Supporting Information (13 pages)

General: ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 500 (500 MHz) or Varian Unity 300 (300 MHz) spectrometer and are referenced to TMS, residual C*H*Cl_3 (^{1}H), residual C*H*D_2OD (^{1}H), *C*DCl_3 (^{13}C) or *C*D_3OD (^{13}C). Mass spectrometric data were obtained on a JOEL SX 102A spectrometer. THF was dried over Na°/benzophenone, and CH_2Cl_2 was dried over CaH_2 prior to use. Other reagents and solvents were obtained commercially and used as received unless otherwise noted.

Octanyl cholate (8): Cholic acid (3.14 g, 7.43 mmol) and 10-camphorsulfonic acid (0.52 g, 2.23 mmol) were dissolved in octanol (3.5 mL, 23.44 mmol). The solution was warmed to 40-50°C in oil bath under vacuum (~13 mm/Hg). After 14 h, the remaining octanol was evaporated under high vacuum. The crude product was purified via chromatography (silica gel, 5% MeOH in CH_2Cl_2) to afford the desired product (2.81 g, 73% yield) as a white powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.06 (t, (*J* = 6.7 Hz, 2 H), 3.98 (s, 1 H), 3.86 (s, 1 H), 3.48 – 3.44 (m, 1 H), 2.41 – 2.34 (m, 1 H), 2.28 – 2.18 (m, 3 H), 1.98 – 1.28 (series of multiplets, 35 H), 0.99 (d, *J* = 3.3 Hz, 3 H), 0.90 (s, 3 H), 0.89 (t, *J* = 7 Hz, 3 H), 0.69 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.38, 73.18, 72.14, 68.63, 56.07, 50.02, 49.32, 47.07, 46.74, 41.96, 41.67, 39.84, 39.76, 35.66, 35.45, 34.95, 34.86, 34.15, 32.97, 32.91, 31.65, 31.11, 30.68, 28.39, 27.78, 26.66, 26.52, 25.82, 25.70, 25.54, 25.15, 24.95, 23.45, 22.69, 17.77, 12.71; HRFAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M+Na]^+$) 543.4015 (100%), cacld. 543.4026.

Representative synthesis of compounds 9 - 11: Octanyl cholate (**8**) (0.266 g, 0.511 mmol), N-t-Boc-glycine (0.403 g, 2.298 mmol), DCC (0.474 g, 2.298 mmol) and DMAP (0.0624 g, 0.051 mmol) were mixed in CH_2Cl_2 (15 mL) for 3 h. The resulting white precipitate was removed by filtration. The filtrate was concentrated, and the product was purified by chromatography (silica gel, EtOAc/Hexane 1:2) to afford the desired product (0.481 g, 95% yield) as a white powder. **Compound 9** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.18 (br, 3 H), 5.01 (s, 1 H), 4.61 (m, 1 H), 4.04 (t, *J* = 6.5 Hz, 2 H), 3.97 – 3.88 (series of multiplets, 6 H), 2.39 – 2.15 (series of multiplets, 2 H), 2.06 – 1.02 (series of multiplets, 35 H), 1.46 (s, 18 H), 1.45 (s, 9 H), 0.93 (s, 3 H), 0.88 (t, *J* = 6.7 Hz, 3 H), 0.81 (d, *J* = 6

Hz, 3 H), 0.74 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.26, 170.19, 169.9, 169.78, 155.87, 155.67, 79.95, 76.47, 75.167, 72.11, 64.55, 47.40, 45.28, 43.17, 42.86, 40.82, 37.94, 34.71, 34.63, 34.43, 31.86, 31.340, 31.20, 30.76, 29.29, 29.25, 28.80, 28.72, 28.42, 28.06, 27.96, 27.19, 26.81, 26.29, 26.012, 25.66, 22.87, 22.71, 22.57, 17.55, 14.18, 12.27; HRFAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M+Na]^+$) 1014.6261 (100%), cacld. 1014.6242. **Compound 10:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.10 (s, 1 H), 4.92 (d, *J* = 2.44 Hz, 1 H), 4.55 (m, 1 H), 4.00 (t, *J* = 6.8 Hz, 2 H), 3.39 – 3.33 (series of multiplets, 6 H), 2.595 – 2.467 (series of multiplets, 6 H), 2.31 – 2.12 (series of multiplets, 2 H), 2.01 – 1.00 (series of multiplets, 37 H), 1.39 (s, 27 H), 0.88 (s, 3 H), 0.84 (t, *J* = 6.8 Hz, 3 H), 0.76 (d, *J* = 6.3 Hz, 3 H), 0.69 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.16, 172.10, 171.78, 171.67, 155.95, 79.45, 75.67, 74.21, 71.10, 64.63, 47.79, 45.27, 43.52, 40.97, 37.92, 36.35, 35.14, 35.05, 34.90, 34.71, 34.46, 31.91, 31.45, 30.95, 29.35, 29.31, 28.96, 28.78, 28.56, 28.55, 27.22, 26.98, 26.269, 25.71, 23.00, 22.77, 22.64, 17.75, 14.24, 12.39; HRFAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M+Na]^+$) 1056.6702 (100%), cacld. 1056.6712. **Compound 11** ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.00, 172.75, 172.41, 172.30, 156.03, 79.00, 75.28, 73.79, 70.77, 64.39, 47.43, 45.04, 43.21, 40.76, 40.00, 39.93, 37.78, 34.74, 34.62, 34.23, 32.19, 32.01, 31.70, 31.24, 30.77, 29.13, 29.10, 28.67, 38.58, 28.38, 25.86, 25.37, 22.56, 22.38, 17.51, 14.05, 12.13; HRFAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M+Na]^+$) 1098.7181 (100%), cacld. 1098.7181.

Representative synthesis of compounds 1 - 3: To compound **9** (0.463 g, 0.467 mmol) was added HCl in dioxane (0.3 mL, 4.0 *M*). After stirring the mixture for 30 min, the excess HCl and solvent were removed in vacuo. The product was isolated, after chromatography (silica gel, CH_2Cl_2/MeOH/NH_3•H_2O 10 : 1.2 : 0.1) as a (0.271 g, 84%) pale oil. The trihydrochloride salt of **1** was prepared by addition of HCl in dioxane and evaporation of excess HCl and dioxane in vacuo giving a white powder. **Compound 1:** ^{1}H NMR ($CDCl_3$ with ~10% CD_3OD, 500 MHz) δ 5.16 (s, 1 H), 4.99 (t, *J* = 3.6 Hz, 1 H), 4.61 (m, 1 H), 4.04 (t, *J* = 6.8 Hz, 2 H), 3.51 – 3.36 (m, 6 H), 2.34 – 2.15 (m, 2 H), 2.00 - 1.05 (series of multiplets, 40 H), 0.93 (s, 3 H), 0.88 (t, *J* = 7.1 Hz, 3 H), 0.80 (d, *J* = 3.2 Hz, 3 H), 0.74 (s, 3 H); ^{13}C NMR ($CDCl_3$ and ~10% CD_3OD, 75 MHz) δ 174.32, 173.92, 173.81, 76.08, 74.67, 71.61, 64.73, 47.64, 45.39, 44.41, 43.49, 40.97,

37.99, 34.99, 34.77, 34.71, 34.52, 31.96, 31.54, 31.35, 30.96, 29.39, 29.36, 29.02, 28.82, 27.32, 27.11, 26.11, 25.83, 23.01, 22.82, 22.69, 17.79, 14.28, 12.41; HRFAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M+Na]^+$) 714.4651 (100%), cacld. 714.4669. **Compound 2:** ^1H NMR ($CDCl_3$ and ~ 10% CD_3OD, 300 MHz) δ 5.142 (s, 1 H), 4.96 (d, *J* = 2.7 Hz, 1 H), 4.60, (m, 1 H), 4.04 (t, *J* = 6.6 Hz, 2 H), 3.07 – 2.95 (series of multiplets, 6 H), 2.56 – 2.43 (series of multiplets, 6 H), 2.38 – 2.13 (series of multiplets, 2 H), 2.07 – 1.02 (series of multiplets, 36 H), 0.92 (s, 3 H), 0.88 (t, *J* = 6.6 Hz, 3 H), 0.82 (d, *J* = 6.6 Hz, 3 H), 0.73 (s, 3 H); ^{13}C NMR ($CDCl_3$ and CD_3OD, 75 MHz) δ 174.29, 172.29, 171.98, 171.92, 75.52, 74.09, 70.98, 64.67, 47.78, 45.26, 43.52, 40.98, 38.73, 38.62, 38.35, 38.07, 38.03, 37.99, 35.01, 34.81, 34.77, 34.49, 31.92, 31.50, 31.40, 30.99, 29.36, 29.33, 28.93, 28.80, 27.43, 26.96, 26.08, 25.56, 23.07, 22.79, 22.62, 17.73, 14.25, 12.34;HRFAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M + Na]^+$) 714.4651 (100%), cacld. 714.4669. **Compound 3:** ^1H NMR ($CDCl_3$ and CD_3OD, 500 MHz) δ 5.12 (s, 1 H) 4.93 (s, 1 H), 4.59 (m, 1 H), 4.04 (t, *J* = 7 Hz, 2 H), 2.79 – 2.69 (series of multiplets, 6 H), 2.4621 – 2.2999 (series of multiplets, 6 H), 2.2033 – 1.0854 (series of multiplets, 42 H), 0.94 (s, 2 H), 0.91 (s, 1 H), 0.88 (t, *J* = 7 Hz, 3 H), 0.82 (d, *J* = 6.4 Hz, 3 H), 0.75 (s, 3 H); ^{13}C NMR ($CDCl_3$ and CD_3OD, 75 MHz) δ 174.70, 171.97, 171.86, 171.75, 76.10, 74.55, 71.56, 64.85, 47.96, 45.31, 43.37, 40.87, 38.09, 34.86, 34.80, 34.73, 34.46, 32.84, 32.62, 32.27, 31.87, 31.75, 31.42, 31.08, 29.31, 29.28, 29.26, 28.78, 28.73, 27.38, 26.91, 26.05, 25.37, 23.24, 23.15, 22.95, 22.74, 22.71, 22.43, 17.78, 14.11, 12.28;HRFAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M+Na]^+$) 798.5624 (100%), cacld. 798.5609.

Benzyl cholate (12): Cholic acid (4.33 g, 10.62 mmol) and 10-caphorsulfonic acid (0.493 g, 2.21 mmol) were dissolved in benzyl alcohol (1.97 mL, 19.3 mmol). The suspension was heated to 50°C in oil bath and stirred under vacuum (~13 mm/Hg) for 16 h. Excess benzyl alcohol was removed in vacuo, and the crude product was chromatographed (silica gel, 5% MeOH in CH_2Cl_2) to give the desired product as a white powder (4.23 g, 81% yield). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34 – 7.33 (m, 5 H), 5.10 (d, *J* = 1.5 Hz, 2 H), 3.92 (s, 1 H), 3.81 (s, 1 H), 3.42 (s, 1 H), 3.40 (br, m, 3 H), 2.44 – 2.38 (m, 1 H), 2.31 – 2.25 (m, 1 H), 2.219 (t, *J* = 12 Hz, 2 H), 0.96 (d, *J* = 5.5 Hz, 3 H), 0.86

(s, 3 H), 0.63 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.25, 136.30, 128.66, 128.63, 128.32, 128.28, 128.24, 73.18, 71.98, 68.54, 66.18, 47.14, 46.56, 41.69, 39.65, 35.51, 35.37, 34.91, 34.84, 31.49, 31.08, 30.50, 28.31, 27.62, 26.47, 23.35, 22.65, 22.60, 17.42, 12.63, 11.57; FAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M+Na]^+$) 521.3235 (100%), cacld. 521.3242.

Representative synthesis of compounds 13-15: Benzyl cholate (**12**) (0.248 g, 0.499 mmol), N-t-Boc-glycine (0.404 g, 2.30 mmol), DCC (0.338 g, 1.49 mmol) and DMAP (0.051 g, 0.399 mmol) were added to CH_2Cl_2 (15 mL), and the suspension was stirred for 16 h. The resulting white precipitate was removed by filtration, and the filtrate was concentrated. The product was obtained after chromatorgraphy (silica gel, EtOAc/Hexane 0.6 :1) as a white powder (0.329 g, 68%). **Compound 13:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 – 7.33 (m, 5 H), 5.16 (s, 1 H), 5.08 (dd, *J* = 22.5 Hz, 12.3 Hz, 4 H), 5.00 (s, 1 H), 4.60 (m, 1 H), 4.04 – 3.81 (series of multiplets, 6 H), 2.43 – 1.01 (series of multiplets, 25 H), 1.46 (s, 9 H), 1.44 (s, 18 H), 0.92 (s, 3 H), 0.797 (d, *J* = 5.7 Hz, 3 H), 0.69 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.99, 170.25, 170.05, 169.85, 155.73, 136.19, 128.69, 128.45, 128.35, 80.06, 77.65, 77.23, 76.80, 76.53, 75.24, 72.19, 66.29, 47.46, 45.35, 43.24, 42.91, 40.89, 38.00, 34.79, 34.66, 34.49, 31.43, 31.25, 30.77, 28.88, 28.40, 27.23, 26.89, 25.74, 22.94, 22.65, 17.61, 12.32; FAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M+Na]^+$) 992.5468 (100%), cacld. 992.5460.

Representative synthesis of compounds 16 – 18: Compound **13** (0.505 g, 0.520 mmol) and Pd (5 wt. % on active carbon, 0.111 g, 0.0521 mmol) were added to MeOH (5 mL). The suspension was stirred under H_2 (50 psi) for 20 h. The solids were removed by filtration and the filtrate was concentrated. Purification of the product via chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave a white powder (0.450 g, 98% yield). **Compound 16:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.20 (s, 1 H), 5.12 (br., 2 H), 4.92 (s, 1 H), 4.55 (m, 1 H), 3.98 – 3.83 (series of multiplets, 6 H), 2.30 – 2.13 (series of multiplets, 2 H), 1.96 – 0.98 (series of multiplets, 30 H), 1.40 (s, 9 H), 1.39 (s, 18 H), 0.87 (s, 3 H), 0.76 (d, *J* = 6.3 Hz, 3 H), 0.68 (s, 3 H); ^{13}C NMR ($CDCl_3$ 75 MHz)

δ 174.11, 165.60, 165.41, 165.22, 151.28, 151.14, 75.48, 75.26, 71.81, 70.57, 67.50, 45.95, 42.58, 40.65, 38.52, 38.16, 36.17, 33.28, 30.01, 29.78, 26.71, 26.42, 25.95, 24.16, 23.78, 23.40, 23.31, 22.55, 22.16, 21.03, 18.23, 17.93, 12.91; FAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M+Na]^+$) 902.4997 (21%), cacld. 902.4990.

Representative synthesis of compounds 19 – 21: Compound **16** (0.375 g, 0.427 mmol), DCC (0.105 g, 0.512 mmol) and DMAP (0.062 g, 0.512 mmol) and N, N-dimethylethanolamine (0.09 ml, 0.896 mmol) were added to CH_2Cl_2 (15 mL). The mixture for 16 h, and solvent and excess N, N-dimethylethanolamine were removed in vacuo. The product was purified via chromatography (silica gel EtOAc/ hexane/ Et_3N, 12 : 10 : 0.6) giving a white powder (0.330 g, 82% yield). ^1H NMR ($CDCl_3$ and ~ 10% CD_3OD, 500 MHz) δ 5.18 (s, 1 H), 5.11 (t, *J* = 9.5 Hz, 1 H), 4.19 (d, *J* = 5.0 Hz, 2 H), 3.92 (s, 3 H), 3.81 (s, 3 H), 2.62 (t, *J* = 10 Hz, 2 H), 2.30 (s, 6 H), 1.47 (s, 9 H), 1.47 (s, 1 H), 1.45 (s, 1 H), 2.12 – 1.05 (series of multiplets, 27 H), 0.96 (s, 3 H), 0.84 (d, *J* = 10.5 Hz, 3 H), 0.78 (s, 3 H); ^{13}C NMR ($CDCl_3$ and ~ 10% CD_3OD, 125 MHz) δ 174.19, 170.05, 169.87, 156.21, 79.36, 79.27, 76.06, 76.90, 71.80, 61.19, 57.04, 46.88, 44.87, 44.67, 44.53, 42.78, 42.15, 42.01, 40.43, 37.47, 34.32, 34.11, 33.92, 33.35, 33.25, 30.74, 30.56, 30.16, 28.40, 27.67, 27.62, 26.73, 26.19, 25.18, 25.10, 24.72, 24.49, 22.29, 21.81, 16.76, 11.56; FAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M + Na]^+$) 973.5723 (100%), cacld. 973.5725. The white solid from the previous reaction (0.680 g, 0.714 mmol) and MeI (1 *M* in CH_2Cl_2, 1.5 mL) were stirred together for 2 h. The solvent and excess MeI were removed in vacuo giving a white solid (0.812 g ~100%). The product was carried on without further purification.

Representative synthesis of compounds 4 – 6: Compound **19** (0.812 g, 0.714 mmol) was dissolved in CH_2Cl_2 (5 mL) and trifluoroacetic acid (0.5 mL) was added. The mixture was stirred for 16 min. The solvent and excess acid were removed in vacuo, and the resulting oil was chromatographed (silica gel, CH_2Cl_2/ MeOH/ $NH_3 \cdot H_2O$ 4 : 4 : 1) to give the desired product as a pale glass (0.437 g, 90% yield). Addition of HCl (2 *M* in ethyl ether, 2.5 mL) gave the trihydrochloride salt of **4** as a pale yellow powder. **Compound 4:** ^1H NMR (50% $CDCl_3$, 50% CD_3OD, 300 MHz) δ 5.43 (s, 1 H), 5.24 (s, 1 H), 4.84 (m, 1 H), 4.66 (m, 2 H), 4.16 – 3.96 (series of multiplets, 6 H), 3.88 (m, 2 H),

3.37 (s, 9 H), 0.67 (s, 3 H), 0.59 (d, *J* = 6.3 Hz, 3 H), 0.56 (s, 3 H); ^{13}C NMR (50% $CDCl_3$, 50% CD_3OD, 75 MHz) δ 173.47, 167.06, 167.01, 166.70, 78.01, 76.49, 73.78, 64.98, 57.67, 53.36, 47.49, 46.99, 45.61, 43.28, 40.83, 40.23, 40.10, 37.69, 34.80, 34.48, 34.28, 31.03, 30.63, 30.44, 28.94, 27.05, 26.56, 25.50, 22.53, 21.56, 16.95, 11.37; FAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M-I]^+$) 665.4475 (85.6%), cacld 665.4489. Compounds **5** and **6** proved too unstable to chromatograph using the basic eluent used for the purification of **4**. Consequently, **5** and **6** were prepared by deprotection of **20** and **21** using HCl (2 *M* in diethyl ether), followed by tituration with ethyl acetate. The compounds were then used without further purification. ^{1}H NMR spectroscopy indicated that compounds **5** and **6** were > 95% pure. **Compound 5:** ^{1}H NMR (50% $CDCl_3$, 50% CD_3OD, 500 MHz) δ 5.21 (s, 1 H), 5.02 (d, *J* = 4 Hz, 1 H), 4.64 (m, 1 H), 4.53 (m, 2 H), 3.74 (m, 2 H), 3.31 – 3.01 (series of multiplets, 6 H), 3.23 (s, 9 H), 2.96 – 2.73 (series of multiples, 6 H), 2.51 – 2.44 (m, 1 H), 2.35 – 2.29 (m, 1 H), 2.14 – 1.09 (series of multiplets, 26 H), 0.99 (s, 3 H), 0.85 (d, *J* = 6.5 Hz, 3 H), 0.80 (s, 3 H); ^{13}C NMR (50% $CDCl_3$, 50% CD_3OD, 125 MHz) δ 172.77, 169.88, 169.56, 169.50, 75.94, 74.44, 71.57, 64.31, 56.94, 52.92, 46.78, 44.59, 42.70, 40.21, 37.16, 34.80, 34.72, 34.66, 34.05, 34.00, 33.78, 33.62, 30.95, 30.91, 30.81, 30.41, 29.96, 29.81, 28.20, 26.37, 26.06, 24.74, 24.24, 22.04, 21.13, 16.54, 10.97; FAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M-I]^+$) 707.4958 (25.6%), cacld 707.4958. **Compound 6:** ^{1}H NMR (50% $CDCl_3$, 50% CD_3OD, 500 MHz) δ 5.12 (s, 1H), 4.94 (d, *J* = 2.5 Hz, 1 H), 4.56 (m. 1 H), 4.51 (t, *J* = 2.3 Hz, 2 H), 3.74 (m, 2 H), 3.23 (s, 9 H), 3.05 – 3.01 (m, 4 H), 2.98 (t, *J* = 7.5 Hz, 2 H), 2.63 – 2.43 (series of multiplets, 6 H), 2.31 - 2.24 (series of multiplets, 2 H), 2.07 – 1.87 (series of multiplets, 12 H), 1.17 - 1.05 (series of multiplets, 23 H), 0.94 (s, 3 H), 0.82 (d, *J* = 6.0 Hz, 3 H), 0.76 (s, 3 H); ^{13}C NMR (50% $CDCl_3$, 50% CD_3OD, 125 MHz) δ 171.87, 169.79, 169.59, 169.50, 76.12, 74.70, 71.65, 65.57, 65.08, 64.40, 57.68, 53.74, 52.78, 45.33 43.54, 41.04, 39.12, 37.92, 43.85, 34.72, 34.56, 34.34, 32.30, 31.47, 31.27, 30.87, 30.58, 29.03, 27.053, 26.84, 25.51, 24.95, 24.91, 22.87, 22.82, 22.65, 21.93, 17.31, 11.81; FAB-MS (thioglycerol + Na^+ matrix) m/e : ($[M-I]^+$) 749.5432 (100%), cacld 749.5436.

Stability tests of compounds 22-24: Compounds **22** – **24** were dissolved in 50 m*M* phosphate buffered water (pH 2.0, 7.0 or 12.0) at approximately 10 m*M* concentrations. Decomposition of the compounds was observed via HPLC (cyano-silica column, 0.15% TFA water-acetonitrile gradient elution).

^{1}H NMR spectra of compounds 1 – 6: