 1.84 (m, 1H, H_{4a}), 1.69 (m, 1H, H_{5a}), 1.57 (m, 5H, $H_{4b\&5b}$ and $H_{\beta\&\gamma}^{Leu}$), 1.37 and 1.25 ($2\times$s, 2×9H, $2\times t$Bu), 0.86 (dd, 6H, $2\times CH_3^{Leu}$ J = 6.2 and 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8–170.9 (C=O ester and amide), 155.4 (C=O Boc), 79.7 (C_q, *t*Bu-Boc), 77.8, 76.6, and 67.9 (C_2, C_3, and C_6), 53.8, 52.0, and 49.7 (C_α^{Leu}, C_α^{Cys} and CO_2CH_3), 47.7 (C_7), 43.2, 41.7, 40.7 (C_q, *t*Bu, C_β^{Leu} and C_β^{Cys}), 30.4 and 26.8 (C_4 and C_5), 29.4 and 27.9 ($2\times t$Bu), 24.5 (C_γ^{Leu}), 22.4 and 21.5 ($2\times CH_3^{Leu}$). LR-MS: *m*/*z* 594.4 $(M+H)^+$, 616.4 $(M+Na)^+$. HR-MS: calculated for $[C_{26}H_{47}N_3O_8S_2–H]^+$ 594.28773, found 594.28687. $[\alpha]_D^{20}$ −42 ($CHCl_3$, *c* 0.5).

4.5. *N*-(6-[(*N*-(*N*-*tert*-Butyloxycarbonyl-glycine))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine methyl ester (5)

Following general procedures 1a and 1b using **4** (94 mg, 0.16 mmol) and Boc–Gly–OH (33.3 mg, 0.19 mmol) gave compound **5** (R_f = 0.51, EtOAc/acetone 1/1, v/v) in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1H, NH, J = 7.4 Hz), 7.30 (m, 1H, NH), 5.40 (br s, 1H, N*H*Boc), 4.78 (dt, 1H, H_α^{Cys}, J = 5.5, 5.6 and 5.7 Hz), 4.65 (m, 1H, H_α^{Leu}), 4.13 (m, 1H, H_6), 4.02 (d, 1H, H_2, J = 8.5 Hz), 3.85 (dd, 1H, H_α^{Gly}, J = 5.7 Hz), 3.76 (m, 5H, H_3, C*H*$_3$CO and H_α^{Gly}), 3.57 and 3.45 ($2\times$m, $2\times$1H, H_{7ab}), 3.34 (m, 1H, H_β^{Cys}), 3.06 (dd, 1H, H_β^{Cys} J = 5.1 Hz), 1.95 (m, 1H, H_{4a}), 1.85 (m, 1H, H_{5a}), 1.67 (m, 5H, $H_{4b\&5b}$, and $H_{\beta\&\gamma}^{Leu}$), 1.45 and 1.33 ($2\times$s, 2×9H, $2\times t$Bu), 0.86 (m, 6H, $2\times CH_3^{Leu}$). ^{13}C NMR (100 MHz, acetone-d_6) δ 173.5–170.6 (C=O ester and amide), 157.2 (C=O Boc), 79.7 (C_q, *t*Bu-Boc), 76.2 (C_2), 72.5 (C_6), 66.7 (C_3), 54.0, 52.4 (CO_2CH_3 and C_α^{Cys}), 50.8 (C_α^{Leu}), 48.3 (C_q, *t*Bu), 44.8 (C_7), 42.8 (C_α^{Gly}), 41.6 (C^{Cys}), 40.9 (C_β^{Leu}), 30.5 and 29.2 ($2\times t$Bu), 27.4 (C_4), 25.4 (C_γ^{Leu}), 24.0 (C_5), 23.3 and 21.6 ($2\times CH_3^{Leu}$). LR-MS: *m*/*z* 651.4 $(M+H)^+$, 673.5 $(M+Na)^+$. HR-MS: calculated for $[C_{28}H_{50}N_4O_9S_2–H]^+$ 651.30920, found 651.30963. $[\alpha]_D^{20}$ −25.6 ($CHCl_3$, *c* 0.25).

4.6. *N*-(6-[(*N*-(*N*-*tert*-Butyloxycarbonyl-glycine))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine methyl ester (15)

Following general procedures 1a and 1b using **14** (70 mg, 0.12 mmol) and Boc–Gly–OH (25 mg, 0.14 mmol) gave compound **15** (R_f = 0.56, EtOAc/acetone 1/1, v/v) in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1H, NH, J = 7.3 Hz), 7.17 (m, 1H, NH), 5.41 (br s, 1H, N*H*Boc), 4.78 (dd, 1H, H_α^{Cys}, J = 6.6 and 6.7 Hz), 4.66 (m, 1H, H_α^{Leu}), 3.81–3.72 (m, 5H, H_α^{Gly} and C*H*$_3$CO), 3.63 (d, H_2, 1H, J = 9.3 Hz), 3.54 (m, H_3 and H_6), 3.46 (m, 1H, H_{7a}), 3.28 and 3.25 ($2\times$dd, 1H, H_{7b}, J = 2.2, 2.5, and 2.6 Hz), 3.20 (dd, 1H, H_β^{Cys}, J = 6.0 and 6.4 Hz), 3.06 (dd, 1H, H_β^{Cys}, J = 6.4 and 6.5 Hz), 2.17 (m, 1H, H_{4a}), 1.67 (m, 4H, H_{4b}, $H_{\beta\&\gamma}^{Leu}$), 1.55–1.40 (m, 2H, H_{4b} and H_{5b}), 1.45 and 1.33 ($2\times$s, 2×9H, $2\times t$Bu), 0.86 (dd, 6H, $2\times CH_3^{Leu}$, J = 6.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 172.2 and 170.3 (C=O ester and amide), 156.1 (C=O Boc), 80.1 (C_q, *t*Bu-Boc), 77.7 (C_2), 76.7 (C_6), 68.2 (C_3), 53.0 and 52.4 (C_α^{Leu} and CO_2CH_3), 49.7 (C_α^{Cys}), 48.1 (C_q, *t*Bu), 44.1 (C_α^{Gly}), 43.6 (C_7), 41.1 and 40.8 (C_β^{Leu} and C_β^{Cys}), 30.5 (C_4), 29.6 and 28.2 ($2\times t$Bu), 27.1 (C_5), 24.7 (C_γ^{Leu}), 22.6 and 21.6 ($2\times CH_3^{Leu}$). LR-MS: *m*/*z* 651.3 $(M+H)^+$, 673.5 $(M+Na)^+$. HR-MS: calculated for $[C_{28}H_{50}N_4O_9S_2–H]^+$ 651.30920, found 651.31061. $[\alpha]_D^{20}$ −67 ($CHCl_3$, *c* 1).

4.7. *N*-(6-[(*N*-(4-*N*-*tert*-Butyloxycarbonyl-aminobutyric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine methyl ester (6)

Following general procedures 1a and 1b using **4** (254 mg, 0.43 mmol) and Boc-4-aminobutyric acid (104 mg, 0.51 mmol) gave compound **6** (R_f = 0.71, EtOAc/acetone 1/1, v/v) in 75% yield. ^{13}C NMR (50 MHz, acetone-d_6) δ 173.4, 172.2, and 170.7 (C=O ester and amide), 157.0 (C=O Boc), 78.5 (C_q, *t*Bu Boc), 76.1 (C_2), 72.4 (C_6), 66.9 (C_3), 54.2 and 52.2 (C_α^{Leu} and CO_2CH_3), 50.7 (C_α^{Cys}), 48.1 (C_q, *t*Bu), 42.8, 41.4. 40.7, and 39.8 (C_7, C_β^{Leu} and C_β^{Cys}, CH_2), 33.0, 27.2, 26.6, and 24.0 (C_4, C_5 and $2\times CH_2$), 29.9 and 28.5 ($2\times t$Bu), 25.3 (C_γ^{Leu}), 23.2 and 21.4 ($2\times CH_3^{Leu}$). LR-MS: *m*/*z* 679.5 $(M+H)^+$, 701.4 $(M+Na)^+$. HR-MS: calculated for $[C_{30}H_{54}N_4O_9S_2–H]^+$ 679.34050, found 679.34375. $[\alpha]_D^{20}$ −16 ($CHCl_3$, *c* 1).

4.8. *N*-(6-[(*N*-(4-*N*-*tert*-butyloxycarbonyl-aminobutyric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine methyl ester (16)

Following general procedures 1a and 1b using **14** (0.25 g, 0.42 mmol) and Boc-4-aminobutyric acid (0.10 g, 0.51 mmol) gave compound **16** (R_f = 0.65, EtOAc/acetone 1/1, v/v) in 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 1H, NH, J = 7.3 Hz), 7.12 (m, 1H, NH), 4.80 (br s, 1H, N*H*Boc), 4.63 (m, 2H, H_α^{Cys} and H_α^{Leu}), 3.71 (s, 3H, C*H*$_3$CO), 3.49–3.42 (m, 3H, H_2, H_3, and H_6), 3.09–3.01 (m, 4H, H_7 and H_β^{Cys}), 2.20 ($2\times CH_2$), 2.10 (m, 1H, H_{4a}), 1.74 (m, 2H, CH_2), 1.63 (m, 4H, H_{5a}, $H_{\beta\&\gamma}^{Leu}$), 1.49–1.27 (m, 2H, H_{4b} and H_{5b}), 1.38 and 1.27 ($2\times$s, 2×9H, $2\times t$Bu),

0.86 (dd, 6H, $2\times CH_3^{Leu}$, $J = 6.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 173.6, 172.4, and 171.3 (C=O ester and amide), 156.4 (C=O Boc), 79.5 (C_q, *t*Bu-Boc), 77.8 (C_6), 76.9 (C_2), 68.2 (C_3), 52.9, 52.3 (C_α^{Leu} and CO_2CH_3), 49.7 (C_α^{Cys}), 47.8 (C_q, S*t*Bu), 43.4, 41.0. 40.7, and 39.3 (C_7, C_β^{Leu}, C_β^{Cys} and CH_2), 29.6 and 28.2 ($2\times$ *t*Bu), 32.9, 30.4, 27.0, 26.1 (C_4, C_5 and $2\times CH_2$), 24.7 (C_γ^{Leu}), 22.6 and 21.5 ($2\times CH_3^{Leu}$). LR-MS: *m/z* 679.7 $(M+H)^+$, 701.4 $(M+Na)^+$. HR-MS: calculated for $[C_{30}H_{54}N_4O_9S_2–H]^+$ 679.34050, found 679.34039. $[\alpha]_D^{20}$ −69 ($CHCl_3$, *c* 1).

4.9. *N*-(6-[(*N*-(*N*-Lauric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine methyl ester (7)

Following general procedures 1a and 1b using **4** (44 mg, 0.07 mmol) and lauric acid (17.8 mg, 0.09 mmol) gave compound **7** ($R_f = 0.5$, DCM/MeOH 9/1, v/v) in >99% yield. ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, 1H, NH, $J = 8.4$ Hz), 6.97 (m, 1H, NH), 6.77 (d, 1H, NH, $J = 7.5$ Hz), 4.77 (dd, 1H, H_α^{Cys}, $J = 7.0$ Hz), 4.65 (m, 1H, H_α^{Leu}), 4.04 (m, 1H, H_6), 3.99 (d, 1H, H_2, $J = 7.9$ Hz), 3.84 (m, 1H, H_3), 3.76 (s, 3H, C*H*$_3$CO), 3.76 (m, 1H, H_{7a}), 3.31 (m, 1H, H_{7b}), 3.20 and 3.08 (ddd, 2H, H_β^{Cys}), 2.35 (t, 2H, CH_2^{lipid}, $J = 7.5$ and 7.6 Hz), 2.27 (t, 2H, CH_2^{lipid}, $J = 7.5$ and 7.7 Hz), 1.95 (m, 1H, H_{4a}), 1.75–1.58 (m, 6H, $H_{\beta\&\gamma}^{Leu}$, H_{5a} and CH_2^{lipid}), 1.42–1.27 (m, *t*Bu, $H_{4b\&5b}$, CH_2^{lipid}), 0.95 (t, 6H, $2\times CH_3^{Leu}$, $J = 6.2$ and 6.3 Hz), 0.88 (t, 3H, CH_3^{lipid}, $J = 6.8$ and 7.1 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 173.4, 171.9, and 170.5 (C=O ester and amide), 73.4 (C_6), 71.7 (C_2), 67.4 (C_3), 52.9, 52.5 (C_α^{Leu} and CO_2CH_3), 50.1 (C_α^{Cys}), 48.5 (C_q, *t*Bu), 42.0 (C_β^{Cys}), 41.0 (C_β^{Leu}), 39.6 (C_7), 36.5, 33.8, and 31.9 ($3\times CH_2^{lipid}$), 29.6 (*t*Bu), 29.6 (CH_2^{lipid}), 26.5, 25.6, 24.0, 24.8, 22.7 (C_4, C_5 and $3\times CH_2^{lipid}$), 24.8 (C_γ^{Leu}), 22.8 and 21.7 ($2\times CH_3^{Leu}$), 14.0 (CH_3^{lipid}). LR-MS: *m/z* 676.5 $(M+H)^+$, 698.5 $(M+Na)^+$. HR-MS: calculated for $[C_{33}H_{61}N_3O_7S_2–H]^+$ 676.40237, found 676.40063. $[\alpha]_D^{20}$ −2.4 ($CHCl_3$, *c* 0.25).

4.10. *N*-(6-[(*N*-(*N*-Lauric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine methyl ester (17)

Following general procedures 1a and 1b using **14** (53 mg, 0.09 mmol) and lauric acid (21.5 mg, 0.11 mmol) gave compound **17** ($R_f = 0.44$, DCM/MeOH 9/1, v/v) in 91% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, 1H, NH, $J = 8.9$ Hz), 7.10 (br t, 1H, NH), 4.73 (dd, 1H, H_α^{Cys}, $J = 7.2$ and 7.4 Hz), 4.69 (dd, 1H, H_α^{Cys}, $J = 7.3$ and 8.3 Hz), 3.77 (s, 3H, C*H*$_3$CO), 3.62–3.42 (m, 4H, H_2, H_3, H_6, and H_{7a}), 3.12 (m, 1H, H_{7b}), 3.02 (dd, 2H, H_β^{Cys}, $J = 6.9$, 7.2, and 7.3 Hz), 2.32–2.17 (m, 4H, $2\times CH_2^{lipid}$), 1.70–1.32 (m, $H_{\beta\&\gamma}^{Leu}$, H_4, H_5, and CH_2^{lipid}), 1.34–1.20 (m, *t*Bu, CH_2^{lipid}), 0.95 (dd, 6H, $2\times CH_3^{Leu}$, $J = 5.9$ Hz), 0.89 (t, 3H, CH_3^{lipid}, $J = 6.8$ and 7.1 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.3, 175.2, 173.1, 172.4 (C=O ester and amide), 78.8 (C_6), 78.2 (C_2), 69.2 (C_3), 53.4 (C_α^{Leu} and CO_2CH_3), 50.6 (C_α^{Cys}), 49.0 (C_q, *t*BuSS), 44.4 (C_7), 42.0. 41.5 (C_β^{Leu} and C_β^{Cys}), 37.1, 32.8, 31.5, 31.0–30.0 (CH_2^{lipid}), 30.2 (*t*Bu), 28.0, 26.6 (C_4, C_5), 23.5 (CH_2^{lipid}), 25.8 (C_γ^{Leu}), 23.7 and 22.6 ($2\times CH_3^{Leu}$), 15.0 (CH_3^{lipid}). LR-MS: *m/z* 676.3 $(M+H)^+$, 698.5 $(M+Na)^+$. HR-MS: calculated for $[C_{33}H_{61}N_3O_7S_2–H]^+$ 676.40237, found 676.40149. $[\alpha]_D^{20}$ −115.2 ($CHCl_3$, *c* 0.25).

4.11. *N*-(6-[(*N*-(*N*-Palmitic acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine methyl ester (8)

Following general procedures 1a and 1b using **4** (91 mg, 0.15 mmol) and palmitic acid (47.2 mg, 0.18 mmol) gave compound **8** ($R_f = 0.67$, EtOAc/acetone 1/1, v/v) in 87% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 2H, $2\times$ NH), 7.00 (d, 1H, NH, $J = 7.8$ Hz), 4.77 (m, 1H, H_α^{Cys}), 4.62 (m, 1H, H_α^{Leu}), 4.06 (m, 2H, H_6 and H_2), 3.84 (m, 1H, H_3), 3.76 (s, 3H, C*H*$_3$CO), 3.60 and 3.30 ($2\times$ m, 2H, H_7), 3.14 (m, 2H, H_β^{Cys}), 2.27 (m, 2H, CH_2^{lipid}), 1.95 (m, 1H, H_{4a}), 1.75 and 1.55 (m, 6H, $H_{\beta\&\gamma}^{Leu}$, H_{5a} and CH_2^{lipid}), 1.42–1.20 (m, *t*Bu, $H_{4b\&5b}$, CH_2^{lipid}), 0.95 (t, 6H, $2\times CH_3^{Leu}$, $J = 5.8$ and 5.9 Hz), 0.88 (t, 3H, CH_3^{lipid}, $J = 6.6$ and 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 173.4, 171.9, and 170.7 (C=O ester and amide), 74.2 (C_6), 71.3 (C_2), 66.6 (C_3), 53.3, 52.6 (C_α^{Leu} and CO_2CH_3), 50.7 (C_α^{Cys}), 48.2 (C_q, *t*Bu), 42.0 (C_β^{Cys}), 40.8 (C_β^{Leu}), 39.7 (C_7), 36.3 and 31.8 ($2\times CH_2^{lipid}$), 29.6 (*t*Bu), 29.6 (CH_2^{lipid}), 26.5, 25.6, 24.0. 22.6 (C_4, C_5 and $2\times CH_2^{lipid}$), 25.1 (C_γ^{Leu}), 22.6 and 21.3 ($2\times CH_3^{Leu}$), 14.0 (CH_3^{lipid}). LR-MS: *m/z* 733.9 $(M+H)^+$, 754.6 $(M+Na)^+$. HR-MS: calculated for $[C_{37}H_{69}N_3O_7S_2–H]^+$ 732.46497, found 732.46338. $[\alpha]_D^{20}$ −2.0 ($CHCl_3$, *c* 0.5).

4.12. *N*-(6-[(*N*-*N*-(Palmitic acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine methyl ester (18)

Following general procedures 1a and 1b using **14** (76 mg, 0.13 mmol) and palmitic acid (39.4 mg, 0.15 mmol) gave compound **18** ($R_f = 0.83$, EtOAc/acetone 1/1, v/v) in 84% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, NH), 7.20 (1H, NH), 7.12 (1H, NH), 4.70 (m, 2H, H_α^{Cys} and H_α^{Leu}), 3.76 (s, 3H, C*H*$_3$CO), 3.53 (m, 4H, H_2, H_3, H_6 and H_{7a}), 3.20 (m, 1H, H_{7b}), 3.00 (m, 2H, H_β^{Cys}), 2.40–2.17 (m, 3H, CH_2^{lipid} and H_{4a}), 1.50–1.40 (m, 6H, $H_{\beta\&\gamma}^{Leu}$, H_{5a} and CH_2^{lipid}), 1.40–1.20 (m, *t*Bu, $H_{4b\&5b}$, CH_2^{lipid}), 0.95 (dd, 6H, $2\times CH_3^{Leu}$, $J = 6.1$ and 6.0 Hz), 0.88 (t, 3H, CH_3^{lipid}, $J = 6.6$ and 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$; 100 MHz MeOD-d_4) δ 174.4, 172.2, 171.4 (C=O ester and amide), 77.9 (C_6), 77.4 (C_2), 68.3 (C_3), 53.6, 52.4 (C_α^{Leu} and CO_2CH_3), 50.7 (C_α^{Cys}), 48.2 (C_q, *t*BuSS), 43.9 (C_7), 42.7. 41.0 (C_β^{Leu} and C_β^{Cys}), 36.5, 32.5, 31.5, 30.0–29.0 (CH_2^{lipid}), 30.2 (*t*Bu), 27.1, 25.7, 24.8, 22.7 (C_4, C_5 and CH_2), 24.8 (C_γ^{Leu}), 22.7 and 21.7 ($2\times CH_3^{Leu}$), 14.1 (CH_3^{lipid}). LR-MS: *m/z* 732.5 $(M+H)^+$, 754.8 $(M+Na)^+$. HR-MS: calculated for $[C_{37}H_{69}N_3O_7S_2–H]^+$ 732.46497, found 732.46295. $[\alpha]_D^{20}$ −43.6 ($CHCl_3$, *c* 0.5).

4.13. *N*-(6-[(*N*-(*N*-(Lauric acid)-glycine))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine methyl ester (9)

Following general procedures 1a and 1b using **5** (34 mg, 0.05 mmol) and lauric acid (12.5 mg, 0.06 mmol) gave

compound **9** (R_f = 0.51, DCM/MeOH 9/1, v/v) in 52% yield. ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.4, 173.5, 171.9 and 169.7 (C=O ester and amide), 73.0, 70.9 (C_2 and C_6), 67.1 (C_3), 53.0, 52.3 (C_α and CO_2CH_3), 49.6 (C_α), 48.2 (C_q, *t*Bu), 43.3, 42.0, 41.7, 39.5 (C_β^{Cys}, C_β^{Leu}, CH_2^{Gly} and C_7), 35.9 and 31.6 ($2\times CH_2^{lipid}$), 29.5 (*t*Bu), 29.6 (CH_2^{lipid}), 26.3, 25.3, 23.7, 22.4 (C_4, C_5, and C_2^{lipid}), 24.6 (C_γ^{Leu}), 22.6 and 21.4 ($2\times CH_3^{Leu}$), 13.8 (CH_3^{lipid}). LR-MS: *m/z* 733.5 $(M+H)^+$, 755.5 $(M+Na)^+$. HR-MS: calculated for $[C_{35}H_{64}N_4O_8S_2–H]^+$ 733.42383, found 733.42206.

4.14. *N*-(6-[(*N*-(*N*-(Lauric acid)-glycine))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine methyl ester (19)

Following general procedures 1a and 1b using **15** (64 mg, 0.10 mmol) and lauric acid (23.6 mg, 0.12 mmol) gave compound **19** (R_f = 0.54, DCM/MeOH 9/1, v/v) in >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, 2H, $2\times$NH, *J* = 5.7 and 6.5 Hz), 7.18 (t, 1H, NH, *J* = 5.8 Hz), 6.54 (t, 1H, NH, *J* = 5.1 Hz), 4.70 (m, 2H, H_α^{Cys} and H_α^{Leu}), 3.92 (dd, 2H, CH_2^{Gly}, *J* = 2.9 and 3.0 Hz), 3.77 (s, 3H, C*H*$_3$CO), 3.66 (d, 1H, H_6), 3.55 (m, 2H, H_2 and H_3), 3.43, 3.26 ($2\times$m, 2H, H_7), 3.14, 3.00 ($2\times$m, 2H, H_β^{Cys}), 2.64-2.14 (m, 4H, $2\times CH_2^{lipid}$), 1.72–1.32 (m, H_β^{Leu}, H_γ^{Leu}, H_4, H_5 and CH_2^{lipid}), 1.32 (s, 9H, *t*Bu), 1.32–1.17 (m, CH_2^{lipid}), 0.95 (dd, 6H, $2\times CH_3^{Leu}$, *J* = 6.0 Hz), 0.88 (t, 3H, CH_3^{lipid}, *J* = 6.6 and 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 174.1, 172.3, 170.2 and 169.7 (C=O ester and amide), 77.6, 76.5 (C_2 and C_6), 68.3 (C_3), 53.2, 52.6 (C_α^{Leu} and CO_2CH_3), 49.6 (C_α^{Cys}), 48.4 (C_q, *t*Bu), 43.8, 43.40, 41.3, 41.0 (C_β^{Cys}, C_β^{Leu}, CH_2^{Gly} and C_7), 36.2, 31.9 and 30.7 ($3\times CH_2^{lipid}$), 29.6 (*t*Bu), 29.3 (CH_2^{lipid}), 27.3, 25.6, 22.6 (C_4, C_5 and CH_2^{lipid}), 24.9 (C_γ^{Leu}), 22.8 and 21.8 ($2\times CH_3^{Leu}$), 14.1 (CH_3^{lipid}). LR-MS: *m/z* 733.5 $(M+H)^+$, 755.5 $(M+Na)^+$. HR-MS: calculated for $[C_{35}H_{64}N_4O_8S_2–H]^+$ 733.42383, found 733.42236. $[\alpha]_D^{20}$ −55.6 ($CHCl_3$, *c* 0.5).

4.15. *N*-(6-[(*N*-(*N*-4-(*N*-Lauric acid)-aminobutyric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine methyl ester (10)

Following general procedures 1a and 1b using **6** (73 mg, 0.11 mmol) and lauric acid (26.0 mg, 0.13 mmol) gave compound **10** (R_f = 0.52, DCM/MeOH 9/1, v/v) in 64% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (m, 1H, NH), 7.27 (m, 1H, NH), 7.17 (d, 1H, NH, *J* = 8.1 Hz), 5.88 (m, 1H, NH), 4.96 (m, 1H, H_α^{Cys}), 4.85–4.60 (m, 3H, H_α^{Leu} and CH_2), 4.17 (m, 1H, H_6), 4.10 (d, 1H, H_2, *J* = 8.2 Hz), 4.06 (m, C*H*$_2$), 3.80 (m, 1H, H_3), 3.75 (s, 3H, C*H*$_3$CO), 3.71–3.25 (m, H_7 and C*H*$_2$), 3.32 (dd, H_β^{Cys}, *J* = 6.5 Hz), 3.12 (m, H_β^{Cys}), 2.31 (m, C*H*$_2$), 2.13 (m, C*H*$_2$), 1.91 (m, H_{4a} and C*H*$_2$), 1.77 (m, 1H, H_{5a}), 1.97–1.55 (m, $H_{\beta\&\gamma}^{Leu}$, $H_{4b\&5b}$ and C*H*$_2$), 1.40 (CH_2), 1.33 (s, 9H, *t*Bu), 1.25 (m, CH_2), 0.95 (m, 6H, $2\times CH_3^{Leu}$), 0.88 (t, 3H, CH_3^{lipid}, *J* = 6.8 and 7.1 Hz). ^{13}C NMR (50 and 150 MHz, $CDCl_3$) δ 174.2, 173.6, 173.0, 172.4 and 170.5 (C=O ester and amide), 72.9, 71.9 (C_2 and C_6), 70.7 (C_3), 53.0, 52.3 (C_α^{Leu} and CO_2CH_3), 50.1 (C_α^{Cys}), 48.3 (C_q, *t*Bu), 42.8, 42.8, 40.9, 39.6, 38.0, 36.9 (C_β^{Cys}, C_β^{Leu}, CH_2 and C_7), 32.5, 31.9 (CH_2), 29.6 (*t*Bu), 29.6 (CH_2), 26.7, 26.6, 26.0, 25.9 (C_4, C_5 and CH_2), 24.8 (C_γ^{Leu}), 22.9 and 21.6 ($2\times CH_3^{Leu}$), 14.0 (CH_3^{lipid}). LR-MS: *m/z* 761.7 $(M+H)^+$, 783.5 $(M+Na)^+$. HR-MS: calculated for $[C_{37}H_{68}N_4O_8S_2–H]^+$ 761.45513, found 761.45355. $[\alpha]_D^{20}$ −8 ($CHCl_3$, *c* 0.25).

4.16. *N*-(6-[(*N*-(*N*-4-(*N*-Lauric acid)-aminobutyric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine methyl ester (20)

Following general procedures 1a and 1b using **16** (55 mg, 0.08 mmol) and lauric acid (19.5 mg, 0.10 mmol) gave compound **20** (R_f = 0.50, DCM/MeOH 9/1, v/v) in 92% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, 1H, NH, *J* = 8.7 Hz), 7.29 (d, 1H, NH, *J* = 8.1 Hz), 7.22 (m, 1H, NH), 5.92 (m, 1H, NH), 4.72–4.62 (m, 2H, H_α^{Cys} and H_α^{Leu}), 3.76 (s, 3H, CH_3CO), 3.61–3.46 (m, 5H, H_2, H_3, H_6, and H_{7a}), 3.25 (m, 2H, CH_2), 3.17 (m, 1H, H_{7b}), 3.06 (m, 2H, H_β^{Cys}), 2.27 (m, 2H, CH_2), 2.17 (t, 2H, CH_2, *J* = 7.7 and 7.2 Hz), 1.90 (m, 2H, CH_2), 1.82–1.39 (m, H_β^{Leu}, H_γ^{Leu}, CH_2^{lipid} and $H_{4\&5}$), 1.33 (s, 9H, *t*Bu), 1.26 (m, CH_2^{lipid}), 0.88 (dd, 6H, $2\times CH_3^{Leu}$, *J* = 5.8 and 5.6 Hz), 0.87 (t, 3H, CH_3^{lipid}, *J* = 6.7 and 7.2 Hz). ^{13}C NMR (150 and 50 MHz, $CDCl_3$) δ 173.8, 173.6, 173.3, 172.1, 170.9 (C=O ester and amide), 77.7 (C_6), 76.7 (C_2), 68.1 (C_3), 52.8, 52.3 (CO_2CH_3 and C_α^{Cys}), 49.7 (C_α^{Leu}), 47.9 (C_q, *t*Bu), 43.4 (C_7), 40.7, 40.6 (C_β^{Leu} and C_β^{Cys}), 38.2, 36.5, 33.0, 31.6, 30.3 (CH_2), 29.6 (*t*Bu), 29.3, 29.1 (CH_2^{lipid}), 27.2, 25.8, 22.7 ($C_{4\&5}$ and CH_2), 24.8 (C_γ^{Leu}), 24.1, 21.7 ($2\times CH_3^{Leu}$), 14.1 (CH_3^{lipid}). LR-MS: *m/z* 761.8 $(M+H)^+$, 783.6 $(M+Na)^+$. HR-MS: calculated for $[C_{37}H_{68}N_4O_8S_2–H]^+$ 761.45513, found 761.45288. $[\alpha]_D^{20}$ −59.2 ($CHCl_3$, *c* 0.25).

4.17. *N*-(6-[(*N*-(*N*-(Palmitic acid)-glycine))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine methyl ester (11)

Following general procedures 1a and 1b using **5** (50 mg, 0.08 mmol) and palmitic acid (23.6 mg, 0.09 mmol) gave compound **11** (R_f = 0.72, EtOAc/acetone 1/1, v/v) in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1H, NH, *J* = 8.2 Hz), 7.30 (m, 2H, $2\times$NH), 6.56 (t, 1H, NH, *J* = 5.0 Hz), 4.77 (dd, 1H, H_α^{Cys}, *J* = 5.8 and 6.0 Hz), 4.66 (m, 1H, H_α^{Leu}), 4.10 (m, 1H, H_6), 4.06 (d, 1H, H_2, *J* = 8.2 Hz), 3.92 (ddd, 2H, CH_2^{Gly}, *J* = 5.0 and 5.4 Hz), 3.77 (m, 4H, H_3 and C*H*$_3$CO), 3.54 (m, 1H, H_{7a}), 3.38 (m, 2H, H_{7b} and H_β^{Cys}), 3.09 (dd, 1H, H_β^{Cys}, *J* = 5.1 and 5.2 Hz), 2.36–2.22 (m, 2H, CH_2^{lipid}), 1.94 (m, 1H, H_{4a}), 1.80 (m, 1H, H_{5a}), 1.70–1.55 (m, 9H, $H_{\beta\&\gamma}^{Leu}$, $H_{4b\&5b}$ and $2\times CH_2^{lipid}$), 1.33 (s, 9H, *t*Bu), 1.39–1.15 (m, CH_2^{lipid}), 0.95 (t, 6H, $2\times CH_3^{Leu}$, *J* = 3.9), 0.88 (t, 3H, CH_3^{lipid}, *J* = 6.6 and 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 173.8, 172.2, and 169.9 (C=O ester and amide), 73.0, 71.0 (C_2 and C_6), 67.5 (C_3), 53.2, 52.6 (C_α^{Leu} and CO_2CH_3), 49.9 (C_α^{Cys}), 48.5 (C_q, *t*Bu), 43.7, 42.3, 41.0, 39.6 (C_β^{Cys}, C_β^{Leu}, CH_2^{Gly} and C_7), 36.1 and 31.9 ($2\times CH_2^{lipid}$), 29.6 (*t*Bu), 29.6 (CH_2^{lipid}), 26.6, 25.5, 24.0, 22.6 (C_4, C_5 and $2\times CH_2^{lipid}$), 24.1 (C_γ^{Leu}), 22.6 and 21.6 ($2\times CH_3^{Leu}$), 14.1 (CH_3^{lipid}). LR-MS: *m/z* 789.5 $(M+H)^+$, 811.6 $(M+Na)^+$. HR-MS: calculated for $[C_{37}H_{72}N_4O_8S_2–H]^+$ 789.48643, found 789.48407. $[\alpha]_D^{20}$ −17.6 ($CHCl_3$, *c* 0.5).

4.18. *N*-(6-[(*N*-(*N*-(Palmitic acid)-glycine))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine methyl ester (21)

Following general procedures 1a and 1b using **15** (63 mg, 0.10 mmol) and palmitic acid (29.8 mg, 0.12 mmol) gave compound **21** (R_f = 0.77, EtOAc/acetone 1/1, v/v) in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (m, 1H, NH), 7.61 (d, 1H, NH, J = 7.8 Hz), 7.52 (d, 1H, NH, J = 8.7 Hz), 7.00 (m, 1H, NH), 4.66 (m, 2H, H_α^{Cys} and H_α^{Leu}), 3.90 (dd, 2H, CH_2^{Gly}), 3.76 (s, 3H, CH_3CO) 3.76–3.27 (m, 4H, H_2, H_3, H_6, H_7, and H_β^{Cys}), 3.09 (dd, 1H, H_β^{Cys}, J = 1.6, 1.9, and 6.4 and 6.7 Hz), 2.27 (m, 2H, CH_2^{lipid}), 2.15 (m, 1H, H_{4a}), 1.74–1.38 (m, 10H, $H_{\beta\&\gamma}^{Leu}$, H_{4b}, H_5 and $2\times CH_2^{lipid}$), 1.32 (s, 9H, *t*Bu), 1.32–1.15 (m, CH_2^{lipid}), 0.95 (m, 6H, $2\times CH_3^{Leu}$), 0.88 (t, 3H, CH_3^{lipid}, J = 6.6 and 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 173.9, 172.4, 170.3, and 169.7 (C=O ester and amide), 78.0, 76.7 (C_2 and C_6), 68.3 (C_3), 53.1, 52.5 (C_α^{Leu} and CO_2CH_3), 49.9 (C_α^{Cys}), 48.2 (C_q, *t*Bu), 43.7, 42.0, 41.6, 40.8 (C_β^{Cys}, C_β^{Leu}, CH_2^{Gly} and C_7), 36.1 and 31.8 ($2\times CH_2^{lipid}$), 29.6 (*t*Bu), 29.6 (CH_2^{lipid}), 27.1, 25.5, 23.8, 21.6 (C_4, C_5 and $2\times CH_2^{lipid}$), 24.8 (C_γ^{Leu}), 22.7 and 21.6 ($2\times CH_3^{Leu}$), 14.0 (CH_3^{lipid}). LR-MS: *m*/*z* 789.5 $(M+H)^+$, 811.6 $(M+Na)^+$. HR-MS: calculated for $[C_{37}H_{72}N_4O_8S_2–H]^+$ 789.48643, found 789.48444. $[\alpha]_D^{20}$ −55.2 ($CHCl_3$, *c* 0.5).

4.19. *N*-(6-[(*N*-(*N*-(Palmitic acid)-4-aminobutyric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine methyl ester (12)

Following general procedures 1a and 1b using **6** (57 mg, 0.08 mmol) and palmitic acid (25.9 mg, 0.1 mmol) gave compound **12** (R_f = 0.50, EtOAc/acetone 1/1, v/v) in 85% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (m, 1H, NH), 7.29 (m, 1H, NH), 7.17 (d, 1H, NH, J = 7.9 Hz), 5.97 (m, 1H, NH), 4.82 (m, 1H, H_α^{Cys}), 4.67 (m, 1H, H_α^{Leu}), 4.16 (m, 1H, H_6), 4.10 (d, 1H, H_2, J = 8.0 Hz), 4.05 (m, CH_2), 3.81 (m, 1H, H_3), 3.75 (s, 3H, CH_3CO), 3.59 (m, 1H, H_{7a}), 3.48, 3.42 (m, CH_2), 3.32 (m, H_{7b}, H_β^{Cys} and CH_2), 3.11 (m, H_β^{Cys} and CH_2), 2.35 (m, CH_2), 2.15 (m, CH_2), 1.91 (m, H_{4a} and CH_2), 1.77 (m, 1H, H_{5a}), 1.68–1.54 (m, $H_{\beta\&\gamma}^{Leu}$, $H_{4b\&5b}$ and CH_2), 1.33 (s, 9H, *t*Bu), 1.39–1.15 (m, CH_2), 0.95 (t, 6H, $2\times CH_3^{Leu}$, J = 5.8 and 5.4 Hz), 0.88 (t, 3H, CH_3^{lipid}, J = 6.9 and 7.1 Hz). ^{13}C NMR (50 and 150 MHz, $CDCl_3$) δ 176.9, 174.2, 173.1, 172.3 and 170.5 (C=O ester and amide), 73.0, 70.7 (C_2 and C_6), 67.4 (C_3), 53.0, 52.4 (C_α^{Leu} and CO_2CH_3), 49.8 (C_α^{Cys}), 48.3 (C_q, *t*Bu), 42.7, 40.7, 39.6, 37.8 (C_β^{Cys}, C_β^{Leu}, CH_2 and C_7), 33.9, 32.5, 31.8 (CH_2), 29.6 (*t*Bu), 29.6 (CH_2), 26.5, 26.0, 25.8, 22.6, 21.6 (C_4, C_5 and CH_2), 24.8 (C_γ^{Leu}), 22.8 and 21.5 ($2\times CH_3^{Leu}$), 14.0 (CH_3^{lipid}). LR-MS: *m*/*z* 817.8 $(M+H)^+$, 839.6 $(M+Na)^+$. HR-MS: calculated for $[C_{41}H_{76}N_4O_8S_2–H]^+$ 817.51773, found 817.51459. $[\alpha]_D^{20}$ −7.6 ($CHCl_3$, *c* 0.5).

4.20. *N*-(6-[(*N*-(*N*-(Palmitic acid)-4-aminobutyric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine methyl ester (22)

Following general procedures 1a and 1b using **16** (44 mg, 0.07 mmol) and palmitic acid (20.0 mg, 0.08 mmol) gave compound **22** (R_f = 0.54, EtOAc/acetone 1/1, v/v) in 78% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.39 (m, 3H, NH), 6.11 (m, 1H, NH), 4.70 (m, 1H, H_α^{Cys}), 4.64 (m, 1H, H_α^{Leu}), 4.00 (m, CH_2), 3.76 (s, 3H, CH_3CO), 3.50–3.57 (m, H_2, H_3, H_6 and CH_2), 3.36–3.18 (m, H_7, CH_2), 3.06 (m, H_β^{Cys} and CH_2), 2.33–2.22 (m, CH_2), 2.16 (m, CH_2), 1.80 (m, CH_2), 1.69 (m, $H_{\beta\&\gamma}^{Leu}$, $H_{4a\&5a}$ and CH_2), 1.33 (s, 9H, *t*Bu), 1.50–1.32 (m, $H_{4b\ \&5b}$ and CH_2), 1.25 (m, CH_2), 0.95 (t, 6H, $2\times CH_3^{Leu}$, J = 5.4 and 5.5 Hz), 0.88 (t, 3H, CH_3^{lipid}, J = 6.8 and 7.1 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.0, 174.6, 174.5, 173.2, and 171.9 (C=O ester and amide), 79.0, 77.7 (C_2 and C_6), 69.2 (C_3), 54.7, 53.3 (C_α^{Leu} and CO_2CH_3), 49.0 (C_α^{Cys}), 48.3 (C_q, *t*Bu), 44.5, 41.9, 41.8, 39.4, 37.6, 34.1, 32.8, 31.5 (C_β^{Cys}, C_β^{Leu}, CH_2 and C_7), 29.6 (*t*Bu), 30.0 (CH_2), 28.1, 26.7, 26.6, 23.5 (C_4, C_5 and CH_2), 24.8 (C_γ^{Leu}), 22.8 and 21.5 ($2\times CH_3^{Leu}$), 14.0 (CH_3^{lipid}). LR-MS: *m*/*z* 817.8 $(M+H)^+$, 839.6 $(M+Na)^+$. HR-MS: calculated for $[C_{41}H_{76}N_4O_8S_2–H]^+$ 817.51773, found 817.51849. $[\alpha]_D^{20}$ −50.8 ($CHCl_3$, *c* 0.5).

4.21. *N*-(6-[(*N*-(*N*-Lauric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine (23)

Compound **23** was prepared from **7** (31 mg, 0.05 mmol) according to general procedure 2. Crude yield: >99%. ^{1}H NMR (400 MHz, MeOD-d_4) δ 4.54 (dd, 1H, H_α^{Cys}, J = 5.6 Hz), 4.36 (m, 1H, H_α^{Leu}), 4.10 (d, 1H, H_2, J = 3.6 Hz), 4.02 (m, 1H, H_3), 3.69 (m, 1H, H_6), 3.26 (m, 2H, H_7), 3.06 (1H, H_β^{Cys}), 2.88 (dd, 1H, H_β^{Cys}, J = 6.0 Hz), 2.16 (m, 2H, CH_2), 1.69–1.42 (m, CH_2^{lipid}, $H_{\beta\&\gamma}^{Leu}$ and $H_{4\&5}$), 1.30–1.10 (m, *t*Bu and CH_2^{lipid}), 0.85 (t, 6H, $2\times CH_3^{Leu}$ J = 6.4 Hz), 0.79 (t, 3H, CH_3^{lipid}, J = 6.8 Hz). ^{13}C NMR (50 MHz, MeOD-d_4) δ 175.2–170.5 (C=O ester and amide), 73.8 (C_6), 72.0 (C_2), 66.7 (C_3), 52.7, 50.2 (C_α^{Leu} and C_α^{Cys}), 48.1 (C_7), 41.7 (C_q, *t*Bu), 40.2, 36.2 (C_β^{Leu} and C_β^{Cys}), 29.5 ($3\times CH_3S$-*t*Bu), 29.4 (CH_2^{lipid}), 25.4 (C_4), 24.7 (C_γ^{Leu}), 22.6 (CH_3^{Leu}), 22.4 (C_5), 21.3 (CH_3^{Leu}), 13.8 ($CH_3^{lipid\gamma}$). LR-MS: *m*/*z* 684.6 $(M+Na)^+$. HR-MS: calculated for $[C_{32}H_{59}N_3O_7S_2–H]^+$ 662.3867, found 662.3922.

4.22. *N*-(6-[(*N*-(*N*-Lauric acid))-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine (35)

Compound **35** was prepared from **23** (7 mg, 11 μmol) according to general procedure 3. LC/MS analysis: t_R 16.3 min, *m*/*z* 574.5 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 30→90% B in 26 min.

4.23. *N*-(6-[(*N*-(*N*-Lauric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine (29)

Compound **29** was prepared from **17** (55 mg, 0.08 mmol) according to general procedure 2. Crude yield: >99%. ^{1}H NMR (400 MHz, MeOD-d_4) δ 4.60 (t, 1H, H_α^{Cys}, J = 6.8 and 7.2 Hz), 4.24 (m, 1H, H_α^{Leu}), 3.52 (m, 2H, $H_{2,3}$ and H_{7a}), 3.35 (m, 1H, H_6), 3.10 (m, 1H,

H_{7b}), 3.00 (dd, 1H, H_β^{Cys}, $J = 6.0$ Hz), 2.84 (dd, 1H, H_β^{Cys}, $J = 6.0$ Hz), 2.14 (m, 2H, CH_2), 2.00 (m, 1H, H_{4a}), 1.69–1.42 (m, CH_2^{lipid}, $H_{\beta\&\gamma}^{Leu}$ and $H_{4\&5}$), 1.30–1.10 (m, *t*Bu and CH_2^{lipid}), 0.83 (br s, 6H, $2 \times CH_3^{Leu}$), 0.76 (t, 3H, CH_3^{lipid}, $J = 6.4$ and 6.8 Hz). ^{13}C NMR (50 MHz, MeOD-d_4) δ 176.0–172.5 (C=O ester and amide), 80.8 (C_6), 77.6 (C_2), 69.2 (C_3), 54.0, 51.3 (C_α^{Leu} and C_α^{Cys}), 44.1 (C_7), 42.7 (C_q, *t*Bu), 41.5, 36.6 (C_β^{Leu} and C_βCys), 30.5 (CH_2^{lipid}), 30.0 ($3 \times CH_3$S-*t*Bu), 28.1 (C_4), 26.7 (C_5),25.9 (C_γ^{Leu}), 23.1, 21.7 ($2 \times CH_3^{Leu}$), 14.2 (CH_3^{lipid}). LR-MS: *m*/*z* 662.3 $(M+H)^+$, 684.6 $(M+Na)^+$. HR-MS: calculated for $[C_{32}H_{59}N_3O_7S_2–H]^+$ 662.3867, found 662.3909.

4.24. *N*-(6-[(*N*-(*N*-Lauric acid))-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine (41)

Compound **41** was prepared from **29** (12 mg, 18 μmol) according to general procedure 3. LC/MS analysis: t_R 4.8 min, *m*/*z* 574.5 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 10→90% B in 26 min.

4.25. *N*-(6-[(*N*-(*N*-Palmitic acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine (24)

Compound **24** was prepared from **8** (98 mg, 0.13 mmol) according to general procedure 2. Crude yield: >99%. ^1H NMR (400 MHz, MeOD-d_4) δ 4.50 (dd, 1H, H_α^{Cys}, $J = 5.6$ Hz), 4.40 (m, 1H, H_α^{Leu}), 4.06 (d, 1H, H_2, $J = 9.6$ Hz), 4.01 (m, 1H, H_3), 3.68 (m, 1H, H_6), 3.25 (m, 2H, H_7), 3.14 (dd, 1H, H_β^{Cys}, $J = 5.6$ Hz), 2.85 (m, 1H, H_β^{Cys}), 2.15 (m, 2H, CH_2), 1.68–1.29 (m, CH_2^{lipid}, $H_{\beta\&\gamma}^{Leu}$ and $H_{4\&5}$), 1.22–1.17 (m, *t*Bu and CH_2^{lipid}), 0.86–0.77 (m, 9H, $2 \times CH_3^{Leu}$), 0.88 (m, 3H, CH_3^{lipid}). ^{13}C NMR (50 MHz, MeOD-d_4) δ 176.0–172.3 (C=O ester and amide), 78.1 (C_6), 72.8 (C_2), 65.8 (C_3), 54.0, 51.5 (C_α^{Leu} and C_α^{Cys}), 43.5 (C_7), 43.3 (C_q, *t*Bu), 41.4, 36.9 (C_β^{Leu} and C_β^{Cys}), 30.6 (CH_2^{lipid}), 30.2 ($3 \times CH_3$*t*Bu), 26.7 (C_4), 26.1 (C_γ^{Leu}), 23.7 (C_5), 23.5, 21.8 ($2 \times CH_3^{Leu}$), 14.4 (CH_3^{lipid}). LC/MS analysis: t_R 24.36 min, *m*/*z* 718.6 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 10→95% B in 26 min. HR-MS: calculated for $[C_{36}H_{67}N_3O_7S_2–H]^+$ 718.4493, found 718.4442.

4.26. *N*-(6-[(*N*-(*N*-Palmitic acid))-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine (36)

Compound **36** was obtained from **24** (25 mg, 35 μmol) according to general procedure 3. LC/MS analysis: t_R 7.0 min, *m*/*z* 630.6 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 10→90% B in 26 min.

4.27. *N*-(6-[(*N*-(*N*-Palmitic acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine (30)

Compound **30** was prepared from **18** (79 mg, 0.11 mmol) according to general procedure 2. Crude yield: >99%. ^1H NMR (400 MHz, MeOD-d_4) δ 4.53 (dd, 1H, H_α^{Cys}, $J = 6.0$ and 6.4 Hz), 4.44 (t, 1H, H_α^{Leu}, $J = 6.4$ and 7.6 Hz), 3.51 (d, 1H, $J = 9.6$ Hz, H_2), 3.43–3.36 (m, 2H, H_3 and H_{7a}), 3.27 (dd, 1H, H_6, $J = 3.0$ and 3.6 Hz), 3.17 (m, 1H, H_{7b}), 3.14 (dd, 1H, H_β^{Cys}, $J = 6.0$ Hz), 2.85 (dd, 1H, H_β^{Cys}, $J = 8.0$ and 9.2 Hz), 2.15 (m, 2H, CH_2), 2.00 (m, 1H, H_{4a}), 1.64–1.60 (m, 4H, $H_{\beta\&\gamma}^{Leu}$, H_{5a}), 1.50–1.27 (m, CH_2^{lipid}, $H_{4b\&5b}$), 1.27–1.17 (m, *t*Bu and CH_2^{lipid}), 0.85–0.77 (dd, 6H, $2 \times CH_3^{Leu}$, $J = 6.0$ Hz), 0.79 (t, 3H CH_3^{lipid}, $J = 6.4$ Hz,). ^{13}C NMR (50 MHz, MeOD-d_4) δ 176–170 (C=O ester and amide), 80.8 (C_6), 77.6 (C_2), 69.2 (C_3), 54.0, 51.4 (C_α^{Leu} and C_α^{Cys}), 44.1 (C_7), 42.8 (C_q, *t*Bu), 41.5, 36.7 (C_β^{Leu} and C_β^{Cys}), 30.5 (CH_2^{lipid}), 30.0 (*t*Bu), 28.1 (C_4), 26.7 (C_5), 25.9 (C_γ^{Leu}), 23.1, 21.7 ($2 \times CH_3^{Leu}$), 14 (CH_3^{lipid}). LC/MS analysis: t_R 23.6, *m*/*z* 718.6 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 10→90% B in 26 min. HR-MS: calculated for $[C_{36}H_{67}N_3O_7S_2–H]^+$ 718.4493, found 718.4420.

4.28. *N*-(6-[(*N*-(*N*-Palmitic acid))-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine (42)

Compound **42** was prepared from **30** (8 mg, 11 mol) according to general procedure 3. LC/MS analysis: t_R 7.0 min, *m*/*z* 630.7 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 10→90% B in 26 min.

4.29. *N*-(6-[(*N*-(*N*-(Lauric acid)-glycine))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine (25)

Compound **25** was prepared from **9** (20 mg, 0.03 mmol) according to general procedure 2. Crude yield: >99%. ^1H NMR (400 MHz, MeOD-d_4) δ 4.51 (dd, 1H, H_α^{Cys}, $J = 5.2$ and 5.6 Hz), 4.40 (dd, 1H, H_α^{Leu}, $J = 4.0$ and 4.4 Hz), 4.10 (d, 1H, H_2, $J = 3.6$ Hz), 4.03 (m, 1H, H_3), 3.77 (s, 2H, H^{Gly}), 3.71 (m, 1H, H_6), 3.25 (br t, 2H, H_7, $J = 5.2$ and 5.6 Hz), 3.110 (dd, 1H, H_β^{Cys}, $J = 5.2$ Hz), 2.94 (dd, 1H, H_β^{Cys}, $J = 8.4$ Hz), 2.17 (t, 2H, CH_2, $J = 7.2$ and 8.0 Hz), 1.68–1.29 (m, CH_2^{lipid}, $H_{\beta\&\gamma}^{Leu}$ and $H_{4\&5}$), 1.28–1.15 (m, *t*Bu and CH_2^{lipid}), 0.85 (dd, 6H, $J = 5.6$ and 6.0 Hz, $2 \times CH_3^{Leu}$), 0.80 (t, 3H, CH_3^{lipid}, $J = 7.2$ and 7.6 Hz). ^{13}C NMR (50 MHz, MeOD-d_4) δ 172.4–171.4 (C=O ester and amide), 78.2 (C_6), 72.7 (C_2), 65.7 (C_3), 54.3, 51.4 (C_α^{Leu} and C_α^{Cys}), 43.6 (C_7), 42.8 (C_q, *t*Bu), 42.4, 37.2 (C_β^{Leu} and C_β^{Cys}), 36.6 (C_α^{Gly}), 30.3 (CH_2^{lipid}), 30.0 (*t*Bu), 26.6 (C_4), 22.8 (C_γ^{Leu}), 21.3 (C_5), 19.6, 18.9 ($2 \times CH_3^{Leu}$), 14.4 (CH_3^{lipid}). LC/MS analysis: t_R 19.9, *m*/*z* 719.5 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 0-95% B in 26 min. HR-MS: calculated for $[C_{34}H_{62}N_4O_8S_2–H]^+$ 719.4081, found 719.4051.

4.30. *N*-(6-[(*N*-(*N*-(Lauric acid)-glycine))-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucurono pyranosyl)-L-leucine (37)

Compound **37** was prepared from **25** (20 mg, 28 μmol) following general procedure 3. LC/MS analysis: t_R

4.3 min, *m/z* 631.7 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 10→90% B in 26 min.

4.31. *N*-(6-[(*N*-(*N*-(Lauric acid)-glycine))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine (31)

Compound **31** was prepared from **19** (44 mg, 0.07 mmol) according to general procedure 2. Crude yield: >99%. ^1H NMR (400 MHz, MeOD-d_4) δ 4.59 (t, 1H, $J = 6.4$ and 7.2 Hz, H_α^{Cys}), 4.27 (dd, 1H, $J = 4.0$ Hz, H_α^{Leu}), 3.77 (dd, 2H, $J = 16.4$ Hz, H_α^{Gly}), 3.52 (d, 1H, $J = 9.6$ Hz, H_2), 3.47 (m, 2H, H_6 and H_{7a}), 3.37 (m, 1H, H_4), 3.07 (m, 2H, $H_{7\,b}$ and H_β^{Cys}), 2.94 (dd, 1H, $J = 7.6$ and 8.0 Hz, H_β^{Cys}), 2.18 (t, 2H, $J = 7.6$ Hz, CH_2^{lipid}), 2.02 (m, 1H, H_{4a}), 1.61–1.40 (m, 8H, $H_{\beta\&\gamma}^{Leu}$, H_{5ab}, CH_2^{lipid}, H_{4b}), 1.25–1.19 (m, *t*Bu and CH_2^{lipid}), 0.87 (d, 6H, $J = 6.0$ Hz, $2\times CH_3^{Leu}$), 0.80 (t, 3H, $J = 6.8$ and 7.2 Hz, CH_3^{lipid}). ^{13}C NMR (50 MHz, MeOD-d_4) δ 175.3–170.1 (C=O ester and amide), 78.0 (C_6), 76.7 (C_2), 68.3 (C_3), 53.4, 50.1 (C_α^{Leu} and C_αCys), 48.4 (C_7), 43.9 (C_q, *t*Bu), 43.3, 41.5 (C_β^{Leu} and C_β^{Cys}), 36.2 (C_α^{Gly}), 30.9 (*t*Bu), 29.8 (CH_2^{lipid}), 25.6 (C_4), 24.9 (C_γ^{Leu}), 22.8 (CH_3^{Leu}), 22.6 (C_5), 21.8 (CH_3^{Leu}), 14.1 (CH_3^{lipid}). LR-MS: *m/z* 719.4 $(M+H)^+$, 741.4 $(M+Na)^+$. HR-MS: calculated for $[C_{34}H_{62}N_4O_8S_2–H]^+$ 719.4081, found 719.4105.

4.32. *N*-(6-[(*N*-(*N*-(Lauric acid)-glycine))-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine (43)

Compound **43** was prepared from **31** (12 mg, 17 mol) according to general procedure 3. LC/MS analysis: t_R 8.7 min, *m/z* 631.7 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 60→90% B in 26 min.

4.33. *N*-(6-[(*N*-(*N*-(Lauric acid)-4-aminobutyric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine (26)

Compound **26** was prepared from **10** (29 mg, 0.04 mmol) according to general procedure 2. Crude yield: >99%. ^1H NMR (400 MHz, MeOD-d_4) δ 4.82 (dd, 1H, H_α^{Cys}, $J = 7.6$ Hz), 4.28 (m, 1H, H_α^{Leu}), 4.14 (m, 2H, $H_{2\&3}$), 3.73 (m, 1H, H_6), 3.44 (m, 1H, H_{7a}), 3.29–3.13 (m, 2H, CH_2^{lipid}, and 2H, H_{7a} and H_β^{Cys}), 3.00 (dd, 1H, H_β^{Cys}, $J = 7.6$ and 8.0 Hz), 2.30 and 2.16 ($2\times$ m, 4H, $2\times CH_2$), 1.82–1.50 (m, CH_2^{lipid}, $H_{\beta\&\gamma}^{Leu}$, $H_{4\&5}$), 1.35–1.20 (m, *t*Bu and CH_2^{lipid}), 0.85 (m, 9H, $2\times CH_3^{Leu}$ and CH_3^{lipid}). ^{13}C NMR (50 MHz, MeOD-d_4) δ 176.2–171.8 (C=O ester and amide), 78.6 (C_6), 73.7 (C_2), 65.5 (C_3), 53.9, 53.6 (C_α^{Leu} and C_α^{Cys}), 44.5 (C_7), 43.8 (C_q, *t*Bu), 43.5, 39.4 (C_β^{Leu} and C_β^{Cys}), 37.0, 33.3, 32.8 (CH_2, 4-aminobutyric acid), 30.5 ($3\times CH_3$*t*Bu), 30.2 (CH_2^{lipid}), 27.6 (C_4), 26.8 (C_5), 26.1 (C_γ^{Leu}), 23.4, 22.2 ($2\times CH_3^{Leu}$), 14 (CH_3^{lipid}). LC/MS analysis: t_R 24.6, *m/z* 747.5 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 0→95% B in 26 min. HR-MS: calculated for $[C_{36}H_{66}N_4O_8S_2–H]^+$ 747.4394, found 747.4446.

4.34. *N*-(6-[(*N*-(*N*-(Lauric acid)-4-aminobutyric acid))-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D- glucuronopyranosyl)-L-leucine (38)

Compound **38** was prepared from **26** (8 mg, 11 μmol) according to general procedure 3. LC/MS analysis: t_R 4.6 min, *m/z* 659.6 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 10→90% B in 26 min.

4.35. *N*-(6-[(*N*-(*N*-(Lauric acid)-4-aminobutyric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine (32)

Compound **32** was prepared from **20** (40 mg, 0.06 mmol) according to general procedure 2. Crude yield: >99%. ^1H NMR (400 MHz, MeOD-d_4) δ 4.61 (t, 1H, H_α^{Cys}, $J = 6.8$ and 7.2 Hz), 4.43 (dd, 1H, H_α^{Leu}, $J = 3.6$ Hz), 3.52 (d, 1H, H_2, $J = 9.2$ Hz), 3.46 (m, 2H, H_3 and H_{7a}), 3.36 (m, 1H, H_6), 3.20–3.02 (m, 4H, CH_2^{lipid}, H_{7b} and H_β^{Cys}), 2.90 (dd, 1H, H_β^{Cys}, $J = 4.8$ and 5.2 Hz), 2.20 (t, 2H, CH_2, $J = 7.2$ Hz), 2.08 (t, 2H, CH_2, $J = 7.6$ Hz), 2.02 (m, 1H, H_{4a}), 1.70 (m, 2H, CH_2^{lipid}), 1.64–1.60 (m, $H_{\beta\&\gamma}^{Leu}$, H_{5a}), 1.52–1.30 (m, CH_2^{lipid}, $H_{4b\&5b}$), 1.30–1.10 (m, *t*Bu and CH_2^{lipid}), 0.87 (m, 6H, $2\times CH_3^{Leu}$), 0.80 (t, 3H, CH_3^{lipid}, $J = 7.2$ Hz). ^{13}C NMR (50 MHz, MeOD-d_4) δ 174.9–170.6 (C=O ester and amide), 77.7 (C_6), 76.9 (C_2), 68.1 (C_3), 53.1, 49.7 (C_α^{Leu} and C_α^{Cys}), 49.4 (C_7), 48.0 (C_q, *t*Bu), 43.6, 41.2 (C_β^{Leu} and C_β^{Cys}), 40.6, 38.8, 36.4 (CH_2, 4-aminobutyric acid), 29.3 ($3\times CH_3$*t*Bu), 29.1 (CH_2^{lipid}), 25.5 (C_4), 24.7 (C_γ^{Leu}), 22.6 (CH_3^{Leu}), 22.4 (C_5), 21.6 (CH_3^{Leu}), 13.8 ($CH_3^{lipid\gamma}$). LC/MS analysis: t_R 25.0, *m/z* 747.5 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 10→90% B in 26 min. HR-MS: calculated for $[C_{36}H_{66}N_4O_8S_2–H]^+$ 747.4394 $(M+H)^+$, found 747.4411.

4.36. *N*-(6-[(*N*-(*N*-(Lauric acid)-4-aminobutyric acid))-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine (44)

Compound **44** was prepared from **32** (20 mg, 27 μmol) according to general procedure 3. LC/MS analysis: t_R 4.7 min, *m/z* 659.6 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 10→90% B in 26 min.

4.37. *N*-(6-[(*N*-(*N*-(Palmitic acid)-glycine))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine (27)

Compound **27** was prepared from **11** (74 mg, 0.09 mmol) according to general procedure 2. Crude yield: >99%. ^1H NMR (400 MHz, MeOD-d_4) δ 4.50 (dd, 1H, $J = 6.4$ Hz, H_α^{Cys}), 4.40 (dd, 1H, $J = 4.0$ and 4.4 Hz, H_α^{Leu}), 4.10 (d, 1H, $J = 3.6$ Hz, H_2), 4.01 (m, 1H, H_3), 3.75 (s, 2H, H_α^{Gly}), 3.70 (m, 1H, H_6), 3.25 (m, 2H, H_7), 3.10 (dd, 1H, $J = 5.2$ Hz, H_β^{Cys}), 2.94 (dd, 1H, H_β^{Cys}, $J = 1.2$ Hz), 2.16 (t, 2H, CH_2, $J = 7.2$ and 8.0 Hz), 1.68–1.29 (m, CH_2^{lipid} $H_{\beta\&\gamma}^{Leu}$, $H_{4\&5}$), 1.26–1.10 (m, *t*Bu and CH_2^{lipid}), 0.85 (dd, 6H, $2\times CH_3^{Leu}$, $J = 5.6$ and 6.0 Hz), 0.79 (t, 3H, CH_3^{lipid}, $J = 6.8$ Hz). ^{13}C

NMR (50 MHz, MeOD-d_4) δ 176.8–171.4 (C═O ester and amide), 78.3 (C_6), 72.7 (C_2), 65.7 (C_3), 54.3, 51.4 (C_α^{Leu} and C_α^{Cys}), 43.6 (C_7), 42.7 (C_q, *t*Bu), 41.2, 36.6 (C_β^{Leu} and C_β^{Cys}), 32.8 (C_α^{Gly}), 30.5 (CH_2^{lipid}), 30.0 ($3\times CH_3$S-*t*Bu), 26.6 (C_4), 25.9 (C_γ^{Leu}), 23.6 (C_5), 23.3, 21.5 ($2\times CH_3^{Leu}$), 14.2 (CH_3^{lipid}). LR-MS: *m/z* 775.5 $(M+H)^+$, 797.4 $(M+Na)^+$. HR-MS: calculated for $[C_{38}H_{70}N_4O_8S_2–H]^+$ 775.4707, found 775.4756.

4.38. *N*-(6-[(*N*-(*N*-(Palmitic acid)-glycine))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine (39)

Compound **39** was prepared from **27** (19 mg, 28 μmol) according to general procedure 3. LC/MS analysis: t_R 8.6 min, *m/z* 687.6 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 80→90% B in 26 min.

4.39. *N*-(6-[(*N*-(*N*-(Palmitic acid)-glycine))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine (33)

Compound **33** was prepared from **21** (48 mg, 0.06 mmol) according to general procedure 2. Crude yield: >99%. ^{1}H NMR (400 MHz, MeOD-d_4) δ 4.55 (dd, 1H, J = 6.0 Hz, H_α^{Cys}), 4.47 (dd, 1H, J = 6.8 and 7.6 Hz, H_α^{Leu}), 3.76 (s, 2H, H_α^{Gly}), 3.53 (d, 1H, J = 9.2 Hz, H_2), 3.40 (m, 2H, H_3 and H_{7a}), 3.29 (dd, 1H, J = 3.2 Hz, H_6), 3.18 (1H, H_{7b}), 3.09 (dd, 1H, J = 5.6 and 6.0 Hz, H_β^{Cys}), 2.92 (dd, 1H, J = 7.6 and 8.0 Hz, H_β^{Cys}), 2.15 (t, 2H, J = 7.2 and 7.6 Hz, CH_2), 2.01 (m, 1H, H_{4a}), 1.64–1.60 (m, 4H, $H_{\beta\&\gamma}^{Leu}$, H_{5a}), 1.50–1.27 (m, CH_2^{lipid}, $H_{4b\&5b}$), 1.25–1.19 (m, *t*Bu and CH_2^{lipid}), 0.87 (dd, 6H, J = 6.0 Hz, $2\times CH_3^{Leu}$), 0.80 (t, 3H, J = 7.2 Hz, CH_3^{lipid}). ^{13}C NMR (50 MHz, MeOD-d_4) δ 176–170 (C═O ester and amide), 80.6 (C_6), 77.6 (C_2), 69.3 (C_3), 54.2, 51.2 (C_α^{Leu} and C_α^{Cys}), 44.3 (C_7), 43.5 (C_q, *t*Bu), 42.6, 41.4 (C_β^{Leu} and C_β^{Cys}), 36.6 (C_α^{Gly}), 30.5 (CH_2^{lipid}), 30.0 ($3\times CH_3$S-*t*Bu), 26.5 (C_4), 25.8 (C_γ^{Leu}), 23.5 (C_5), 23.2, 21.7 ($2\times CH_3^{Leu}$), 15.2 (CH_3^{lipid}). LR-MS: *m/z* 775.6 $(M+H)^+$, 797.4 $(M+Na)^+$. HR-MS: calculated for $[C_{38}H_{70}N_4O_8S_2–H]^+$ 775.4707, found 775.4690.

4.40. *N*-(6-[(*N*-(*N*-(Palmitic acid)-glycine))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine (45)

Compound **45** was prepared from **33** (10 mg, 15 μmol) according to general procedure 3. LC/MS analysis: t_R 6.8 min, *m/z* 687.6 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 10→90% B in 26 min.

4.41. *N*-(6-[(*N*-(*N*-4-(Palmitic acid)-aminobutyric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine (28)

Compound **28** was prepared from **12** (58 mg, 0.07 mmol) according to general procedure 2. Crude yield: >99%. ^{1}H NMR (400 MHz, MeOD-d_4) δ 4.50 (dd, 1H, H_α^{Cys}, J = 5.2 Hz), 4.40 (m, 1H, H_α^{Leu}), 4.11 (d, 1H, H_2, J = 3.6 Hz), 4.03 (m, 1H, H_3), 3.72 (m, 1H, H_6), 3.26 (m, 2H, H_7), 3.12–3.06 (m, 2H, CH_2^{lipid}, and 1H, H_β^{Cys}), 2.92 (dd, 1H, H_β^{Cys}, J = 6.0 Hz), 2.16 and 2.06 ($2\times$ t, 4H, $2\times CH_2$, J = 7.2 and 7.6 Hz), 1.73–1.42 (m, CH_2^{lipid}, $H_{\beta\&\gamma}^{Leu}$, $H_{4\&5}$), 1.30–1.10 (m, *t*Bu and CH_2^{lipid}), 0.85 (dd, 6H, J = 5.6 and 6.0 Hz, $2\times CH_3^{Leu}$), 0.79 (t, 3H, CH_3^{lipid}, J = 6.8 Hz). ^{13}C NMR (50 MHz, MeOD-d_4) δ 176.1–172.4 (C═O ester and amide), 78.3 (C_6), 72.7 (C_2), 65.7 (C_3), 54.2, 51.4 (C_α^{Leu} and C_α^{Cys}), 43.5 (C_7), 43.0 (C_q, *t*Bu), 41.1, 39.3 (C_β^{Leu} and C_β^{Cys}), 37.0, 33.7, 32.8 (CH_2), 30.5 (CH_2^{lipid}), 30.0 ($3\times CH_3$*t*Bu), 26.4 (C_4), 26.0 (C_γ^{Leu}), 23.6 (C_5), 23.3, 21.5 ($2\times CH_3^{Leu}$), 14.2 (CH_3^{lipid}). LR-MS: *m/z* 803.5 $(M+H)^+$, 825.5 $(M+Na)^+$. HR-MS: calculated for $[C_{40}H_{74}N_4O_8S_2–H]^+$ 803.5020 $(M+H)^+$, found 803.4991.

4.42. *N*-(6-[(*N*-(*N*-4-(Palmitic acid)-aminobutyric acid))-L-cysteinyl]-aminomethyl-4,5-dideoxy-α-D-glucuronopyranosyl)-L-leucine (40)

Compound **40** was prepared from **28** (17 mg, 21 μmol) according to general procedure 3. LC/MS analysis: t_R 6.6 min, *m/z* 715.5 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 10→95% B in 26 min.

4.43. *N*-(6-[(*N*-(*N*-4-(Palmitic acid)-aminobutyric acid))-*S*-*tert*-butylthio-L-cysteinyl]-aminomethyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine (34)

Compound **34** was prepared from **22** (44 mg, 0.05 mmol) according to general procedure 2. Crude yield: >99%. ^{1}H NMR (400 MHz, MeOD-d_4) δ 4.54 (dd, 1H, H_α^{Cys}, J = 6.0 Hz), 4.43 (t, 1H, H_α^{Leu}, J = 6.8 and 7.2 Hz), 3.50 (d, 1H, H_2, J = 9.2 Hz), 3.42 (m, 2H, H_3 and H_{7a}), 3.29 (dd, 1H, H_6, J = 3.2 and 3.6 Hz), 3.18 (1H, H_{7b}), 3.12–3.02 (m, 2H, CH_2^{lipid}, and 1H, H_β^{Cys}), 3.09 (dd, 1H, H_β^{Cys}, J = 8.0 Hz), 2.92 (dd, 1H, H_β^{Cys}, J = 7.6 and 8.0 Hz), 2.18 (t, 2H, CH_2, J = 7.2 and 7.6 Hz), 2.08 (t, 2H, CH_2, J = 7.2 and 8.0 Hz), 2.01 (m, 1H, H_{4a}), 1.70 (m, 2H, CH_2^{lipid}), 1.64–1.60 (m, $H_{\beta\&\gamma}^{Leu}$, H_{5a}), 1.52–1.30 (m, CH_2^{lipid}, $H_{4b\&5b}$), 1.25–1.19 (m, *t*Bu and CH_2^{lipid}), 0.87 (dd, 6H, $2\times CH_3^{Leu}$, J = 5.2 and 5.6 Hz), 0.80 (t, 3H, CH_3^{lipid}, J = 6.4 and 7.2 Hz). ^{13}C NMR (50 MHz, MeOD-d_4) δ 176.0–172.5 (C═O ester and amide), 80.7 (C_6), 77.6 (C_2), 69.3 (C_3), 54.2, 51.6 (C_α^{Leu} and C_α^{Cys}), 44.2 (C_7), 42.8 (C_q, *t*Bu), 42.3, 41.6 (C_β^{Leu} and C_β^{Cys}), 39.4, 36.9, 33.8 (CH_2, 4-aminobutyric acid), 30.5 (CH_2^{lipid}), 30.0 ($3\times CH_3$*t*Bu), 26.4 (C_4), 25.9 (C_γ^{Leu}), 23.5 (C_5), 23.2, 21.2 ($2\times CH_3^{Leu}$), 14.4 (CH_3^{lipid}). LC/MS analysis: t_R 23.1, *m/z* 803.5 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 10→90% B in 26 min. HR-MS: calculated for $[C_{40}H_{74}N_4O_8S_2–H]^+$ 803.5020, found 803.5039 $(M+H)^+$.

4.44. *N*-(6-[(*N*-(*N*-4-(Palmitic acid)-aminobutyric acid))-*S*-*tert*-butylthio-L-cysteinyl]-amino methyl-4,5-dideoxy-β-D-glucuronopyranosyl)-L-leucine (46)

Compound **46** was prepared from **34** (11 mg, 14 μmol) according to general procedure 3. LC/MS analysis: t_R 7.0 min, *m/z* 715.6 $(M+H)^+$. Buffers: A: 50% aq MeOH, B: CH_3CN, C: 0.1% methanolic TFA, 70→90% B in 26 min.

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