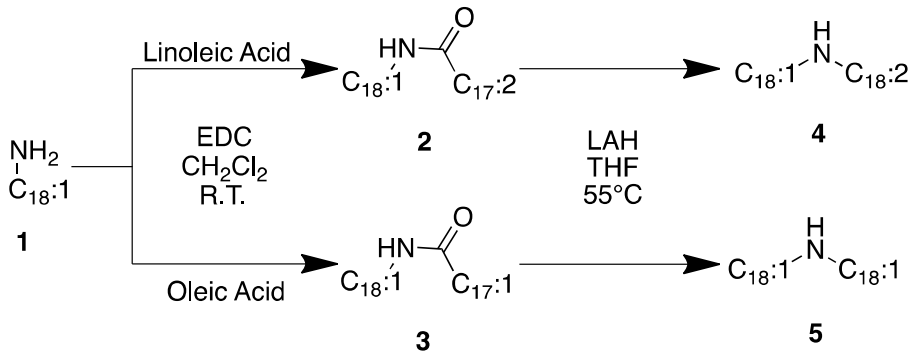
Supplemental Information

MATERIALS AND METHODS

Synthetic Procedures



Scheme 1: Synthesis of dialkylamine precursors

*Synthesis of **2***

2.3g of linoleic acid (280.45g/mol, 8.2mmol, 1.1eq) and 1.8g 1-Ethyl-3-3-(3-dimethylaminopropyl)carbodiimide (EDC) (155.24g/mol, 11.6mmol, 1.5 eq) were added to 30 mL CH_2Cl_2 and the solution was cooled on ice to 4°C. In a separate vessel, 2g of **1** (oleylamine, 267.49g/mol, 7.48mmol, 1.0 eq) was dissolved in 10 mL CH_2Cl_2. The solution of **1** was then added dropwise over 20 minutes. The reaction was allowed to gradually warm to room temperature while stirring overnight. CH_2Cl_2 was removed by rotary evaporation, and the resulting oil was solubilized in 100mL ethyl acetate (EtOAc) and washed 3x with 20mL 1MHCl and 2x with 20mL brine. The organic layer was then dried over Na_2SO_4 and concentrated to an oil. Further purification was not carried out on this compound. 3.8g (96%). MW calc. ($C_{36}H_{67}NO$) = 529.92 found 530.76. TLC: R_f = 0.7 (99:1 CH_2Cl_2:MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 6H), 3.30-3.20 (m, 2H), 2.90-2.80 (m, 2H), 2.20-2.10 (m, 2H) 2.10-1.90 (m, 8H), 1.70-1.60 (m, 2H), 1.60-1.50 (m, 2H), 1.40-1.10 (m, 36H), 0.90 (m, 6H).

*Synthesis of **3***

1g of oleic acid (282.46g/mol, 3.5mmol, 1.1 eq) and 0.82g EDC (155.24g/mol, 5.25mmol, 1.5 eq) were added to 20mL CH_2Cl_2, and the solution was cooled on ice to 4°C. In a separate vessel, 0.85g **1** (oleylamine, 267.49g/mol, 3.2mmol, 1.0 eq) was dissolved in 10 mL CH_2Cl_2. The solution of **1** was then added dropwise over 20 minutes. The reaction was allowed to gradually warm to room temperature while stirring overnight. CH_2Cl_2 was removed by rotary evaporation, and the resulting oil was solubilized in 50mL EtOAc and washed 3x with 20mL 1MHCl and 2x with 20mL brine. The organic layer was then dried over Na_2SO_4 and concentrated to an oil. Further purification was not carried out on this compound. 1.58g (93%). MW calc. ($C_{36}H_{69}NO$) = 531.94 found 532.81. TLC: R_f = 0.7 (99:1 CH_2Cl_2:MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 4H), 3.30-3.20 (m, 2H), 2.20-2.10 (m,2H), 2.10-1.90 (m, 8H), 1.70-1.60 (m, 2H), 1.60-1.50 (m, 2H), 1.40-1.10 (m, 42H), 0.90 (m, 6H).

*Synthesis of **4***

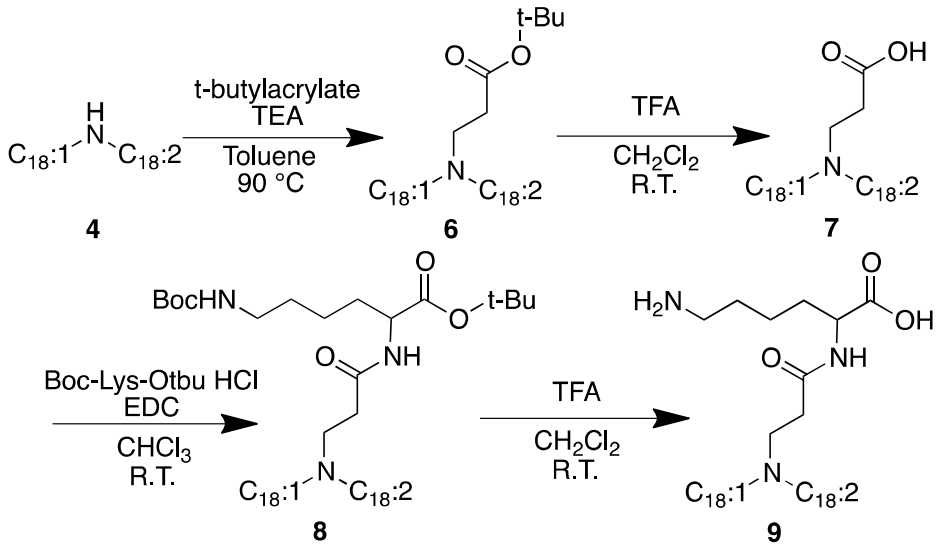
0.82g of lithium aluminum hydride (LAH) (37.95g/mol, 21.5mmol, 3.0 eq) was suspended in 25mL anhydrous THF and cooled in an ice bath to 4°C. 3.8g of **2** (529.92g/mol, 7.2mmol, 1.0 eq) was solubilized in 20mL anhydrous THF and added dropwise to the LAH solution over 1 hour. The reaction was allowed to warm to room temperature, then heated to 55°C and stirred overnight. After 24 hours, the reaction was cooled back to 4°C in an ice bath, and excess LAH was quenched by the slow addition of 5mL deionized H_2O followed by 1 hour of stirring at 4°C. The solid salts were removed by filtration, and the THF:H_2O mixture was removed by rotary evaporation. The remaining oily solid was solubilized in 100mL diethyl ether and washed 2x with 20mL 1M HCl, 2x with 20mL brine. The organic layer was then dried over Na_2SO_4 and concentrated to an oil. Further purification was not carried out on this compound. 3.35g (91%). MW calc. ($C_{36}H_{69}N$) = 515.94 found 516.18. TLC: R_f = 0.15 (99:1 CH_2Cl_2:MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 6H), 3.00-2.80 (m, 4H), 2.80-2.70 (m, 2H), 2.10-1.90 (m, 8H), 1.90-1.70 (m, 4H), 1.40-1.10 (m, 38H), 0.90 (m, 6H).

*Synthesis of **5***

0.34g of LAH (37.95g/mol, 8.9mmol, 3.0 eq) was suspended in 20mL anhydrous THF and cooled in an ice bath to 4°C. 1.58g of **3** (531.94g/mol, 3.0mmol, 1.0 eq) was solubilized in 15mL anhydrous THF and added dropwise to the LAH solution over 1 hour. The reaction was allowed to warm to room temperature, then heated to 55°C and stirred overnight. After 24 hours, the reaction was cooled back to 4°C in an ice bath, and excess LAH was quenched by the slow addition of 5mL deionized H_2O followed by 1 hour of stirring at 4°C. The solid salts were removed by filtration, and the THF:H_2O mixture was removed by rotary evaporation. The remaining oily solid was solubilized in 100mL diethyl ether and washed 2x with 20mL 1M HCl, 2x with 20mL brine. The organic layer was then dried over Na_2SO_4 and concentrated to an oil. Further purification was not carried out on this compound. 1.35g (87%). MW calc. ($C_{36}H_{69}N$) = 517.96 found 518.78. TLC: R_f = 0.15 (99:1 CH_2Cl_2:MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 4H), 2.70-2.50 (m, 4H), 2.10-1.90 (m, 8H), 1.60-1.40 (m, 4H), 1.40-1.10 (m, 44H), 0.90 (m, 6H).



Scheme 2: Synthesis of LOA-LysC2

*Synthesis of **6***

3.3g of **4** (515.94g/mol, 6.4mmol, 1.0 eq), 1.6g of t-butylacrylate (128.17g/mol, 12.8mmol, 2.0 eq), and 2.6g triethylamine (TEA) (101.19g/mol, 25.6mmol, 4.0 eq) were solubilized in 10mL toluene and stirred at 90°C for 72 hours. Solvent was removed by rotary evaporation, and the resulting oil was solubilized in 100 mL EtOAc, washed 2x with 20mL 1M HCl and 2x with 20mL brine. The organic layer was then dried over Na_2SO_4 and concentrated to an oil. The crude product was purified by HPFC using an elution gradient of 0-8% MeOH in $CHCl_3$. MW calc. ($C_{43}H_{81}NO_2$) = 644.11 found 645.01. 2.76g (67%). TLC: R_f = 0.9 (95:4.5:0.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 6H), 3.50-3.40 (m, 2H), 3.30-3.20 (m, 2H), 3.00-2.80 (m, 4H), 2.80-2.70 (m, 2H), 2.10-1.90 (m, 8H), 1.90-1.70 (m, 4H), 1.50 (s, 9H) 1.40-1.10 (m, 38H), 0.90 (m, 6H).

*Synthesis of **7***

2.7g of **6** (644.11g/mol, 4.2mmol) was stirred in 15mL 1:1 TFA:CH_2Cl_2 at room temperature for 1 hour. TFA and CH_2Cl_2 were removed by rotary evaporation, and the resulting oil was solubilized in 100 mL EtOAc, washed 2x with 20mL 1M $NaHCO_3$ and 2x with 20mL brine. The organic layer was dried over Na_2SO_4 and concentrated to an oil. MW calc. ($C_{39}H_{73}NO_2$) = 588.0 found 588.91. 2.32g (94%). TLC: R_f = 0.3 (95:4.5:0.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 6H), 3.50-3.40 (m, 2H), 3.30-3.20 (m, 2H), 3.00-2.80 (m, 4H), 2.80-2.70 (m, 2H), 2.10-1.90 (m, 8H), 1.90-1.70 (m, 4H), 1.40-1.10 (m, 38H), 0.90 (m, 6H).

*Synthesis of **8***

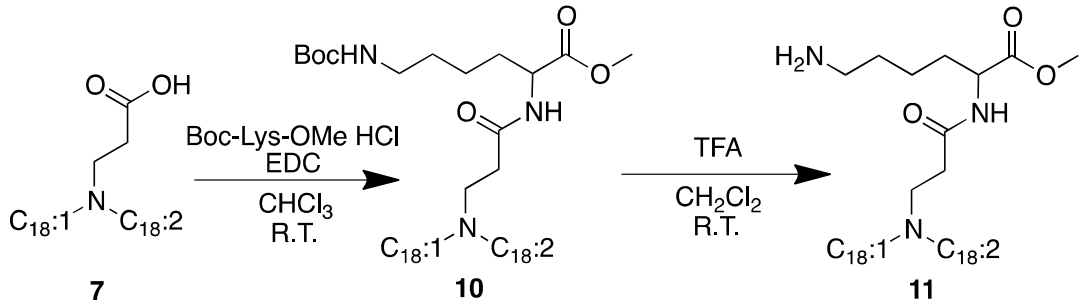
1.05g of **7** (588.0g/mol, 1.8mmol, 1.0 eq), 0.68g Boc-Lys-Otbu HCl (338.87g/mol, 2mmol, 1.1 eq), 0.42g EDC (155.24g/mol, 2.7mmol, 1.5 eq) were added to 30mL $CHCl_3$ and stirred at room temperature for 24 hours. Solvent was removed by rotary evaporation. The resulting oily solid was solubilized in 100mL EtOAc and washed 2x with 20mL 1M HCl and 2x with 20mL brine. The organic layer was dried over Na_2SO_4 and concentrated to an oil. The crude product was purified by HPFC using an elution gradient of 0-10% MeOH in $CHCl_3$. MW calc ($C_{54}H_{101}N_3O_5$) = 872.40 found 873.31. 1.04g (66%). TLC: R_f = 0.45 (95:4.5:0.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 6H), 4.40 (m, 1H), 3.50-3.40 (m, 2H), 3.30-3.20 (m, 2H), 3.20-3.10 (m, 2H), 3.00-2.80 (m, 4H), 2.80-2.70 (m, 2H), 2.10-1.90 (m, 8H), 1.90-1.70 (m, 8H), 1.55 (m, 2H), 1.40 (s, 18H), 1.40-1.10 (m, 38H), 0.90 (m, 6H).

*Synthesis of **9***

1.04g of **8** (872.40g/mol, 1.2mmol, 1.0 eq) was stirred in 10mL 1:1 TFA:CH_2Cl_2 at room temperature for 1 hour. TFA and CH_2Cl_2 were removed by rotary evaporation, and the resulting oil was solubilized in 50 mL EtOAc, washed 2x with 10mL 1M $NaHCO_3$ and 2x with 10mL brine. The organic layer was dried over Na_2SO_4 and concentrated to an oil. The crude product was purified by HPFC using an elution gradient of 0-30% MeOH in $CHCl_3$. MW calc. ($C_{45}H_{85}N_3O_{3)}$ = 716.17 found 717.12. 0.64g (75%). TLC: R_f = 0.15 (72.5:25:2.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 6H), 4.40 (m, 1H), 3.50-3.40 (m, 2H), 3.30-3.20 (m, 2H), 3.20-3.10 (m, 2H), 3.00-2.80 (m, 4H), 2.80-2.70 (m, 2H), 2.10-1.90 (m, 8H), 1.80-1.60 (m, 6H) 1.40-1.10 (m, 42H), 0.90 (m, 6H).



Scheme 4: Synthesis of LOA-LysC2-OMe

*Synthesis of **10***

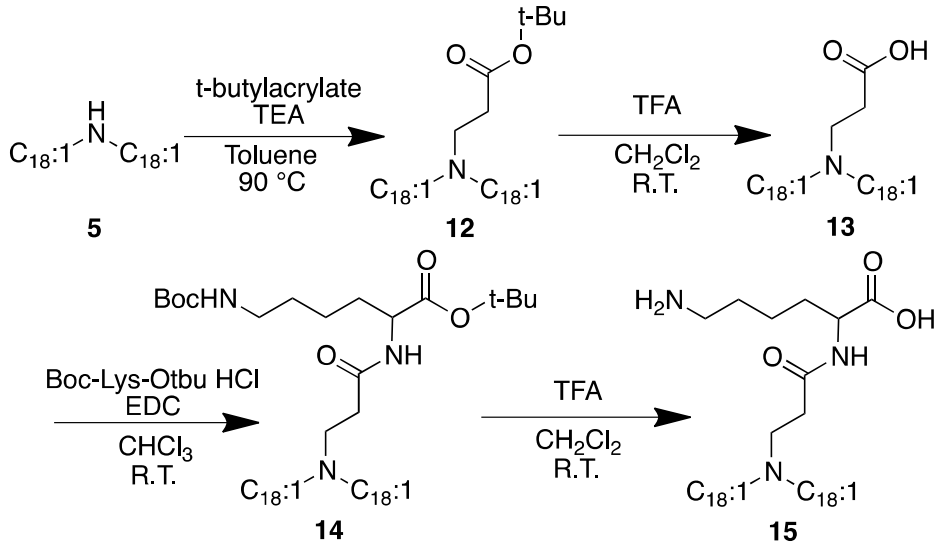
1g of **7** (588.0g/mol, 1.7mmol, 1.0 eq), 0.56g Boc-Lys-OMe HCl (296.79g/mol, 1.9mmol, 1.1 eq), 0.41g EDC (155.24g/mol, 2.6mmol, 1.5 eq) were added to 30mL $CHCl_3$ and stirred at room temperature for 24 hours. Solvent was removed by rotary evaporation. The resulting oily solid was solubilized in 100mL EtOAc and washed 2x with 20mL 1M HCl and 2x with 20mL brine. The organic layer was dried over Na_2SO_4 and concentrated to an oil. The crude product was purified by HPFC using an elution gradient of 0-10% MeOH in $CHCl_3$. MW calc ($C_{54}H_{95}N_3O_5$) = 830.32 found 831.29. 0.85g (60%). TLC: R_f = 0.45 (95:4.5:0.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 6H), 4.40 (m, 1H), 3.70 (s, 3H), 3.50-3.40 (m, 2H), 3.30-3.20 (m, 2H), 3.20-3.10 (m, 2H) 3.00-2.80 (m, 4H), 2.80-2.70 (m, 2H), 2.10-1.90 (m, 8H), 1.90-1.70 (m, 8H), 1.55 (m, 2H), 1.40 (s, 9H), 1.40-1.10 (m, 38H), 0.90 (m, 6H).

*Synthesis of **11***

0.85g of **10** (830.32g/mol, 1.0mmol, 1.0 eq) was stirred in 10mL 1:1 TFA:CH_2Cl_2 at room temperature for 1 hour. TFA and CH_2Cl_2 were removed by rotary evaporation, and the resulting oil was solubilized in 50 mL EtOAc, washed 2x with 10mL 1M $NaHCO_3$ and 2x with 10mL brine. The organic layer was dried over Na_2SO_4 and concentrated to an oil. The crude product was purified by HPFC using an elution gradient of 0-20% MeOH in $CHCl_3$. MW calc. ($C_{45}H_{85}N_3O_{3)}$ = 730.20 found 730.73. 0.6g (82%). TLC: R_f = 0.15 (90:9:1 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 6H), 4.40 (m, 1H), 3.70 (s, 3H) 3.50-3.40 (m, 2H), 3.30-3.20 (m, 2H), 3.20-3.10 (m, 2H) 3.00-2.80 (m, 4H), 2.80-2.70 (m, 2H), 2.10-1.90 (m, 8H), 1.80-1.60 (m, 6H) 1.40-1.10 (m, 42H), 0.90 (m, 6H).



Scheme 3: Synthesis of DOA-LysC2

*Synthesis of **12***

2g of **5** (517.96 g/mol, 3.9mmol, 1.0 eq), 1g of t-butylacrylate (128.17g/mol, 7.8mmol, 2.0 eq), and 1.6g triethylamine (TEA) (101.19g/mol, 11.2mmol, 4.0 eq) were solubilized in 10mL toluene and stirred at 90°C for 72 hours. Solvent was removed by rotary evaporation, and the resulting oil was solubilized in 50 mL EtOAc, washed 2x with 10mL 1M HCl and 2x with 10mL brine. The organic layer was then dried over Na_2SO_4 and concentrated to an oil. The crude product was purified by HPFC using an elution gradient of 0-5% MeOH in $CHCl_3$. MW calc. ($C_{43}H_{83}NO_2$) = 646.12 found 647.02. 1.4g (56%). TLC: R_f = 0.9 (95:4.5:0.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 4H), 3.20 (m, 2H), 3.00-2.80 (m, 4H), 2.80-2.60 (m, 2H), 2.10-1.90 (m, 8H), 1.90-1.70 (m, 4H), 1.50 (s, 9H) 1.40-1.10 (m, 44H), 0.90 (m, 6H).

*Synthesis of **13***

1.35g **12** (646.12g/mol, 2.1mmol) was stirred in 10mL 1:1 TFA:CH_2Cl_2 at room temperature for 1 hour. TFA and CH_2Cl_2 were removed by rotary evaporation, and the resulting oil was solubilized in 50 mL EtOAc, washed 2x with 10mL 1M $NaHCO_3$ and 2x with 10mL brine. The organic layer was dried over Na_2SO_4 and concentrated to an oil. MW calc. ($C_{39}H_{75}NO_2$) = 590.02 found 590.86. 1.05g (85%). TLC: R_f = 0.3 (95:4.5:0.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 4H), 3.20 (m, 2H), 3.00-2.80 (m, 4H), 2.80-2.60 (m, 2H), 2.10-1.90 (m, 8H), 1.90-1.70 (m, 4H), 1.40-1.10 (m, 44H), 0.90 (m, 6H).

*Synthesis of **14***

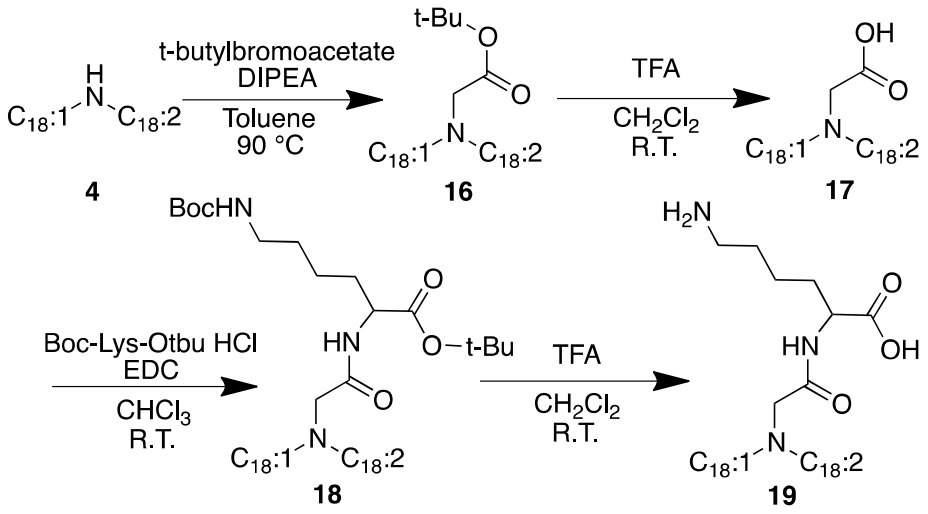
1g of **13** (590.02g/mol, 1.7mmol, 1.0 eq), 0.64g Boc-Lys-Otbu HCl (338.87g/mol, 1.9mmol, 1.1 eq), 0.4g EDC (155.24g/mol, 2.55mmol, 1.5 eq) were added to 30mL $CHCl_3$ and stirred at room temperature for 24 hours. Solvent was removed by rotary evaporation. The resulting oily solid was solubilized in 100mL EtOAc and washed 2x with 20mL 1M HCl and 2x with 20mL brine. The organic layer was dried over Na_2SO_4 and concentrated to an oil. The crude product was purified by HPFC using an elution gradient of 0-10% MeOH in $CHCl_3$. MW calc ($C_{54}H_{103}N_3O_5$) = 874.41 found 874.68. 1.05g (71%). TLC: R_f = 0.45 (95:4.5:0.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 4H), 4.40 (m, 1H), 3.50-3.40 (m, 2H), 3.30-3.20 (m, 2H), 3.20-3.10 (m, 2H) 3.00-2.80 (m, 6H), 2.10-1.90 (m, 8H), 1.90-1.70 (m, 8H), 1.40 (s, 18H), 1.40-1.10 (m, 44H), 0.90 (m, 6H).

*Synthesis of **15***

1.05g of **14** (874.41g/mol, 1.2mmol, 1.0 eq) was stirred in 10mL 1:1 TFA:CH_2Cl_2 at room temperature for 1 hour. TFA and CH_2Cl_2 were removed by rotary evaporation, and the resulting oil was solubilized in 50 mL EtOAc, washed 2x with 10mL 1M $NaHCO_3$ and 2x with 10mL brine. The organic layer was dried over Na_2SO_4 and concentrated to an oil. The crude product was purified by HPFC using an elution gradient of 0-30% MeOH in $CHCl_3$. MW calc. ($C_{45}H_{87}N_3O_{3)}$ = 718.19 found 719.04. 0.61g (71%). TLC: R_f = 0.15 (72.5:25:2.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 4H), 4.40 (m, 1H), 3.50-3.40 (m, 2H), 3.30-3.20 (m, 2H), 3.20-3.10 (m, 2H) 3.00-2.80 (m, 4H), 2.10-1.90 (m, 8H), 1.80-1.60 (m, 6H) 1.40-1.10 (m, 46H), 0.90 (m, 6H).



Scheme 5: Synthesis of LOA-LysC1

*Synthesis of **16***

2g of **4** (515.94g/mol, 3.9mmol, 1.0 eq), 1.5g of t-butylbromoacetate (195.05g/mol, 7.8mmol, 2.0 eq), and 1.3g DIPEA (129.24g/mol, 9.8mmol, 2.5 eq) were solubilized in 10mL toluene and stirred at 80°C for 48 hours. Solvent was removed by rotary evaporation, and the resulting oil was solubilized in 100 mL EtOAc, washed 2x with 20mL 1M HCl and 2x with 20mL brine. The organic layer was then dried over Na_2SO_4 and concentrated to an oil. The crude product was purified by HPFC using an elution gradient of 0-8% MeOH in $CHCl_3$. MW calc. ($C_{42}H_{79}NO_2$) = 630.08 found 630.36. 1.89g (77%). TLC: R_f = 0.85 (95:4.5:0.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 6H), 3.70-3.60 (s, 2H), 3.30-3.20 (m, 4H), 2.80-2.70 (m, 2H), 2.10-1.90 (m, 8H), 1.90-1.70 (m, 4H), 1.50 (s, 9H), 1.40-1.10 (m, 38H), 0.90 (m, 6H).

*Synthesis of **17***

1.8g of **16** (630.08g/mol, 2.9mmol) was stirred in 10mL 1:1 TFA:CH_2Cl_2 at room temperature for 1 hour. TFA and CH_2Cl_2 were removed by rotary evaporation, and the resulting oil was solubilized in 100 mL EtOAc, washed 2x with 20mL 1M $NaHCO_3$ and 2x with 20mL brine. The organic layer was dried over Na_2SO_4 and concentrated to an oil. MW calc. ($C_{38}H_{71}NO_2$) = 573.98 found 574.42. 1.55g (93%). TLC: R_f = 0.3 (95:4.5:0.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 6H), 3.90-3.80 (s, 2H), 3.40-3.20 (m, 4H), 2.80-2.70 (m, 2H), 2.10-1.90 (m, 8H), 1.90-1.70 (m, 4H), 1.40-1.10 (m, 38H), 0.90 (m, 6H).

*Synthesis of **18***

0.9g of **17** (574.42g/mol, 1.6mmol, 1.0 eq), 0.61g Boc-Lys-Otbu HCl (338.87g/mol, 1.8mmol, 1.1 eq), 0.38g EDC (155.24g/mol, 2.4mmol, 1.5 eq) were added to 30mL $CHCl_3$ and stirred at room temperature for 24 hours. Solvent was removed by rotary evaporation. The resulting oily solid was solubilized in 100mL EtOAc and washed 2x with 20mL 1M HCl and 2x with 20mL brine. The organic layer was dried over Na_2SO_4 and concentrated to an oil. The crude product was purified by HPFC using an elution gradient of 0-10% MeOH in $CHCl_3$. MW calc ($C_{53}H_{99}N_3O_5$) = 858.37 found 859.24. 0.93g (68%). TLC: R_f = 0.45 (95:4.5:0.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 6H), 4.40 (m, 1H), 3.50-3.40 (s, 2H), 3.40-3.30 (m, 2H), 3.20-3.10 (m, 4H), 2.80-2.70 (m, 2H), 2.10-1.90 (m, 8H), 1.90-1.70 (m, 8H), 1.55 (m, 2H), 1.40 (s, 18H), 1.40-1.10 (m, 38H), 0.90 (m, 6H).

*Synthesis of **19***

0.9g of **18** (858.37g/mol, 1.0mmol, 1.0 eq) was stirred in 10mL 1:1 TFA:CH_2Cl_2 at room temperature for 1 hour. TFA and CH_2Cl_2 were removed by rotary evaporation, and the resulting oil was solubilized in 50 mL EtOAc, washed 2x with 10mL 1M $NaHCO_3$ and 2x with 10mL brine. The organic layer was dried over Na_2SO_4 and concentrated to an oil. The crude product was purified by HPFC using an elution gradient of 0-30% MeOH in $CHCl_3$. MW calc. ($C_{44}H_{83}N_3O_{3)}$ = 702.15 found 703.01. 0.51g (72%). TLC: R_f = 0.15 (72.5:25:2.5 CH_2Cl_2:MeOH:NH_3OH).

^{1}H NMR (300 MHz, $CDCl_3$): 5.50-5.30 (m, 6H), 4.40 (m, 1H), 3.50-3.40 (s, 2H), 3.30-3.20 (m, 2H), 3.00-2.80 (m, 4H), 2.80-2.70 (m, 2H), 2.10-1.90 (m, 8H), 1.80-1.60 (m, 6H) 1.40-1.10 (m, 42H), 0.90 (m, 6H).

siRNA Sequences

Lowercase = 2'-fluoro modified nucleotides
Asterisk = phosphorothioate linkage

Anti-Luciferase
Sense: 5' –GCUACAUUCUGGAGAGAUAdTdT-3'
Antisense: 5'-UAUGUCUCCAGAAUGUAGCdTdT-3'
Non-specific control provided by Pfizer

Factor VII
Sense: 5'-GGAucAucucAAGucuuAcT*T-3'
Antisense: 5'-GuAAGAcuuGAGAuGAuccT*T-3'
Non-specific: siGenome Non-Targeting siRNA #5 (Dharmacon, Lafeyette, CO)

SUPPLEMENTAL TABLES AND FIGURES

Ionizable Lysine Lipid	Size (nm)	PDI	Encapsulation Efficiency (%)
LOA-LysC2	89.7	0.16	91.6
DOA-LysC2	98.0	0.18	93.6
LOA-LysC1	85.8	0.13	83.5
LOA-LysC2-OMe	103.6	0.15	92.7

Table S1: Size, PDI, and encapsulation efficiency of ILL liposomes (40:40:10:10 ILL:Chol:DSPC:PEG-DMG)

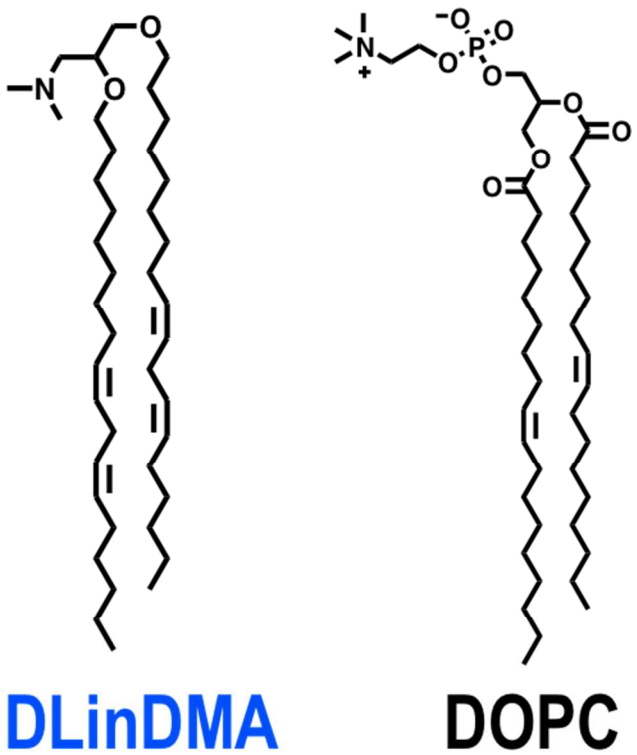


Figure S1: Lipid structures for positive (DLinDMA) and negative (DOPC) control lipids.

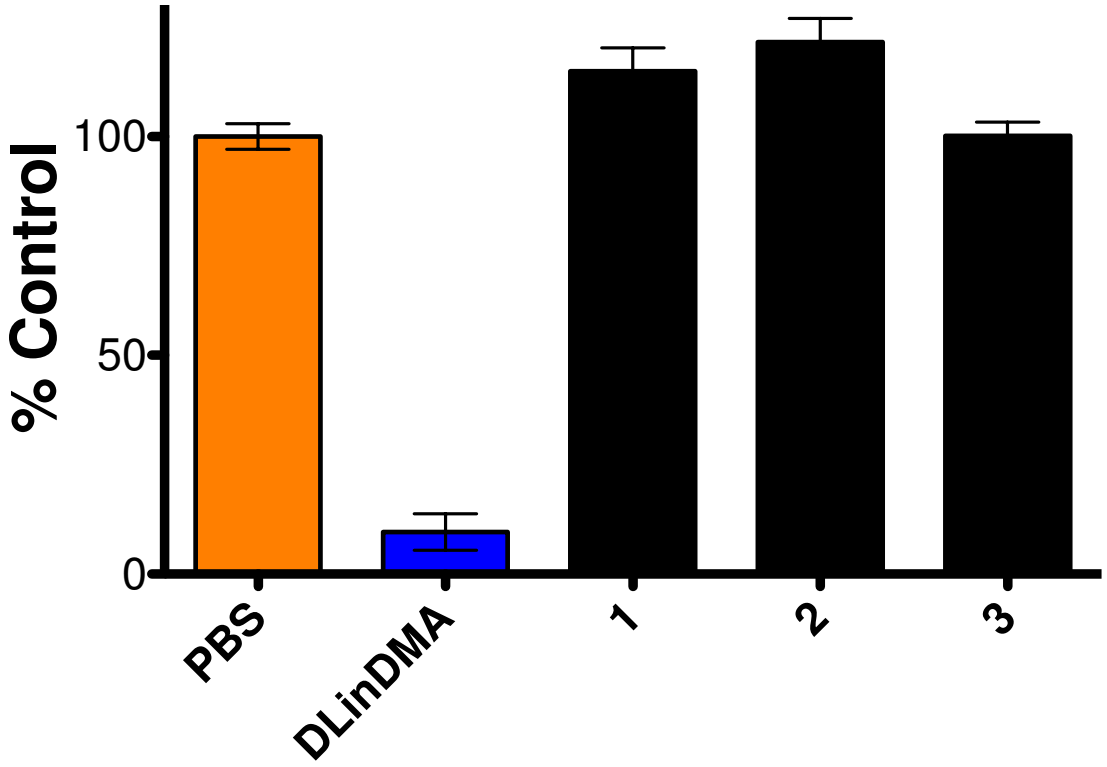


Figure S2: Factor VII knockdown experiments with LOA-LysC2 containing liposomal siRNA formulations. DLinDMA containing formulations (40:40:10:10 DLinDMA:Chol:DSPC:PEG-DMG) were used as a positive control. LOA-LysC2 containing formulations were:

1. 40:40:10:10 LOA-LysC2:Chol:DSPC:PEG-DMG
2. 40:40:10:10 LOA-LysC2:Chol:POPC:PEG-DMG
3. 40:40:10:10 LOA-LysC2:Chol:POPE:PEG-DMG

No significant knockdown was observed for any LOA-LysC2 containing formulation.

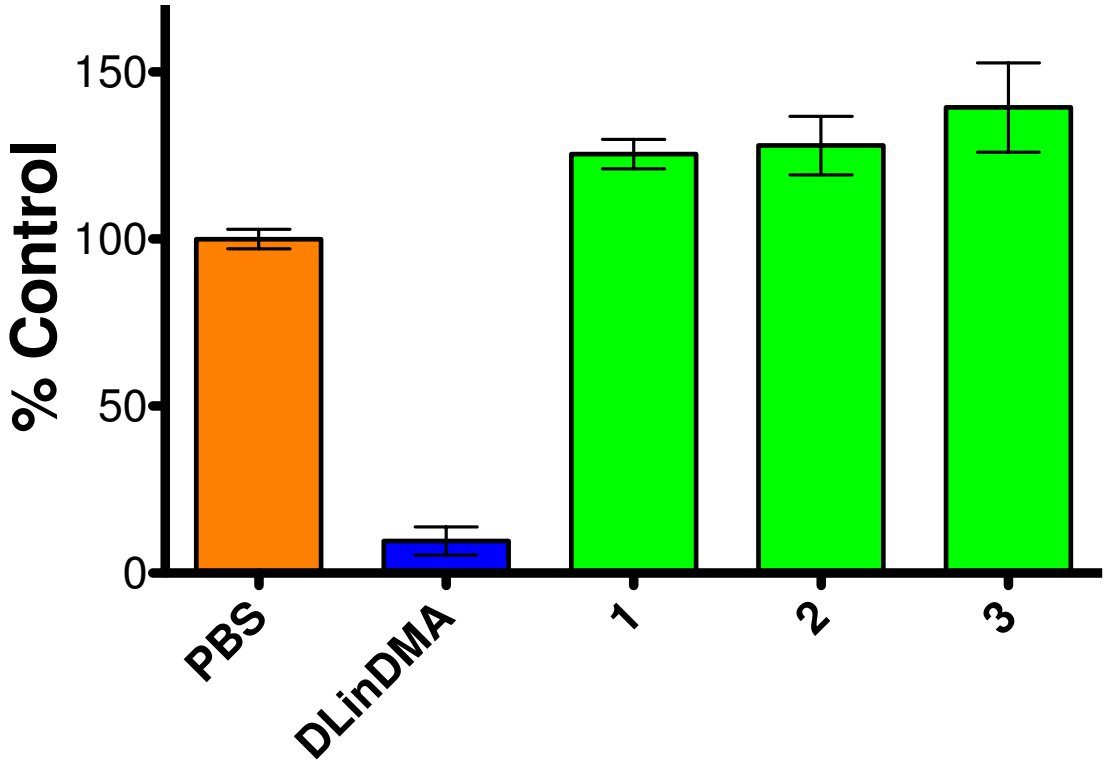


Figure S3: Factor VII knockdown experiments with LOA-LysC2-OMe containing liposomal siRNA formulations. DLinDMA containing formulations (40:40:10:10 DLinDMA:Chol:DSPC:PEG-DMG) were used as a positive control. LOA-LysC2 containing formulations were:

1. 40:40:10:10 LOA-LysC2:Chol:DSPC:PEG-DMG
2. 40:40:10:10 LOA-LysC2:Chol:POPC:PEG-DMG
3. 48:40:10:2 LOA-LysC2:Chol:POPC:PEG-DMG

No significant knockdown was observed for any LOA-LysC2-OMe containing formulation.