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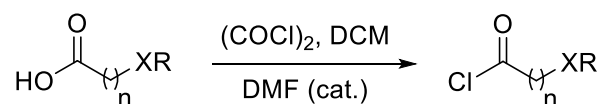
General information

Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous CH_2Cl_2 , toluene, THF and DMF were obtained from an Innovative Technology Inc. PureSolv[®] solvent purification system. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz. All spectral data was acquired at 295 K unless stated otherwise. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peaks, δ_{H} 7.26 and δ_{C} 77.16 for CDCl_3 were used as a reference. Coupling constants (J) are reported in Hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used are: br s broad singlet, s singlet, d doublet, br d broad doublet, t triplet, br t broad triplet, q quartet, p pentet, dd, doublet of doublets, ddd doublet of doublet of doublets, dddd doublet of doublet of doublet of doublets, dt doublet of triplets, ddt doublet of doublet of triplets, td triplet of doublets, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 spectrometer as a thin film dispersed from either CH_2Cl_2 or CDCl_3 . Mass spectra (high-resolution) were obtained by the University of York Mass Spectrometry Service, using Electrospray Ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus. Thin layer chromatography was carried out on Merck silica gel 60F₂₅₄ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. In most cases, flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 μm , 60 Å, under a light positive pressure, eluting with the specified solvent system. When noted in the procedures, products were purified by using a Teledyne ISCO NextGen 300+ automated flash column chromatography unit equipped with UV–Vis (200–800 nm) and evaporative light scattering (ELS) detectors. Crude materials were loaded onto pre-packed RediSep Rf Gold columns (SiO_2 : 40–60 mesh) either by direct liquid injection or dry loading from adsorbed Celite.

X-ray crystallography

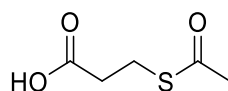
Diffraction data were collected at 110 K on an Oxford Diffraction SuperNova diffractometer with Cu- K_{α} radiation ($\lambda = 1.54184 \text{ \AA}$) using an EOS CCD camera. The crystal was cooled with an Oxford Instruments Cryojet. Diffractometer control, data collection, initial unit cell determination, frame integration and unit-cell refinement was carried out with "Crysalis".¹ Face-indexed absorption corrections were applied using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.² OLEX2³ was used for overall structure solution, refinement and preparation of computer graphics and publication data. Within OLEX2, the algorithms used for structure solution were Superflip charge-flipping⁴ (**24b**) or ShelXT dual-space⁵ (**20_{RE}** & **24I**). Refinement by full-matrix least-squares used the SHELXL-97⁶ algorithm within OLEX2.³ All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using a "riding model" and included in the refinement at calculated positions. **24b** was a non-merohedral twin modelled using Crysalis¹ with two components in the ratio 0.6144:0.3856(11). The asymmetric unit of **24I** contained two molecules, one of which exhibited disorder of two of the carbons (C6 & C7). These were modelled in two positions in a refined ration of 0.901:0.099(3). The ADP of each pair of disordered atoms were constrained to be equal (C6 & C6a, C7 & C7a). CCDC 2040347 (**24b**), 1921223 (**20_{RE}**) and 2040346 (**24I**) contain the crystallographic data for these macrocyclic thiolactones, see: www.ccdc.cam.ac.uk/data_request/cif

General procedure for acid chloride formation



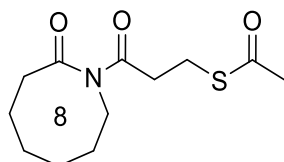
Oxalyl chloride (3 mmol) was added to a suspension of carboxylic acid (1 mmol) in DCM (5 mL), followed by a catalytic amount of DMF (1 drop/mmol of carboxylic acid). The resulting mixture was stirred at RT for 1 h and concentrated *in vacuo* to remove all the solvent and excess oxalyl chloride.

3-(Acetylthio)propanoic acid (28)



3-Bromopropionic acid (3.84 g, 25.1 mmol) was added to a stirring solution of potassium thioacetate (3.41 g, 29.9 mmol) in acetone (500 mL) and allowed to stir at RT for 6 h. Afterwards, all solvent was removed *in vacuo* and the residue taken up in ethyl acetate (250 mL) and water (250 mL). The organic layer was collected and the aqueous layer extracted with ethyl acetate (3 × 250 mL). The combined organics were dried over MgSO₄ and concentrated *in vacuo* to afford the *title compound* as a brown solid (3.44 g, 92%); R_f 0.43 (2:3 ethyl acetate: hexane); m.p. 49–53 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2925, 1687, 1408, 1355, 1244, 1200, 1131, 1040, 944, 804, 689, 623, 532, 488; δ_{H} (400 MHz, CDCl₃) 10.10 (1H, br s, COOH), 3.10 (2H, t, *J* = 6.9 Hz, CH₂), 2.69 (2H, t, *J* = 6.9 Hz, CH₂), 2.33 (3H, s, CH₃); δ_{C} (100 MHz, CDCl₃) 195.7 (SCO), 177.9 (COOH), 34.3 (CH₂), 30.7 (CH₃), 23.9 (CH₂); HRMS (ESI): calcd. for C₅H₈NaO₃S, 171.0086. Found: [MNa]⁺, 171.0086 (−0.1 ppm error). This procedure was adapted from a literature method.⁷

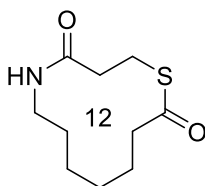
1-[3-(Acetylsulfanyl)propanoyl]azocan-2-one (23a)



A mixture of 1-aza-2-cyclooctanone **21a** (381 mg, 2.97 mmol), DMAP (103 mg, 0.840 mmol) and pyridine (1.44 mL, 17.8 mmol) in DCM (30 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (4.49 mmol, prepared using the general procedure) in DCM (30 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then

diluted with DCM (50 mL) and washed with 10% aq. HCl (50 mL). The aqueous layer was then extracted with DCM (3 × 25 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as a light orange oil (610 mg, 80%); R_f 0.43 (2:5 ethyl acetate: hexane); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2928, 2859, 1687, 1445, 1372, 1247, 1198, 1175, 1126, 1092, 998, 893, 774, 692, 628, 594; δ_{H} (400 MHz, CDCl₃) 3.92–3.83 (2H, m, CH₂N), 3.19–3.09 (4H, m, COCH₂CH₂S and COCH₂CH₂S), 2.66–2.58 (2H, m, CH₂CON), 2.29–2.25 (3H, m, CH₃), 1.88–1.79 (2H, m, CH₂), 1.71–1.63 (2H, m, CH₂), 1.60–1.52 (2H, m, CH₂), 1.46–1.37 (2H, m, CH₂); δ_{C} (100 MHz, CDCl₃), 195.9 (COS), 178.3 (CON), 174.8 (COCH₂CH₂), 43.5 (CH₂N), 39.9 (COCH₂CH₂S), 37.2 (CH₂CON), 30.6 (CH₃), 29.5 (CH₂), 29.1 (CH₂), 26.3 (CH₂), 24.5 (COCH₂CH₂S), 24.0 (CH₂); HRMS (ESI): calcd. for C₁₂H₁₉NNaO₃S, 280.0978. Found: [MNa]⁺, 280.0976 (0.8 ppm error).

1-Thia-5-azacyclododecane-4,12-dione (**20_{RE}**)

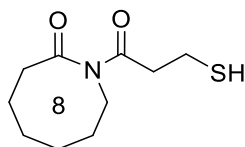


A mixture of 1-[3-(acetylsulfanyl)propanoyl]azocan-2-one **23a** (130 mg, 0.505 mmol) and piperidine (0.148 mL, 1.50 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 22 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* **20_{RE}** as an off white solid (31.7 mg, 29%), along with recovered **23a** (8.3 mg, 6%) and **20_{RO}** (3.4 mg, 3%; for characterisation data for **20_{RO}** see next page). Data for **20_{RE}**: m.p. 152–155 °C; R_f 0.28 (9:1 ethyl acetate: methanol); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3294, 3096, 2924, 2856, 1688, 1638, 1562, 1456, 1434, 1352, 1263, 1244, 1219, 1183, 1144, 1105, 1071, 1035, 977, 936, 883, 858, 784, 729, 629, 566, 587; All ¹H signals are broadened due to rotamer interconversion. δ_{H} (400 MHz, CDCl₃) 5.71 (1H, br s, NH), 3.42–3.10 (3H, m, 1.5 × CH₂), 2.85–2.32 (5H, m, 2.5 × CH₂), 1.67–1.56 (1H, m, 0.5 × CH₂), 1.56–1.28 (7H, m, 3.5 × CH₂); δ_{C} (100 MHz, CDCl₃) 200.5 (SCO), 169.9 (CO), 43.5 (CH₂COS), 38.4 (CH₂NH), 37.7 (CH₂), 27.6 (CH₂), 26.2 (CH₂), 24.1 (CH₂), 23.5 (CH₂), 22.3 (CH₂); HRMS (ESI): calcd. for C₁₀H₁₈NO₂S, 216.1053. Found: [MH]⁺, 216.1051 (0.6 ppm error). For X-ray crystallographic data, see CCDC 1921223.

The same product **20_{RE}** was also prepared using the S-Fm strategy, using the following procedure:

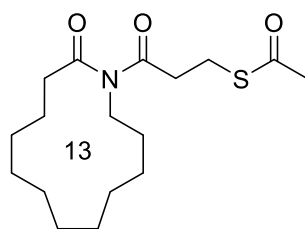
A mixture of 1-aza-2-cyclooctanone (63.7 mg, 0.501 mmol), DMAP (7.5 mg, 0.062 mmol) and pyridine (0.240 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **34** (1.50 mmol, prepared from **S1** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.75 mL, 5.00 mmol) was added, followed by stirring at RT for 14 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO₂, 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded the *title compound* as a yellow crystalline solid (16.2 mg, 15%).

1-(3-Mercaptopropanoyl)azocan-2-one (**20_{RO}**)



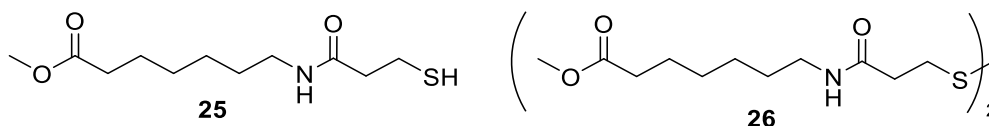
Data for **20_{RO}** (for synthesis see above): colorless oil; R_f 0.74 (9:1 ethyl acetate: methanol); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2925, 2857, 1685, 1445, 1370, 1339, 1285, 1258, 1197, 1174, 1125, 1091, 1018, 867, 799, 686, 591, 504; δ_H (400 MHz, CDCl₃) 3.94–3.88 (2H, m, CH₂N), 3.20 (2H, t, $J = 6.6$ Hz, CH₂CH₂SH), 2.79 (2H, dt, $J = 8.5, 6.6$ Hz, CH₂CH₂SH), 2.67–2.61 (2H, m, CH₂CON), 1.90–1.82 (2H, m, CH₂), 1.74–1.66 (2H, m, CH₂), 1.63 (1H, t, $J = 8.5$ Hz, CH₂SH), 1.61–1.55 (2H, m, CH₂), 1.48–1.40 (2H, m, CH₂); δ_C (100 MHz, CDCl₃) 178.4 (CON), 174.8 (COCH₂CH₂), 43.8 (COCH₂CH₂S), 43.5 (CH₂N), 37.2 (CH₂CON), 29.6 (CH₂), 29.2 (CH₂), 26.3 (CH₂), 24.1 (CH₂), 20.1 (CH₂SH); HRMS (ESI): calcd. for C₁₀H₁₇NNaO₂S, 238.0872. Found: [MNa]⁺, 238.0869 (1.3 ppm error).

1-[3-(Acetylsulfanyl)propanoyl]-1-azacyclotridecan-2-one (**23b**)



A mixture of lauro lactam **21b** (592 mg, 3.00 mmol), DMAP (57.4 mg, 0.473 mmol) and pyridine (1.45 mL, 18.0 mmol) in DCM (50 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (4.49 mmol, 1.50 eqv. prepared using the general procedure) in DCM (10 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (50 mL) and washed with 10% aq. HCl (50 mL). The aqueous layer was then extracted with DCM (3 × 25 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as a colorless oil (323 mg, 33%); R_f 0.53 (2:3 ethyl acetate: hexane); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2930, 2861, 1690, 1364, 1180, 1133, 1047, 952, 626; δ_{H} (400 MHz, CDCl₃) 3.67 – 3.53 (2H, m, CH₂N), 3.14 – 2.95 (4H, m, COCH₂CH₂S and COCH₂CH₂S), 2.61 – 2.45 (2H, m, CH₂CON), 2.24 – 2.22 (3H, m, CH₃), 1.84 – 1.62 (2H, m, CH₂), 1.58 (2H, p, *J* = 6.6 Hz, CH₂), 1.44 – 1.18 (14H, m, CH₂); δ_{C} (100 MHz, CD₂Cl₃), 195.7 (COS), 176.5 (CON), 174.4 (COCH₂CH₂), 43.0 (CH₂N), 39.0 (COCH₂CH₂S), 35.9 (CH₂CON), 30.4 (CH₃), 25.8 (CH₂), 25.7 (CH₂), 25.6 (CH₂), 24.9 (CH₂), 24.5 (COCH₂CH₂S), 24.5 (CH₂), 24.4 (CH₂), 24.0 (CH₂), 23.8 (CH₂), 23.7 (CH₂); HRMS (ESI): calcd. for C₁₇H₂₉NNaO₃S, 350.1760. Found: [MNa]⁺, 350.1760 (0.1 ppm error).

Methyl 7-(3-sulfanylpropanamido)heptanoate (**25**) and methyl 7-[(2-[(7-methoxy-7-oxoheptyl)carbamoyl]ethyl)disulfanyl]propanamido]heptanoate (**26**)



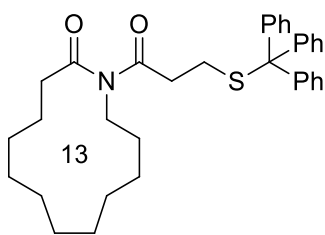
1-[3-(Acetylsulfanyl)propanoyl]azocan-2-one **21a** (25.7 mg, 0.100 mmol) was dissolved in MeOH (1 mL) and sparged for 5 min with argon to remove oxygen. To this stirring solution was added NaOH (4N aq., 0.03 mL, 1.2 eqv.) and the solution was stirred for 2 hours at RT. The reaction mixture was then acidified with HCl (10% aq.) to pH 1 and diluted with ethyl acetate (3 mL) and water (5 mL). This was then extracted with ethyl acetate (3 × 5 mL) and the organics washed with NaHCO₃ and sat. NaCl. The mixture was dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:1 ethyl acetate:

hexane → ethyl acetate → 1:19 methanol: ethyl acetate) afforded crude thiol **25** (containing 8% disulfide **26** in ^1H NMR) as an off white solid (4.7 mg, 19%) and disulfide **26** (as a 4.6:1 mixture of rotamers) as light yellow oil (4.0 mg, 16%);

Data for **25**: R_f 0.49 (9:1 ethyl acetate: methanol); δ_{H} (400 MHz, CDCl_3), 5.56 (1H, br s, NH), 3.65 (3H, s, CH_3), 3.25 (2H, q, $J = 6.8$ Hz, CH_2N), 2.80 (2H, dt, $J = 8.2, 6.7$ Hz, CH_2SH), 2.46 (2H, t, $J = 6.7$ Hz, CH_2CON), 2.29 (2H, t, $J = 7.5$ Hz, $\text{CH}_2\text{CO}_2\text{CH}_3$), 1.65 – 1.56 (3H, m, CH_2 and SH), 1.55 – 1.45 (2H, m, CH_2), 1.37 – 1.27 (4H, m, CH_2); δ_{C} (100 MHz, CDCl_3), 174.3 (CO_2CH_3), 170.7 (CON), 51.6 (CH_3), 40.6 (CH_2CON), 39.6 (CH_2N), 34.0 ($\text{CH}_2\text{CO}_2\text{CH}_3$), 29.5 (CH_2), 28.8 (CH_2), 26.6 (CH_2), 24.8 (CH_2), 20.6 (CH_2SH); HRMS (ESI): calcd. for $\text{C}_{11}\text{H}_{21}\text{NNaO}_3\text{S}$, 270.1134. Found: $[\text{MNa}]^+$, 270.1134 (0.0 ppm error).

Data for **26**: R_f 0.39 (9:1 ethyl acetate: methanol); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 3307, 2927, 2853, 1735, 1636, 1546, 1438, 1416, 1365, 1260, 1196, 1018, 800, 726; δ_{H} (400 MHz, CDCl_3) 5.98 (4H, br m, NH, both), 3.65 (12H, s, CH_3 , both rotamers), 3.24 (8H, td, $J = 7.1, 5.8$ Hz, CH_2N , both rotamers), 3.15 (4H, t, $J = 7.0$ Hz, CH_2S , minor), 2.97 (4H, dt, $J = 6.9$ Hz, CH_2S , major), 2.64 (4H, t, $J = 7.0$ Hz, CH_2CON , minor), 2.55 (4H, t, $J = 6.9$ Hz, CH_2CON , major), 2.29 (8H, t, $J = 7.5$ Hz, $\text{CH}_2\text{CO}_2\text{CH}_3$, both rotamers), 1.67 – 1.56 (8H, m, CH_2), 1.55 – 1.46 (8H, m, CH_2), 1.38 – 1.27 (16H, m, CH_2); Only one rotamer was clearly observable by ^{13}C NMR: δ_{C} (100 MHz, CDCl_3), 174.3 (CO_2CH_3), 171.0 (CON), 51.6 (CH_3), 39.6 (CH_2N), 35.9 (CH_2CON), 34.4 (CH_2S), 34.0 ($\text{CH}_2\text{CO}_2\text{CH}_3$), 29.4 (CH_2), 28.8 (CH_2), 26.6 (CH_2), 24.8 (CH_2); HRMS (ESI): calcd. for $\text{C}_{22}\text{H}_{40}\text{N}_2\text{NaO}_6\text{S}_2$, 515.2220. Found: $[\text{MNa}]^+$, 515.2224 (–0.8 ppm error).

1-[3-(Tritylthio)propanoyl]-1-azacyclotridecan-2-one (**31b**)

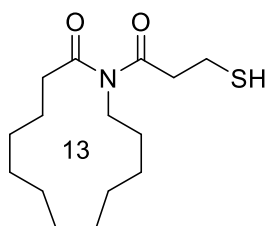


Oxalyl chloride (1.14 mL, 13.3 mmol) was added to a suspension of 3-(tritylthio)propanoic acid (1.57 g, 4.51 mmol) in toluene (45 mL), followed by a catalytic amount of DMF (4 drops). The resulting mixture was stirred at RT for 1 h and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride. The resulting 3-(tritylthio)propanoyl chloride **30** was added to a pre-stirred mixture of lauro lactam **21b** (577 mg, 2.92 mmol), DMAP (49.0 mg, 0.401 mmol) and pyridine (1.44 mL, 17.9 mmol) in DCM (50 mL) under an argon atmosphere. The reaction mixture was then heated to 50 °C and stirred for 18 hours. The mixture was then cooled, diluted with DCM (30 mL) and washed with 10% aq. HCl (90 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined

organic extracts dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , 1:19 ethyl acetate: hexane \rightarrow 1:9 ethyl acetate: hexane) afforded the *title compound* as a clear viscous oil (1.21 g, 78%)*; R_f 0.74 (1:9 methanol: ethyl acetate); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 2929, 2859, 1691, 1595, 1489, 1445, 1364, 1229, 1180, 1132, 1099, 1034, 909, 737, 699, 676, 620; δ_{H} (400 MHz, CDCl_3) 7.46–7.40 (5H, m, ArH), 7.34–7.18 (10H, m, ArH), 3.65–3.56 (2H, m, CH_2N), 2.70 (2H, t, $J = 6.9$ Hz, $\text{COCH}_2\text{CH}_2\text{S}$), 2.61–2.49 (2H, m, CH_2CON [overlapping]), 2.53 (2H, t, $J = 6.9$ Hz, $\text{COCH}_2\text{CH}_2\text{S}$ [overlapping]), 1.75 (2H, p, $J = 6.9$ Hz, CH_2), 1.65–1.56 (2H, m, CH_2), 1.48–1.25 (14H, m, CH_2); δ_{C} (100 MHz, CDCl_3), 176.8 (CON), 174.8 (COCH_2CH_2), 144.9 ($3 \times \text{ArC}$), 129.8 ($6 \times \text{ArCH}$), 128.0 ($6 \times \text{ArCH}$), 126.7 ($3 \times \text{ArCH}$), 66.9 (CPh_3), 43.1 (CH_2N), 38.2 (CH_2CON), 36.3 ($\text{COCH}_2\text{CH}_2\text{S}$), 27.3 ($\text{COCH}_2\text{CH}_2\text{S}$), 26.0 (CH_2), 25.9 (CH_2), 25.7 (CH_2), 25.1 (CH_2), 24.9 (CH_2), 24.7 (CH_2), 24.2 (CH_2), 24.1 (CH_2), 23.9 (CH_2); HRMS (ESI): calcd. for $\text{C}_{34}\text{H}_{41}\text{NNaO}_2\text{S}$, 550.2750. Found: $[\text{MNa}]^+$, 550.2753 (–0.5 ppm error).

*The purified product also contains traces of triphenylmethanol that we were unable to remove completely, although the purity of **31b** was sufficient for the product to be used in subsequent steps. Characteristic NMR data for triphenylmethanol can be seen at: δ_{C} (100 MHz, CDCl_3), 147.0 (ArC), 128.04 (ArCH), 127.37 (ArCH), 81.9 (Ph_3COH).

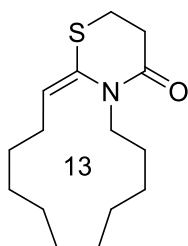
1-(3-Mercaptopropanoyl)azacyclotridecan-2-one (**32**)



To a solution of 1-(3-(tritylthio)propanoyl)azacyclotridecan-2-one **31b** (1.02 g, 1.94 mmol) in DCM (10 mL) under an argon atmosphere was added TFA (1.20 mL, 15.7 mmol) and the solution stirred for 3 min. Next, triisopropylsilane (0.550 mL, 2.69 mmol) was added and the solution stirred for a further 30 min. The mixture was then diluted with DCM (5 mL) and washed with water (20 mL). The aqueous layer was then extracted with DCM (3×10 mL) and the combined organic extracts dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , 1:19 ethyl acetate: hexane \rightarrow 1:9 ethyl acetate: hexane \rightarrow 1:1 ethyl acetate: hexane \rightarrow ethyl acetate \rightarrow 1:19 methanol: ethyl acetate) afforded the *title compound* as a yellow oil (268 mg, 48%), along with a small amount of compound **33** (38.0 mg, 7%; data for **33** is given below). Data for **32**: R_f 0.64 (1:1 ethyl acetate: hexane); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 2928, 2860, 1689, 1463, 1445, 1365, 1247, 1230, 1179, 1132, 1121, 1099, 1047, 762, 716, 605; δ_{H} (400 MHz, CDCl_3) 3.63–3.56 (2H, m, CH_2N), 3.03 (2H, t, $J = 6.6$ Hz, $\text{COCH}_2\text{CH}_2\text{SH}$), 2.71 (2H, dt, $J = 8.4, 6.6$ Hz, $\text{COCH}_2\text{CH}_2\text{SH}$), 2.53–2.47 (2H, m, CH_2CON), 1.73–1.64 (2H, m, CH_2), 1.63–

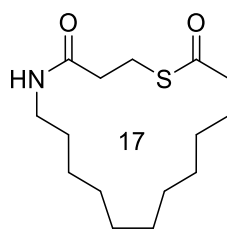
1.54 (2H, m, CH₂ [overlapping]), 1.58 (1H, t, *J* = 8.4 Hz, SH [overlapping]), 1.41–1.15 (14H, m, CH₂); δ_c (100 MHz, CDCl₃), 176.5 (CON), 174.3 (COCH₂CH₂), 42.9 (2 × CH₂ (CH₂N and COCH₂CH₂S)), 35.8 (CH₂CON), 25.8 (CH₂), 25.6 (CH₂), 25.5 (CH₂), 24.8 (CH₂), 24.5 (CH₂), 24.4 (CH₂), 24.0 (CH₂), 23.8 (CH₂), 23.6 (CH₂), 19.8 (COCH₂CH₂SH); HRMS (ESI): calcd. for C₁₅H₂₇NNaO₂S, 308.1655. Found: [MNa]⁺, 308.1646 (2.7 ppm error).

(E)-6,7,8,9,10,11,12,13,14,15-Decahydro-2H-[1,3]thiazino[3,2-a][1]azacyclotridecin-4(3H)-one (33)



Data for **33** (for synthesis see above): off white pasty solid; R_f 0.55 (ethyl acetate); ν_{max}/cm⁻¹ (thin film) 3317, 2927, 2856, 1651, 1549, 1443, 1355, 1258, 1117, 1028, 918, 733, 702, 605; δ_H (400 MHz, CDCl₃), 5.47 (1H, t, *J* = 7.8 Hz, CHCH₂), 3.82–3.74 (2H, m, CH₂N), 3.01–2.96 (2H, m, COCH₂CH₂S), 2.71–2.65 (2H, m, COCH₂CH₂S), 2.22–2.15 (2H, m, CHCH₂), 1.69–1.58 (2H, m, CH₂), 1.54–1.45 (2H, m, CH₂), 1.38–1.24 (12H, m, 6 × CH₂); δ_c (100 MHz, CDCl₃), 169.8 (CON), 133.0 (C quat), 121.1 (CHCH₂), 46.2 (CH₂N), 35.5 (COCH₂CH₂S), 28.7 (CHCH₂), 27.4 (CH₂), 27.2 (CH₂), 25.6 (CH₂), 25.5 (CH₂), 25.3 (CH₂), 25.1 (CH₂), 24.80 (CH₂), 24.75 (COCH₂CH₂S), 24.1 (CH₂); HRMS (ESI): calcd. for C₁₅H₂₅NNaOS, 290.1549. Found: [MNa]⁺, 290.1546 (1.1 ppm error).

1-Thia-5-azacycloheptadecane-4,17-dione (24b)

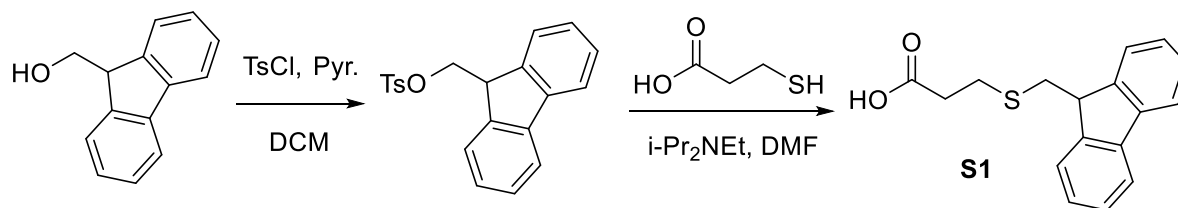


To a solution of 1-(3-(tritylthio)propanoyl)azacyclotridecan-2-one **31b** (1.02 g, 1.93 mmol) in DCM (20 mL) under an argon atmosphere was added TFA (1.95 mL, 25.5 mmol) and the solution stirred for 3 min. Next, triisopropylsilane (0.44 mL, 2.15 mmol) was added and the solution stirred for a further 30 min. The solvent and TFA were removed *in vacuo*. The crude material was then re-dissolved in DCM (20 mL) and DBU (2.87 mL, 19.3 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. The reaction mixture was then diluted with DCM (20 mL) and washed with 10% aq. HCl (50 mL). The aqueous layer was then extracted with DCM (3 × 50 mL) and the

combined organic extracts dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , 1:9 ethyl acetate: hexane \rightarrow 1:4 ethyl acetate: hexane \rightarrow 1:1 ethyl acetate: hexane \rightarrow ethyl acetate) afforded the *title compound* as a white crystalline solid (307 mg, 56%), along with a small amount of lauro lactam **21b** (13.3 mg, 4%). Data for **24b**: m.p. 88–95°C; R_f 0.17 (1:1 ethyl acetate: hexane); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 3299, 2927, 2856, 1684, 1647, 1555, 1459, 1355, 1261, 1203, 1026, 717; δ_{H} (400 MHz, CDCl_3) 5.88 (1H, br s, NH), 3.31–3.23 (2H, m, CH_2NH), 3.17–3.09 (2H, m, CH_2SCO), 2.55–2.47 (4H, m, $\text{COCH}_2\text{CH}_2\text{S}$ and CH_2COS), 1.64 (2H, apparent pentet, $J = 7.0$ Hz, CH_2), 1.51–1.40 (2H, m, CH_2), 1.37–1.18 (14H, m, $7 \times \text{CH}_2$); δ_{C} (100 MHz, CDCl_3): 201.1 (SCO), 171.0 (CO), 43.7 (CH_2COS), 39.4 (CH_2NH), 36.1 ($\text{COCH}_2\text{CH}_2\text{S}$), 28.8 (CH_2), 27.5 (CH_2), 27.43 (CH_2), 27.40 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 26.4 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 25.0 (CH_2); HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{27}\text{NNaO}_2\text{S}$, 308.1655. Found: $[\text{MNa}]^+$, 308.1646 (2.9 ppm error). For X-ray crystallographic data see CCDC 2040347.

The same product **24b** was also prepared using the S-Fm strategy- see compound **37** on pages 12 and 13.

3-(((9H-Fluoren-9-yl)methyl)thio)propanoic acid (**S1**)

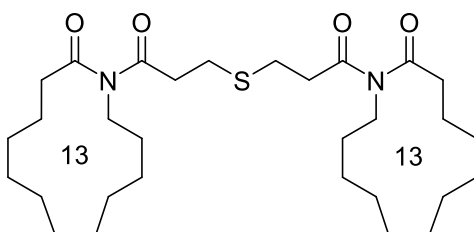


Tosyl chloride (19.6 g, 100 mmol) in anhydrous pyridine (16.1 mL) was added slowly to a solution of 9-fluorenylmethanol (19.6 g, 100 mmol) in CHCl_3 (100 mL) at 0 °C. After stirring for 2 h, the solution was washed with 10% aq. NaHCO_3 (2 \times 25 mL), and brine (2 \times 25 mL) and dried over anhydrous MgSO_4 . After filtration, the solvent was removed *in vacuo*. The product was recrystallized by dissolving in CHCl_3 and adding hexane until loss of transparency in the solution was starting to become apparent. At this point, the mixture was left to stand at room temperature overnight to crystallize. The crystals were filtered by vacuum filtration to yield fluorenylmethyl *p*-toluenesulfonate (26.8 g, 76%); δ_{H} (400 MHz, CDCl_3) 7.78–7.69 (4H, m, ArH), 7.53 (2H, dt, $J = 7.5, 1.0$ Hz, ArH), 7.68 (2H, td, $J = 7.5, 1.0$ Hz, ArH), 7.32–7.23 (4H, m, ArH), 4.28–4.18 (3H, m, CH and CH_2), 2.41 (3H, s, CH_3); δ_{C} (100 MHz, CDCl_3) 145.0 (ArC), 142.6 (2 \times ArC), 141.3 (2 \times ArC), 132.8 (ArC), 130.0 (2 \times ArCH), 128.2 (2 \times ArCH), 128.0 (2 \times ArCH), 127.3 (2 \times ArCH), 125.3 (2 \times ArCH), 120.2 (2 \times ArCH), 72.0 (CH_2), 46.8 (CH), 21.8 (CH_3).⁸

To a solution of 3-thiopropionic acid (2.48 mL, 28.5 mmol) and fluorenyl methanol *p*-toluenesulfonate (9.99 g, 28.5 mmol) in DMF (50 mL) was added $i\text{-Pr}_2\text{NEt}$ (9.93 mL, 57.0 mmol). The reaction was stirred

at room temperature for 16 h and DMF was removed under reduced pressure (high vacuum). The residue was dissolved in ethyl acetate (300 mL), washed with 0.2N aq. HCl (5 × 100 mL), sat. aq. NaHCO₃ (2 × 100 mL), water (100 mL), brine (100 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the crude material was then suspended in chloroform and filtered to remove insoluble material (2 × 150 mL). The combined chloroform fractions were then concentrated and the solvent removed *in vacuo* to afford the *title compound* **S1** as a yellow solid (3.85 g, 48%); R_f 0.27 (ethyl acetate); m.p. 91–95 °C; $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3039, 2912, 1706, 1477, 1448, 1263, 1197, 940, 739, 621; δ_{H} (400 MHz, CDCl₃) 7.76 (2H, dt, $J = 7.6, 1.0$ Hz, ArH), 7.68 (2H, dq, $J = 7.5, 1.0$ Hz, ArH), 7.40 (2H, tt, $J = 7.6, 1.0$ Hz, ArH), 7.32 (2H, td, $J = 7.5, 1.0$ Hz, ArH), 4.12 (1H, t, $J = 6.4$ Hz, SCH₂CH), 3.11 (2H, d, $J = 6.4$ Hz, SCH₂CH), 2.80 (2H, t, $J = 7.3$ Hz, CH₂CH₂S), 2.63 (2H, t, $J = 7.3$ Hz, CH₂CH₂S); δ_{C} (100 MHz, CDCl₃) 177.6 (COOH), 146.0 (2 × ArC), 141.2 (2 × ArC), 127.8 (2 × ArCH), 127.2 (2 × ArCH), 124.9 (2 × ArCH), 120.1 (2 × ArCH), 47.0 (SCH₂CH), 36.9 (SCH₂CH), 34.7 (CH₂CH₂S), 27.9 (CH₂CH₂S); HRMS (ESI): calcd. for C₁₇H₁₆NaO₂S, 307.0763. Found: [MNa]⁺, 307.0763 (0.2 ppm error). The synthetic procedure was adapted from a literature report.⁹

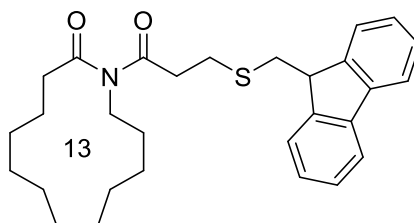
1,1'-(3,3'-Thiobis(propanoyl))bis(azacyclotridecan-2-one) (**37**)



A mixture of lauro lactam (98.1 mg, 0.497 mmol), DMAP (7.4 mg, 0.061 mmol) and pyridine (0.24 mL, 3.00 mmol) in DCM (10 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **34** (1.66 mmol, prepared from **S1** using the general procedure) in DCM (5 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. TLC analysis indicated that acylation was incomplete at this stage, therefore, an additional acylation reaction was performed. Thus, the reaction mixture was dissolved in DCM (15 mL) and to it was added DMAP (11.8 mg, 0.097 mmol) and pyridine (0.240 mL, 3.00 mmol). Then, another solution of acid chloride **34** (1.70 mmol, prepared from **S1** using the general procedure) in DCM (15 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.75 mL, 5.00 mmol) was added, followed

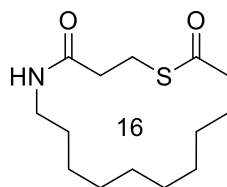
by stirring at RT for 18 h, before the solvent was removed *in vacuo*. The crude product was dry loaded onto Celite and purified by automated flash column chromatography (using a 24 g pre-packed SiO₂ column, 0% → 100% ethyl acetate in hexanes) affording 17-membered ring thiolactone **24b** (76.7 mg, 54%; for data see pages 10 and 11) and the *title compound* **37** as a yellow crystalline solid (40.0 mg, 30%). Data for **37**: m.p. 53–59 °C; R_f 0.73 (ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2928, 2860, 1689, 1463, 1446, 1363, 1243, 1179, 1121, 1099, 1047, 916, 732, 647; δ_{H} (400 MHz, CDCl₃) 3.70–3.62 (4H, m, CH₂N), 3.08 (4H, t, $J = 7.2$ Hz, CH₂), 2.83 (4H, t, $J = 7.2$ Hz, CH₂), 2.60–2.53 (4H, m, CH₂CON), 1.80–1.71 (4H, m, CH₂), 1.70–1.60 (4H, m, CH₂), 1.50–1.22 (28H, m, CH₂); δ_{C} (100 MHz, CDCl₃), 176.9 (2 × CON), 174.9 (2 × COCH₂CH₂), 43.2 (2 × CH₂N), 39.4 (2 × CH₂), 36.1 (2 × CH₂CON), 27.6 (2 × CH₂), 26.0 (2 × CH₂), 25.8 (2 × CH₂), 25.7 (2 × CH₂), 25.0 (2 × CH₂), 24.6 (4 × CH₂), 24.2 (2 × CH₂), 24.0 (2 × CH₂), 23.8 (2 × CH₂); HRMS (ESI): calcd. for C₃₀H₅₂N₂NaO₄S, 559.3540. Found: [MNa]⁺, 559.3543 (–0.5 ppm error).

1-(3-(((9H-Fluoren-9-yl)methyl)thio)propanoyl)azacyclotridecan-2-one (35b)



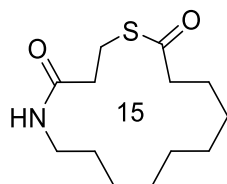
A mixture of lauro lactam (198 mg, 1.00 mmol), DMAP (14.4 mg, 0.118 mmol) and pyridine (0.48 mL, 5.99 mmol) in DCM (10 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **34** (1.50 mmol, prepared from **S1** using the general procedure) in DCM (10 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. Purification by flash column chromatography (SiO₂, 1:9 ethyl acetate: hexane → 1:3 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 3:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a yellow-white solid (380 mg, 82%); R_f 0.31 (1:4 ethyl acetate: hexane); m.p. 79–85 °C; $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2930, 2851, 1689, 1447, 1364, 1244, 1179, 1121, 907, 726, 647, 621, 580; δ_{H} (400 MHz, CDCl₃) 7.75 (2H, dt, $J = 7.6, 1.0$ Hz, ArH), 7.68 (2H, dq, $J = 7.4, 1.0$ Hz, ArH), 7.40 (2H, tt, $J = 7.6, 1.0$ Hz, ArH), 7.32 (2H, td, $J = 7.4, 1.0$ Hz, ArH), 4.12 (1H, t, $J = 6.6$ Hz, SCH₂CH), 3.70–3.62 (2H, m, CH₂N), 3.12–3.06 (4H, m, COCH₂CH₂S and SCH₂CH), 2.89 (4H, t, $J = 7.1$ Hz, COCH₂CH₂S), 2.60–2.52 (2H, m, CH₂CON), 1.82–1.73 (2H, m, CH₂), 1.70–1.61 (2H, m, CH₂), 1.50–1.24 (14H, m, 7 × CH₂); δ_{C} (100 MHz, CDCl₃) 176.8 (CON), 174.8 (COCH₂CH₂), 146.2 (2 × ArC), 141.1 (2 × ArC), 127.6 (2 × ArCH), 127.1 (2 × ArCH), 125.0 (2 × ArCH), 119.9 (2 × ArCH), 47.0 (SCH₂CH), 43.1 (CH₂N), 39.4 (COCH₂CH₂S), 37.0 (SCH₂CH), 36.0 (CH₂CON), 28.4 (COCH₂CH₂S), 25.9 (CH₂), 25.8 (CH₂), 25.7 (CH₂), 24.9 (CH₂), 24.6 (CH₂), 24.5 (CH₂), 24.2 (CH₂), 24.0 (CH₂), 23.7 (CH₂); HRMS (ESI): calcd. for C₂₉H₃₈NO₂S, 464.2618. Found: [MH]⁺, 464.2617 (0.2 ppm error).

1-Thia-5-azacyclohexadecane-4,16-dione (24c)



A mixture of azacyclododecan-2-one¹⁰ (27.5 mg, 0.150 mmol), DMAP (1.8 mg, 0.015 mmol) and pyridine (73 μ L, 0.90 mmol) in DCM (1 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **34** (0.469 mmol, prepared from **S1** using the general procedure) in DCM (2 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (5 mL) and washed with 10% aq. HCl (5 mL). The aqueous layer was then extracted with DCM (3 \times 5 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. The mixture was then re-dissolved in DCM (3 mL) and DBU (0.22 mL, 1.50 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed under a flow of nitrogen gas. Purification by flash column chromatography (SiO₂, hexane \rightarrow 1:19 ethyl acetate: hexane \rightarrow 1:9 ethyl acetate: hexane \rightarrow 1:2 ethyl acetate: hexane \rightarrow 1:1 ethyl acetate: hexane \rightarrow 2:1 ethyl acetate: hexane \rightarrow ethyl acetate) afforded the *title compound* as a yellow crystalline solid (15.2 mg, 37%); m.p. 76–83 °C; R_f 0.38 (ethyl acetate); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 3302, 2927, 2856, 1682, 1647, 1552, 1448, 1373, 1259, 1161, 1019, 733, 585; δ_{H} (400 MHz, CDCl₃) 5.53 (1H, br s, NH), 3.33–3.26 (2H, m, CH₂NH), 3.21–3.13 (2H, m, CH₂SCO), 2.58–2.53 (2H, m, CH₂COS), 2.52–2.47 (2H, m, COCH₂CH₂S), 1.74–1.66 (2H, m, CH₂), 1.54–1.46 (2H, m, CH₂), 1.36–1.27 (2H, m, 6 \times CH₂); δ_{C} (100 MHz, CDCl₃) 200.8 (SCO), 170.6 (CO), 43.0 (CH₂COS), 39.3 (CH₂NH), 36.2 (COCH₂CH₂S), 28.6 (CH₂), 27.4 (CH₂), 26.81 (CH₂), 26.79 (CH₂), 26.71 (CH₂), 26.4 (CH₂), 25.3 (CH₂), 25.2 (CH₂), 25.0 (CH₂); HRMS (ESI): calcd. for C₁₄H₂₅NNaO₂S, 294.1498. Found: [MNa]⁺, 294.1499 (–0.4 ppm error).

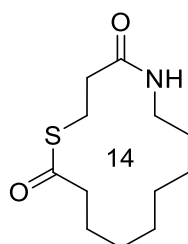
1-Thia-5-azacyclopentadecane-4,15-dione (24d)



A mixture of azacycloundecan-2-one¹⁰ (86.7 mg, 0.512 mmol), DMAP (6.8 mg, 0.056 mmol) and pyridine (0.240 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **34** (1.51 mmol, prepared from **S1** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture

was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.75 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO₂, 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded the *title compound* as a yellow crystalline solid (40.8 mg, 31%); m.p. 102–104 °C; R_f 0.34 (ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3299, 3089, 2928, 2856, 1680, 1646, 1552, 1442, 1398, 1355, 1258, 1202, 1140, 1008, 960, 919, 732, 583; δ_{H} (400 MHz, CDCl₃) 5.53 (1H, br s, NH), 3.33–3.26 (2H, m, CH₂NH), 3.17–3.12 (2H, m, CH₂SCO), 2.58–2.51 (4H, m, CH₂COS and COCH₂CH₂S), 1.73–1.64 (2H, m, CH₂), 1.56–1.48 (2H, m, CH₂), 1.42–1.22 (10H, m, 5 × CH₂); δ_{C} (100 MHz, CDCl₃) 201.3 (SCO), 170.6 (CO), 43.1 (CH₂COS), 38.7 (CH₂NH), 35.3 (COCH₂CH₂S), 28.3 (CH₂), 27.3 (CH₂), 26.5 (CH₂), 26.42 (CH₂), 26.39 (CH₂), 26.0 (CH₂), 25.5 (CH₂), 24.3 (CH₂); HRMS (ESI): calcd. for C₁₃H₂₃NNaO₂S, 280.1342. Found: [MNa]⁺, 280.1344 (−0.9 ppm error).

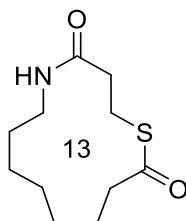
1-Thia-5-azacyclotetradecane-4,14-dione (24e)



A mixture of azacyclodecan-2-one¹⁰ (77.6 mg, 0.500 mmol), DMAP (6.4 mg, 0.052 mmol) and pyridine (0.24 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **34** (1.51 mmol, prepared from **S1** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.75 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO₂, hexane → 1:19 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded the *title compound* as a yellow crystalline solid (26.7 mg, 22%); m.p. 55–61 °C; R_f 0.31 (ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3304, 2929, 2858, 1679, 1649, 1551, 1444, 1376, 1258, 1168, 1043, 920, 731, 595; δ_{H} (400 MHz, CDCl₃) 5.69 (1H, br s, NH), 3.30–3.24 (2H, m, CH₂NH), 3.20–3.14 (2H, m,

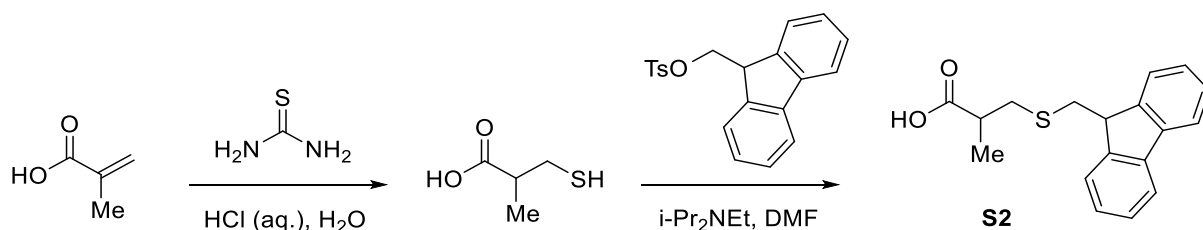
CH₂SCO), 2.58–2.52 (4H, m, 2 × CH₂ (CH₂COS and COCH₂CH₂S), 1.77–1.59 (4H, m, 2 × CH₂), 1.47–1.31 (8H, m, 4 × CH₂); δ_c (100 MHz, CDCl₃) 201.4 (SCO), 170.6 (CO), 43.9 (CH₂COS), 39.1 (CH₂NH), 35.5 (COCH₂CH₂S), 28.0 (CH₂), 25.7 (CH₂), 25.45 (CH₂), 25.36 (CH₂), 25.29 (CH₂), 25.26 (CH₂), 23.2 (CH₂); HRMS (ESI): calcd. for C₁₂H₂₂NO₂S, 244.1366. Found: [MH]⁺, 244.1362 (1.4 ppm error).

1-Thia-5-azacyclotridecane-4,13-dione (24f)



A mixture of azonan-2-one¹⁰ (87.1 mg, 0.617 mmol), DMAP (8.5 mg, 0.070 mmol) and pyridine (0.240 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **34** (1.51 mmol, prepared from **51** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.75 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO₂, 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a yellow crystalline solid (66.9 mg, 47%); m.p. 129–131 °C; R_f 0.19 (ethyl acetate); ν_{max}/cm⁻¹ (thin film) 3243, 3080, 2924, 2857, 1678, 1634, 1562, 1459, 1434, 1412, 1360, 1286, 1269, 1204, 1174, 1151, 1123, 1042, 1018, 983, 960, 901, 853, 802, 771, 731, 690, 622, 604, 464; δ_H (400 MHz, CDCl₃) 5.93 (1H, br s, NH), 3.27–3.20 (2H, m, CH₂NH), 3.19–3.13 (2H, m, CH₂SCO), 2.65–2.56 (2H, m, COCH₂CH₂S), 2.54–2.45 (2H, m, CH₂COS), 1.78–1.67 (2H, m, CH₂), 1.55–1.47 (2H, m, CH₂), 1.39 (2H, apparent p, J = 6.5 Hz, CH₂), 1.34–1.25 (4H, m, 2 × CH₂); δ_c (100 MHz, CDCl₃) 201.6 (SCO), 170.3 (CO), 44.3 (CH₂COS), 39.6 (CH₂NH), 35.6 (COCH₂CH₂S), 27.9 (CH₂), 27.4 (2 × CH₂), 25.5 (CH₂), 25.1 (CH₂), 24.5 (CH₂); HRMS (ESI): calcd. for C₁₁H₂₀NO₂S, 230.1209. Found: [MH]⁺, 230.1209 (0.1 ppm error).

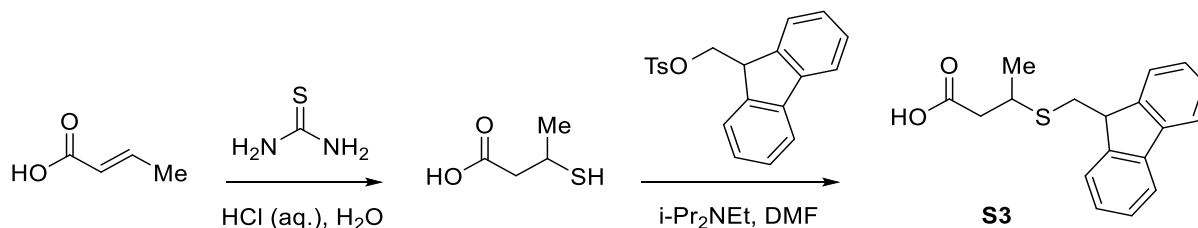
3-(((9H-Fluoren-9-yl)methyl)thio)-2-methylpropanoic acid (**S2**)



A solution of thiourea (2.65 g, 34.5 mmol), water (5 mL), and concentrated aq. HCl (37%, 3.16 mL) was stirred at 45 °C for 30 min. To this was added methacrylic acid (2.50 g, 2.46 mL) dropwise over 30 min and the temperature was then raised to 90 °C for 2 h with stirring. An aqueous solution of NaOH (4.03 g in 5 mL H₂O) was prepared and added dropwise over 30 min. The reaction mixture was stirred for 30 min and allowed to cool to RT. Concentrated HCl was added to adjust the pH to 5–6 and the reaction mixture extracted using ethyl acetate (3 × 10 mL). The combined organic fractions were collected and the solvent removed *in vacuo* to afford 3-mercapto-2-methylpropanoic acid as a yellow oil which was used without further purification (559 mg, 16%). [Data for 3-mercapto-2-methylpropanoic acid: R_f 0.47 (ethyl acetate); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 2976, 2936, 1701, 1622, 1461, 1412, 1236, 1185, 1118, 1075, 918, 831, 620, 525; δ_{H} (400 MHz, CDCl₃) 12.04 (1H, s, COOH), 2.81–2.56 (3H, m, CH and CH₂), 1.55 (1H, t, J = 8.5 Hz, SH), 1.25 (3H, d, J = 6.8 Hz, CH₃); δ_{C} (100 MHz, CDCl₃) 181.5 (COOH), 43.5 (CH), 27.5 (CH₂), 16.3 (CH₃); HRMS (ESI): calcd. for C₄H₇O₂S, 119.0172 Found: [M-H]⁻, 119.0170 (1.6 ppm error)]. To a solution of 3-mercapto-2-methylpropanoic acid (457 mg, 3.81 mmol) and fluorenyl methanol p-toluenesulfonate (1.41 g, 4.02 mmol- see **S1** for its preparation) in DMF (7 mL) was added *i*-Pr₂NEt (1.39 mL, 8.00 mmol). The reaction was stirred at room temperature for 25 h. The reaction mixture was dissolved in ethyl acetate (40 mL), washed with 0.2N aq. HCl (5 × 15 mL), sat. aq. NaHCO₃ (2 × 15 mL), water (15 mL), brine (15 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the crude material was then suspended in chloroform and filtered to remove insoluble material (2 × 10 mL). The combined chloroform fractions were concentrated and solvent removed *in vacuo* to afford the *title compound* **S2** as an orange solid (637 mg, 56%); R_f 0.40 (ethyl acetate); m.p. 59–70 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 2933, 1704, 1610, 1477, 1448, 1294, 1232, 1101, 1006, 919, 765, 734, 621; δ_{H} (400 MHz, CDCl₃) 7.81–7.61 (4H, m, ArH), 7.44–7.27 (4H, m, ArH), 4.10 (1H, t, J = 6.5 Hz, SCH₂CH), 3.14–3.02 (2H, m, SCH₂CH), 2.89 (1H, dd, J = 12.8, 6.8 Hz, CH(CH₃)CHH'), 2.69 (1H, apparent sextet, J = 6.9 Hz, CH(CH₃)CHH'), 2.60 (1H, dd, J = 12.8, 6.8 Hz, CH(CH₃)CHH'), 1.25 (3H, d, J = 6.9 Hz, CH₃); δ_{C} (100 MHz, CDCl₃) 181.1 (COOH), 146.1 (2 × ArC), 141.1 (2 × ArC), 127.7 (2 × ArCH), 127.1 (2 × ArCH), 125.0 (ArCH), 124.9 (ArCH), 120.0 (2 × ArCH), 47.0 (SCH₂CH), 40.2 ((CH(CH₃)CH₂),), 37.2 (SCH₂CH), 36.3 (CH(CH₃)CH₂), 16.7 (CH₃); HRMS (ESI): calcd. for C₁₈H₁₈NaO₂S, 321.0920. Found:

[MNa]⁺, 321.0917 (1.0 ppm error). The synthetic procedure was adapted from a method reported in a patent.^{11a}

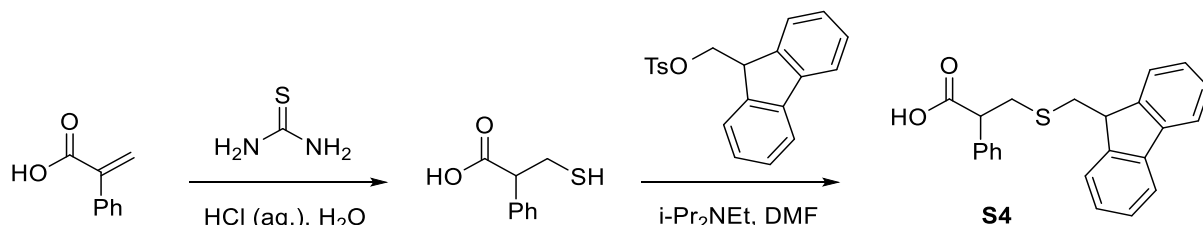
3-(((9H-Fluoren-9-yl)methyl)thio)-butanoic acid (**S3**)



A solution of thiourea (1.75 g, 23.0 mmol), water (25 mL), and concentrated HCl (37%, 15.8 mL) was stirred at 45 °C for 30 min. To this was added crotonic acid (12.5 g, 145 mmol) and the temperature was then raised to 90 °C for 2 h. An aqueous solution of NaOH (20 g in 25 mL of H₂O) was prepared and added dropwise over 30 min. The reaction mixture was stirred for 30 min and allowed to cool to RT. Concentrated aq. HCl was added to adjust the pH to 5–6 and the reaction mixture extracted using ethyl acetate (3 × 50 mL). The combined organic fractions were collected, and the solvent removed *in vacuo* to afford 3-mercapto-butanoic acid as a yellow oil which was used without further purification (14.6 g, 84%) [Data for 3-mercapto-butanoic acid: R_f 0.33 (ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2969, 2926, 1704, 1408, 1380, 1296, 1263, 1228, 1176, 1115, 1086, 1028, 917, 886, 691, 642, 488; δ_{H} (400 MHz, CDCl₃) 10.47 (1H, s, COOH), 3.42–3.29 (1H, m, CH), 2.72–2.57 (2H, m, CH₂), 1.86 (1H, t, *J* = 6.9 Hz, SH), 1.39 (3H, d, *J* = 6.9 Hz, CH₃); δ_{C} (100 MHz, CDCl₃) 177.5 (COOH), 45.7 (CH₂), 31.0 (CH), 24.9 (CH₃); HRMS (ESI): calcd. for C₄H₇O₂S, 119.0172 Found: [M-H]⁻, 119.0171 (1.1 ppm error)]. To a solution of 3-mercapto-butanoic acid (484 mg, 4.03 mmol) and fluorenyl methanol p-toluenesulfonate (1.40 g, 4.03 mmol- see **S1** for its preparation) in DMF (7.0 mL) was added ⁱPr₂NEt (1.39 mL, 8.06 mmol). The reaction was stirred at room temperature for 17 h. The reaction mixture was dissolved in ethyl acetate (40 mL), washed with 0.2N aq. HCl (5 × 15 mL), sat. aq. NaHCO₃ (2 × 15 mL), water (15 mL), brine (15 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure to afford the *title compound* as a yellow solid (582 mg, 48%); R_f 0.51 (ethyl acetate); m.p. 140–152 °C; $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2916, 1706, 1477, 1447, 1374, 1293, 1241, 1166, 1100, 1021, 938, 726, 637, 621, 571; δ_{H} (400 MHz, CDCl₃) 7.77–7.64 (4H, m, ArH), 7.43–7.27 (4H, m, ArH), 4.11 (1H, t, *J* = 6.6 Hz, SCH₂CH), 3.29–3.18 (1H, m, CHH'CH(CH₃)), 3.10 (2H, d, *J* = 6.6 Hz, SCH₂CH), 2.67 (1H, dd, *J* = 15.9, 6.4 Hz, CHH'CH(CH₃)), 2.51 (1H, dd, *J* = 15.9, 8.0 Hz, CHH'CH(CH₃)), 1.34 (3H, d, *J* = 6.8 Hz, CH₃); δ_{C} (100 MHz, CDCl₃) 176.0 (COOH), 146.1 (2 × ArC), 141.1 (2 × ArC), 127.7 (2 × ArCH), 127.2 (2 × ArCH), 125.00 (ArCH), 124.97 (ArCH), 120.0 (2 × ArCH), 47.0 (SCH₂CH), 42.0 (CH₂CH(CH₃)), 37.2 (CH₂CH(CH₃)), 35.4 (SCH₂CH), 21.6

(CH₃); HRMS (ESI): calcd. for C₁₈H₁₈NaO₂S, 321.0920. Found: [MNa]⁺, 321.0926 (–2.0 ppm error). The synthetic procedure was adapted from a method reported in a patent.^{11a}

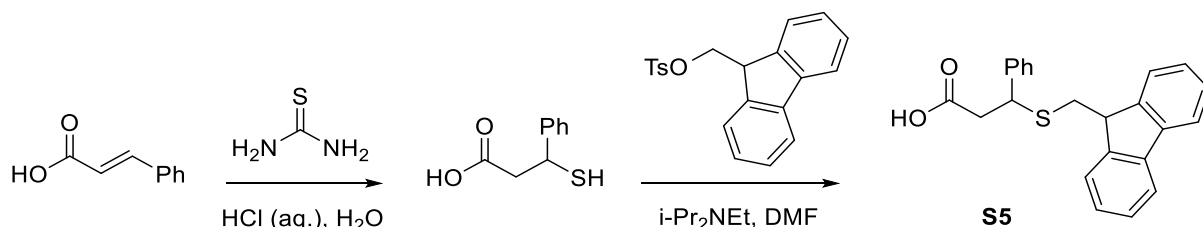
3-(((9H-Fluoren-9-yl)methyl)thio)-2-phenylpropanoic acid (**S4**)



A solution of thiourea (13.3 g, 174 mmol), water (25 mL), and concentrated aq. HCl (37%, 15.8 mL) was stirred at 45 °C for 30 min. To this was added atropic acid (2.96 g, 30.0 mmol) and the temperature was then raised to 90 °C for 2 h. An aqueous solution of NaOH (20 g in 25 mL of H₂O) was prepared and added dropwise over 30 min. The reaction mixture was stirred for 30 min and allowed to cool to RT. Concentrated HCl was added to adjust the pH to 5–6 and the reaction mixture extracted using ethyl acetate (3 × 50 mL). The combined organic fractions were collected and the solvent removed *in vacuo* to afford 3-mercapto-2-phenylpropanoic acid as a white paste which was used without further purification (3.72 g, 70%) [Data for 3-mercapto-2-phenylpropanoic acid: R_f 0.37 (ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3019, 2259, 1705, 1601, 1496, 1455, 1419, 1277, 1242, 1180, 1005, 924, 717, 697, 645, 615, 503; δ_{H} (400 MHz, CDCl₃) 9.81 (1H, s, COOH), 7.40 – 7.22 (5H, m, ArH), 3.77 (1H, dd, *J* = 9.0, 6.4 Hz, CH), 3.15 (1H, dt, *J* = 13.8, 9.0 Hz, CHCHH'SH), 2.84 (1H, ddd, *J* = 13.8, 7.9, 6.4 Hz, CHCHH'SH), 1.54 (1H, dd, *J* = 9.0, 7.9 Hz, SH); δ_{C} (100 MHz, CDCl₃) 178.2 (COOH), 136.9 (ArC), 129.1 (2 × ArCH), 128.3 (ArCH), 128.1 (2 × ArCH), 55.8 (CH), 27.2 (CH₂); HRMS (ESI): calcd. for C₉H₉O₂S, 181.0329 Found: [M-H]⁻, 181.0324 (2.4 ppm error)]. To a solution of 3-mercapto-2-phenylpropanoic acid (1.46 g, 8.00 mmol) and fluorenyl methanol p-toluenesulfonate (2.82 g, 8.04 mmol- see **S1** for its preparation) in DMF (14 mL) was added ⁱPr₂NEt (2.78 mL, 16.0 mmol). The reaction was stirred at room temperature for 16 h. The reaction mixture was dissolved in ethyl acetate (80 mL), washed with 0.2N HCl (5 × 30 mL), sat. NaHCO₃ (2 × 30 mL), water (30 mL), brine (30 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure. The combined organics were concentrated and solvent removed *in vacuo* to afford the *title compound* as a yellow solid (1.93 g, 67%); R_f 0.45 (ethyl acetate); m.p. 69–85 °C; $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3052, 1714, 1611, 1450, 1012, 736; δ_{H} (400 MHz, CDCl₃) 7.73 (2H, dt, *J* = 7.5, 0.9 Hz, ArH), 7.61 (2H, ddt, *J* = 13.8, 7.5, 0.9 Hz, ArH), 7.44–7.24 (9H, m, ArH), 4.04 (1H, t, *J* = 6.6 Hz, SCH₂CH), 3.77 (1H, dd, *J* = 8.9, 6.4 Hz, CH(Ph)CHH'), 3.23 (1H, dd, *J* = 13.3, 8.9 Hz, CH(Ph)CHH'), 3.06–2.95 (2H, m, SCH₂CH), 2.88 (1H, dd, *J* = 13.3, 6.4 Hz, CH(Ph)CHH'); δ_{C} (100 MHz, CDCl₃) 177.7 (COOH), 146.1 (ArC), 146.0 (ArC), 141.1 (2 × ArC), 137.4 (ArC), 129.0 (2 × ArCH), 128.1 (3 × ArCH), 127.7

(2 × ArCH), 127.2 (ArCH), 127.1 (ArCH), 125.0 (2 × ArCH), 120.0 (2 × ArCH), 52.5 ((CH(Ph)CH₂), 46.9 (SCH₂CH), 37.3 (SCH₂CH), 36.0 (CH(Ph)CH₂); HRMS (ESI): calcd. for C₂₃H₁₉O₂S, 359.1111. Found: [M-H]⁻, 359.1118 (-1.9 ppm error). The synthetic procedure was adapted from a method reported in a patent.^{11a}

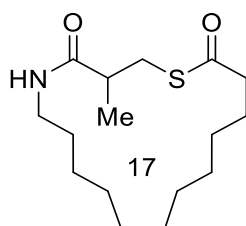
3-(((9H-Fluoren-9-yl)methyl)thio)-3-phenylpropanoic acid (S5)



A solution of thiourea (12.2 g, 160 mmol), water (80 mL), and concentrated aq. HCl (37%, 70.4 mL) was stirred at 120 °C for 2 h. The reaction mixture was then cooled to RT. *Trans*-cinnamic acid (5.92 g, 40 mmol) was added and the temperature was then raised back to 120 °C and stirred for 18 h, before the reaction mixture was then cooled to 0 °C. An aqueous solution of NaOH (62.6 g in 244 mL H₂O) was prepared and added dropwise at 0 °C until the pH was 14. The reaction mixture was stirred and heated to 90 °C for 1.5 h and then was cooled to 0 °C. Concentrated aq. HCl was added to adjust the pH to 5–6 and the reaction mixture extracted using toluene (3 × 100 mL). The combined organic fractions were collected, washed with water (300 mL), dried over anhydrous MgSO₄, filtered, and the solvent removed *in vacuo* to afford a sample that is predominantly made up of *3-mercapto-3-phenylpropanoic acid*, contaminated with a small amount (*ca.* 20%) *trans*-cinnamic acid, as a white solid, with this mixture was used without further purification (5.21 g of material isolated). [Data for *3-mercapto-3-phenylpropanoic acid*: R_f 0.33 (ethyl acetate); δ_H (400 MHz, CDCl₃) 11.21 (1H, s, COOH), 7.40–7.17 (5H, m, ArH), 4.50 (1H, ddd, *J* = 8.0, 7.0, 6.1 Hz, CH), 3.10–3.05 (2H, m, CH₂), 2.30 (1H, t, *J* = 6.1 Hz, SH); HRMS (ESI): calcd. for C₉H₉O₂S, 181.0329 Found: [M-H]⁻, 181.0329 (1.1 ppm error)]. To a portion of this mixture (calculated to contain 1.19 g, 6.54 mmol, of *3-mercapto-3-phenylpropanoic acid*) and fluorenyl methanol *p*-toluenesulfonate (2.33 g, 6.64 mmol- see **S1** for its preparation) in DMF (12 mL) was added ⁱPr₂NEt (2.31 mL, 13.3 mmol). The reaction was stirred at room temperature for 72 h. The reaction mixture was dissolved in ethyl acetate (65 mL), washed with 0.2N aq. HCl (5 × 25 mL), sat. aq. NaHCO₃ (2 × 25 mL), water (25 mL), brine (25 mL) and dried over anhydrous Na₂SO₄. The combined organics were concentrated and solvent removed *in vacuo* to afford the *title compound* as a light orange solid (1.63 g, 69%); R_f 0.48 (ethyl acetate); m.p. 126–140 °C; ν_{max}/cm⁻¹ (thin film) 3031, 1704, 1448, 1297, 1153, 918, 733, 698, 666, 621, 528; δ_H (400 MHz, CDCl₃) 7.77–7.69 (2H, m, ArH), 7.65 (1H, d, *J* = 7.6 Hz, ArH), 7.43–7.21 (10H, m, ArH), 4.38 (1H, t, *J* = 7.6 Hz, SCH₂CH), 3.94 (1H, dd, *J* = 6.7 Hz, CHH'CH(Ph)), 2.95–2.87 (3H, m, SCH₂CH and CHH'CH(Ph)), 2.73 (1H, dd, *J* = 13.0, 7.3 Hz,

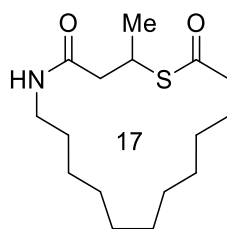
CHH'CH(Ph)); δ_c (100 MHz, CDCl₃) 176.4 (COOH), 146.1 (ArC), 146.0 (ArC), 141.1 (3 × ArC), 128.9 (2 × ArCH), 128.0 (2 × ArCH), 127.9 (ArCH), 127.64 (ArCH), 127.60 (ArCH), 127.1 (2 × ArCH), 125.1 (ArCH), 124.8 (ArCH), 119.9 (2 × ArCH), 46.4 (CH₂CH(Ph)), 45.6 (SCH₂CH), 41.4 (SCH₂CH), 35.5 (CH₂CH(Ph)); HRMS (ESI): calcd. for C₂₃H₂₀NaO₂S, 383.1076. Found: [MNa]⁺, 383.1077 (−0.2 ppm error). The synthetic procedure was adapted from a method reported in a patent.^{11b}

3-Methyl-1-thia-5-azacycloheptadecane-4,17-dione (24g)



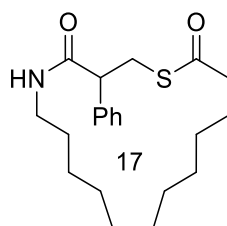
A mixture of lauro lactam **21b** (98.5 mg, 0.499 mmol), DMAP (6.1 mg, 0.05 mmol) and pyridine (0.24 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 3-(((9H-fluoren-9-yl)methyl)thio)-2-methylpropanoyl chloride (1.50 mmol, prepared from **S2** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.750 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO₂, hexane → 1:19 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded the *title compound* as a yellow crystalline solid (86.7 mg, 58%); m.p. 73–80 °C; R_f 0.53 (ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3297, 2927, 2856, 1684, 1643, 1549, 1456, 1367, 1248, 1189, 1122, 1028, 947, 732; δ_H (400 MHz, CDCl₃) 5.74 (1H, br s, NH), 3.62–3.52 (1H, m, CHH'NH), 3.06–2.91 (3H, m, CHH'NH and CH₂SCO), 2.62–2.36 (3H, m, COCH(CH₃)CH₂S and CH₂COS), 1.76–1.50 (3H, m, 1.5 × CH₂), 1.45–1.24 (15H, m, 7.5 × CH₂), 1.21 (3H, d, *J* = 6.9 Hz, CH₃); δ_c (100 MHz, CDCl₃) 201.1 (SCO), 174.3 (CO), 43.7 (CH₂COS), 42.2 (COCH(CH₃)CH₂S), 39.4 (CH₂NH), 32.7 (CH₂SCO), 28.9 (CH₂), 27.50 (CH₂), 27.47 (CH₂), 27.3 (CH₂), 27.1 (CH₂), 27.0 (CH₂), 26.4 (CH₂), 25.3 (CH₂), 25.2 (CH₂), 18.3 (CH₃); HRMS (ESI): calcd. for C₁₆H₂₉NNaO₂S, 322.1811. Found: [MNa]⁺, 322.1808 (1.0 ppm error).

2-Methyl-1-thia-5-azacycloheptadecane-4,17-dione (24h)



A mixture of lauro lactam **21b** (98.6 mg, 0.500 mmol), DMAP (6.2 mg, 0.051 mmol) and pyridine (0.24 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 3-(((9H-fluoren-9-yl)methyl)thio)-butanoyl chloride (1.50 mmol, prepared from **S3** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.75 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO₂, hexane → 1:19 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded the *title compound* as a yellow crystalline solid (87.2 mg, 58%); m.p. 54–56 °C; R_f 0.48 (ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3299, 2926, 2856, 1683, 1645, 1553, 1447, 1373, 1291, 1118, 1020, 732; δ_{H} (400 MHz, CDCl₃) 5.86 (1H, br s, NH), 3.90–3.80 (1H, m, COCH₂CH(CH₃)S), 3.38–3.16 (2H, m, CH₂NH), 2.62–2.41 (4H, m, 2 × CH₂(CH₂CON and CH₂COS)), 1.78–1.55 (3H, m, 1.5 × CH₂), 1.54–1.45 (2H, m, CH₂), 1.42 (3H, d, *J* = 7.0 Hz, CH₃), 1.40–1.22 (13H, m, 6.5 × CH₂); δ_{C} (100 MHz, CDCl₃) 200.5 (COS), 170.3 (CON), 43.9 (CH₂CO), 43.7 (CH₂CO), 39.4 (CH₂NH), 37.0 (COCH₂CH(CH₃)S), 29.0 (CH₂), 27.6 (CH₂), 27.4 (CH₂), 27.1 (CH₂), 26.99 (CH₂), 26.97 (CH₂), 26.4 (CH₂), 25.5 (CH₂), 24.6 (CH₂), 21.8 (CH₃); HRMS (ESI): calcd. for C₁₆H₂₉NNaO₂S, 322.1811. Found: [MNa]⁺, 322.1812 (−0.2 ppm error).

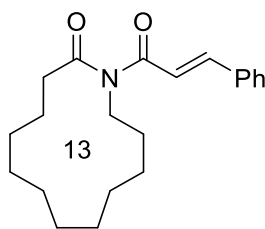
3-Phenyl-1-thia-5-azacycloheptadecane-4,17-dione (24i)



A mixture of lauro lactam **21b** (99.3 mg, 0.503 mmol), DMAP (8.0 mg, 0.066 mmol) and pyridine (0.24 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a

solution of 3-(((9H-fluoren-9-yl)methyl)thio)-2-phenylpropanoyl chloride (1.50 mmol, prepared from **S4** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.75 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by repeated flash column chromatography (SiO₂, hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a yellow solid (52.5 mg, 29%); m.p. 82–86 °C; R_f 0.73 (ethyl acetate); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 3301, 3063, 2927, 2856, 1682, 1647, 1548, 1495, 1450, 1393, 1353, 1243, 1187, 1030, 909, 760, 729, 697; δ_{H} (400 MHz, CDCl₃) 7.42–7.26 (5H, m, ArH), 5.46 (1H, br d, $J = 8.3$ Hz, NH), 3.75 (1H, dddd, $J = 13.3, 8.3, 8.3, 3.4$ Hz, CHH'NH), 3.58 (1H, dd, $J = 9.2, 5.4$ Hz, COCH(Ph)CH₂S), 3.31–3.26 (2H, m, CH₂SCO), 2.84–2.74 (1H, m, CHH'NH), 2.64 (1H, ddd, $J = 14.2, 8.7, 5.4$, CHH'COS), 2.50 (1H, ddd, $J = 14.2, 7.2, 5.4$, CHH'COS), 1.84–1.71 (2H, m, CH₂), 1.70–1.52 (2H, m, CH₂), 1.45–1.21 (14H, m, 7 × CH₂); δ_{C} (100 MHz, CDCl₃) 201.3 (COS), 171.5 (CON), 139.3 (ArC), 129.0 (2 × ArCH), 127.8 (ArCH), 127.7 (2 × ArCH), 53.5 (COCH(Ph)CH₂S), 43.8 (CH₂COS), 39.5 (CH₂NH), 32.6 (CH₂SCO), 29.1 (CH₂), 27.8 (CH₂), 27.51 (CH₂), 27.49 (2 × CH₂), 27.46 (CH₂), 26.5 (CH₂), 25.7 (CH₂), 25.1 (CH₂); HRMS (ESI): calcd. for C₂₁H₃₁NNaO₂S, 384.1968. Found: [MNa]⁺, 384.1970 (−0.5 ppm error).

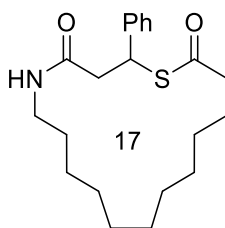
1-[(2E)-3-Phenylprop-2-enoyl]azacyclotridecan-2-one (**S6**)



A mixture of lauro lactam **21b** (98.2 mg, 0.498 mmol), DMAP (6.1 mg, 0.050 mmol) and pyridine (0.24 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 3-(((9H-fluoren-9-yl)methyl)thio)-3-phenylpropanoyl chloride (1.51 mmol, prepared from **S5** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.75 mL,

5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO₂, hexane → 3:97 ethyl acetate: hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) afforded the *title compound* **S6** as a yellow crystalline solid (115 mg, 70%); m.p. 45–51 °C; R_f 0.40 (1:4 ethyl acetate: hexane); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2929, 2859, 1675, 1616, 1577, 1449, 1332, 1178, 1135, 1098, 1071, 1047, 910, 763, 729, 684, 563; δ_{H} (400 MHz, CDCl₃) 7.71 (1H, d, $J = 15.5$ Hz, ArCHCHCON), 7.57–7.52 (2H, m, ArH), 7.41–7.33 (3H, m, ArH), 7.14 (1H, d, $J = 15.5$ Hz, ArCHCHCON), 3.81 (2H, t, $J = 7.0$ Hz, CH₂N), 2.69 (2H, t, $J = 7.2$ Hz, CH₂CON), 1.84–1.75 (2H, m, CH₂), 1.71 (2H, apparent p, $J = 7.0$ Hz, CH₂), 1.51–1.24 (14H, m, 7 × CH₂); δ_{C} (100 MHz, CDCl₃), 177.5 (CON), 169.5 (COCHCH), 144.1 (ArCHCHCON), 134.9 (ArC), 130.3 (ArCH), 128.9 (2 × ArCH), 128.3 (2 × ArCH), 121.3 (ArCHCHCON), 43.7 (CH₂N), 36.6 (CH₂CON), 26.5 (CH₂), 26.1 (CH₂), 25.4 (2 × CH₂), 25.3 (CH₂), 25.0 (CH₂), 24.6 (CH₂), 24.2 (CH₂), 23.8 (CH₂); HRMS (ESI): calcd. for C₂₁H₂₉NNaO₂, 350.2090. Found: [MNa]⁺, 350.2091 (–0.1 ppm error).

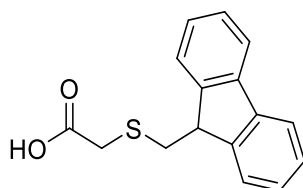
2-Phenyl-1-thia-5-azacycloheptadecane-4,17-dione (**24j**)



A mixture of lauro lactam **21b** (156mg, 0.792 mmol), DMAP (10.5 mg, 0.086 mmol) and pyridine (0.36 mL, 4.50 mmol) in DCM (10 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 3-(((9H-fluoren-9-yl)methyl)thio)-3-phenylpropanoyl chloride (2.25 mmol, prepared from **S5** using the general procedure) in DCM (5 mL) was added and the resulting mixture was stirred at RT for 18 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted (SiO₂, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo* to afford the crude imide product 1-(3-(((9H-fluoren-9-yl)methyl)thio)3-phenylpropanoyl)azacyclotridecan-2-one as a yellow oil (273 mg). The crude material was then re-dissolved in DCM (10 mL) and DBU (0.75 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO₂, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as an orange solid (22.6 mg, 8%); m.p. 79–82 °C; R_f 0.35 (1:1 ethyl acetate: hexane); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3295, 3078, 2927, 2856, 1689, 1645, 1554, 1494, 1452, 1361, 766, 733, 698; δ_{H} (400 MHz, CDCl₃) 7.38–7.19 (5H, m, ArCH), 5.86 (1H,

br t, $J = 5.6$ Hz, NH), 5.02 (1H, dd, $J = 9.7, 5.1$ Hz, COCH₂CH(Ph)S), 3.53–3.41 (1H, m, CHH'NH), 3.14 (1H, app dq, $J = 13.2, 5.6$ Hz, CHH'NH), 2.90–2.74 (2H, m, CH₂CON), 2.62–2.43 (2H, m, CH₂COS), 1.90–1.67 (1H, m, 0.5 × CH₂), 1.61–1.47 (3H, m, 1.5 × CH₂), 1.45–1.21 (14H, m, 7 × CH₂); δ_c (100 MHz, CDCl₃) 198.7 (COS), 169.5 (CON), 142.0 (ArC), 128.8 (2 × ArCH), 127.7 (ArCH), 127.5 (2 × ArCH), 44.7 (COCH₂CH(Ph)S), 43.4 (CH₂CO), 43.3 (CH₂CO), 39.5 (CH₂NH), 29.0 (CH₂), 27.7 (CH₂), 27.2 (CH₂), 27.1 (2 × CH₂), 26.9 (CH₂), 26.5 (CH₂), 25.5 (CH₂), 24.5 (CH₂); HRMS (ESI): calcd. for C₂₁H₃₁NNaO₂S, 384.1968. Found: [MNa]⁺, 384.1966 (0.5 ppm error).

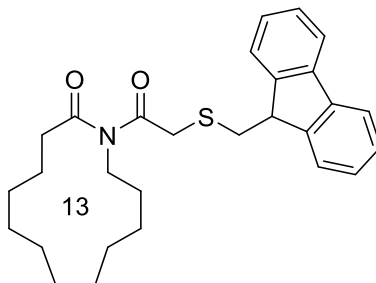
2-(((9H-Fluoren-9-yl)methyl)thio)acetic acid (S7)



To 9-fluorenemethanol (9.80 g, 50 mmol) was added thionyl chloride (50 mL) and the solution was heated at reflux at 80 °C for 2 h. Excess thionyl chloride was removed *in vacuo* and the residue was taken up in a pentane: DCM (60:40) mixture. Purification by flash column chromatography (SiO₂, 85:15 pentane: DCM) afforded 9-fluorenylmethyl chloride as a pale yellow oil (1.88 g, 17%) [Data for 9-fluorenylmethyl chloride: R_f 0.35 (85:15 pentane: DCM); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3066, 2952, 1477, 1448, 1303, 1263, 1100, 1031, 936, 814, 763, 736, 706, 638, 621, 579, 530; δ_H (400 MHz, CDCl₃) 7.81 – 7.67 (4H, m, ArH), 7.46 – 7.32 (4H, m, ArH), 4.27 (1H, t, $J = 6.6$ Hz, CH), 3.92 (1H, t, $J = 6.6$ Hz, CH₂); δ_c (100 MHz, CDCl₃) 144.2 (2 × ArC), 141.3 (2 × ArC), 128.2 (2 × ArCH), 127.3 (2 × ArCH), 125.1 (2 × ArCH), 120.2 (2 × ArCH), 49.5 (CH₂CH), 47.1 (CH₂CH); HRMS (APCI): calcd. for C₁₄H₁₂Cl, 215.062204. Found: [MH]⁺, 215.062158 (–0.2 ppm error)].¹² To a solution of thioglycolic acid (86 μL , 1.23 mmol) and 9-fluorenylmethyl chloride (245 mg, 1.14 mmol) in THF (5 mL) was added ⁱPr₂NEt (0.61 mL, 3.51 mmol). The reaction was stirred at room temperature for 17 h and THF was removed under reduced pressure. The residue was taken up in sat. aq. Na₂CO₃ (10 mL) bringing the pH to 8. The mixture was extracted with CHCl₃ (3 × 30 mL), and the aqueous layer acidified with aq. HCl (10%) to pH 1 and extracted with ethyl acetate (5 × 30 mL). The combined ethyl acetate extracts were dried over MgSO₄ and concentrated *in vacuo* to afford the *title compound* as an orange-yellow solid paste (310 mg, 100%); R_f 0.20 (ethyl acetate); m.p. 94–101 °C; $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2919, 1703, 1477, 1448, 1295, 1129, 1155, 1031, 765, 736, 621; δ_H (400 MHz, CDCl₃) 10.24 (1H, br s, COOH), 7.80 – 7.64 (4H, m, ArH), 7.44 – 7.29 (4H, m, ArH), 4.17 (1H, t, $J = 6.3$ Hz, SCH₂CH), 3.25 (2H, d, $J = 6.3$ Hz, SCH₂CH), 3.23 (2H, s, SCH₂COOH); δ_c (100 MHz, CDCl₃) 176.2 (COOH), 145.7 (2 × ArC), 141.2 (2 × ArC), 127.8 (2 × ArCH), 127.2 (2 × ArCH),

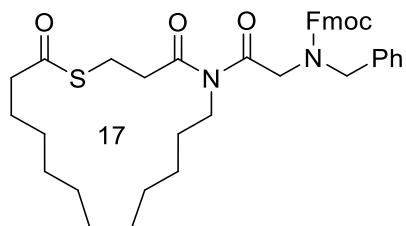
124.9 (2 × ArCH), 120.1 (2 × ArCH), 46.6 (SCH₂CH), 36.8 (SCH₂CH), 34.2 (SCH₂COOH); HRMS (ESI): calcd. for C₁₆H₁₄NaO₂S, 293.0607. Found: [MNa]⁺, 293.0604 (0.9 ppm error).¹³

1-(2-(((9H-Fluoren-9-yl)methyl)thio)acetyl)azacyclotridecan-2-one (S8)



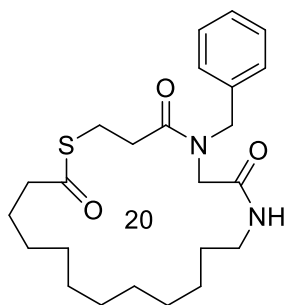
A mixture of lauro lactam **21b** (198 mg, 1.00 mmol), DMAP (13.6 mg, 0.111 mmol) and pyridine (0.480 mL, 6.00 mmol) in DCM (20 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 2-(((9H-fluoren-9-yl)methyl)thio)acetyl chloride (3.14 mmol, prepared from **S7** using the general procedure) in DCM (20 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. Purification by flash column chromatography (SiO₂, hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 3:1 ethyl acetate: hexane) afforded the *title compound* as an orange solid (299 mg, 66%); R_f 0.31 (1:3 ethyl acetate: hexane); m.p. 65 – 71 °C; ν_{max}/cm⁻¹ (thin film) 2929, 2860, 1682, 1447, 1360, 1276, 1177, 1120, 1047, 909, 764, 736, 621; δ_H (400 MHz, CDCl₃) 7.73 (4H, t, *J* = 16.3, 7.5 Hz, ArH), 7.42–7.28 (4H, m, ArH), 4.13 (1H, t, *J* = 6.7 Hz, SCH₂CH), 3.84 (2H, s, SCH₂CON), 3.71–3.63 (2H, m, CH₂N), 3.12 (2H, t, *J* = 6.7 Hz, SCH₂CH), 2.59–2.50 (2H, m, CH₂CON), 1.83–1.72 (2H, m, CH₂), 1.71–1.58 (2H, m, CH₂), 1.52–1.41 (4H, m, 2 × CH₂), 1.40–1.21 (10H, m, 5 × CH₂); δ_C (100 MHz, CDCl₃) 176.8 (CON), 172.6 (CON), 146.1 (2 × ArC), 141.1 (2 × ArC), 127.7 (2 × ArCH), 127.1 (2 × ArCH), 125.1 (2 × ArCH), 120.0 (2 × ArCH), 46.7 (SCH₂CH), 43.4 (CH₂N), 39.1 (SCH₂CON), 36.3 (SCH₂CH), 35.7 (CH₂CON), 25.92 (CH₂), 25.87 (CH₂), 25.4 (CH₂), 24.9 (CH₂), 24.6 (CH₂), 24.4 (CH₂), 24.1 (CH₂), 23.9 (CH₂), 23.7 (CH₂); HRMS (ESI): calcd. for C₂₈H₃₆NO₂S, 450.2461. Found: [MH]⁺, 450.2462 (–0.2 ppm error).

(9H-Fluoren-9-yl)methyl benzyl(2-(4,17-dioxo-1-thia-5-azacycloheptadecan-5-yl)-2-oxoethyl)carbamate (S9)



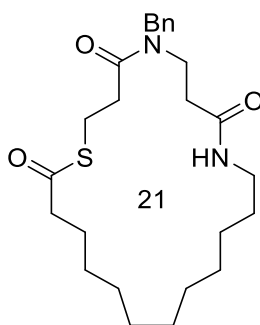
A mixture of 1-thia-5-azacycloheptadecane-4,17-dione **24b** (150 mg, 0.526 mmol), DMAP (6.1 mg, 0.050 mmol) and pyridine (0.240 mL, 3.00 mmol) in DCM (2.5 mL) under an argon atmosphere was stirred for 5 mins. Next, a solution of (9H-fluoren-9-yl)methyl benzyl(2-chloro-2-oxoethyl)carbamate (0.754 mmol, prepared from *N*-(((9H-fluoren-9-yl)methoxy)carbonyl)-*N*-benzylglycine¹⁰ using the general procedure) in DCM (5 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The crude mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* **S9** as a 1:1 mixture of rotamers as a fluffy white solid; m.p. 44–59 °C (261 mg, 76%); R_f 0.56 (1:1 ethyl acetate: hexane); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2927, 2856, 1694, 1451, 1424, 1389, 1220, 1112, 1004, 953, 892, 759, 740, 699, 621, 598, 534; δ_{H} (400 MHz, CDCl₃) ¹H NMR signals are for both rotamers unless stated 7.74 (2H, d, $J = 7.4$ Hz, ArH), 7.72 (2H, d, $J = 7.6$ Hz, ArH), 7.53 (2H, d, $J = 7.5$ Hz, ArH), 7.47 (2H, d, $J = 7.5$ Hz, ArH), 7.42–7.12 (18H, m, ArH), 4.58–4.54 (4H, m, 2 × CH₂Ph), 4.51 (2H, d, $J = 6.5$ Hz, COCH₂CH), 4.49–4.47 (2H, m, NCH₂CNO, [overlapping]), 4.48–4.45 (2H, m, COCH₂CH, [overlapping]), 4.26 (2H, s, NCH₂CNO), 4.26–4.19 (2H, m, 2 × COCH₂CH), 3.62–3.56 (2H, m, CH₂CH₂NCO, rotamer A), 3.51–3.44 (2H, m, CH₂CH₂NCO, rotamer B), 3.11 (4H, apparent q, $J = 6.4$ Hz, 2 × SCH₂CH₂CON), 2.83 (4H, apparent dt, $J = 13.8, 6.6$ Hz, 2 × SCH₂CH₂CON), 2.60 – 2.52 (4H, m, 2 × CH₂CH₂COS), 1.73 – 1.62 (4H, m, 2 × CH₂), 1.56 – 1.47 (2H, m, CH₂), 1.45 – 1.14 (30H, m, 15 × CH₂); δ_{C} (100 MHz, CDCl₃), 200.02 (SCO), 199.99 (SCO), 173.9 (CO), 173.8 (CO), 172.4 (CO), 172.2 (CO), 156.72 (NCO₂), 156.70 (NCO₂), 144.01 (2 × ArC), 143.95 (2 × ArC), 141.35 (2 × ArC), 141.33 (2 × ArC), 137.3 (ArC), 137.1 (ArC), 128.8 (2 × ArCH), 128.6 (2 × ArCH), 128.0 (2 × ArCH), 127.7 (4 × ArCH), 127.53 (ArCH), 127.51 (ArCH), 127.4 (2 × ArCH), 127.1 (4 × ArCH), 125.1 (2 × ArCH), 124.9 (2 × ArCH), 119.98 (2 × ArCH), 119.95 (2 × ArCH), 67.9 (CH₂CH), 67.3 (CH₂CH), 54.2 (NCH₂CNO), 53.3 (NCH₂CNO), 51.7 (CH₂Ph), 51.6 (CH₂Ph), 47.4 (CH), 47.2 (CH), 44.5 (CH₂CH₂N), 44.4 (CH₂CH₂N), 43.7 (2 × CH₂COS), 37.4 (2 × COCH₂CH₂S), 27.80 (2 × CH₂), 27.75 (CH₂), 27.71 (2 × CH₂), 27.64 (CH₂), 27.3 (2 × CH₂), 27.2 (2 × CH₂), 26.70 (CH₂), 26.66 (2 × CH₂), 26.60 (CH₂), 25.10 (CH₂), 25.07 (CH₂), 25.01 (CH₂), 24.97 (CH₂), 23.59 (2 × COCH₂CH₂S); HRMS (ESI): calcd. for C₃₉H₄₆N₂NaO₅S, 677.3020. Found: [MNa]⁺, 677.3012 (1.1 ppm error).

5-Benzyl-5,8-diaza-1-thiacycloicosane-4,7,20-trione (**24l**)



To a solution of (9H-fluoren-9-yl)methyl benzyl(2-(4,17-dioxo-1-thia-5-azacycloheptadecan-5-yl)-2-oxoethyl)carbamate **S9** (261 mg, 0.398 mmol) in DCM (10 mL) under an argon atmosphere DBU (0.75 mL, 0.50 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO₂, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a white crystalline solid (106 mg, 62%; 47% over 2 steps from **24b**) as a 5:4 (A:B) mixture of rotamers; m.p. 84–98 °C; R_f 0.67 (9:1 ethyl acetate: methanol); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 3318, 2927, 2856, 1655, 1543, 1496, 1443, 1358, 1265, 1236, 1198, 1081, 1021, 910, 730, 699; δ_{H} (400 MHz, CDCl₃) 7.34–7.17 (8H, m, ArH), 7.13–7.07 (2H, m, ArH), 6.49 (1H, t, $J = 5.7$ Hz, NH, rotamer A), 6.09 (1H, t, $J = 5.8$ Hz, NH, rotamer B), 4.60 (2H, s, PhCH₂, rotamer B), 4.58 (2H, s, PhCH₂, rotamer A), 3.96 (2H, s, NCH₂CO, rotamer A), 3.87 (2H, s, NCH₂CO, rotamer B), 3.20–3.09 (8H, m, 4 × CH₂), 2.71 (2H, t, $J = 6.2$ Hz, CH₂), 2.61–2.43 (6H, m, 3 × CH₂), 1.71–1.56 (4H, m, 2 × CH₂), 1.50–1.12 (32H, m, 16 × CH₂); δ_{C} (100 MHz, CDCl₃): 200.2 (SCO), 200.1 (SCO), 172.7 (CO), 171.8 (CO), 168.9 (CO), 167.7 (CO), 136.7 (ArC), 135.5 (ArC), 129.2 (2 × ArCH), 128.9 (2 × ArCH), 128.6 (2 × ArCH), 128.1 (ArCH), 128.0 (ArCH), 126.6 (2 × ArCH), 52.7 (PhCH₂, rotamer A), 51.5 (NCH₂CO, rotamer A), 50.7 (NCH₂CO, rotamer B), 50.3 (PhCH₂, rotamer B), 43.4 (CH₂), 43.3 (CH₂), 39.5 (2 × CH₂), 33.9 (CH₂), 33.5 (CH₂), 29.2 (CH₂), 29.1 (CH₂), 28.6 (CH₂), 28.4 (CH₂), 27.9 (CH₂), 27.8 (CH₂), 27.6 (CH₂), 27.4 (CH₂), 27.18 (CH₂), 27.15 (CH₂), 26.99 (2 × CH₂), 26.95 (CH₂), 26.6 (CH₂), 26.3 (CH₂), 25.9 (CH₂), 25.0 (CH₂), 24.8 (CH₂), 24.7 (CH₂), 24.6 (CH₂); HRMS (ESI): calcd. for C₂₄H₃₆N₂NaO₃S, 455.2339. Found: [MNa]⁺, 455.2332 (1.5 ppm error). For X-ray crystallographic data, see CCDC 2040346.

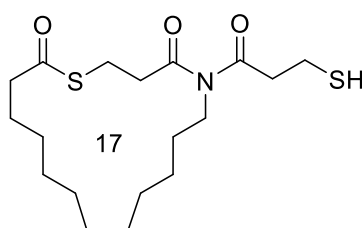
5-Benzyl-1-thia-5,9-diazacycloheptadecane-4,8,21-trione (24m)



A mixture of 1-thia-5-azacycloheptadecane-4,17-dione **24b** (143 mg, 0.502 mmol), DMAP (8.6 mg, 0.070 mmol) and pyridine (0.24 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred for 5 mins. Next, a solution of 3-(((9*H*-fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)propanoyl chloride (0.755 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)propanoic acid using the general procedure) in DCM (5 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. TLC analysis indicated that the acylation was incomplete, and so another solution of 3-(((9*H*-fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)propanoyl chloride (0.748 mmol) in DCM (10 mL) was prepared and added to the reaction mixture, with heating at reflux for an additional 18 h at 50 °C. The crude mixture was then concentrated *in vacuo*. Rough purification by flash column chromatography (SiO₂, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded a crude product consisting of predominantly (9*H*-fluoren-9-yl)methyl benzyl(3-(4,17-dioxo-1-thia-5-azacycloheptadecan-5-yl)-3-oxopropyl)carbamate, as a roughly 1:1 mixture of rotamers, as a light yellow paste (283 mg of material isolated, used directly in the next step). [Selected data for the intermediate (9*H*-fluoren-9-yl)methyl benzyl(3-(4,17-dioxo-1-thia-5-azacycloheptadecan-5-yl)-3-oxopropyl)carbamate: R_f 0.71 (ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2927, 2856, 1688, 1451, 1420, 1369, 1210, 1112, 1031, 910, 759, 729, 700, 621; Diagnostic ¹H NMR resonances: δ_H (400 MHz, CDCl₃), 4.56 (2H, d, $J = 6.1$ Hz, COCH₂CH), 4.50 – 4.47 (2H, m, CH₂Ph, [overlapping]), 4.50 – 4.45 (2H, m, COCH₂CH, [overlapping]), 4.43 (2H, s, CH₂Ph), 4.27 (1H, t, $J = 6.1$ Hz, COCH₂CH), 4.20 (1H, t, $J = 6.4$ Hz, COCH₂CH); Diagnostic ¹³C NMR resonances: δ_C (100 MHz, CDCl₃), 200.2 (2 × SCO), 174.3 (CO), 174.0 (CO), 173.9 (CO), 173.7 (CO), 156.6 (NCO₂), 156.2 (NCO₂), 67.5 (CH₂CH), 67.3 (CH₂CH), 51.1 (PhCH₂), 50.9 (PhCH₂), 47.5 (CH), 47.4 (CH); HRMS (ESI): calcd. for C₄₀H₄₈N₂NaO₅S, 691.3176 Found: [MNa]⁺, 691.3176 (0.0 ppm error)]. To a solution of this sample of (9*H*-fluoren-9-yl)methyl benzyl(3-(4,17-dioxo-1-thia-5-azacycloheptadecan-5-yl)-3-oxopropyl)carbamate in DCM (8.2 mL) under an argon atmosphere, DBU (0.610 mL, 4.04 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by

flash column chromatography (SiO₂, hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → 4:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a 2:1 mixture of rotamers as a white pasty solid (31.6 mg, 14% from **24b**); m.p. 62–75°C; R_f 0.34 (ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3311, 2925, 2854, 1638, 1549, 1439, 1365, 1197, 1026, 727, 698; δ_{H} (400 MHz, CDCl₃), 7.37 – 7.22 (8H, m, ArCH, both rotamers), 7.15–7.08 (2H, m, ArCH, both rotamers), 6.46 (1H, br t, $J = 5.7$ Hz, NH, major rotamer), 5.77 (1H, br t, $J = 5.7$ Hz, NH, minor rotamer), 4.60 (2H, s, CH₂Ph, minor rotamer), 4.57 (2H, s, CH₂Ph, major rotamer), 3.70–3.64 (2H, m, CON(CH₂Ph)CH₂, major rotamer), 3.60–3.54 (2H, m, CON(CH₂Ph)CH₂, minor rotamer), 3.30–3.17 (4H, m, 2 × CH₂), 3.14 (2H, t, $J = 6.7$ Hz, CH₂), 2.75–2.69 (2H, m, CH₂, minor rotamer), 2.63 (2H, t, $J = 6.7$ Hz, CH₂, major rotamer), 2.58 (2H, t, $J = 7.0$ Hz, CH₂, minor rotamer), 2.55–2.47 (4H, m, 2 × CH₂), 2.39 – 2.33 (2H, m, CH₂, minor rotamer), 1.74–1.61 (4H, m, 2 × CH₂), 1.59–1.43 (4H, m, 2 × CH₂), 1.38–1.21 (30H, m, 15 × CH₂, both rotamers); δ_{C} (100 MHz, CDCl₃) data for major rotamer A, 200.1 (COS), 172.4 (CON), 171.0 (CON), 136.4 (ArC), 129.1 (2 × ArCH), 127.8 (ArCH), 126.3 (2 × ArCH), 52.0 (CH₂Ph), 43.5 (CH₂), 43.2 (CON(CH₂Ph)CH₂), 39.8 (CH₂), 35.5 (CH₂), 33.9 (CH₂), 29.4 (CH₂), 28.9 (CH₂), 28.2 (CH₂), 27.8 (CH₂), 27.52 (CH₂), 27.49 (CH₂), 27.2 (CH₂), 26.7 (CH₂), 24.9 (CH₂), 24.6 (CH₂); Diagnostic ¹³C NMR resonances for the minor rotamer: δ_{C} (100 MHz, CDCl₃), 201.1 (COS), 171.2 (CON), 169.7 (CON), 49.2 (CH₂Ph); HRMS (ESI): calcd. for C₂₅H₃₈N₂NaO₃S, 469.2495 Found: [MNa]⁺, 469.2500 (–0.9 ppm error).

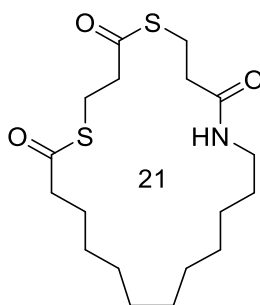
5-(3-Mercaptopropanoyl)-1-thia-5-azacycloheptadecane-4,17-dione (**39**)



Oxalyl chloride (0.19 mL, 2.25 mmol) was added to a suspension of 3-(tritylthio)propanoic acid (525 mg, 1.51 mmol) in DCM (7.5 mL), followed by a catalytic amount of DMF (1 drop). The resulting mixture was stirred at RT for 30 min and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride. The resulting 3-(tritylthio)propanoyl chloride **30** was dissolved in DCM (3 mL) and added to a pre-stirred mixture of 1-thia-5-azacycloheptadecane-4,17-dione **24b** (149 mg, 0.521 mmol), DMAP (7.0 mg, 0.057 mmol) and pyridine (0.240 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere. The reaction mixture was then heated to 50 °C and stirred for 18 h. The solvent was removed *in vacuo*, and the product mixture was loaded onto a short silica plug and eluted (SiO₂, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) to remove the majority of the excess carboxylic acid and pyridine

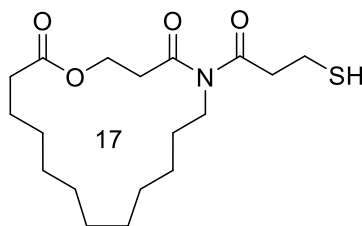
residues, and concentrated *in vacuo* to afford a sample of crude 5-(3-(tritylthio)propanoyl)-1-thia-5-azacycloheptadecane-4,17-dione (**38**) as a white solid, which was used without further purification, 274 mg of this crude material was obtained. [Data for crude **38**: m.p. 31 – 45 °C; R_f 0.79 (ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3058, 2928, 2856, 1819, 1690, 1595, 1489, 1444, 1370, 1132, 1106, 1034, 908, 730, 698, 676, 619, 506; δ_{H} (400 MHz, CDCl₃), 7.49 – 7.41 (5H, m, ArH), 7.33 – 7.18 (10H, m, ArH), 3.59 – 3.51 (2H, m, CH₂CH₂CH₂NCO), 3.15 (2H, t, $J = 6.5$ Hz, COSCH₂CH₂CON), 2.90 (2H, t, $J = 6.5$ Hz, COSCH₂CH₂CON), 2.76 (2H, t, $J = 7.0$ Hz, CH₂CH₂SC(Ph)₃), 2.62 – 2.57 (2H, m, CH₂CH₂COS), 2.54 (2H, t, $J = 7.0$ Hz, CH₂CH₂SC(Ph)₃), 1.76 – 1.66 (2H, m, CH₂), 1.53 – 1.43 (2H, m, CH₂), 1.41 – 1.18 (14H, m, 7 × CH₂); δ_{C} (100 MHz, CDCl₃), 200.1 (COS), 174.5 (CO), 173.7 (CO), 144.8 (3 × ArC), 129.7 (6 × ArCH), 127.9 (6 × ArCH), 126.7 (3 × ArCH), 66.9 (CPh₃), 44.1 (CH₂CH₂CH₂NCO), 43.7 (CH₂COS), 38.5 (CH₂CH₂SC(Ph)₃), 37.9 (COSCH₂CH₂CON), 27.9 (CH₂), 27.84 (CH₂), 27.77 (CH₂), 27.2 (2 × CH₂), 27.1 (CH₂), 26.8 (CH₂), 26.6 (CH₂), 25.14 (CH₂), 25.05 (CH₂), 23.8 (COSCH₂); HRMS (ESI): calcd. for C₃₇H₄₅NNaO₃S₂, 638.2733. Found: [MNa]⁺, 638.2738 (–0.7 ppm error)]. This mixture was then dissolved in DCM (4.4 mL) under an argon atmosphere, before TFA (0.44 mL, 5.7 mmol) was added and the solution stirred for 3 min. Next, triisopropylsilane (0.11 mL, 0.53 mmol) was added and the solution stirred for a further 30 min. The mixture was then diluted with DCM (1.5 mL) and washed with water (5 mL). The aqueous layer was then extracted with DCM (3 × 1.5 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, hexane → 3:97 ethyl acetate: hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane) afforded the *title compound* as a colorless oil (52.6 mg, 27% from **24b**); R_f 0.27 (4:1 hexane: ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2926, 2855, 1687, 1460, 1371, 1206, 1132, 1105, 1016, 948, 732, 698, 600; δ_{H} (400 MHz, CDCl₃), 3.63–3.56 (2H, m, CH₂CH₂CH₂NCO), 3.18–3.11 (4H, m, CH₂CH₂SH and COSCH₂), 2.90 (2H, t, $J = 6.6$ Hz, COSCH₂CH₂CON), 2.78 (2H, dt, $J = 8.4, 6.6$ Hz, CH₂CH₂SH), 2.59–2.53 (2H, m, CH₂CH₂CO₂), 1.72–1.60 (2H, m, CH₂ [overlapping]), 1.64 (1H, t, $J = 8.4$ Hz, CH₂CH₂SH [overlapping]), 1.55–1.45 (2H, m, CH₂), 1.38–1.15 (14H, m, 7 × CH₂); δ_{C} (100 MHz, CDCl₃), 200.2 (COS), 174.3 (CO), 173.9 (CO), 44.3 (CH₂CH₂CH₂NCO), 43.8 (CH₂COS), 43.6 (CH₂CH₂SH), 37.9 (COSCH₂CH₂CON), 27.94 (CH₂), 27.85 (CH₂), 27.8 (CH₂), 27.3 (CH₂), 27.2 (CH₂), 26.8 (CH₂), 26.7 (CH₂), 25.2 (CH₂), 25.1 (CH₂), 23.9 (COSCH₂), 19.9 (CH₂CH₂SH); HRMS (ESI): calcd. for C₁₈H₃₂NO₃S₂, 374.1818. Found: [MH]⁺, 374.1819 (–0.1 ppm error).

1,5-Dithia-9-azacyclohenicosane-4,8,21-trione (**40**)



5-(3-Mercaptopropanoyl)-1-thia-5-azacycloheptadecane-4,17-dione (**39**) (45 mg, 0.120 mmol) was dissolved in CDCl_3 (0.7 mL) and transferred to an NMR tube. To it was added triethylamine (33 μL , 0.240 mmol) in CDCl_3 (0.2 mL), and then the reaction mixture was heated to 55 $^\circ\text{C}$ in an oil bath for 8 h (doing the reaction in an NMR tube enabled us to monitor progress of the rearrangement using ^1H NMR). The mixture was then concentrated and purified by flash column chromatography (SiO_2 , hexane \rightarrow 3:97 ethyl acetate: hexane \rightarrow 1:19 ethyl acetate: hexane \rightarrow 1:9 ethyl acetate: hexane \rightarrow 1:4 ethyl acetate: hexane \rightarrow 1:1 ethyl acetate: hexane \rightarrow 2:1 ethyl acetate: hexane) afforded some recovered starting material **39** (6.6 mg, 15%) and the *title compound* **40** a pasty white solid (13.9 mg, 31%). Data for **40**: m.p. 87–89 $^\circ\text{C}$; R_f 0.12 (1:1 ethyl acetate: hexane); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 3300, 2925, 2854, 1687, 1645, 1549, 1409, 1262, 1161, 1052, 958, 731, 698, 601; δ_{H} (400 MHz, CDCl_3), 5.79 (1H, br t, $J = 6.0$ Hz, NH), 3.28 (2H, q, $J = 6.0$ Hz, CH_2NHCO), 3.22–3.17 (2H, m, $\text{SCH}_2\text{CH}_2\text{CONH}$), 3.14 (2H, t, $J = 6.7$ Hz, $\text{COSCH}_2\text{CH}_2\text{COS}$), 2.83 (2H, t, $J = 6.7$ Hz, $\text{COSCH}_2\text{CH}_2\text{COS}$), 2.58–2.51 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{COS}$), 2.50–2.44 (2H, m, $\text{SCH}_2\text{CH}_2\text{CONH}$), 1.70 (2H, t, $J = 6.7$ Hz, CH_2), 1.55–1.44 (2H, m, CH_2), 1.38–1.18 (14H, m, $7 \times \text{CH}_2$); δ_{C} (100 MHz, CDCl_3), 199.6 (COS), 197.8 (COS), 170.9 (CON), 44.0 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{COS}$), 43.8 ($\text{COSCH}_2\text{CH}_2\text{COS}$), 39.7 (CH_2NHCO), 36.6 ($\text{SCH}_2\text{CH}_2\text{CONH}$), 29.3 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 28.0 (CH_2), 26.5 (CH_2), 25.6 ($\text{COSCH}_2\text{CH}_2\text{CONH}$), 25.3 (CH_2), 24.3 ($\text{COSCH}_2\text{CH}_2\text{COS}$); HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{32}\text{NO}_3\text{S}_2$, 374.1818. Found: $[\text{MH}]^+$, 374.1812 (1.5 ppm error).

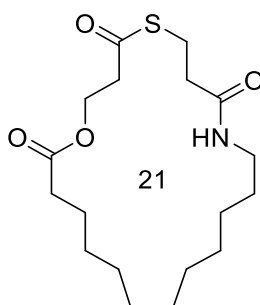
5-(3-Mercaptopropanoyl)-1-oxa-5-azacycloheptadecane-4,17-dione (43)



Oxalyl chloride (0.340 mL, 4.00 mmol) was added to a suspension of 3-(tritylthio)propanoic acid (467 mg, 1.34 mmol) in DCM (13.5 mL), followed by a catalytic amount of DMF (1 drop). The resulting mixture was stirred at RT for 30 min and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride. The resulting 3-(tritylthio)propanoyl chloride was added to a pre-stirred mixture of 1-oxa-5-azacycloheptadecane-4,17-dione **41**¹⁴ (120 mg, 0.445 mmol), DMAP (6.7 mg, 0.055 mmol) and pyridine (0.220 mL, 2.67 mmol) in DCM (9.0 mL) under an argon atmosphere. The reaction mixture was then heated at reflux at 50 °C and stirred for 18 h. The solvent was removed *in vacuo*, and the reaction mixture loaded onto a short silica plug and eluted (SiO₂, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) to remove the majority of the excess carboxylic acid and pyridine residues, and then concentrated *in vacuo* to afford crude 5-(3-(tritylthio)propanoyl)-1-thia-5-azacycloheptadecane-4,17-dione (**42**) as a colorless oil which was used without further purification, with 220 mg of this crude material obtained. [Data for crude **42**: R_f 0.67 (1:1 hexane: ethyl acetate); v_{max}/cm⁻¹ (thin film) 3057, 2929, 2857, 1733, 1696, 1642, 1489, 1445, 1368, 1104, 1034, 910, 742, 699, 676, 620; δ_H (400 MHz, CDCl₃), 7.51–7.42 (5H, m, ArH), 7.35–7.17 (10H, m, ArH), 4.42 (2H, t, *J* = 6.0 Hz, CO₂CH₂CH₂CON), 3.53 (2H, m, CH₂CH₂CH₂NCO), 3.01 (2H, t, *J* = 6.0 Hz, CO₂CH₂CH₂CON), 2.59 (4H, m, CH₂CH₂S and CH₂CH₂S), 2.33 (2H, m, CH₂CH₂CO₂), 1.70–1.60 (2H, m, CH₂), 1.53–1.43 (2H, m, CH₂), 1.42–1.24 (14H, m, 7 × CH₂); Diagnostic ¹³C NMR resonances: δ_C (100 MHz, CDCl₃), 174.4 (CO), 173.8 (CO), 172.7 (CO), 59.6 (CO₂CH₂CH₂CON), 43.8 (CH₂CH₂CH₂NCO), 37.6 (CH₂), 37.2 (CO₂CH₂CH₂CON), 34.1 (CH₂CH₂CO₂); HRMS (ESI): calcd. for C₃₇H₄₅NNaO₄S, 622.2962. Found: [MNa]⁺, 622.2973 (–1.2 ppm error)]. This mixture was then dissolved in DCM (4.3 mL) under an argon atmosphere, before TFA (0.420 mL, 5.6 mmol) was added and the solution stirred for 3 min. Next, triisopropylsilane (0.100 mL, 0.47 mmol) was added and the solution stirred for a further 30 min. The mixture was then diluted with DCM (1.5 mL) and washed with water (5 mL). The aqueous layer was then extracted with DCM (3 × 1.5 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, hexane → 3:97 ethyl acetate: hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) afforded the *title compound* as a colorless oil (47.3 mg, 30% from **41**); R_f 0.14 (4:1 hexane: ethyl acetate); v_{max}/cm⁻¹ (thin film) 2927, 2856, 1732, 1693, 1460, 1367, 1208, 1131, 1102, 732; δ_H (400 MHz, CDCl₃), 4.43 (2H, t, *J* = 6.3 Hz, CO₂CH₂CH₂CON), 3.66–3.60

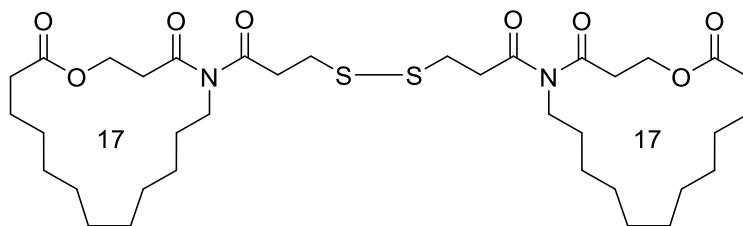
(2H, m, CH₂CH₂CH₂NCO), 3.09 (2H, t, *J* = 6.5 Hz, CH₂CH₂SH), 3.01 (2H, t, *J* = 6.3 Hz, CO₂CH₂CH₂CON), 2.80 (2H, dt, *J* = 8.5, 6.5 Hz, CH₂CH₂SH), 2.35–2.29 (2H, m, CH₂CH₂CO₂), 1.67 (1H, t, *J* = 8.5 Hz, CH₂CH₂SH [overlapping]), 1.68–1.60 (2H, m, CH₂ [overlapping]), 1.59–1.50 (2H, m, CH₂), 1.41–1.21 (14H, m, 7 × CH₂); δ_c (100 MHz, CDCl₃), 174.2 (CO), 174.0 (CO), 172.9 (CO), 59.6 (CO₂CH₂CH₂CON), 44.0 (CH₂CH₂CH₂NCO), 42.8 (CH₂CH₂SH), 36.9 (CO₂CH₂CH₂CON), 34.2 (CH₂CH₂CO₂), 27.92 (CH₂), 27.85 (CH₂), 27.6 (CH₂), 27.2 (CH₂), 27.1 (CH₂), 27.0 (CH₂), 26.7 (CH₂), 25.1 (CH₂), 24.8 (CH₂), 19.8 (CH₂CH₂SH); HRMS (ESI): calcd. for C₁₈H₃₂NO₄S, 358.2047. Found: [MH]⁺, 358.2029 (5.0 ppm error).

1-Oxa-5-thia-9-azacyclohenicosane-4,8,21-trione (**44**)



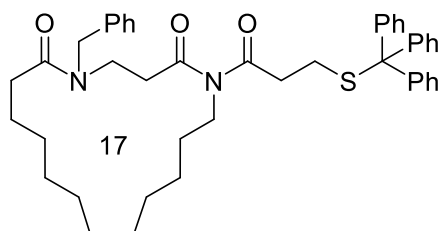
5-(3-Mercaptopropanoyl)-1-oxa-5-azacycloheptadecane-4,17-dione (**43**) (47.3 mg, 0.132 mmol) was dissolved in CDCl₃ (1.5 mL) and transferred to a round bottomed flask under argon. To it was added triethylamine (37 μL, 0.265 mmol) in CDCl₃ (0.5 mL). The reaction mixture was heated to 55 °C in an oil bath for 12 h. Purification by flash column chromatography (SiO₂, hexane → 3:97 ethyl acetate: hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* **44** (8.0 mg, 17%) as an off white solid, along with disulfide **45** (7.3 mg, 16%; see next page for data for **45**). Data for **44**: m.p. 78 – 80 °C; R_f 0.14 (1:1 ethyl acetate: hexane); ν_{max}/cm⁻¹ (thin film) 3301, 2926, 2855, 1737, 1690, 1647, 1551, 1459, 1256, 1167, 1097, 1020, 715; δ_H (400 MHz, CDCl₃), 5.80 (1H, br s, NH), 4.38 (2H, t, *J* = 5.9 Hz, CO₂CH₂CH₂COS), 3.30 (2H, q, *J* = 5.8 Hz, CH₂NHCO), 3.18 (2H, t, *J* = 6.8 Hz, SCH₂CH₂), 2.85 (2H, t, *J* = 5.9 Hz, CO₂CH₂CH₂COS), 2.47 (2H, t, *J* = 6.8 Hz, SCH₂CH₂), 2.34 – 2.27 (2H, m, CH₂CH₂CO₂), 1.67 – 1.58 (2H, m, CH₂), 1.55 – 1.46 (2H, m, CH₂), 1.39 – 1.21 (14H, m, 7 × CH₂); δ_c (100 MHz, CDCl₃), 197.0 (COS), 173.8 (CO₂), 170.9 (CON), 59.7 (CO₂CH₂CH₂COS), 43.4 (CO₂CH₂CH₂COS), 39.6 (CH₂NHCO), 36.8 (SCH₂CH₂), 34.1 (CH₂CH₂CO₂), 28.9 (CH₂), 28.5 (CH₂), 28.32 (2 × CH₂), 28.28 (2 × CH₂), 27.9 (CH₂), 26.0 (CH₂), 25.7 (SCH₂CH₂), 24.7 (CH₂); HRMS (ESI): calcd. for C₁₈H₃₁NNaO₄S, 380.1866. Found: [MNa]⁺, 380.1866 (0.1 ppm error).

5,5'-(3,3'-Disulfanediy)bis(propanoyl)bis(1-oxa-5-azacycloheptadecane-4,17-dione) (45)



Data for **45** (for synthetic procedure, see above): R_f 0.58 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2926, 2855, 1733, 1695, 1459, 1366, 1260, 1131, 1100, 1020, 913, 802, 732, 470; δ_H (400 MHz, $CDCl_3$), 4.43 (4H, t, $J = 6.2$ Hz, $2 \times CO_2CH_2CH_2CON$), 3.68 – 3.56 (4H, m, $2 \times CH_2CH_2CH_2NCO$), 3.18 (4H, t, $J = 6.8$ Hz, $2 \times CH_2CH_2S$), 3.01 (4H, t, $J = 6.2$ Hz, $2 \times CO_2CH_2CH_2CON$), 2.96 (4H, t, $J = 6.8$ Hz, $2 \times CH_2CH_2S$), 2.34–2.28 (4H, m, $2 \times CH_2CH_2CO_2$), 1.70–1.60 (4H, m, $2 \times CH_2$), 1.59–1.50 (4H, m, $2 \times CH_2$), 1.39–1.18 (28H, m, $14 \times CH_2$); δ_C (100 MHz, $CDCl_3$), 174.4 ($2 \times CO$), 174.0 ($2 \times CO$), 173.0 ($2 \times CO$), 59.7 ($2 \times CO_2CH_2CH_2CON$), 44.2 ($2 \times CH_2CH_2CH_2NCO$), 38.4 ($2 \times CH_2CH_2S$), 37.0 ($2 \times CO_2CH_2CH_2CON$), 34.2 ($2 \times CH_2CH_2CO_2$), 33.3 ($2 \times CH_2CH_2S$), 28.0 ($2 \times CH_2$), 27.9 ($2 \times CH_2$), 27.7 ($2 \times CH_2$), 27.23 ($2 \times CH_2$), 27.19 ($2 \times CH_2$), 27.0 ($2 \times CH_2$), 26.7 ($2 \times CH_2$), 25.2 ($2 \times CH_2$), 24.8 ($2 \times CH_2$); HRMS (ESI): calcd. for $C_{36}H_{60}N_2NaO_8S_2$, 735.3683. Found: $[MNa]^+$, 735.3709 (–3.5 ppm error).

5-Benzyl-1-(3-(tritylthio)propanoyl)-1,5-diazacycloheptadecane-2,6-dione (47)

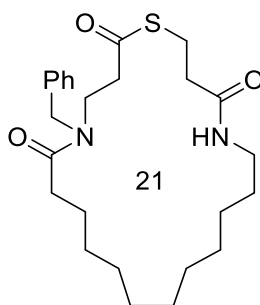


A mixture of 5-benzyl-1,5-diazacycloheptadecane-2,6-dione¹⁰ (327.0 mg, 0.912 mmol), DMAP (11.2 mg, 0.092 mmol) and pyridine (0.44 mL, 5.47 mmol) in DCM (10 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **30** (1.37 mmol, prepared from 3-(tritylthio)propanoic acid using the general procedure) in DCM (13 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (5 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 \times 10 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. TLC analysis indicated that acylation was incomplete at this stage, so an additional acylation sequence was performed. Thus, the crude reaction mixture was dissolved in DCM (10 mL) and to it was added DMAP (11.2 mg, 0.092 mmol) and pyridine (0.44 mL, 5.47 mmol). Then, another solution of acid chloride **30** (1.36 mmol, 1.5 eqv. prepared using the general procedure) in DCM (13 mL) was added and the resulting mixture was

heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (5 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as a 2:1 mixture of rotamers as a fluffy white solid (343mg, 55 %)*; m.p. 38–48 °C; R_f 0.45 (1:1 ethyl acetate: hexane); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 2929, 1694, 1637, 1445, 1371, 1131, 1105, 1034, 907, 726, 698, 647, 619, 506; δ_{H} (400 MHz, CDCl₃) 7.47–7.15 (40H, m, ArH, both rotamers), 4.65 (2H, s, NCH₂Ph, major), 4.58 (2H, s, NCH₂Ph, minor), 3.66–3.60 (4H, m, CH₂, both), 3.54–3.47 (2H, m, CH₂, major), 3.37–3.30 (2H, m, CH₂, minor), 2.87 (2H, t, *J* = 6.5 Hz, CH₂, major), 2.83 (2H, t, *J* = 6.8 Hz, CH₂, minor), 2.69 (2H, t, *J* = 7.1 Hz, CH₂, major), 2.54 (2H, t, *J* = 7.0 Hz, CH₂, minor), 2.51–2.39 (6H, m, CH₂, both), 2.38–2.33 (2H, m, CH₂, major), 1.81–1.62 (4H, m, CH₂, both), 1.53–1.18 (32H, m, CH₂, both); δ_{C} (100 MHz, CDCl₃), 174.4 (CO), 174.2 (CO), 174.1 (CO), 174.0 (CO), 173.6 (CO), 173.4 (CO), 144.8 (ArC), 144.7 (ArC), 138.2 (ArC), 137.1 (ArC), 129.7 (ArCH), 129.6 (ArCH), 129.0 (ArCH), 128.6 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.7 (ArCH), 127.2 (ArCH), 126.8 (ArCH), 126.6 (ArCH), 126.5 (ArCH), 67.0 (CPh₃), 66.8 (CPh₃), 52.7 (NCH₂Ph, major), 48.7 (NCH₂Ph, minor), 44.3 (CH₂), 43.8 (CH₂), 43.2 (CH₂), 43.1 (CH₂), 38.4 (CH₂), 37.3 (CH₂), 37.2 (CH₂), 35.6 (CH₂), 33.3 (CH₂), 32.5 (CH₂), 31.7 (CH₂), 27.8 (CH₂), 27.5 (CH₂), 27.3 (CH₂), 27.2 (CH₂), 27.1 (CH₂), 27.0 (CH₂), 26.9 (CH₂), 26.8 (CH₂), 26.6 (CH₂), 26.5 (CH₂), 26.3 (CH₂), 26.1 (CH₂), 24.9 (CH₂), 24.8 (CH₂), 24.3 (CH₂); HRMS (ESI): calcd. for C₄₄H₅₂N₂NaO₃S, 711.3591. Found: [MNa]⁺, 711.3614 (–3.2 ppm error).

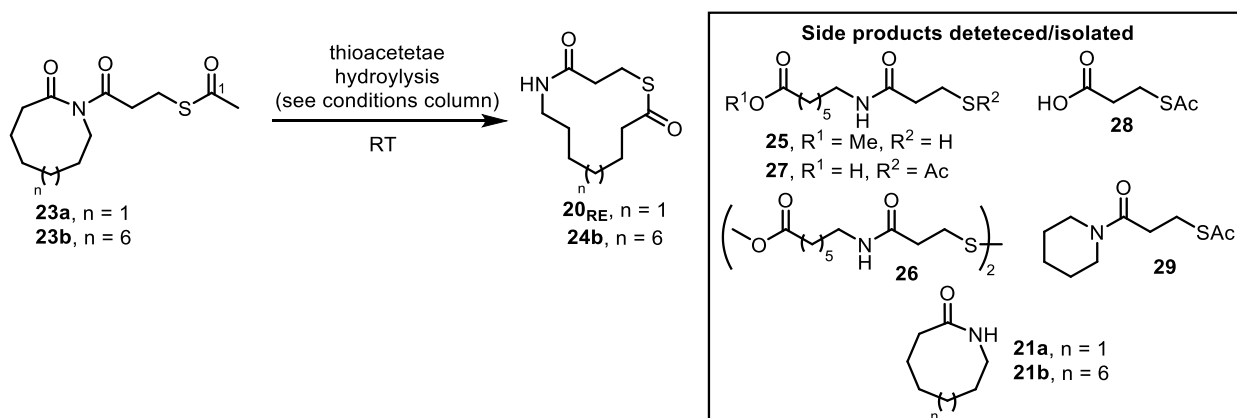
*Trace trityl impurities were visible in the NMR spectra of this product, but its purity was judged to be sufficient to proceed with the ring expansion sequence.

5-Benzyl-1-thia-5,18-diazacyclohenicosane-2,6,19-trione (49)



A mixture of 5-benzyl-1-(3-(tritylthio)propanoyl)-1,5-diazacycloheptadecane-2,6-dione (307 mg, 0.445 mmol) in DCM (5 mL) under an argon atmosphere was added TFA (0.46 mL, 6.01 mmol) and the solution stirred for 3 min. Next, triisopropylsilane (0.10 mL, 0.495 mmol) was added and the solution stirred for a further 30 min. The solvent and TFA were removed *in vacuo*. The crude material (containing thiol **48**) was then re-dissolved in DCM (5 mL) and DBU (0.67 mL, 4.50 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. The reaction mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a 5:3:1 (A:B:C) mixture of rotamers as a colorless oil (33.5 mg, 17%); R_f 0.34 (ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3308, 2925, 2854, 1635, 1551, 1495, 1432, 1363, 1260, 1201, 1163, 1059, 1030, 978, 915, 803, 728, 698, 645, 613; δ_{H} (400 MHz, CDCl₃), 7.39 – 7.09 (15H, m, ArCH, all rotamers), 7.03 (1H, br t, $J = 5.7$ Hz, NH, rotamer C), 6.79 (1H, br t, $J = 5.9$ Hz, NH, rotamer A), 5.76 (1H, br m, NH, rotamer B), 4.63 (2H, s, CH₂Ph, rotamer C), 4.59 (2H, s, CH₂Ph, rotamer B), 4.57 (2H, s, CH₂Ph, rotamer A), 3.72 – 3.67 (2H, m, CON(CH₂Ph)CH₂, rotamer A), 3.66 – 3.61 (2H, m, CON(CH₂Ph)CH₂, rotamer C), 3.59 – 3.52 (2H, m, CON(CH₂Ph)CH₂, rotamer B), 3.33 – 3.24 (6H, m, 3 × CH₂, all rotamers), 3.19 – 3.08 (4H, m, 2 × CH₂), 2.76 – 2.66 (4H, m, 2 × CH₂), 2.57 – 2.47 (4H, m, 2 × CH₂, rotamer C), 2.45 – 2.28 (10H, m, 5 × CH₂), 1.78 – 1.57 (8H, m, 4 × CH₂), 1.55 – 1.43 (6H, m, 3 × CH₂), 1.41 – 1.19 (42H, m, 21 × CH₂, all rotamers); δ_{C} (100 MHz, CDCl₃) data for major rotamer A, 197.5 (COS), 174.2 (CON), 171.4 (CON), 136.6 (ArC), 129.1 (2 × ArCH), 127.8 (ArCH), 126.5 (2 × ArCH), 51.2 (CH₂Ph), 42.7 (CH₂), 42.1 (CH₂), 39.4 (CH₂), 36.0 (CH₂), 33.0 (CH₂), 28.9 (CH₂), 28.0 (CH₂), 27.9 (CH₂), 27.8 (CH₂), 27.6 (CH₂), 27.4 (CH₂), 27.0 (CH₂), 26.1 (CH₂), 25.7 (CH₂), 24.6 (CH₂); Diagnostic ¹³C NMR resonances of rotamer B: δ_{C} (100 MHz, CDCl₃), 197.0 (COS), 173.4 (CON), 170.4 (CON), 48.4 (CH₂Ph); Diagnostic ¹³C NMR resonances of rotamer C: δ_{C} (100 MHz, CDCl₃), 175.1 (CON), 171.2 (CON), 52.1 (CH₂Ph); HRMS (ESI): calcd. for C₂₅H₃₈N₂NaO₃S, 469.2495 Found: [MNa]⁺, 469.2495 (0.0 ppm error).

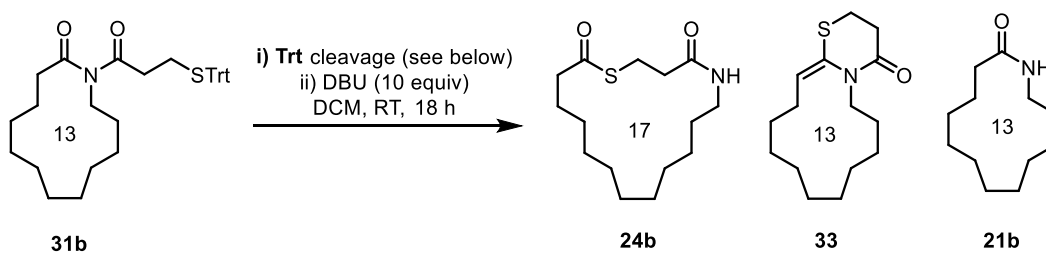
Table S1. Optimisation experiments for the S-Ac strategy



Entry	Conditions	Solvent	Time / h	Yield of 20_{RE} ^a /%	Side products ^b
1	4M NaOH _(aq)	MeOH	2	0	25 (19%) and 26 (16%)
2	0.3M LiOH _(aq)	THF	3	trace	27 , 28 (13%), 21a and 23a (21%)
3	0.3M LiOH _(aq)	THF	0.33	6	21a (10%) and 23a (20%)
4	DIPA	THF	24	0	No reaction
5	DIPA	DCM	24	0	No reaction
6	Et ₂ NH, DTT	DCM	18	16	20_{RO} (43%)
7	piperidine	THF	24	0	No reaction
8	piperidine	DCM	22	29	29 , 21a , 23a (6%) and 20_{RO} (3%)
9	piperidine	DCM	18	36 (24b) (from 23b)	29 , 21b and 23b (34%)

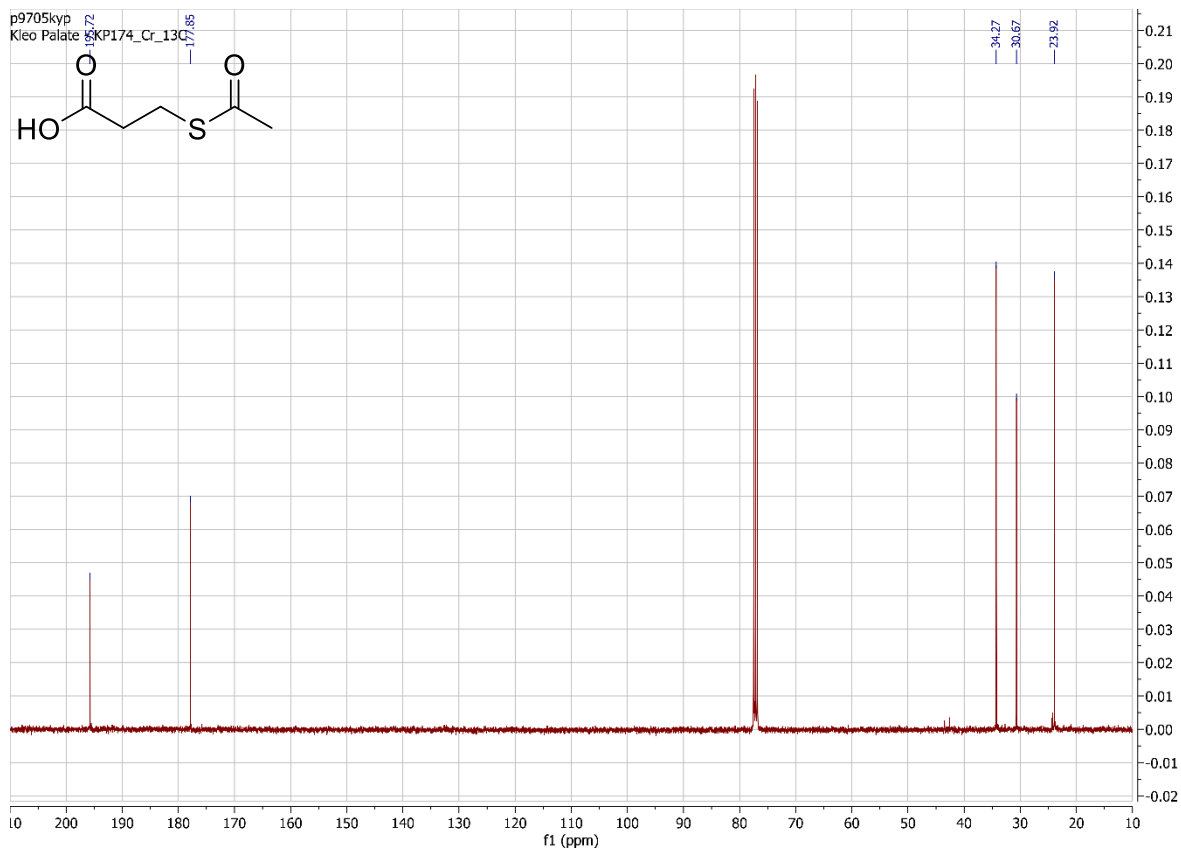
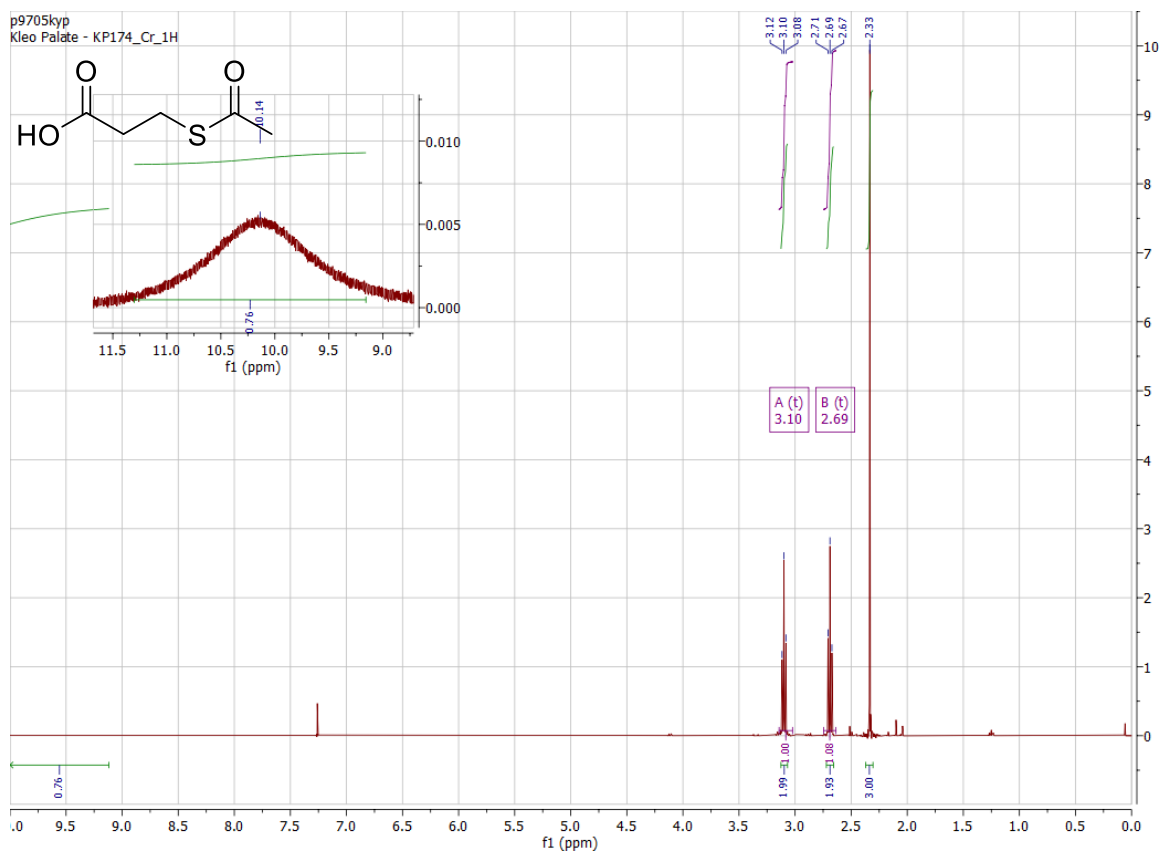
All reactions were performed at RT. ^a Isolated following column chromatography. ^b Yield (in parentheses) is only reported for side products when the product was isolated without impurities; see ESI spectroscopic characterisation data relating to the side products **25**, **26** and **28**.

Table S2: Optimisation experiments for the S-Trt strategy^a

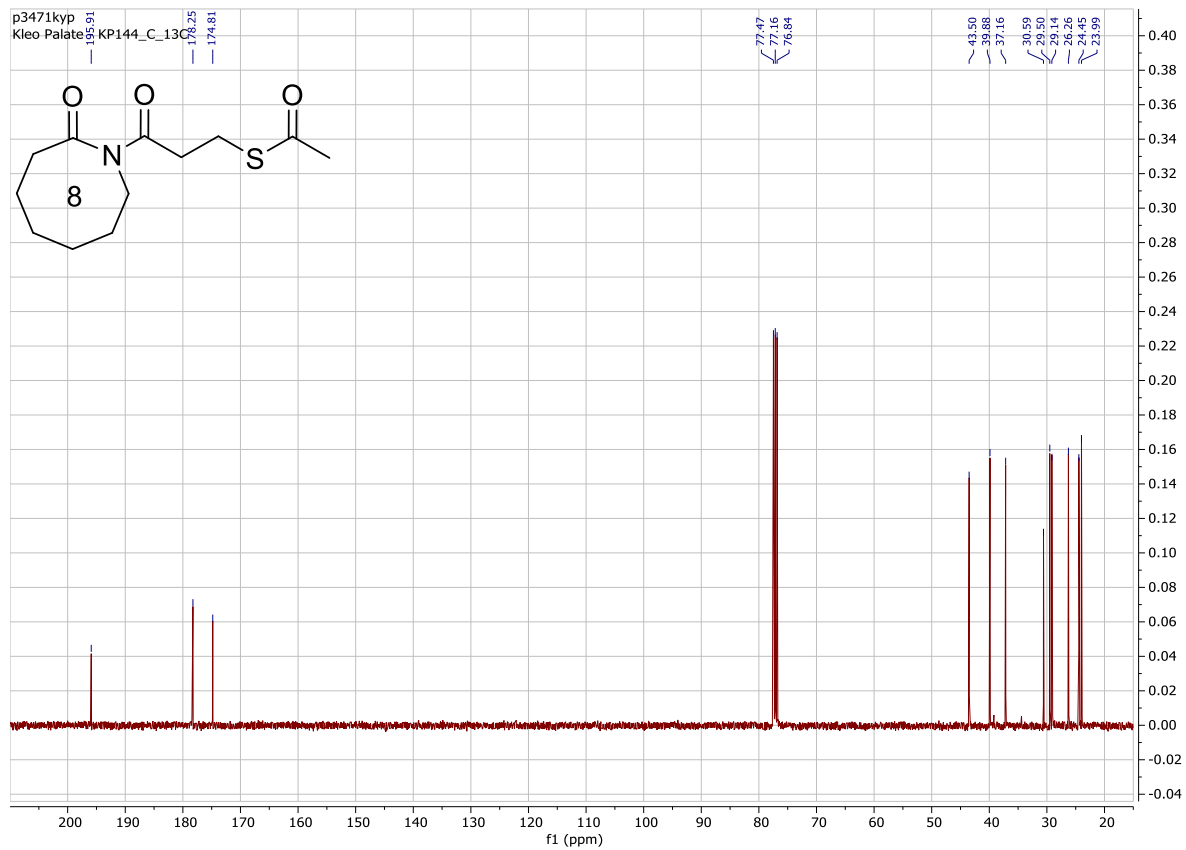
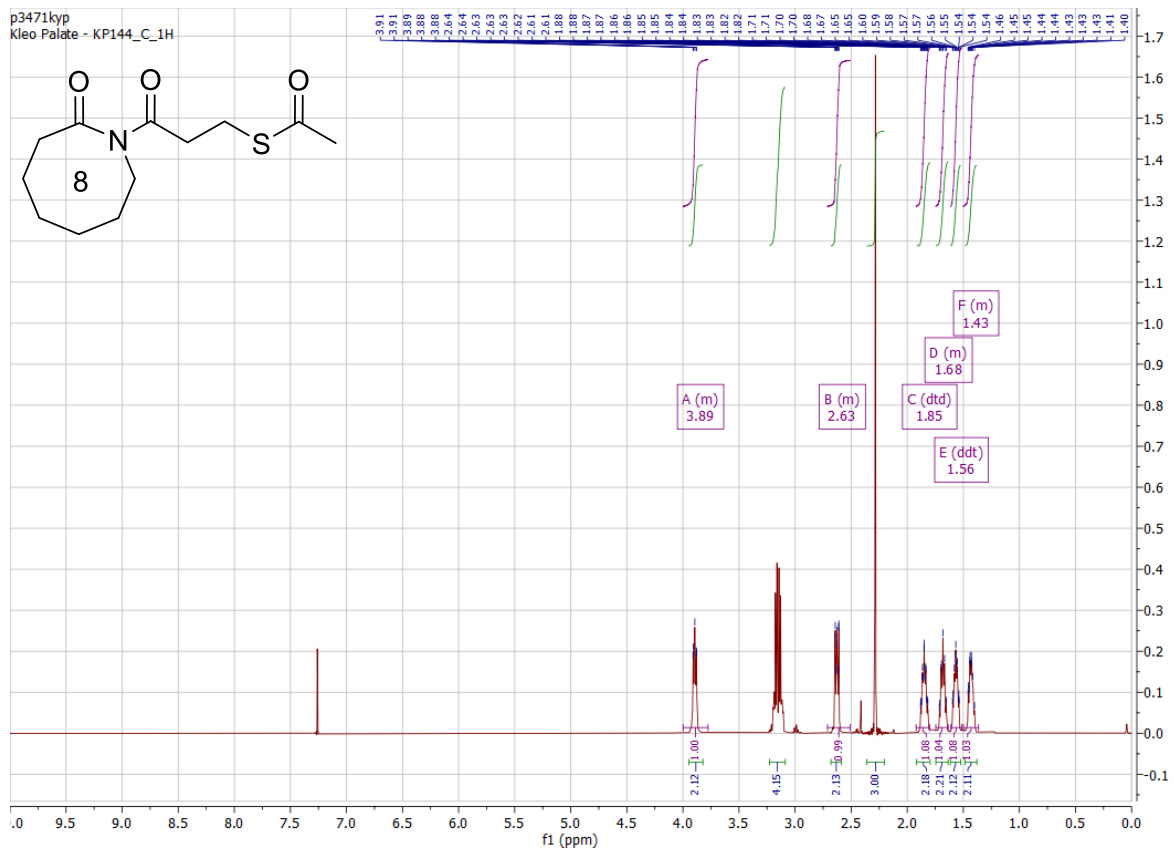


Entry	Step ii performed	Acid	Scavenger reagent	Yield ^b 24b /%	Side products ^b
1	No	TFA (8 equiv.)	<i>i</i> -Pr ₃ SiH (1.4 equiv.)	12	32 (48%), 33 (7%)
2	Yes	TFA (13 equiv.)	<i>i</i> -Pr ₃ SiH (1.2 equiv.)	56	21b (4%), 33 ^c
3	Yes	AcOH	<i>i</i> -Pr ₃ SiH (1.2 equiv.)	0	No reaction
4	Yes	HCl ^d	<i>i</i> -Pr ₃ SiH (1.2 equiv.)	0	No reaction
5	Yes	TFA ^e (1.1 equiv.)	<i>i</i> -Pr ₃ SiH (1.2 equiv.)	trace	21b (3%), 31b (80%)
6	Yes	TFA (13 equiv.)	Et ₃ SiH (1.3 equiv.)	36	21b (4%), 33 (7%)

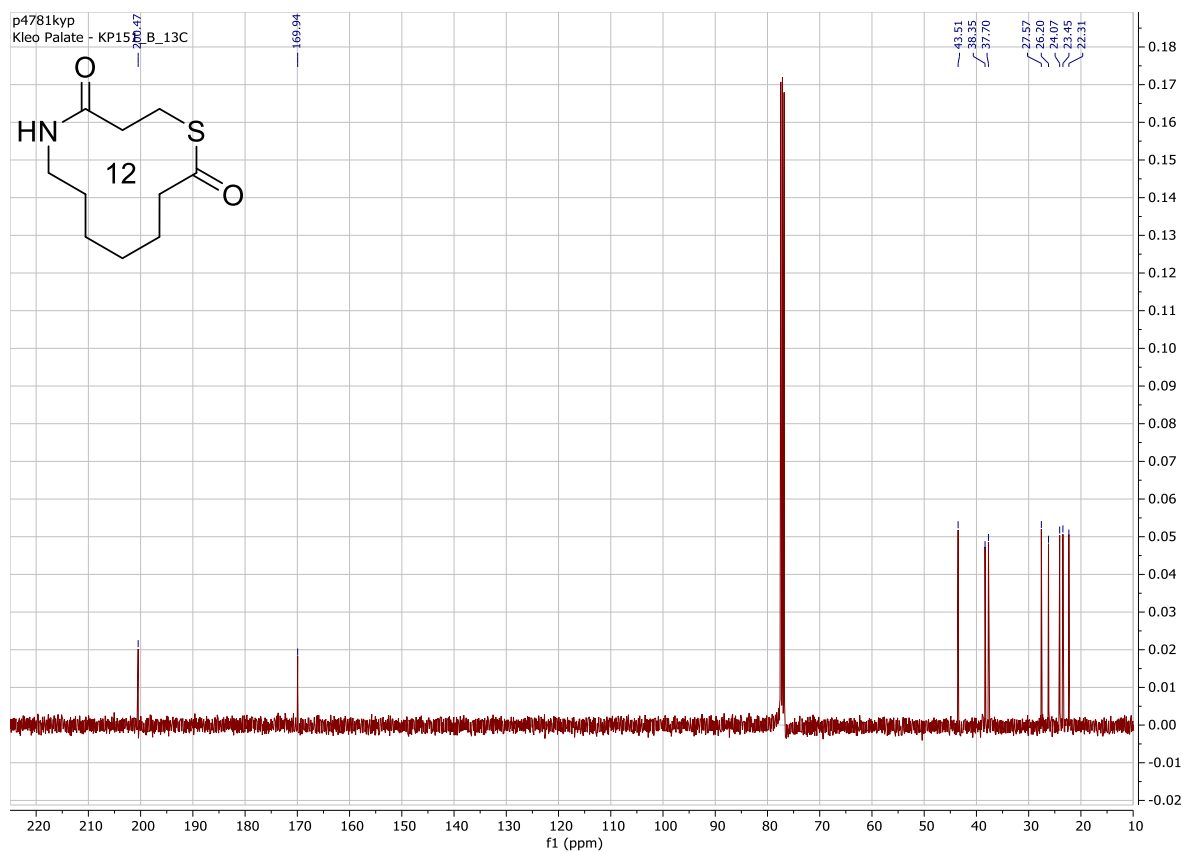
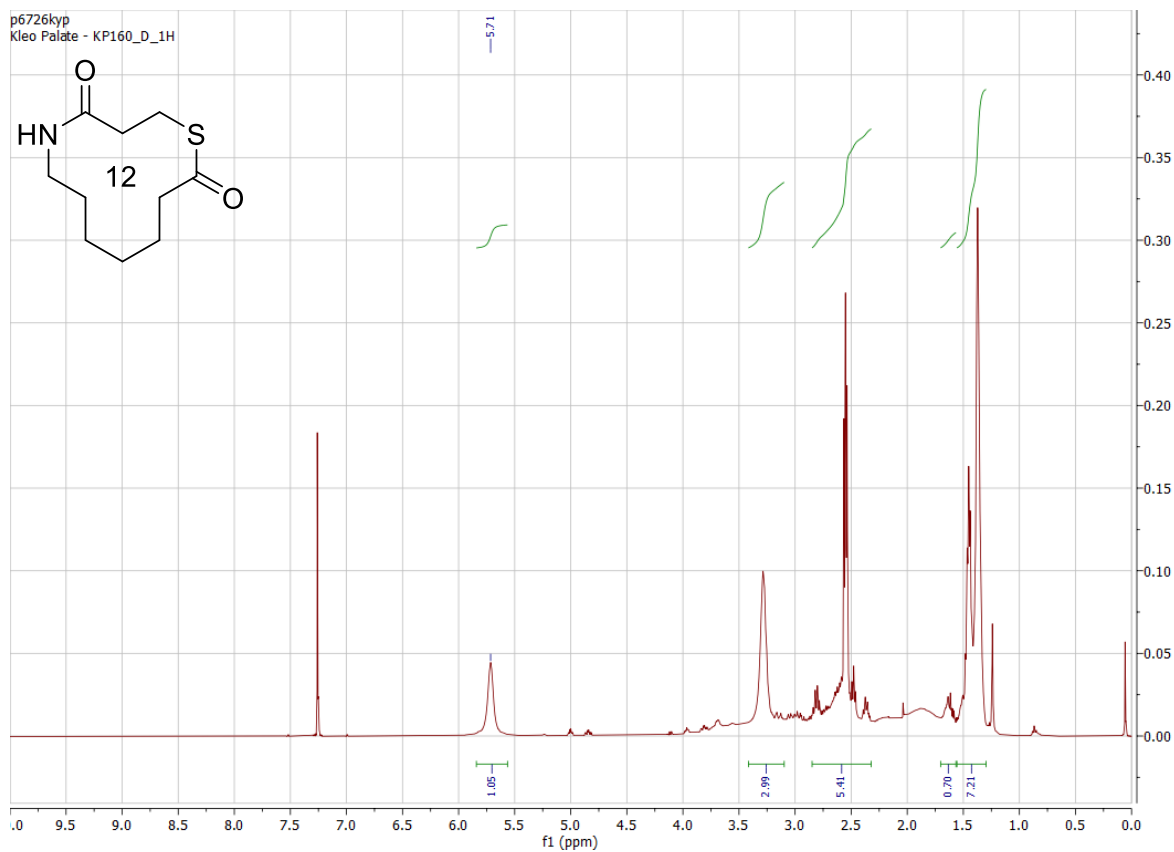
^a Unless stated, the following protocol was used for step i) - the stated acid was added to **31b** in DCM at RT and stirred for 3 min, before adding the scavenger reagent and stirring at RT for a further 30 min (for full synthetic procedures, see ESI). ^b Yields refer to material isolated cleanly following column chromatography. ^c **33** observed by TLC but not isolated. ^d 4 M in 1,4-dioxane. ^e at 0 °C

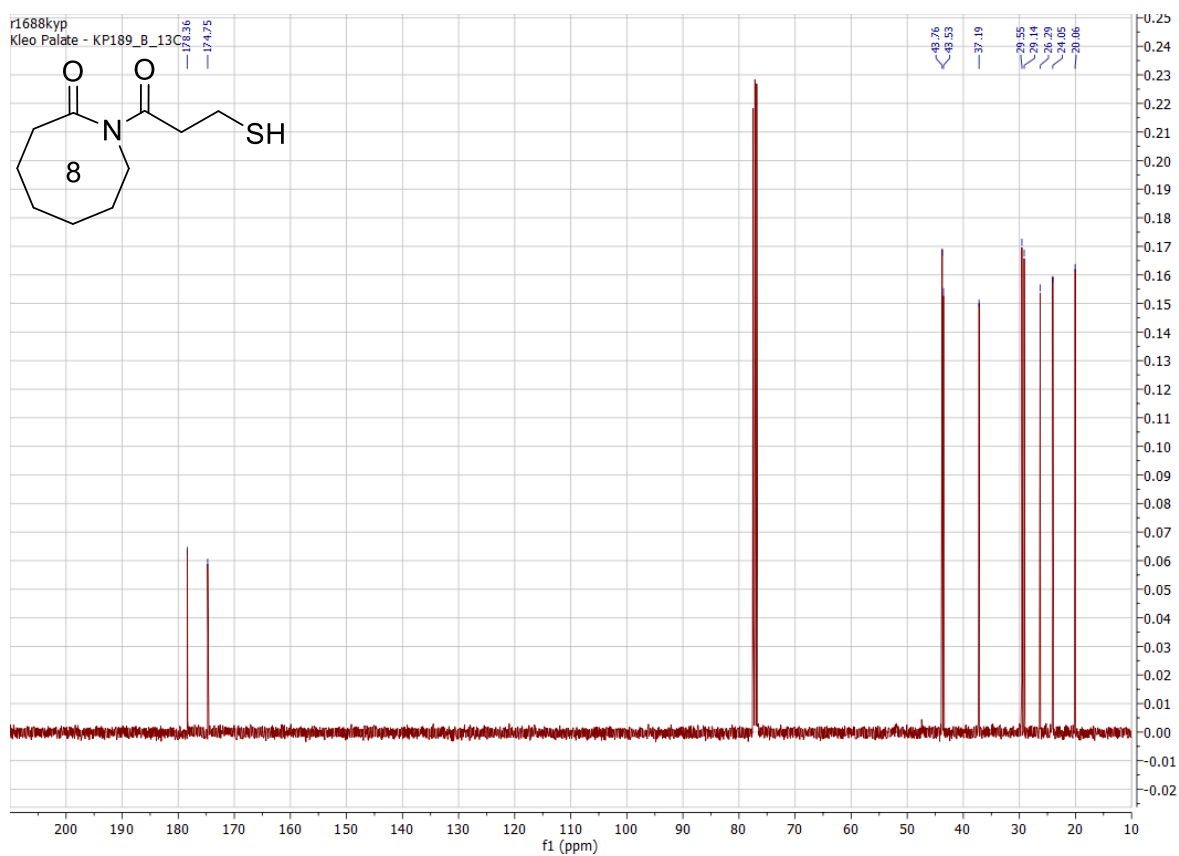
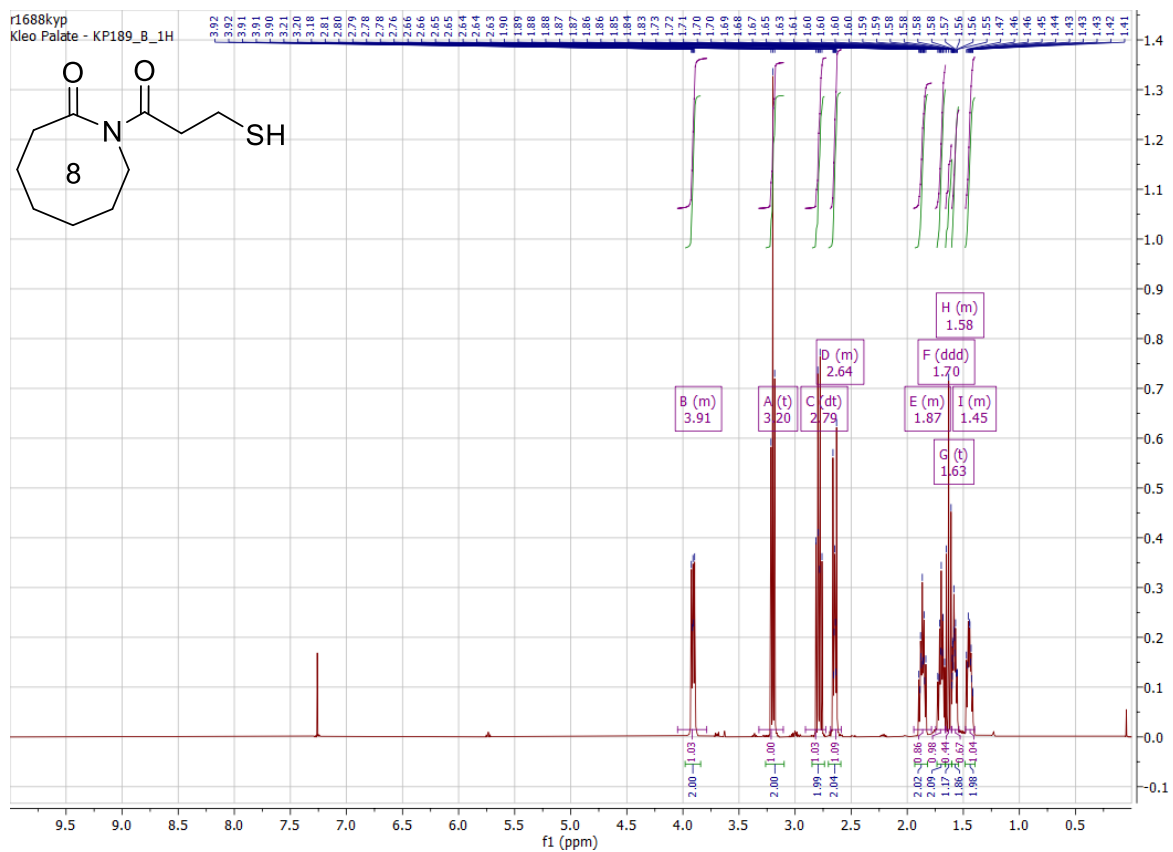


23a

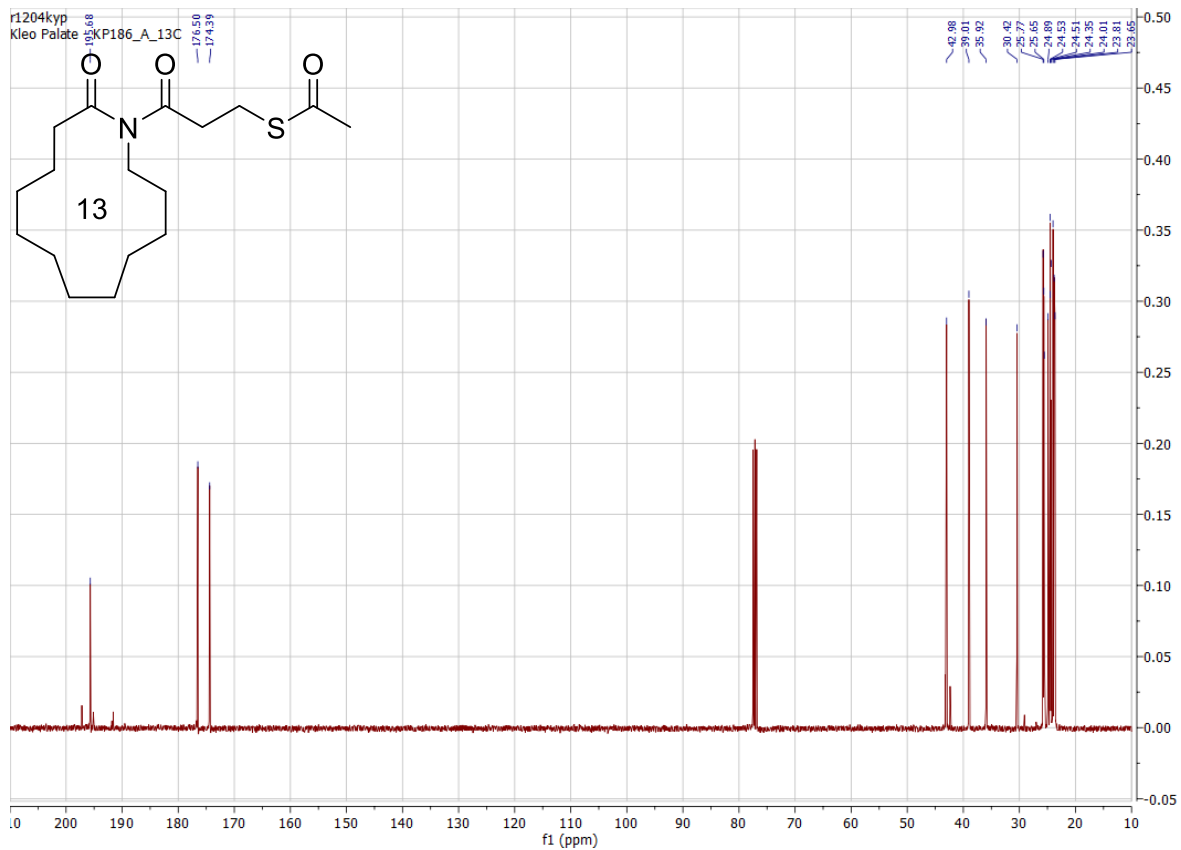
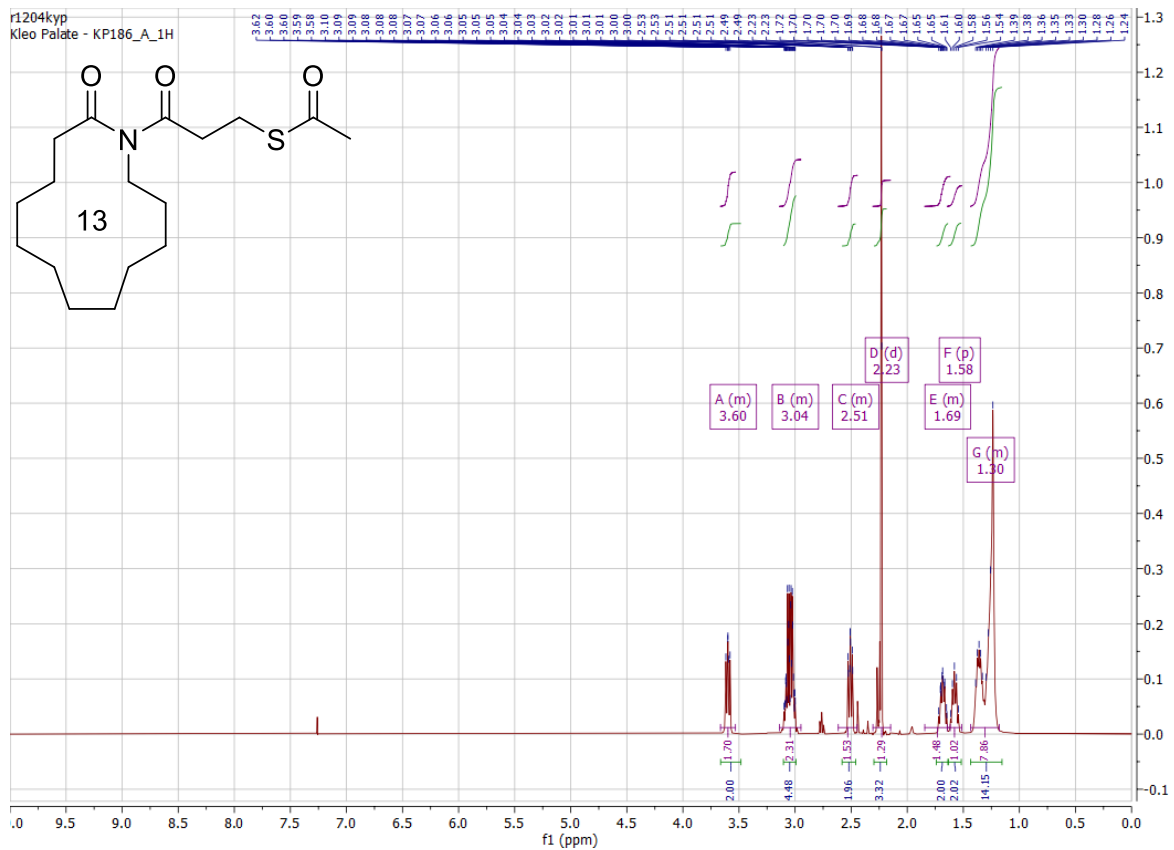


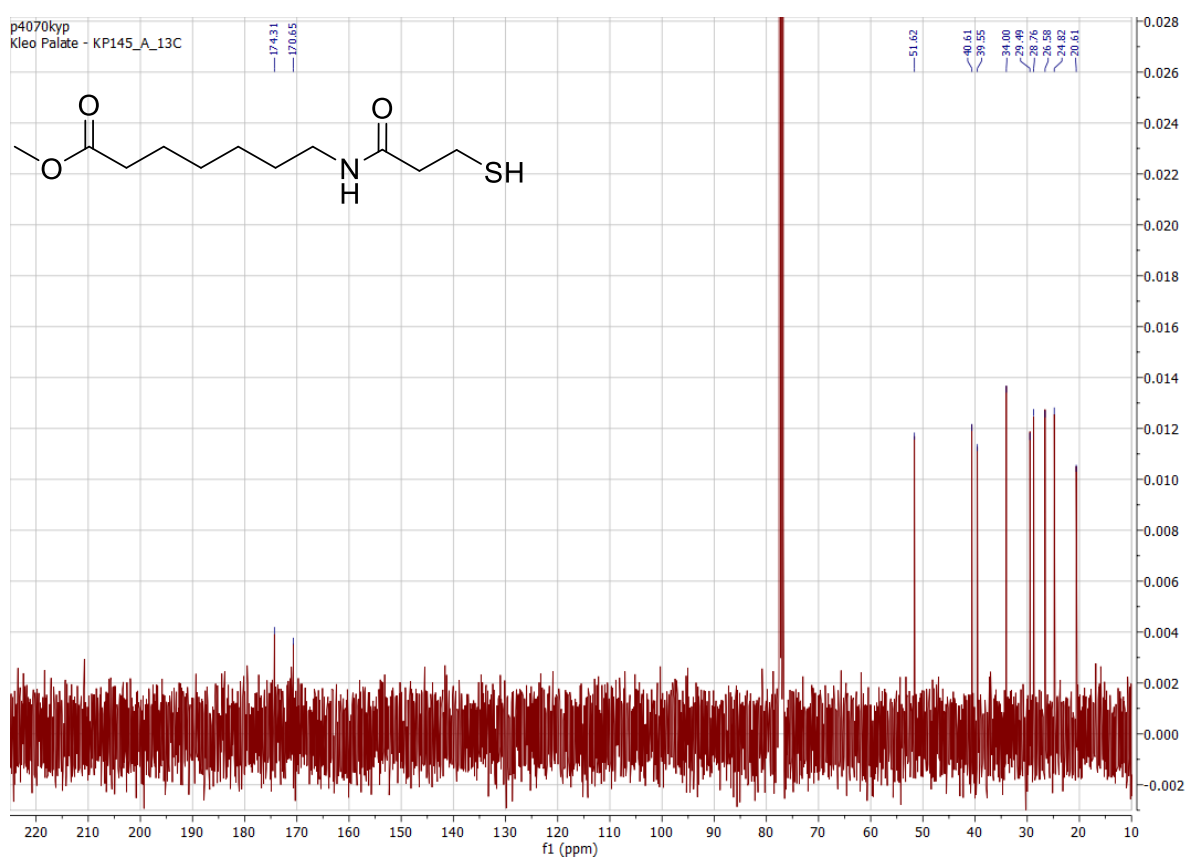
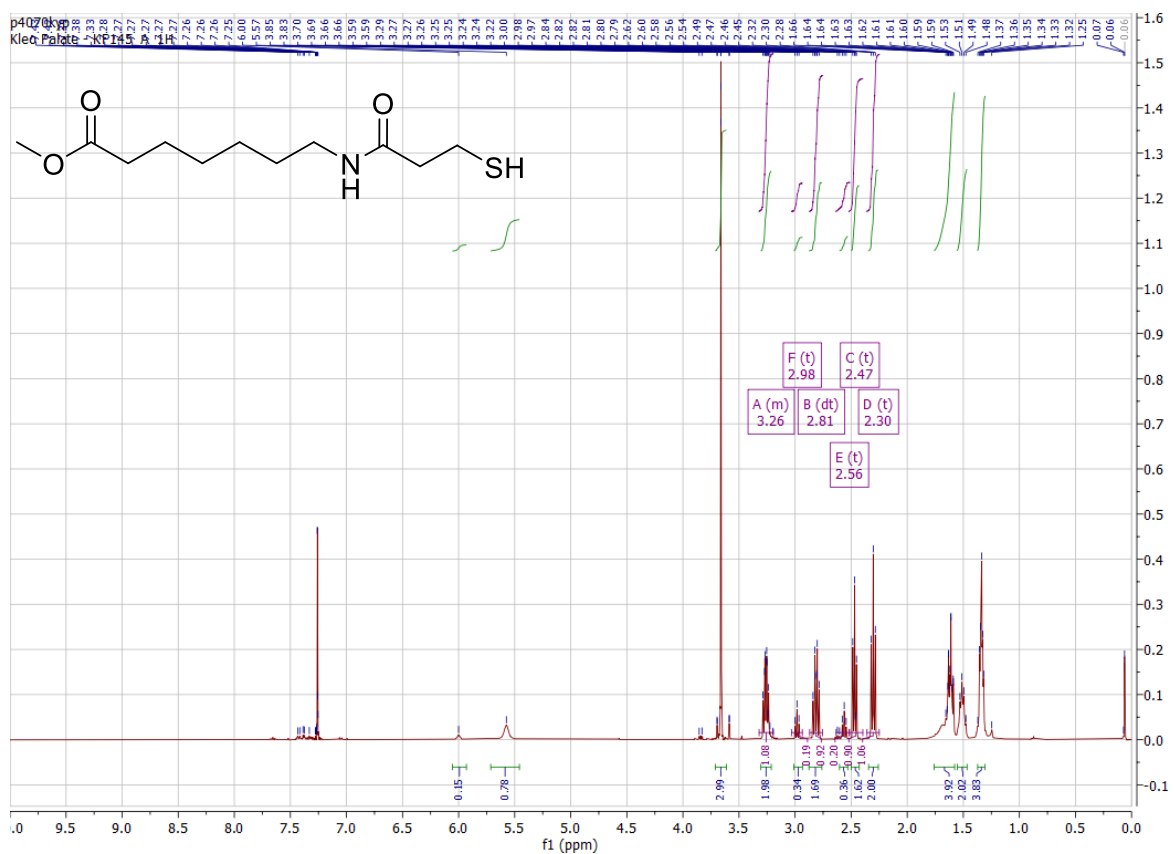
20RE

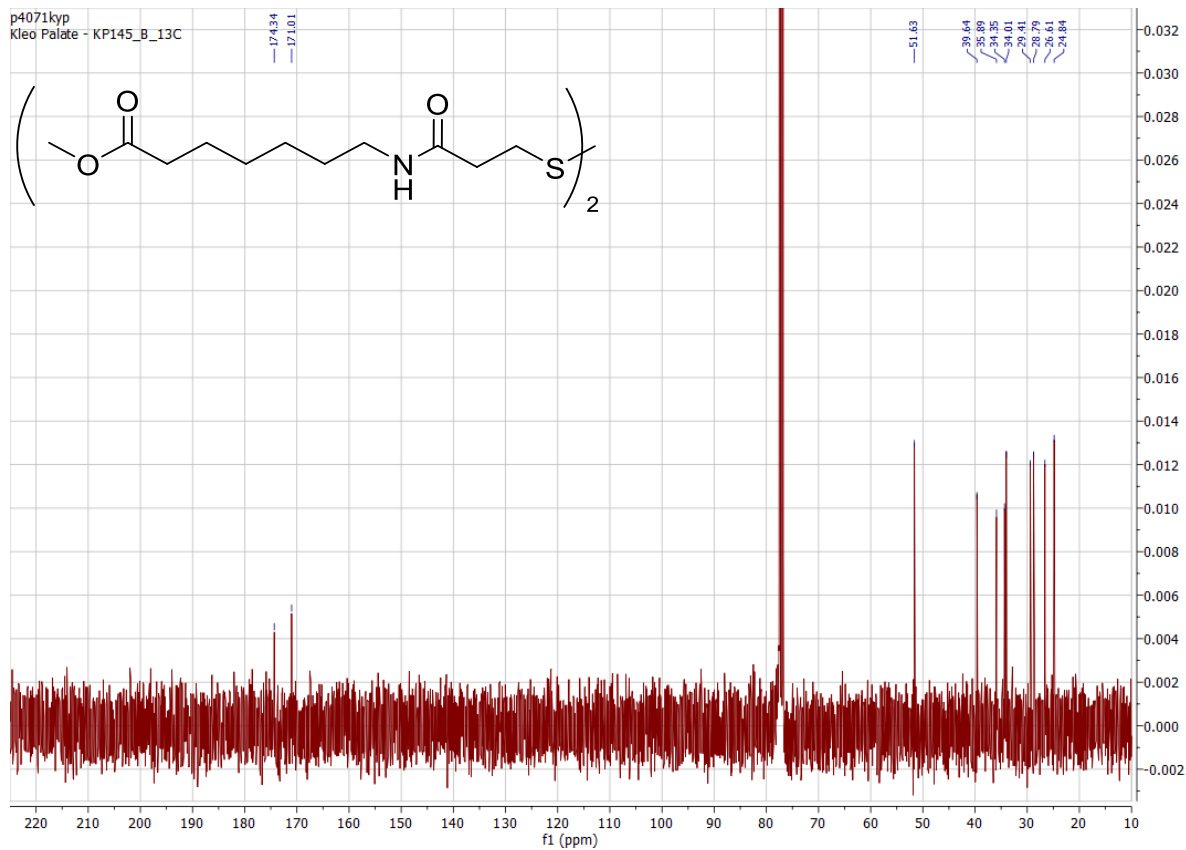
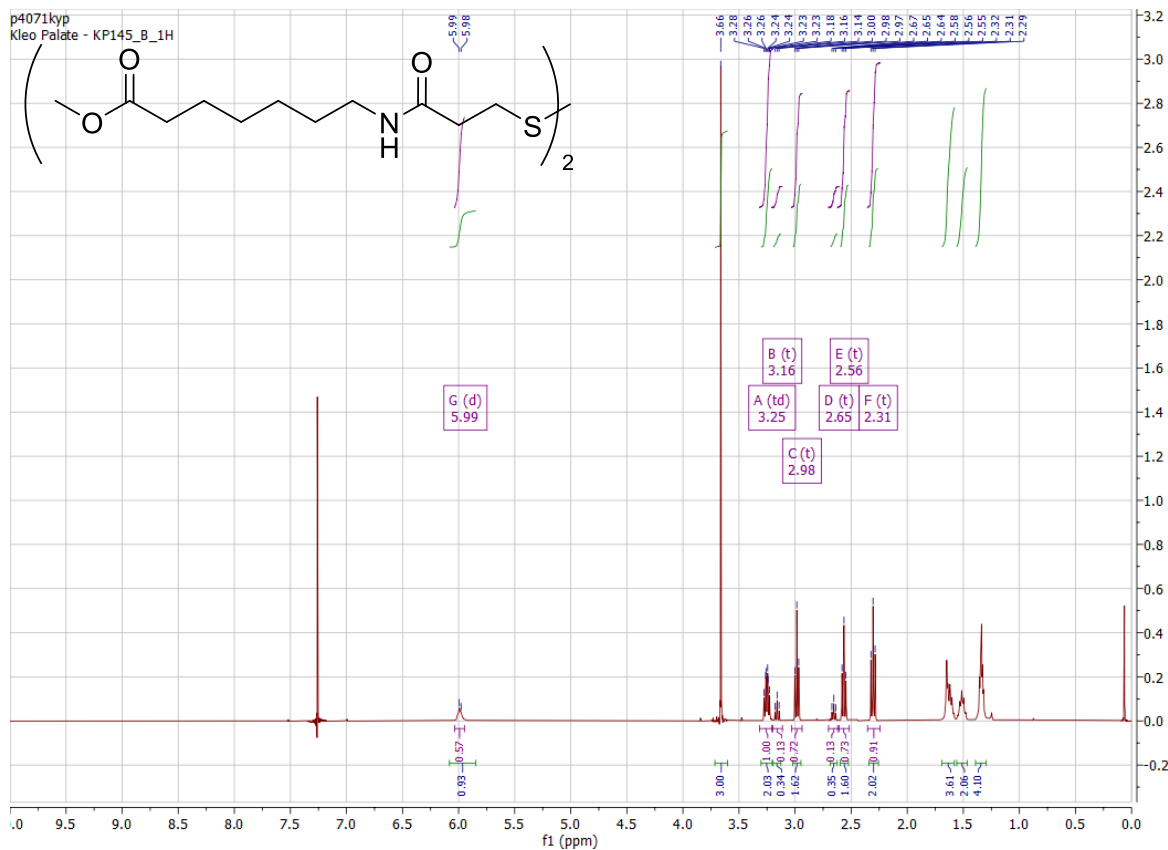




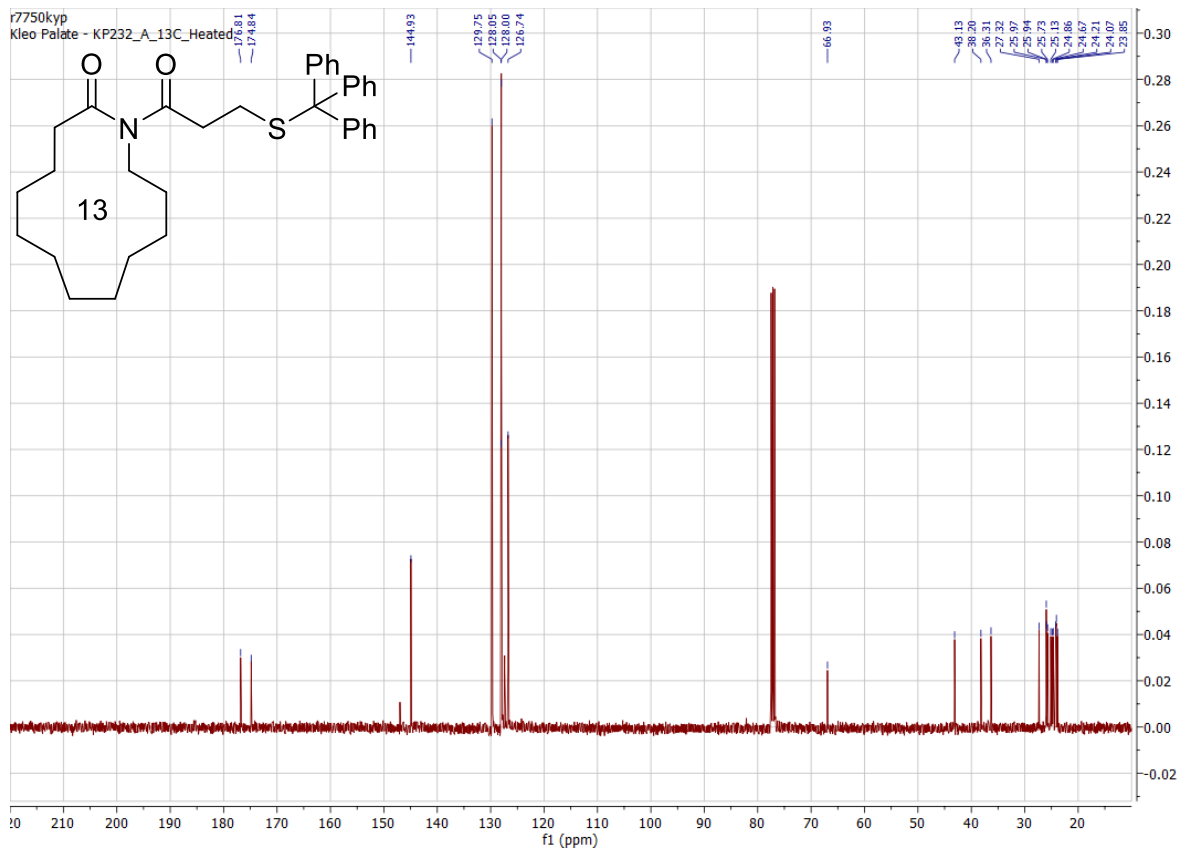
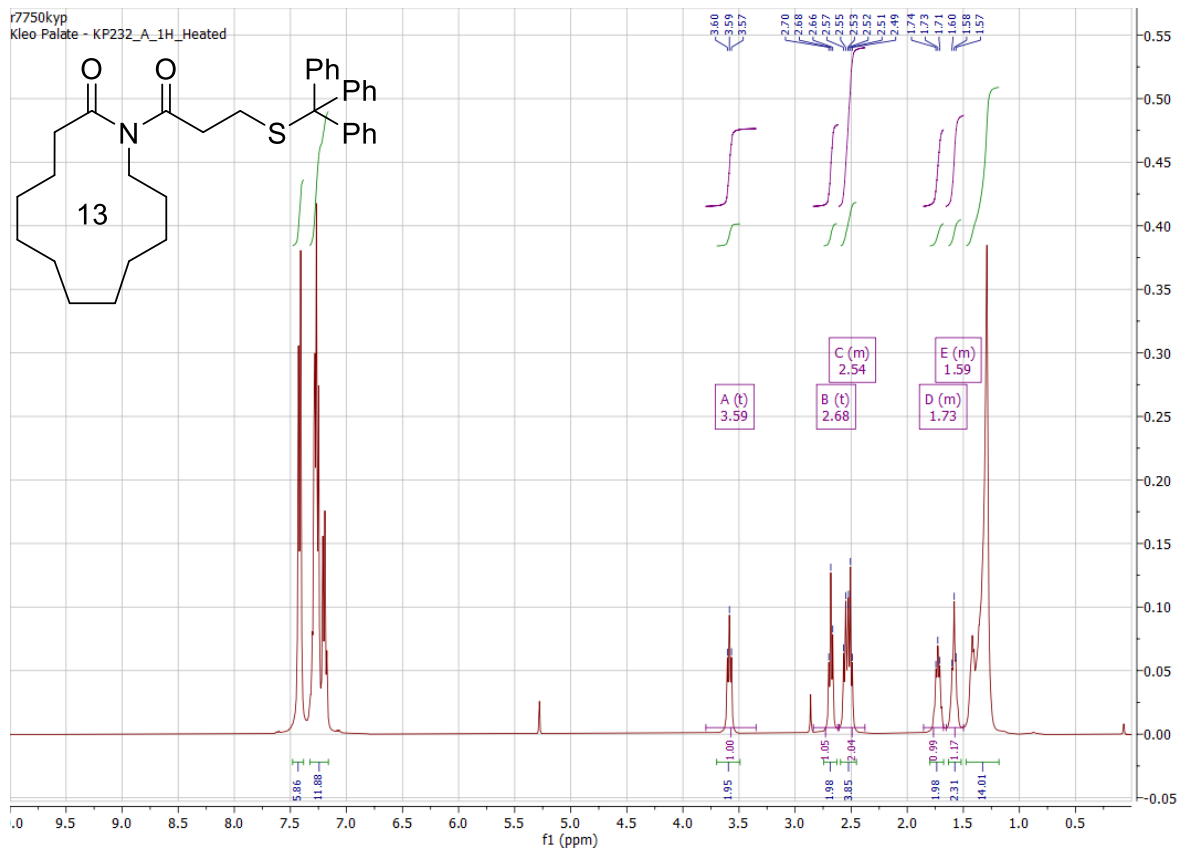
23b

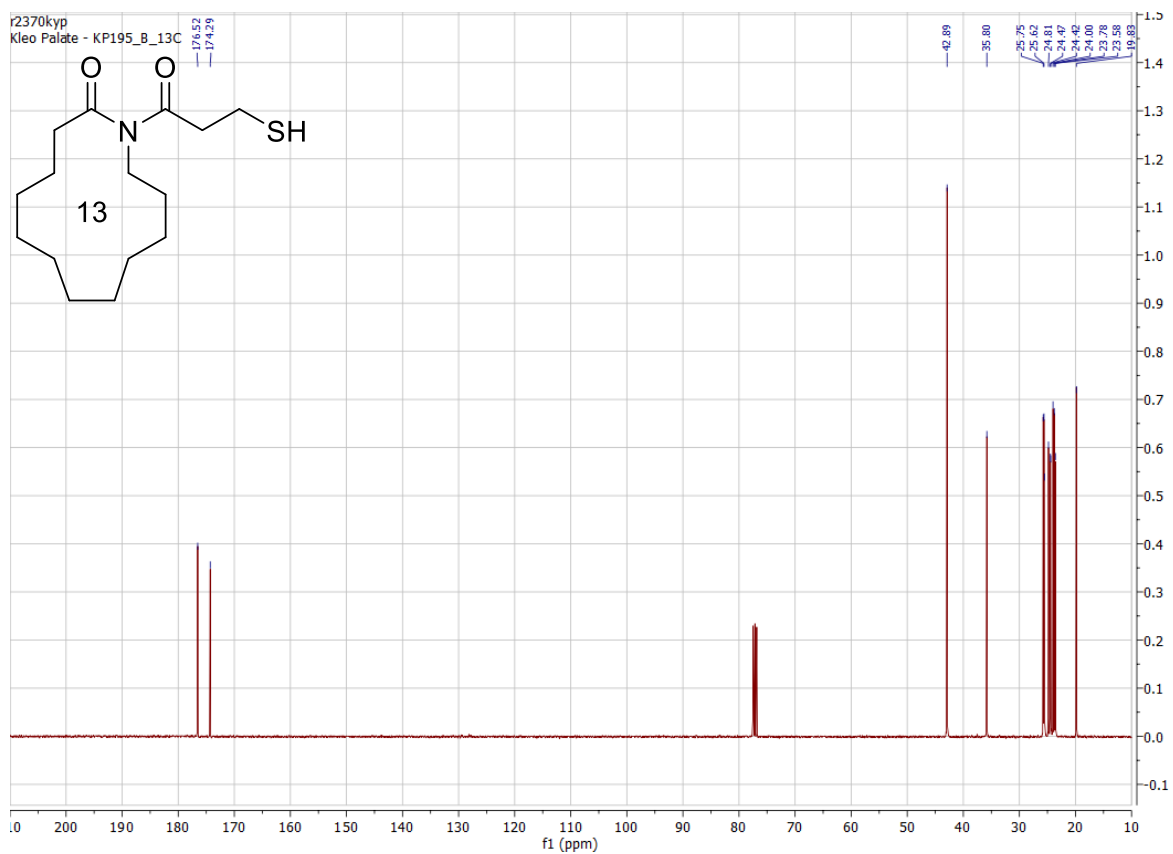
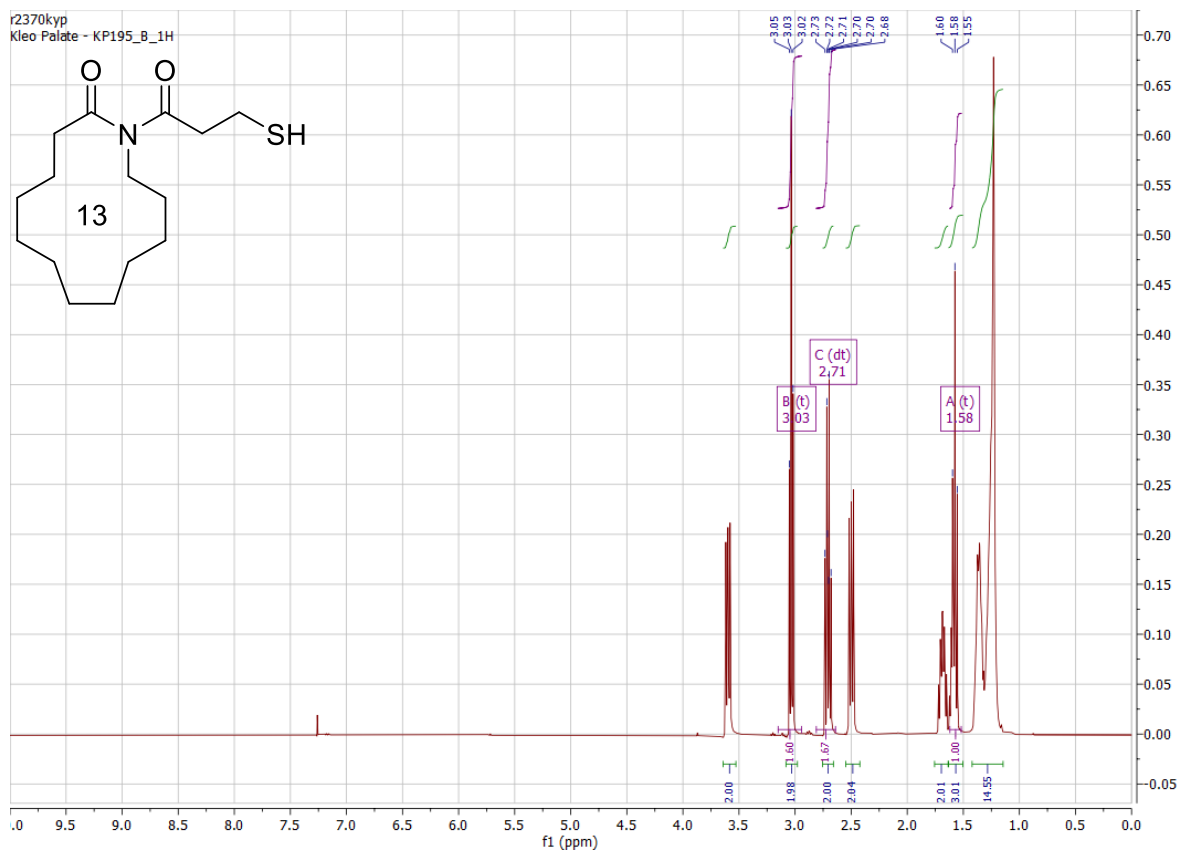


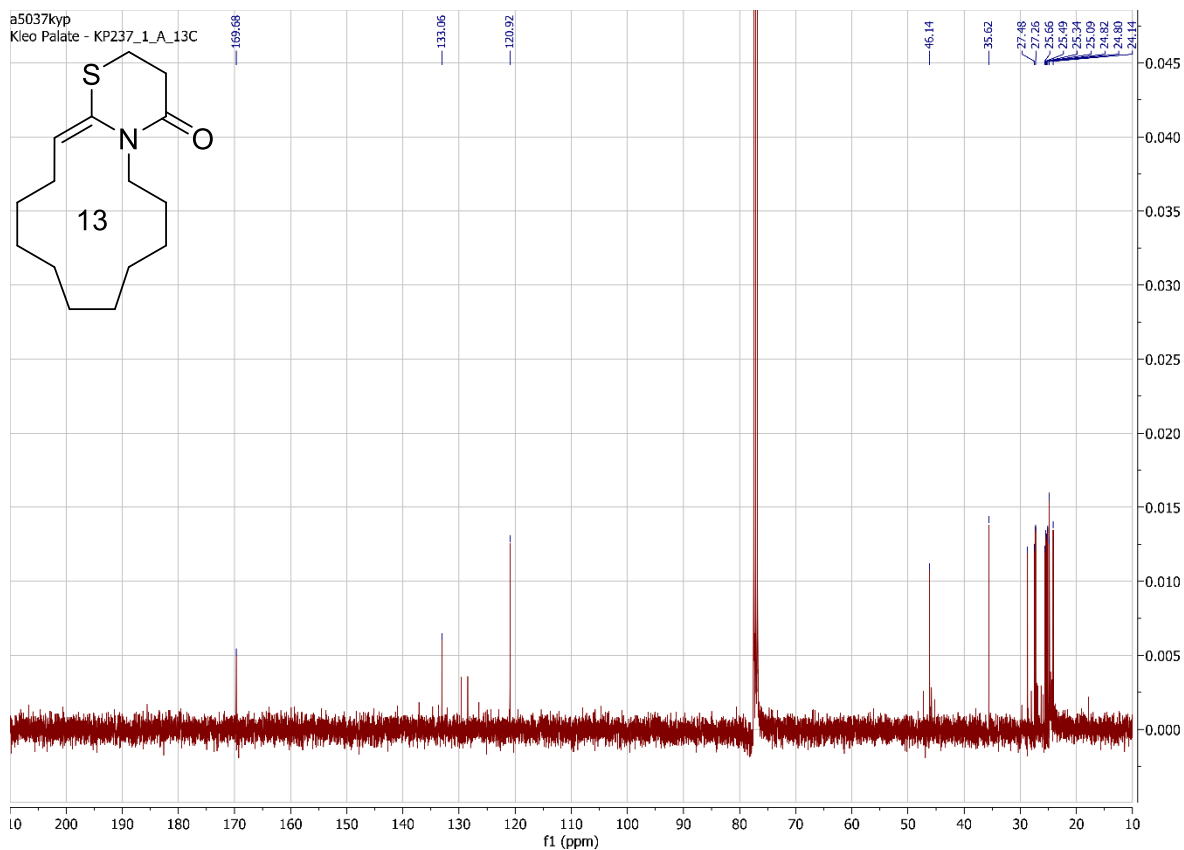
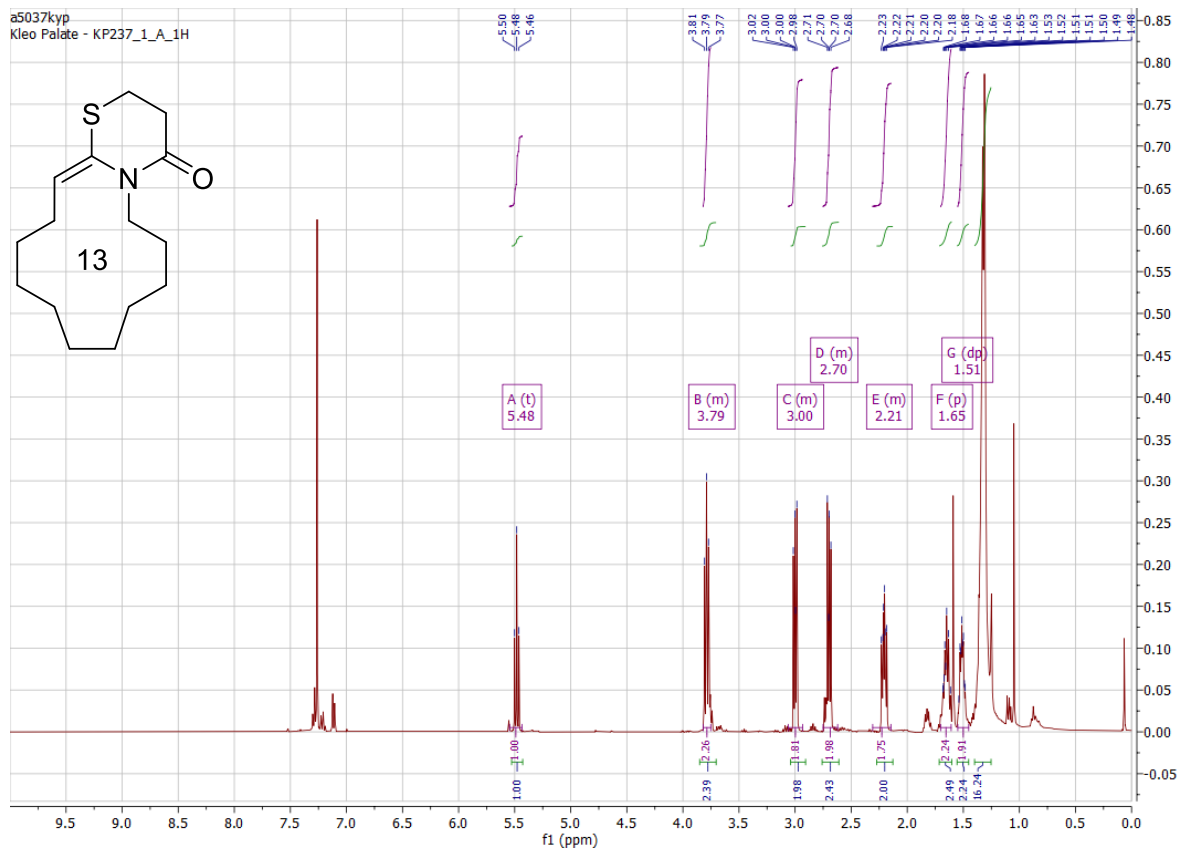




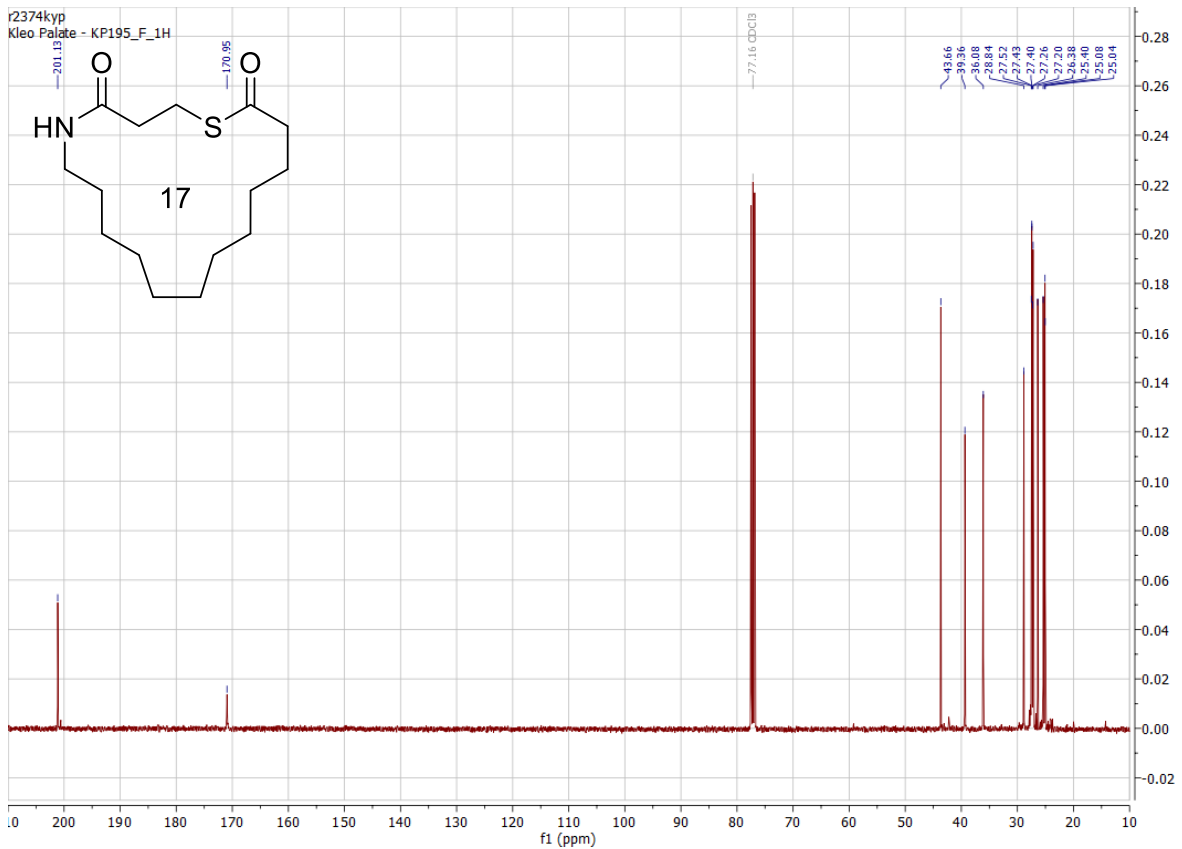
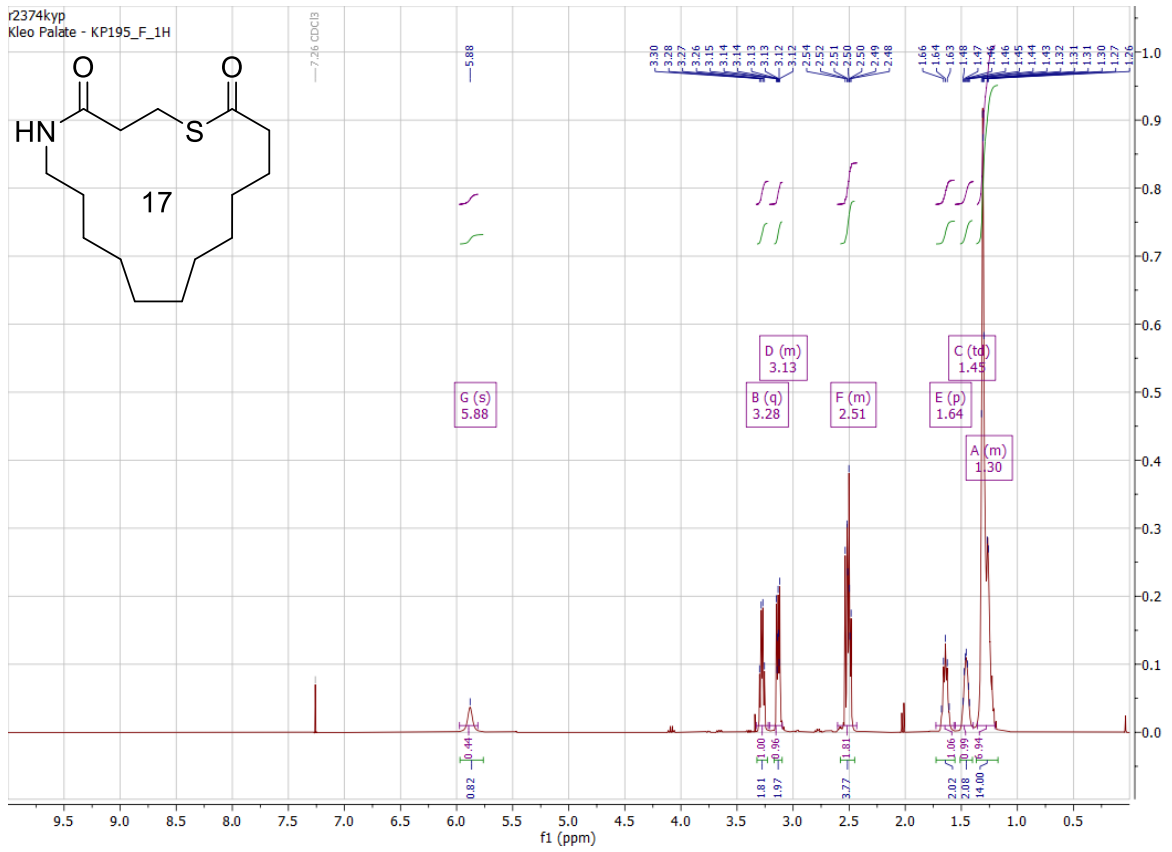
31b



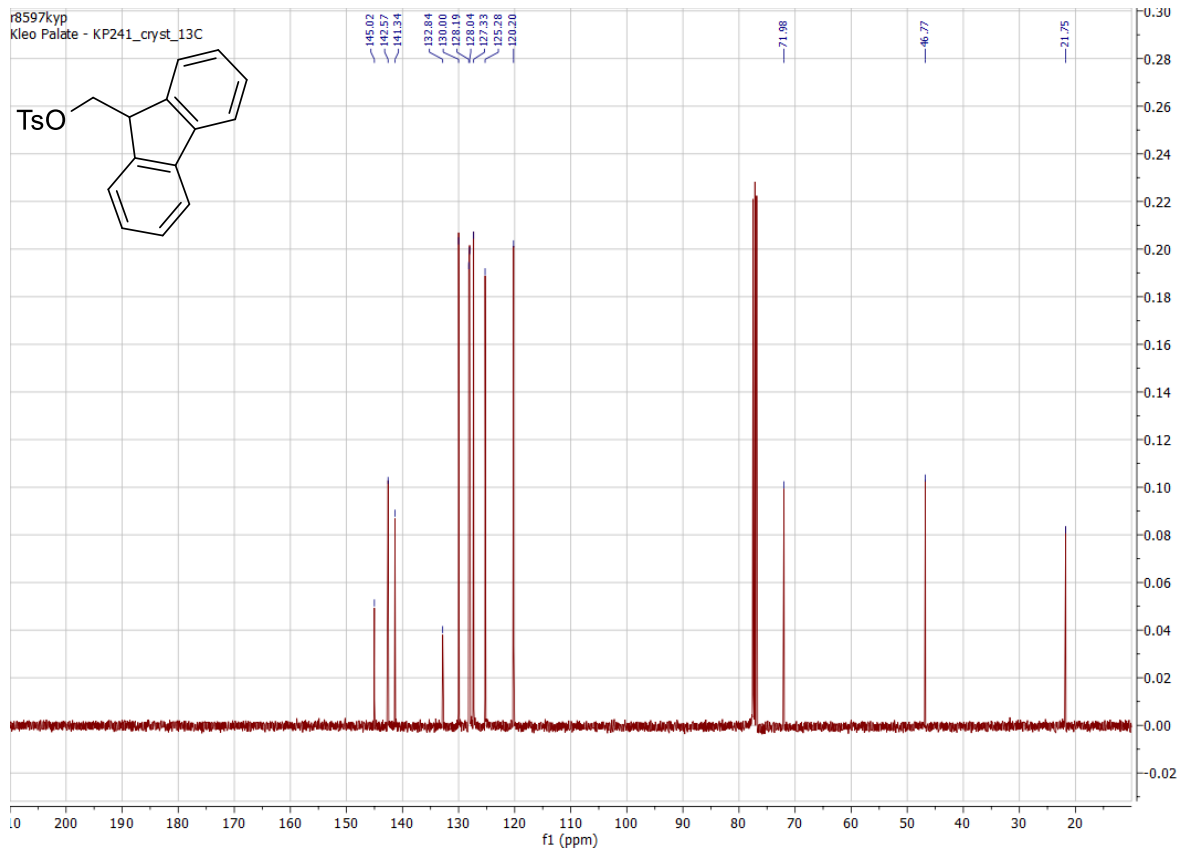
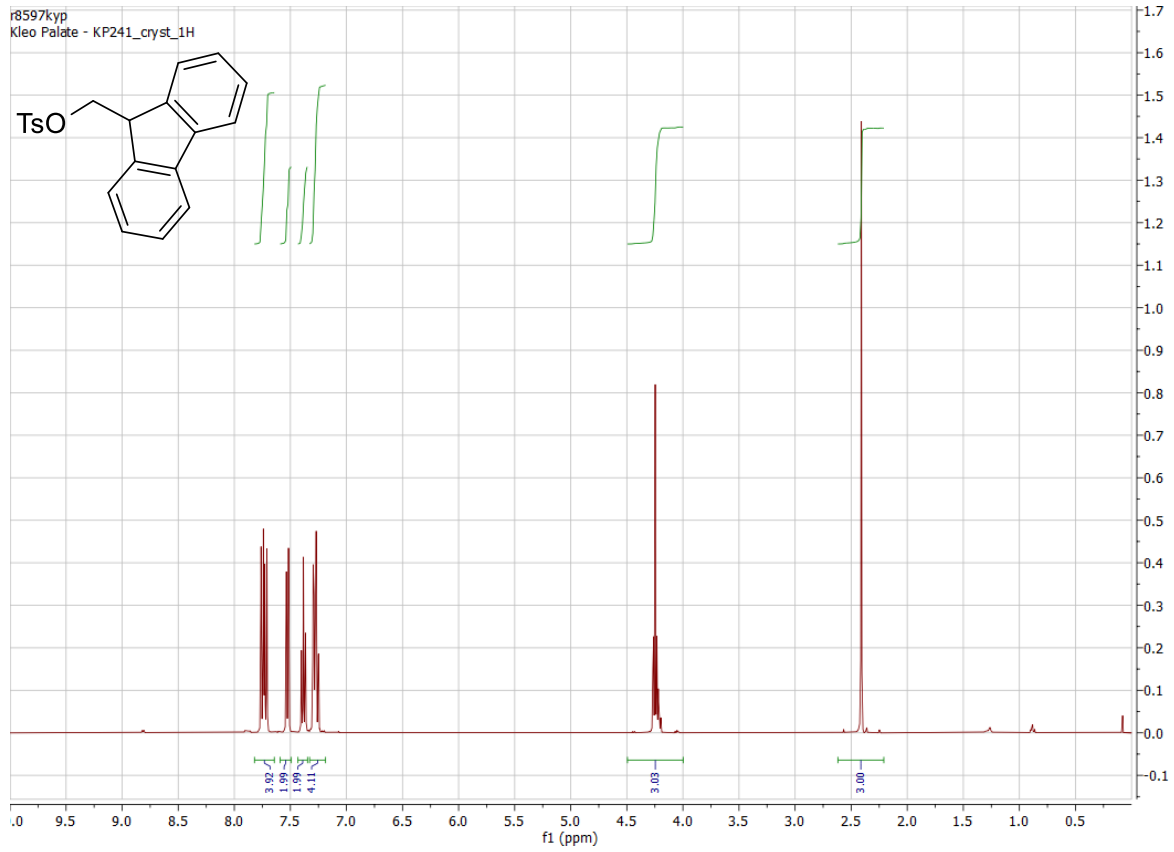




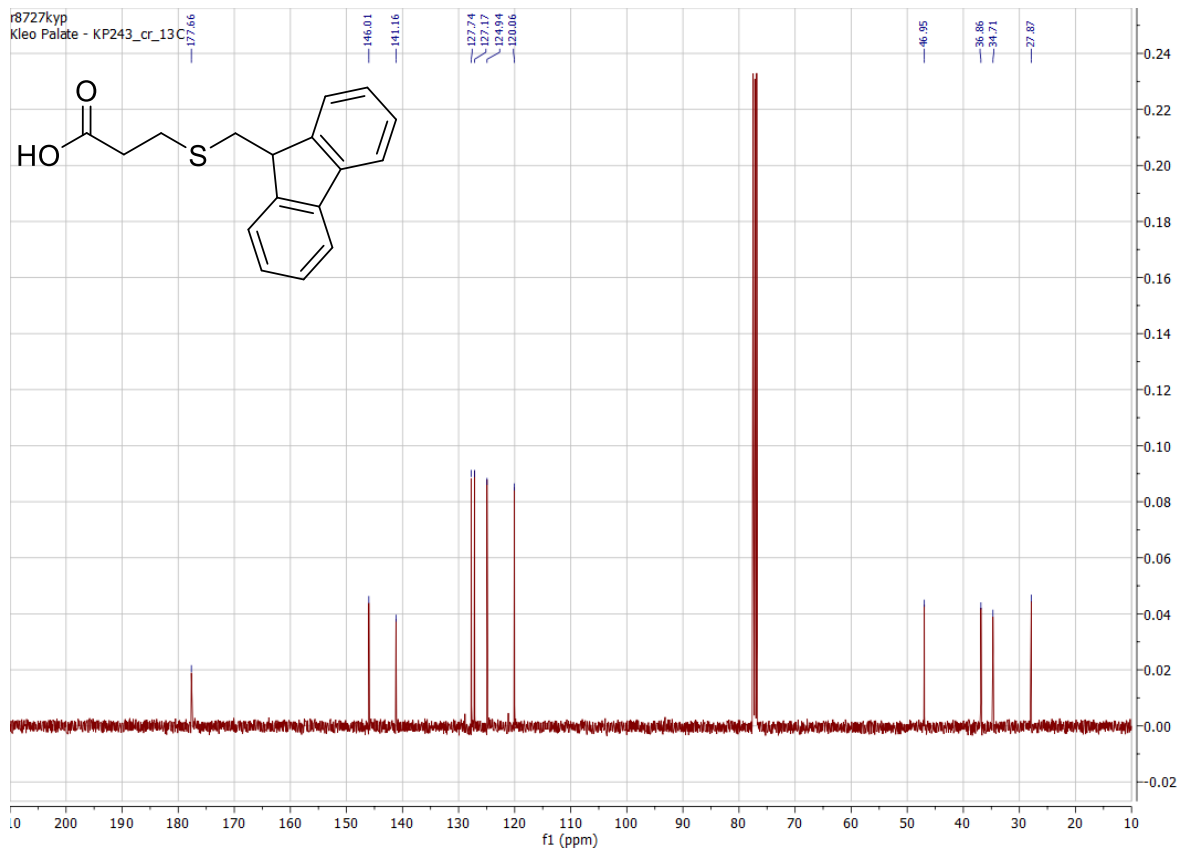
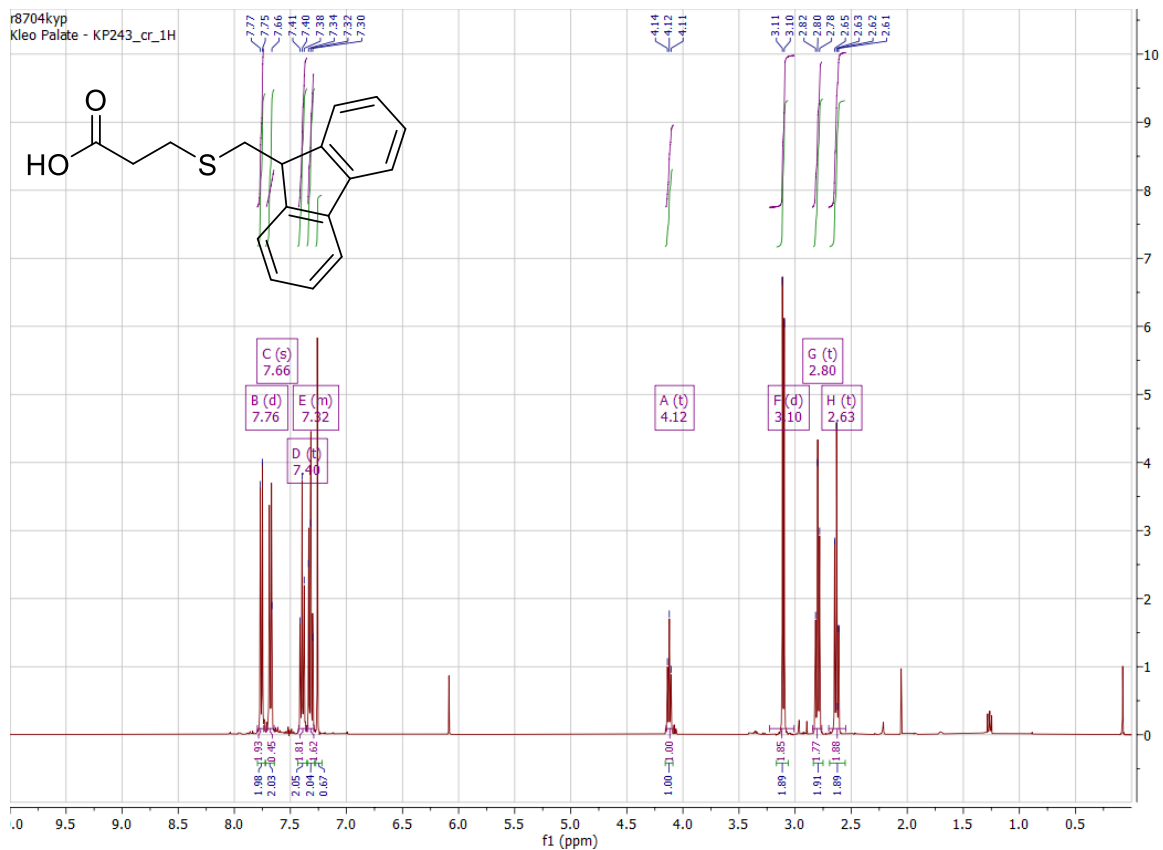
24b

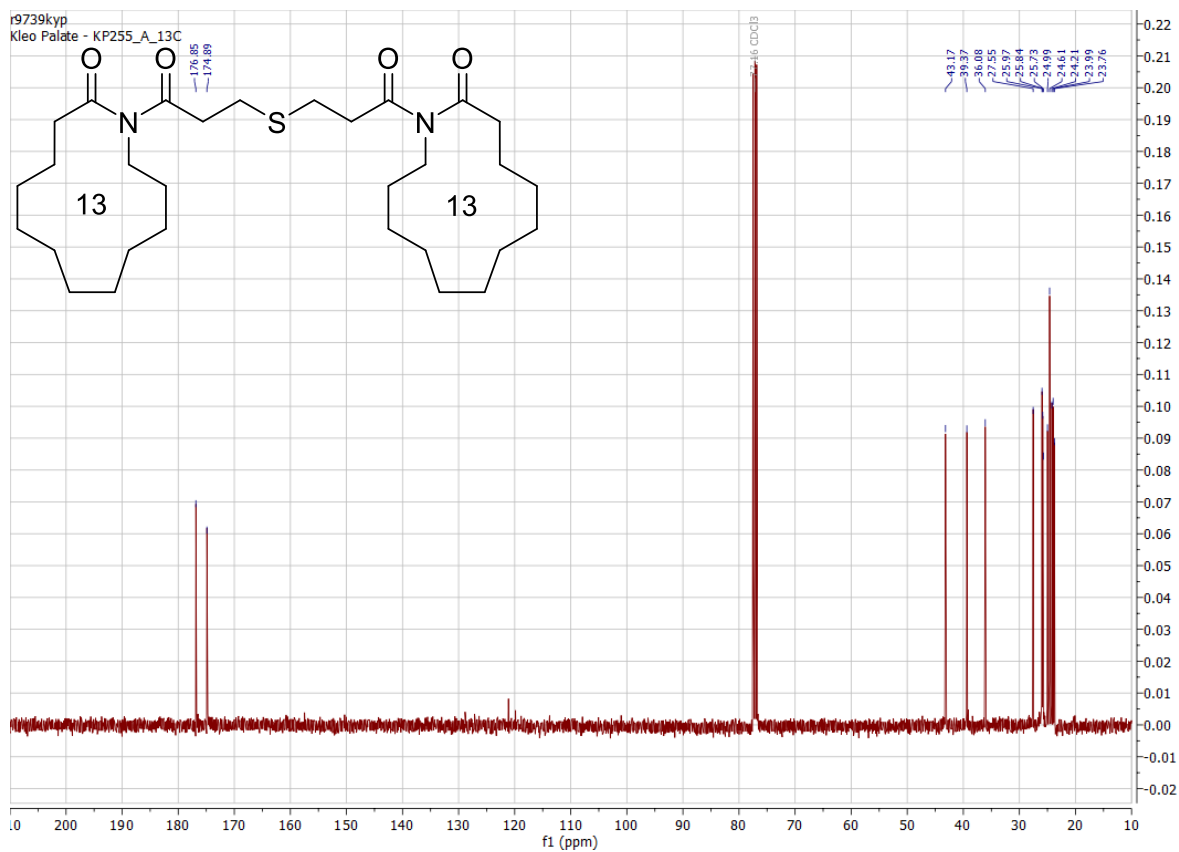
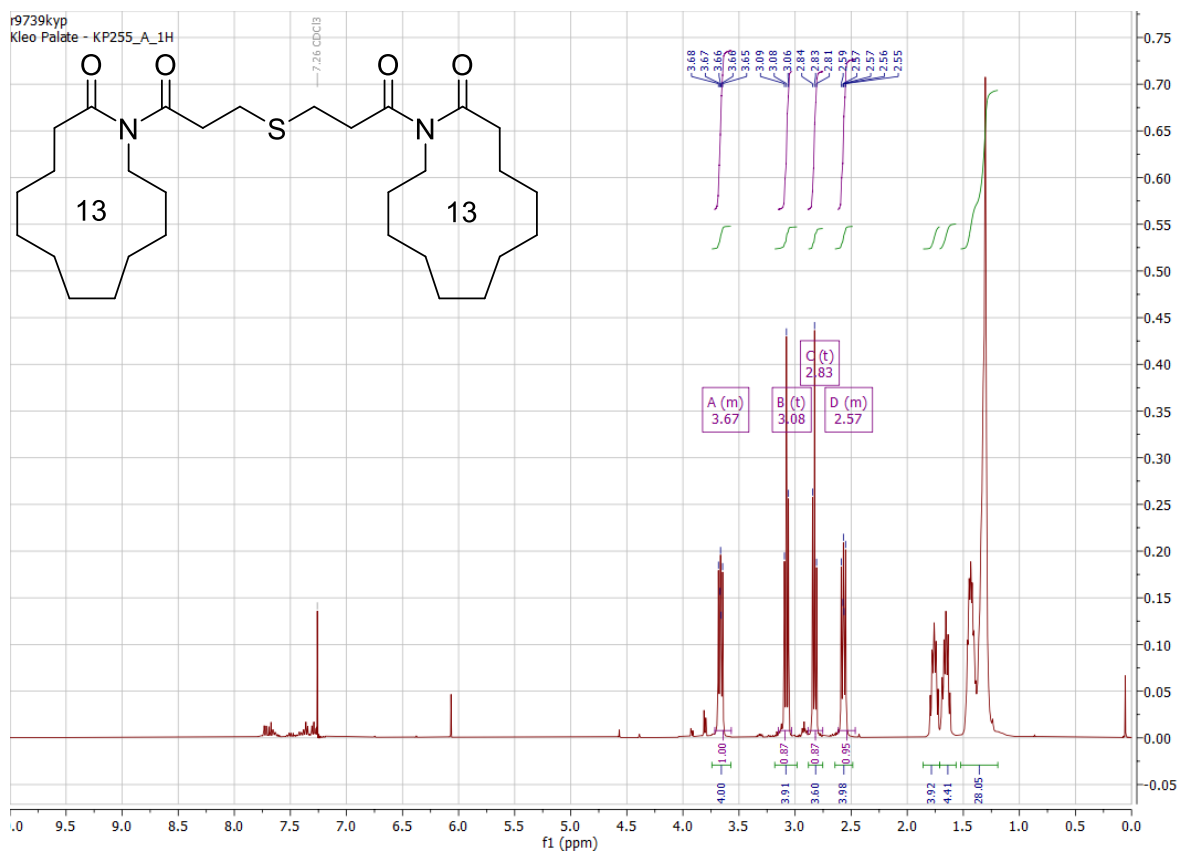


Fluorenylmethyl *p*-toluenesulfonate

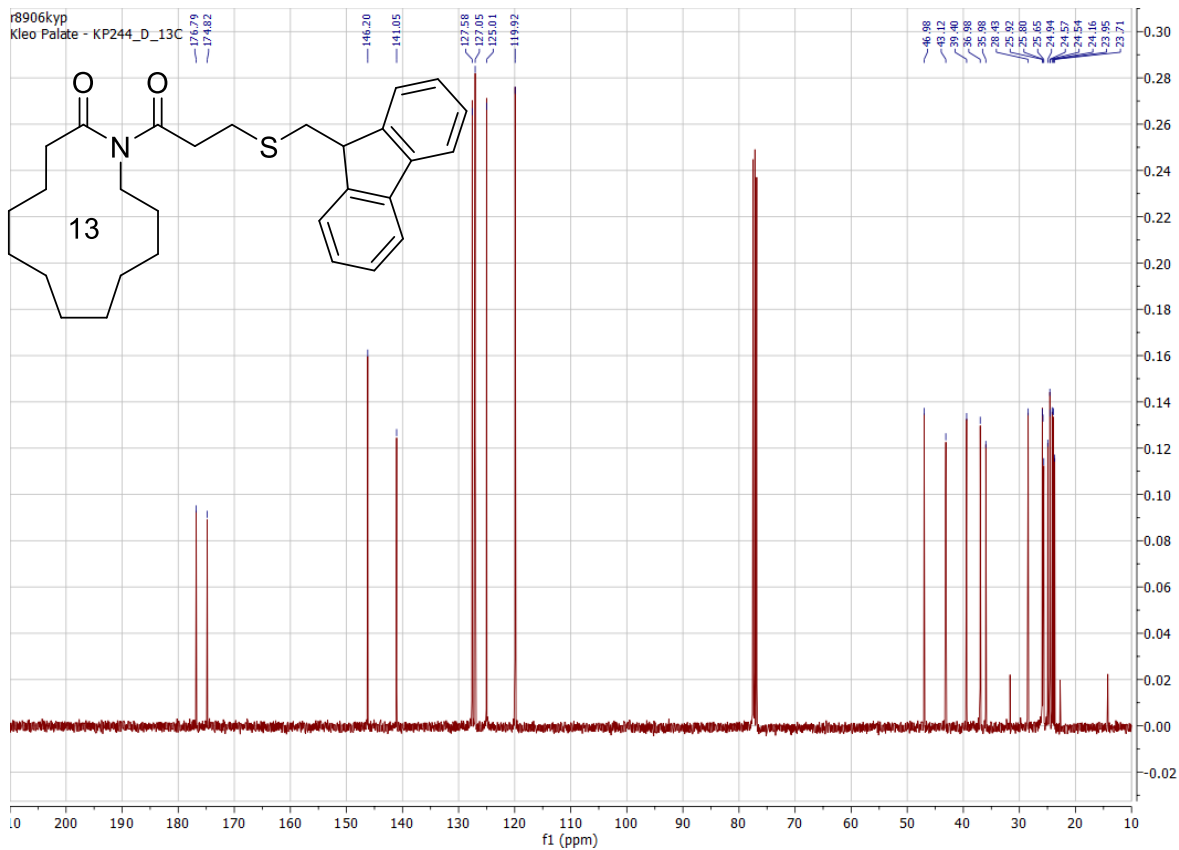
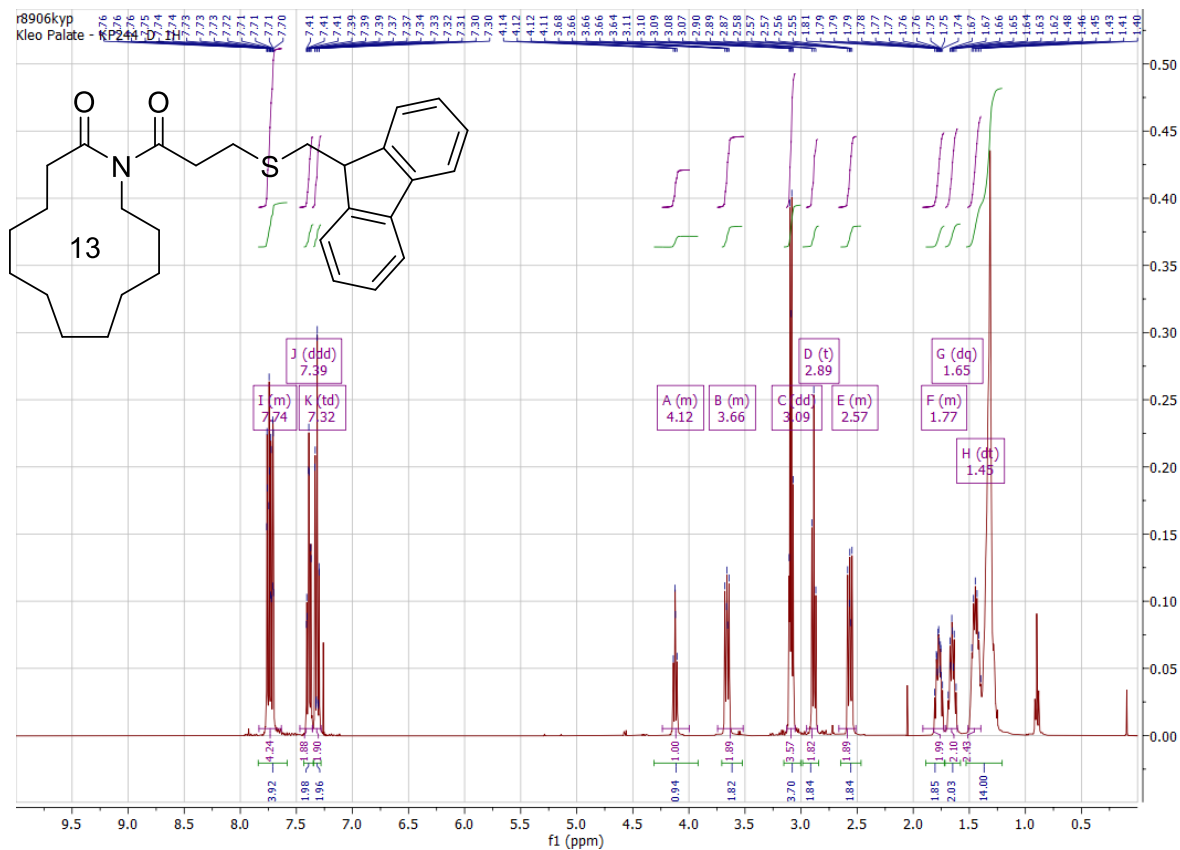


S1

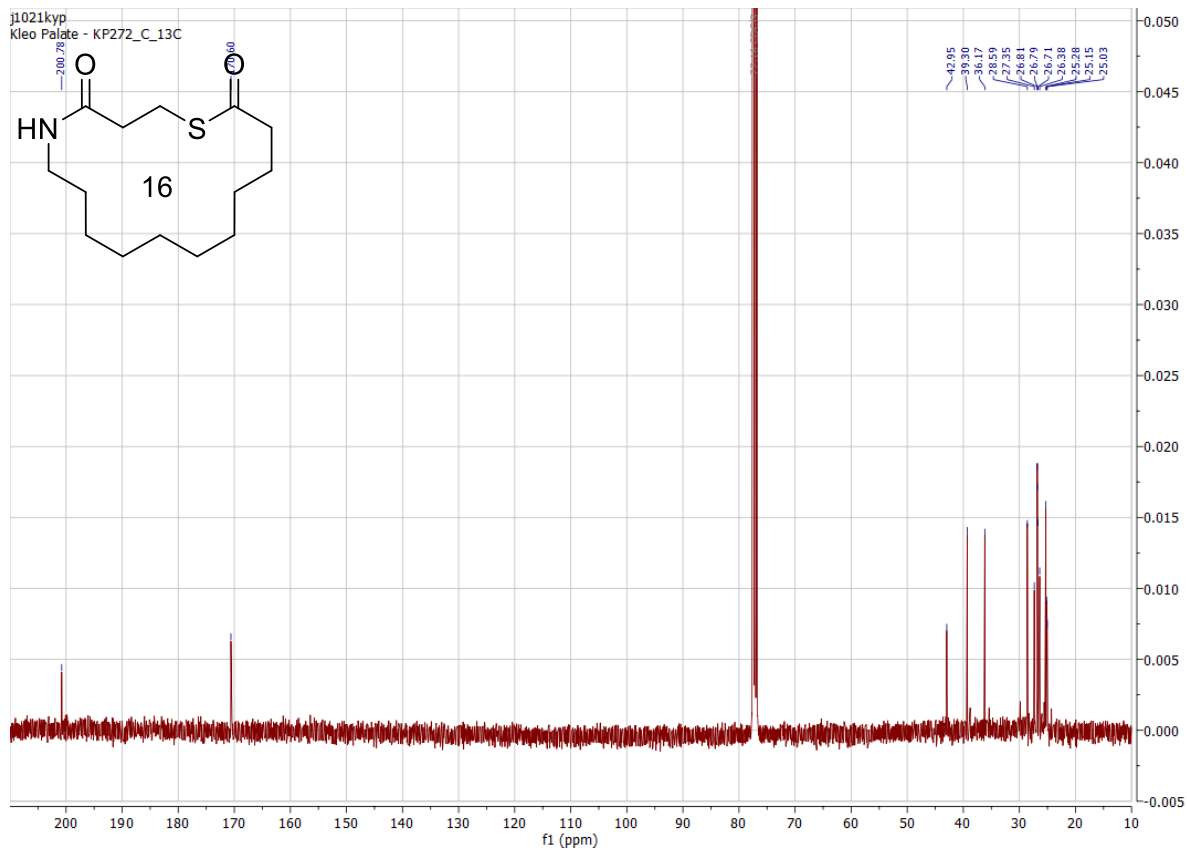
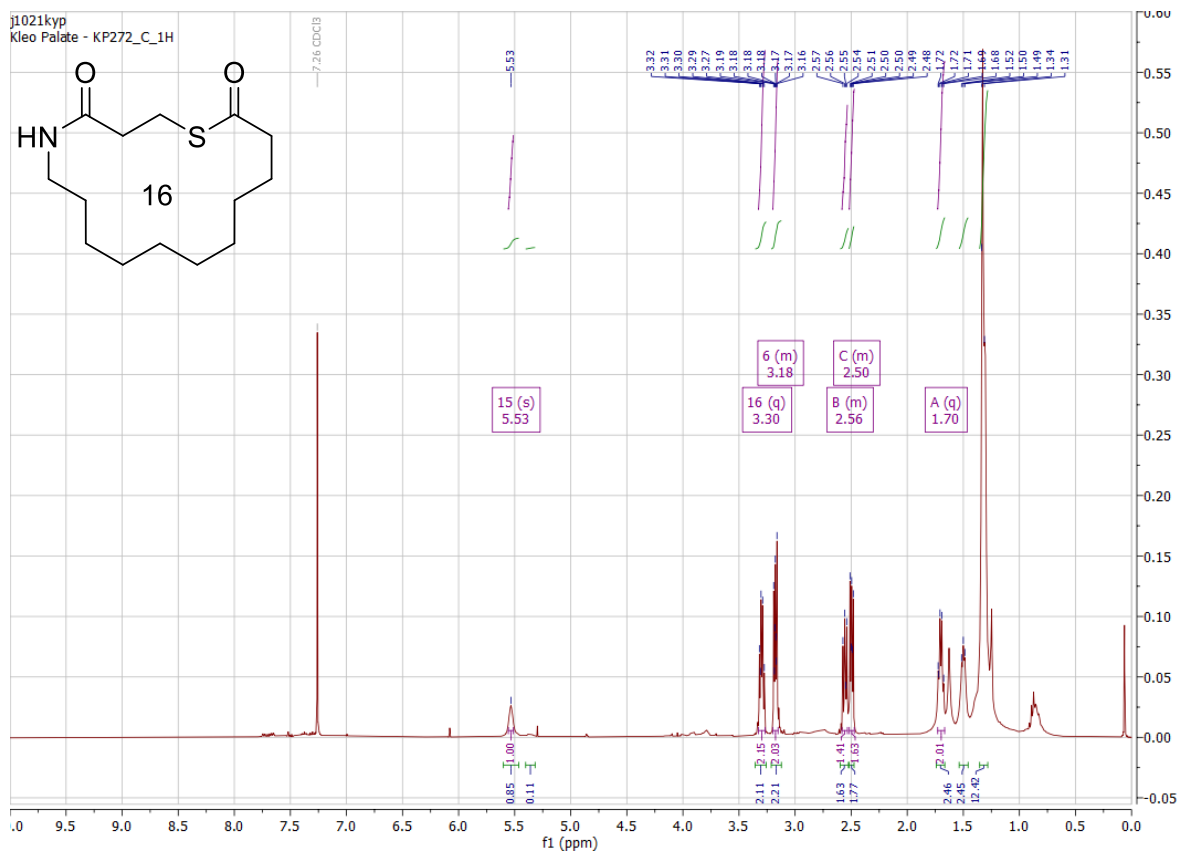




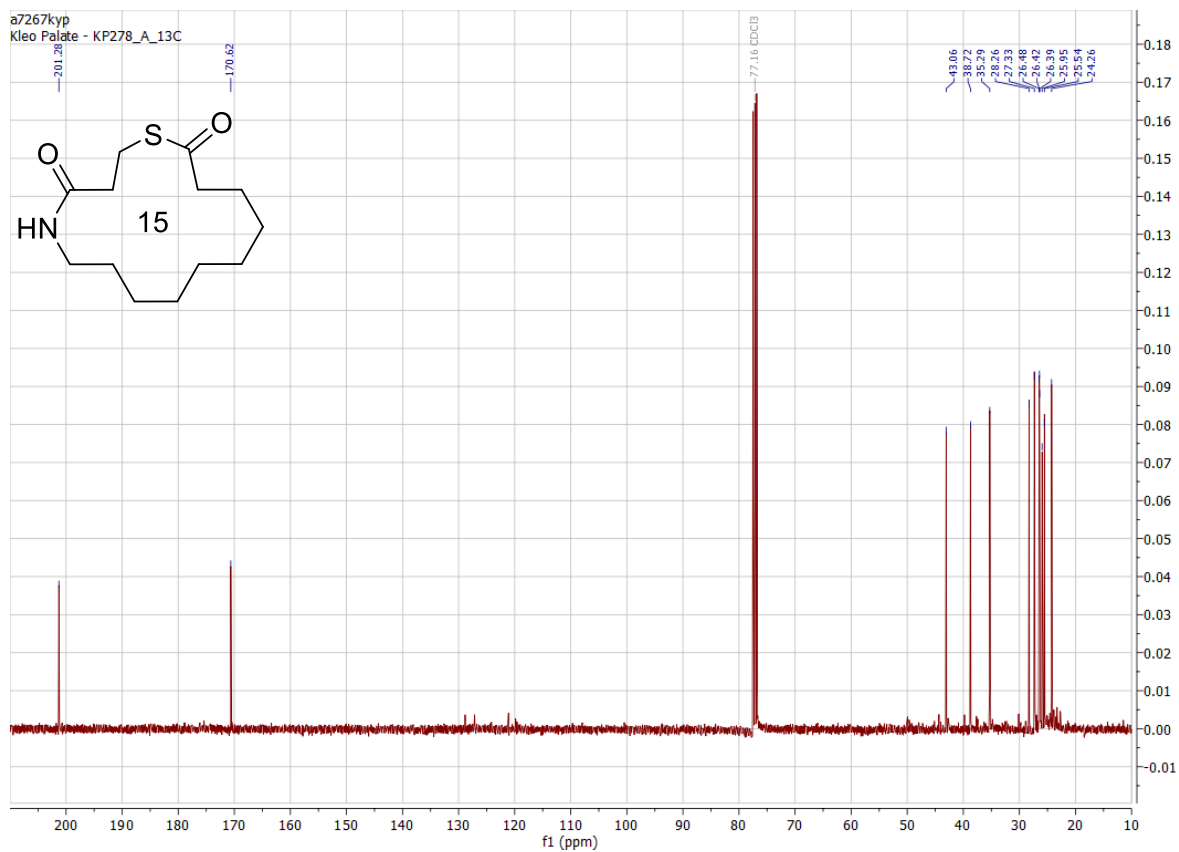
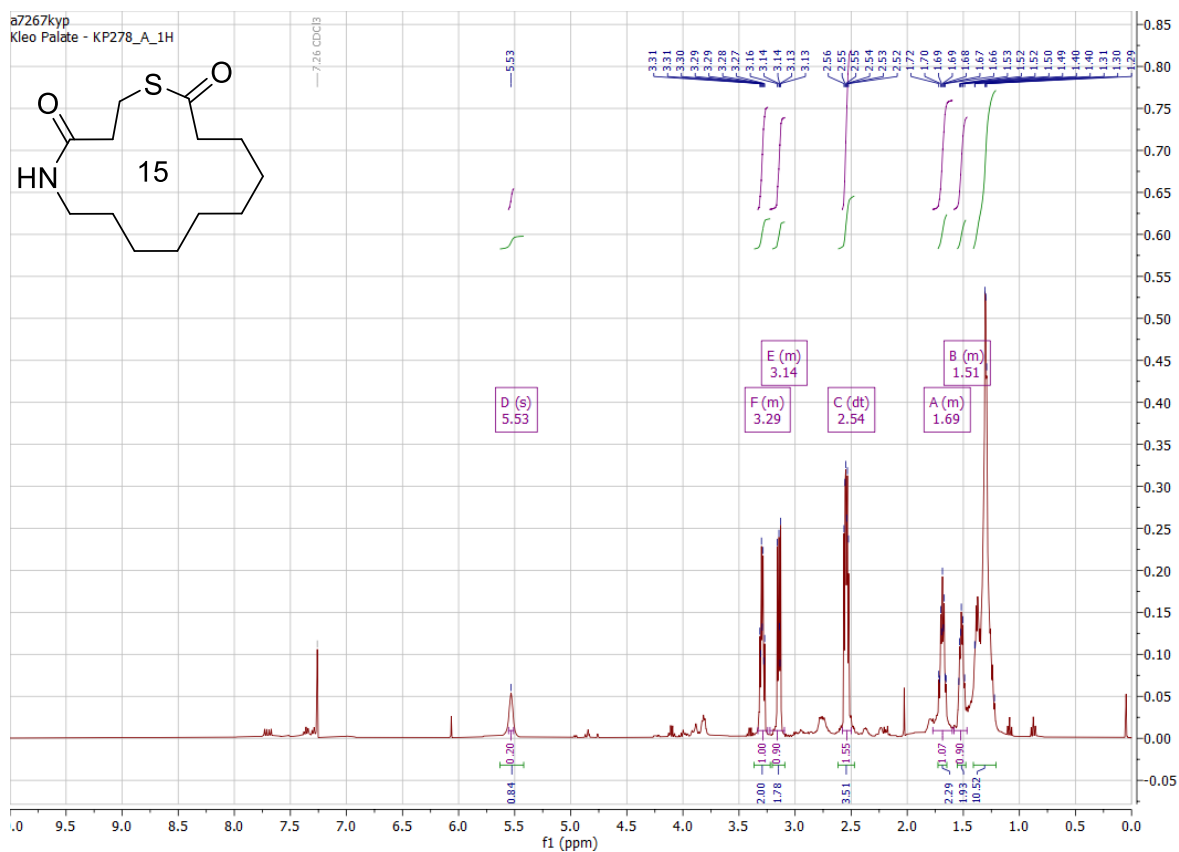
35b



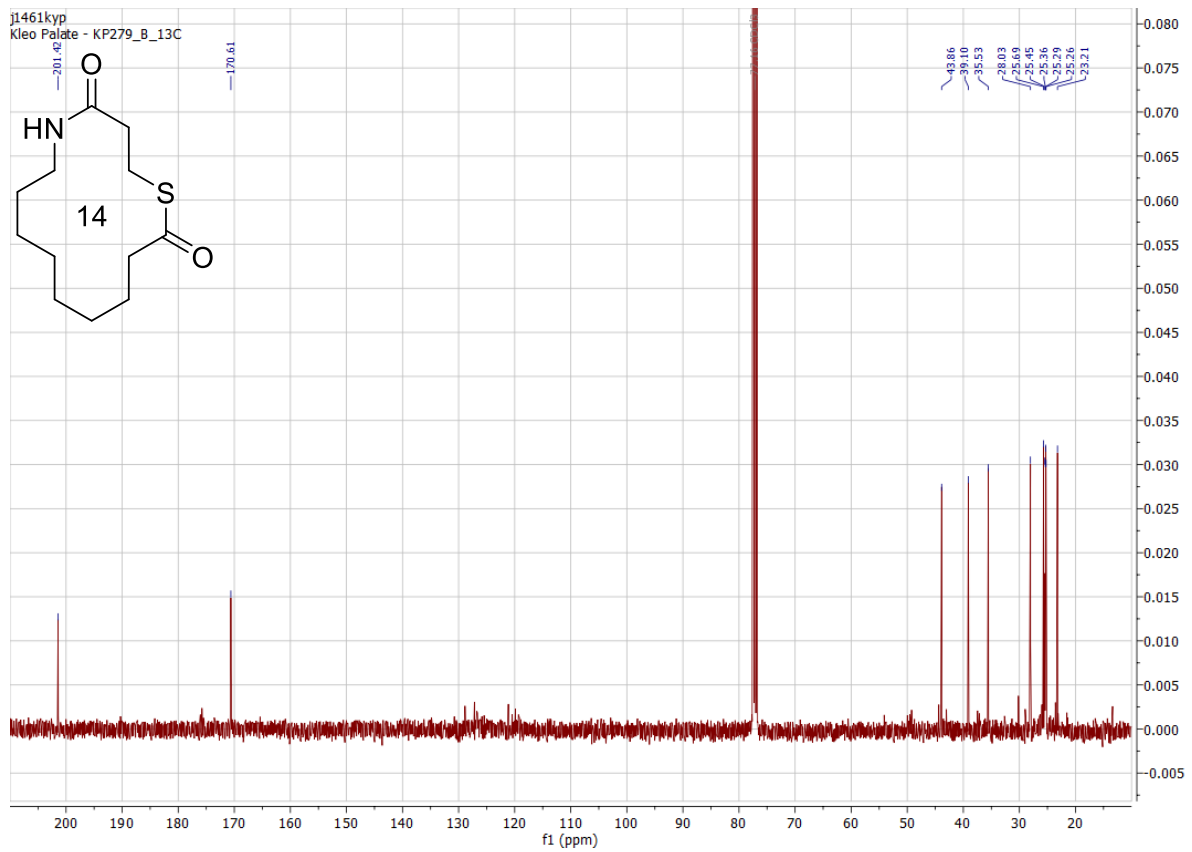
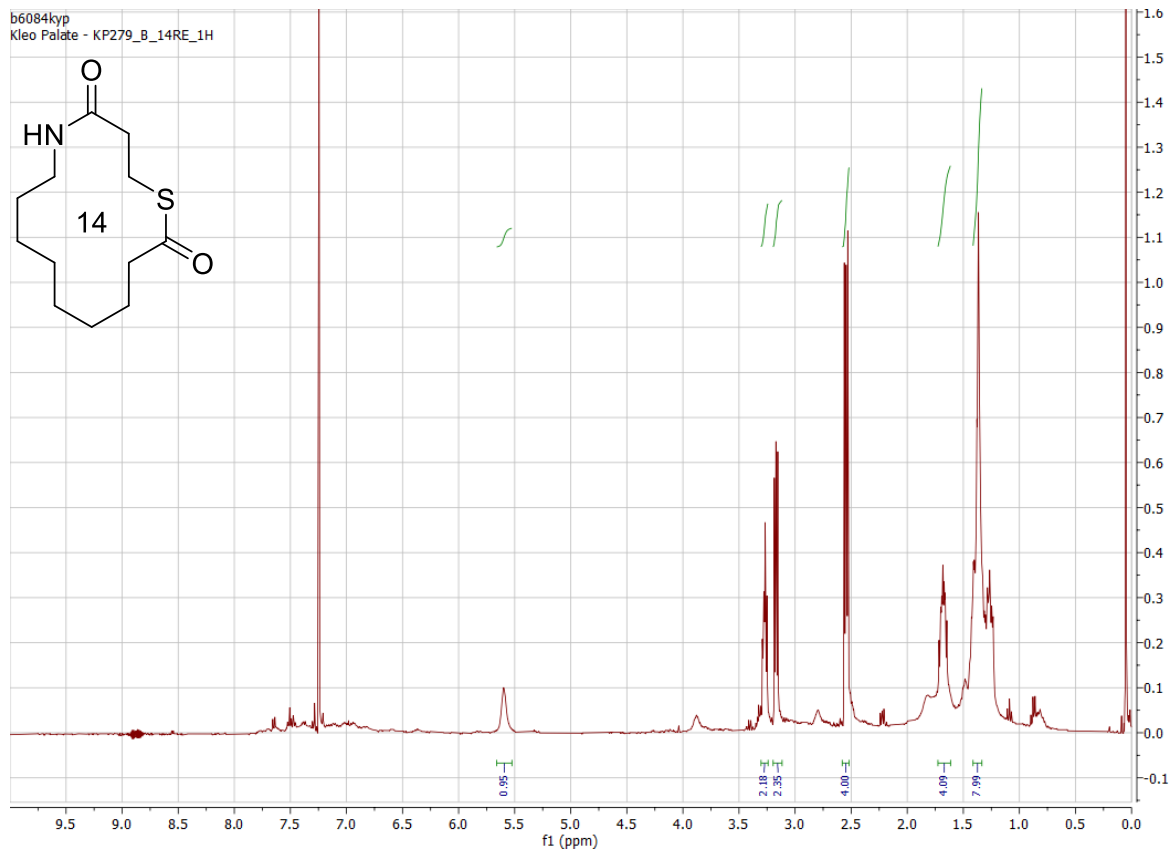
24c



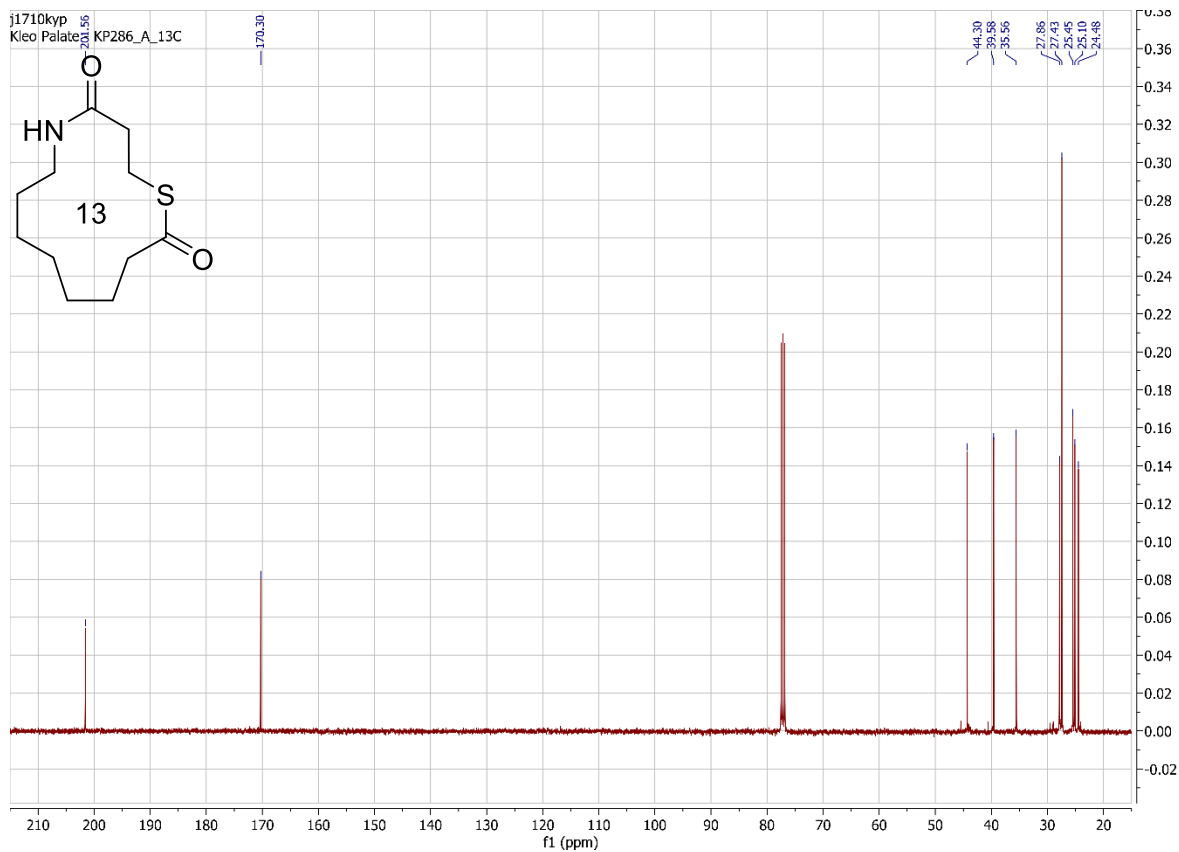
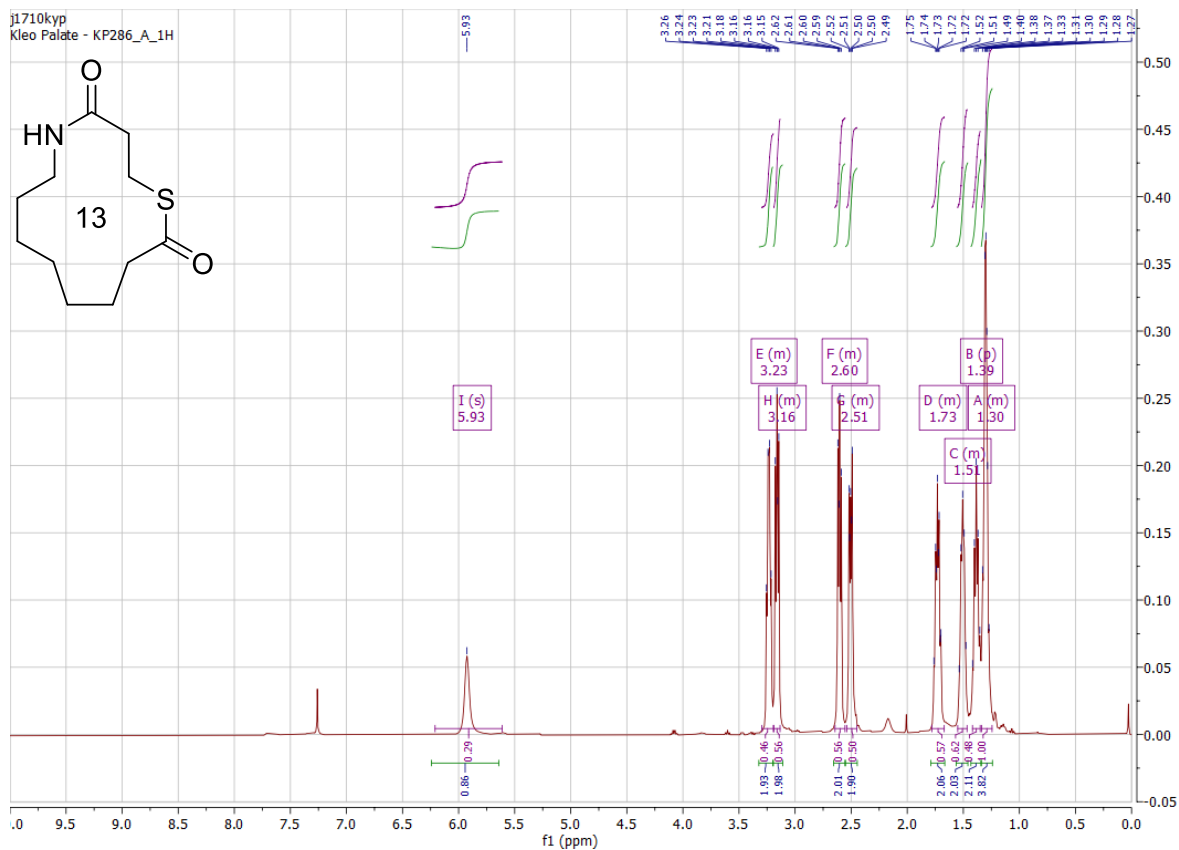
24d

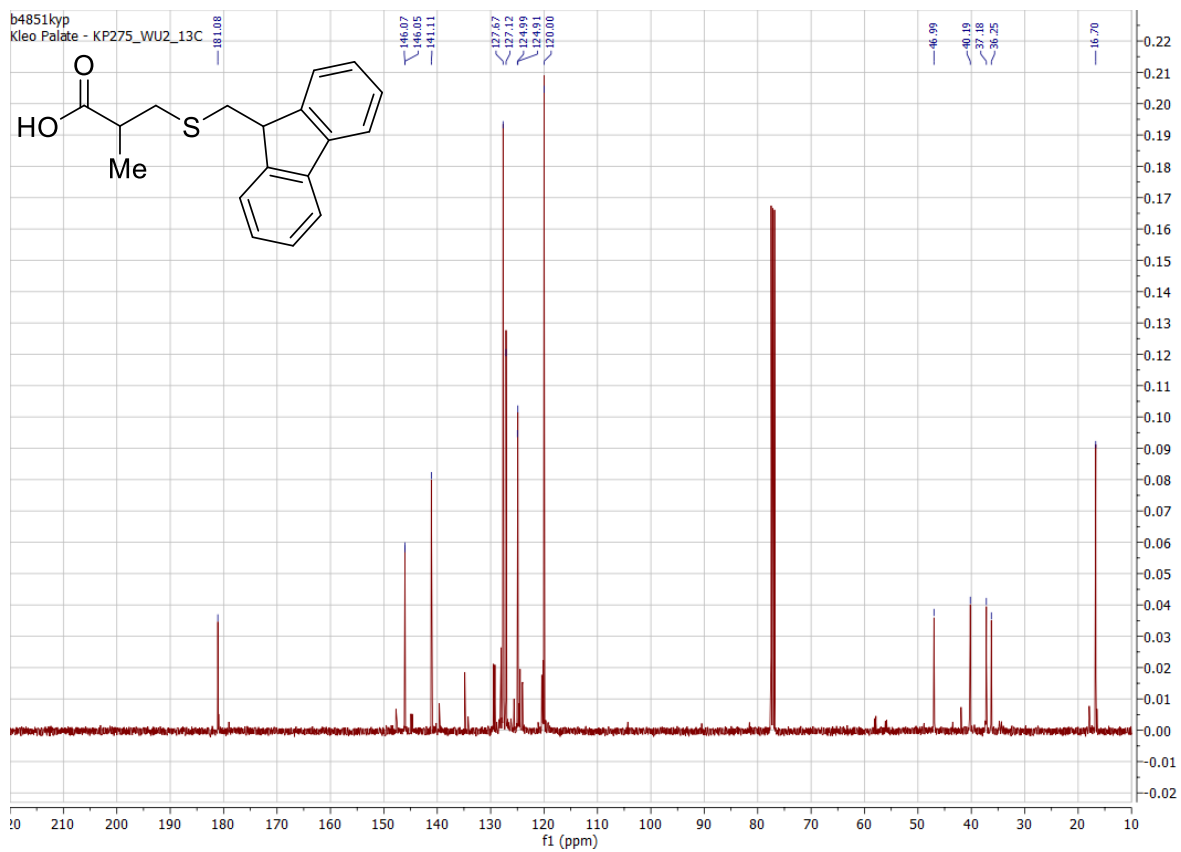
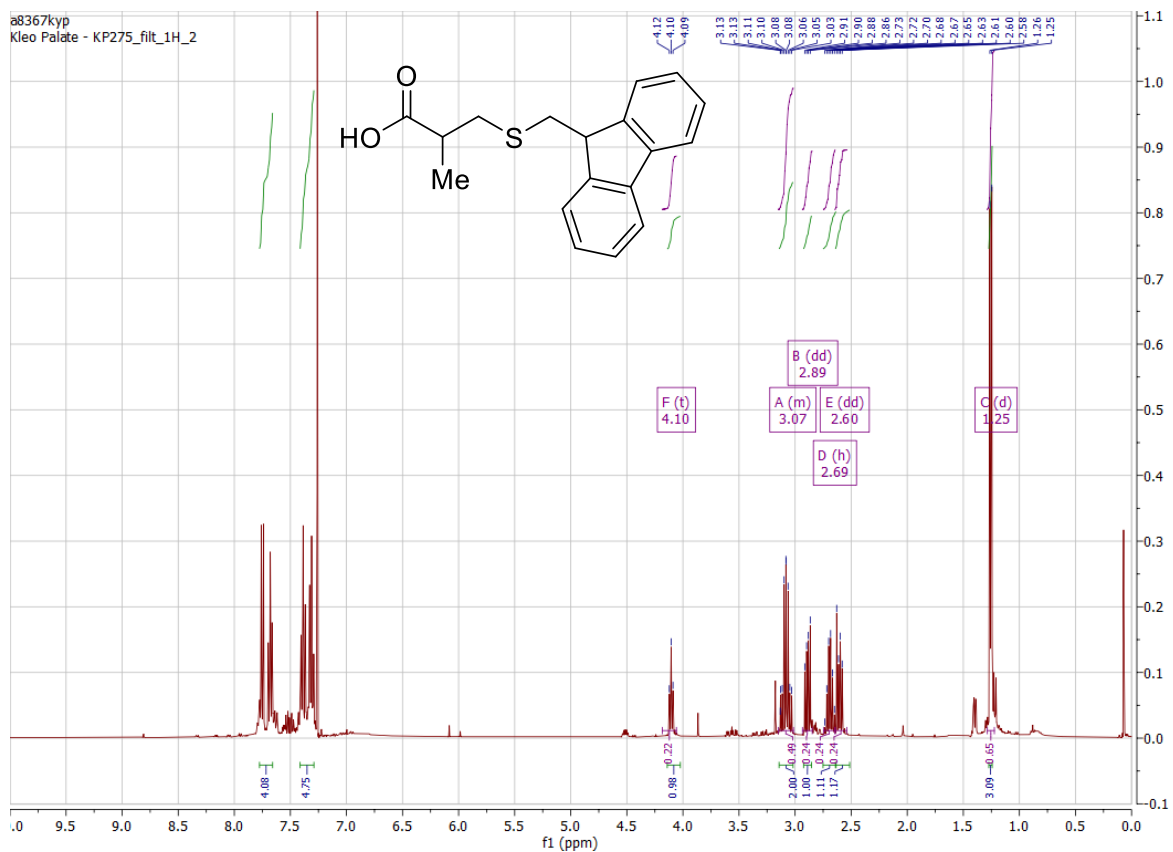


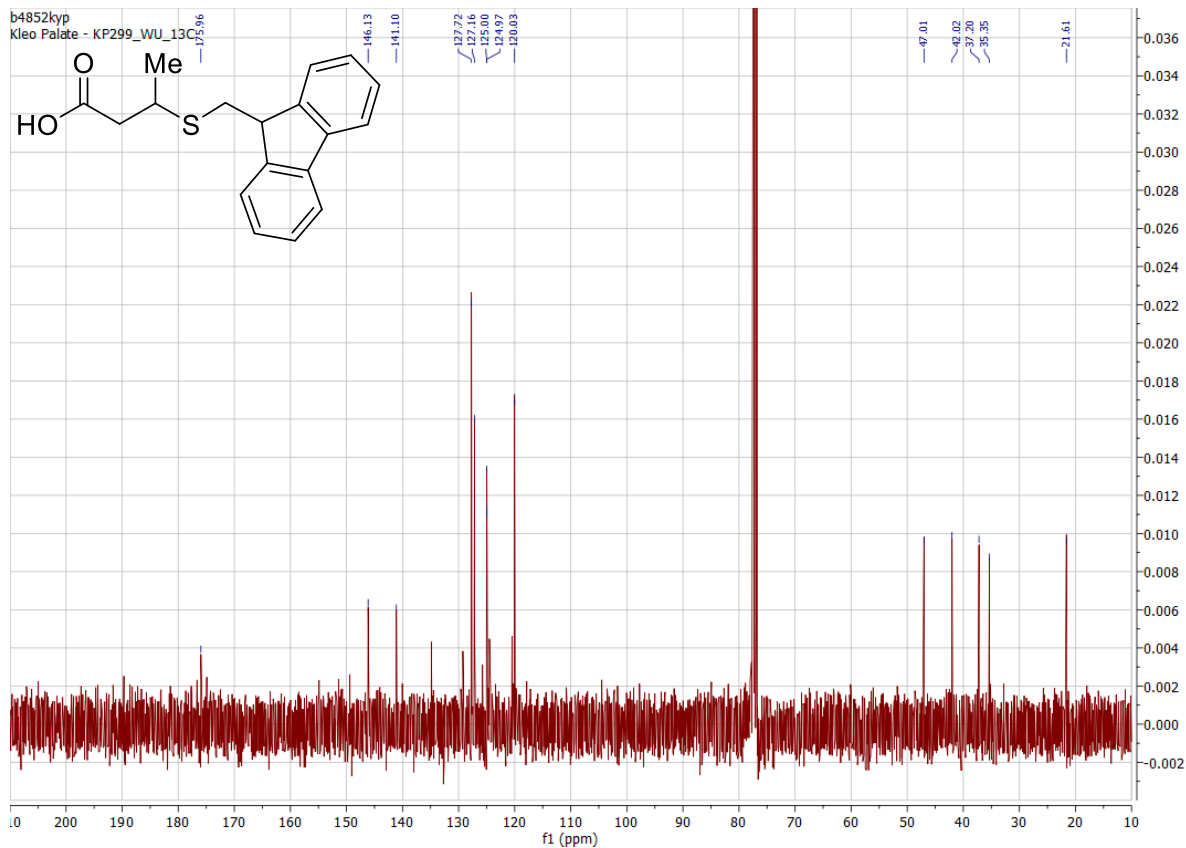
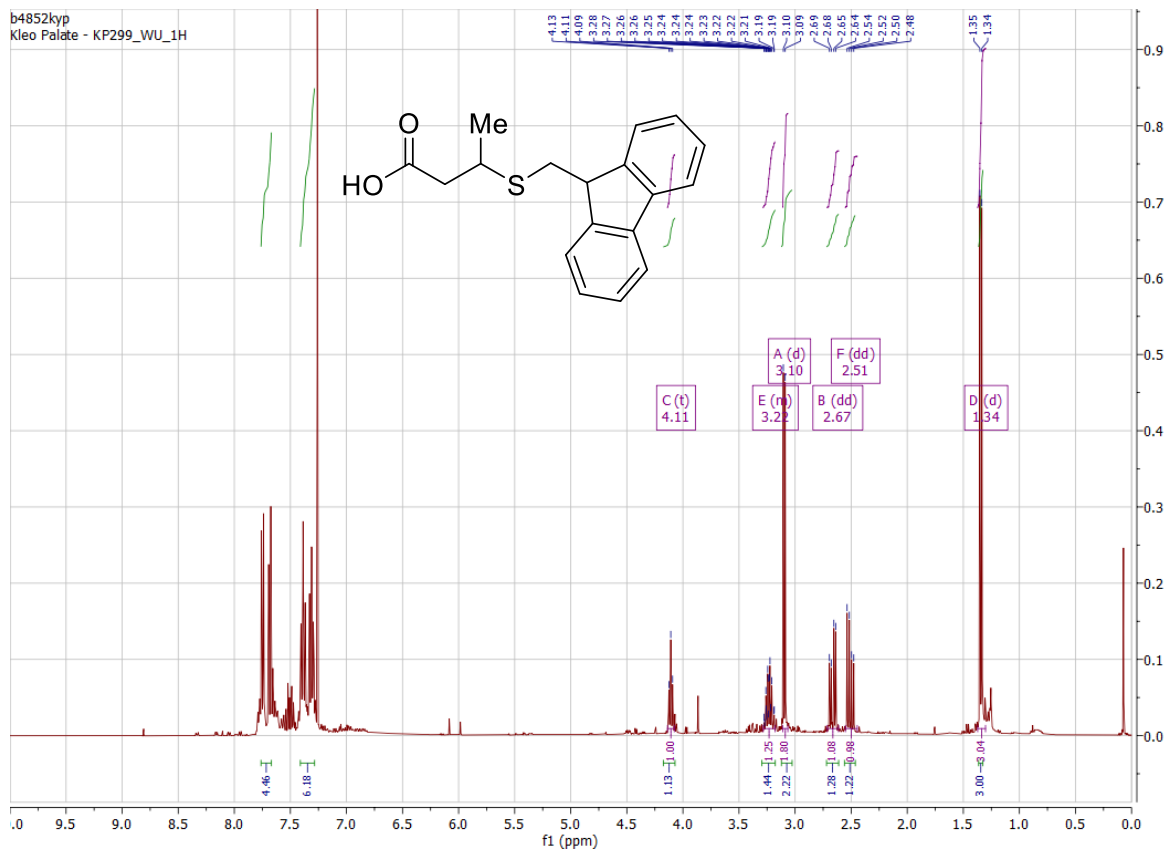
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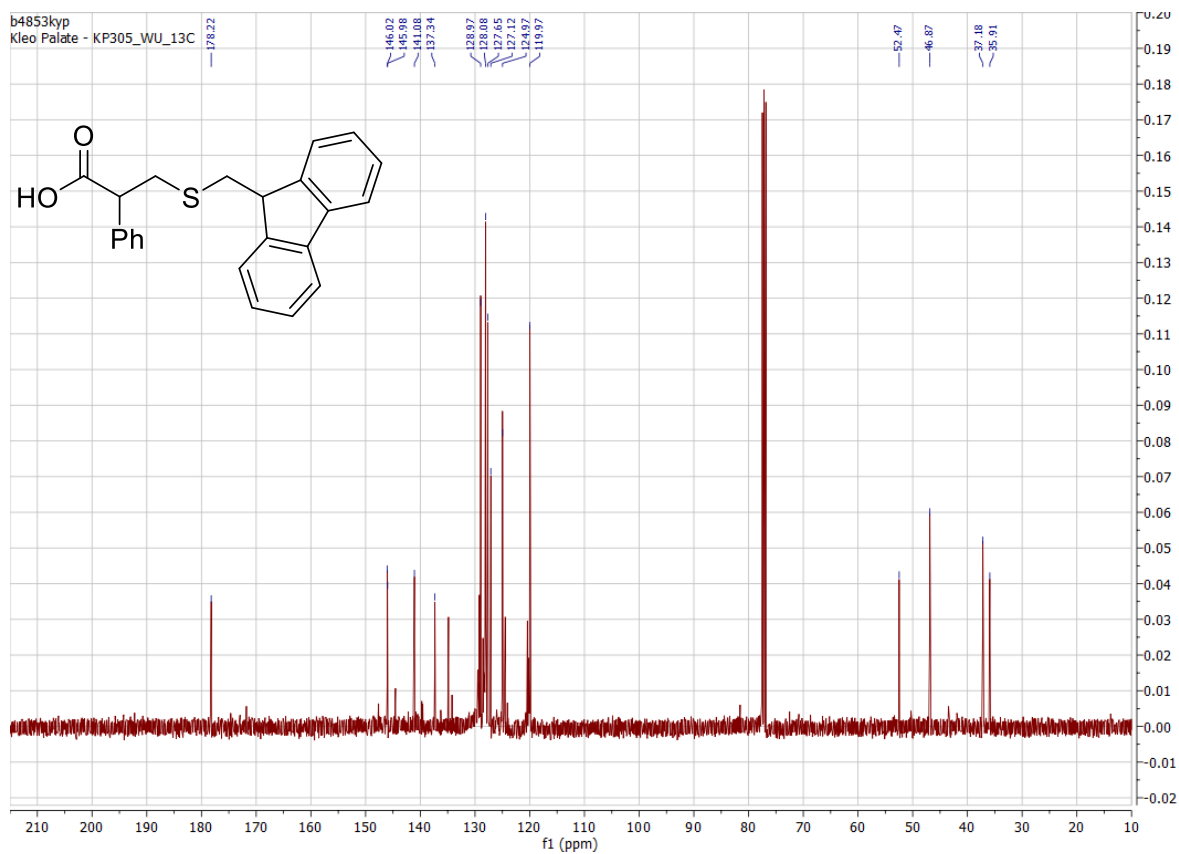
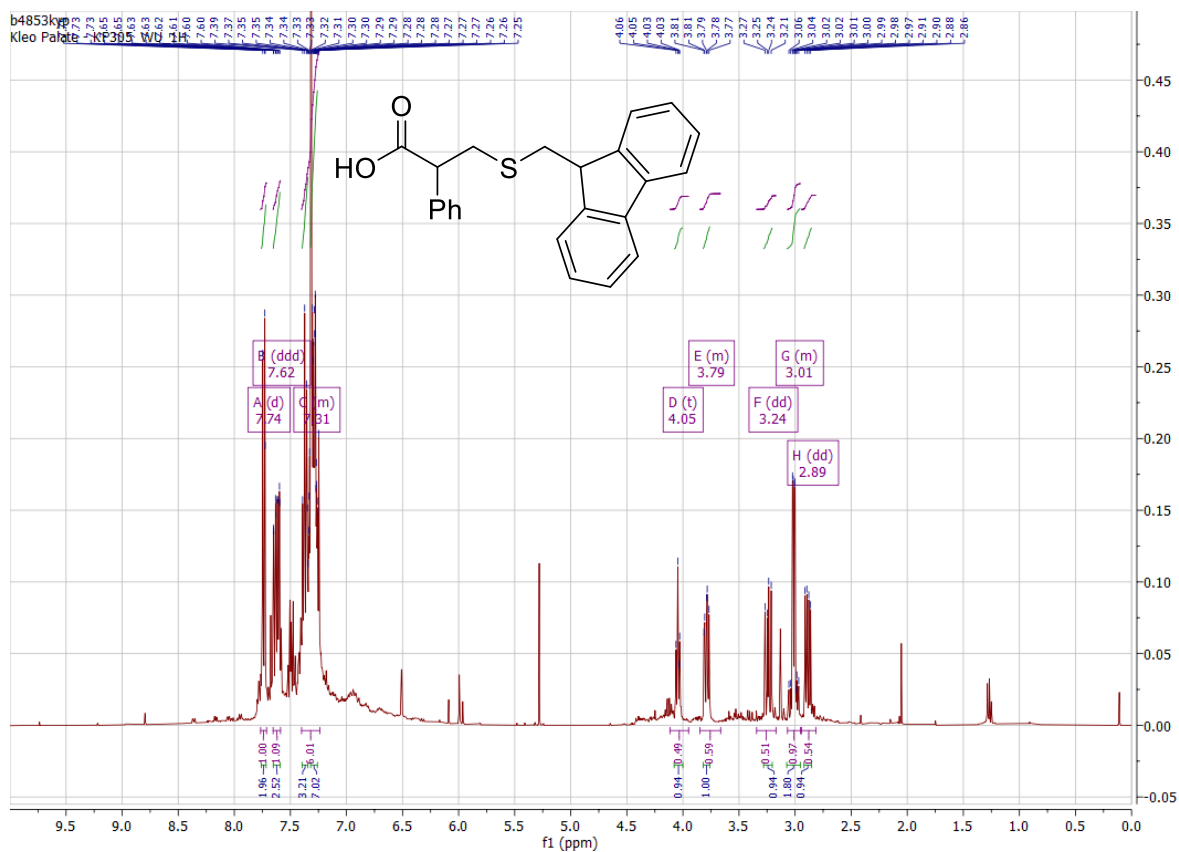


24f

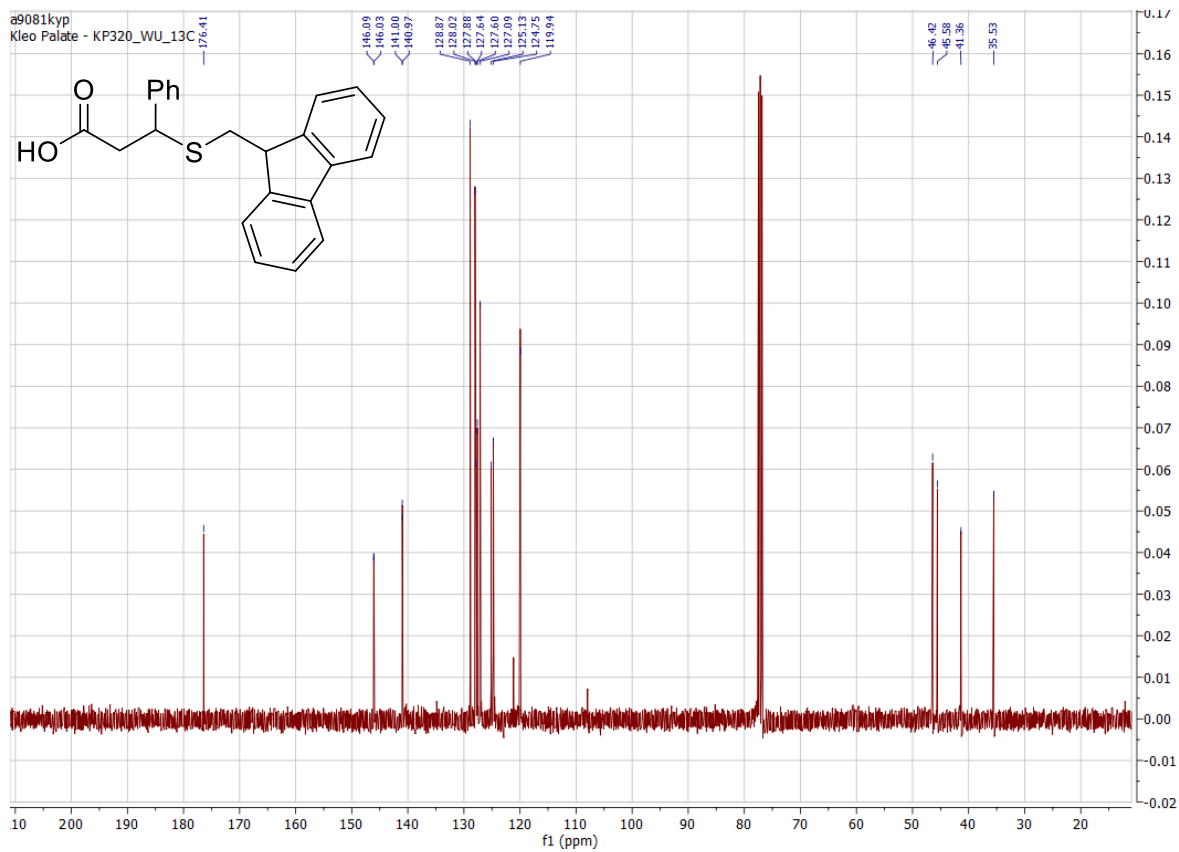
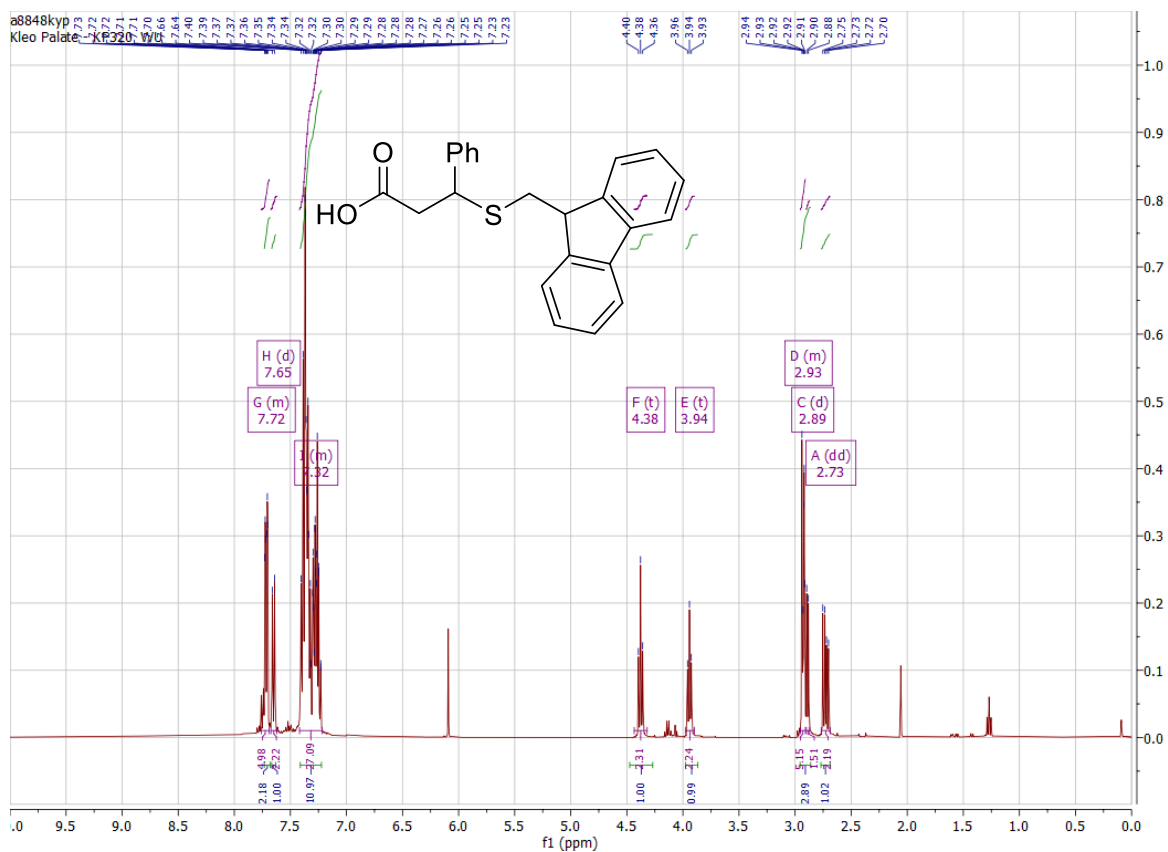




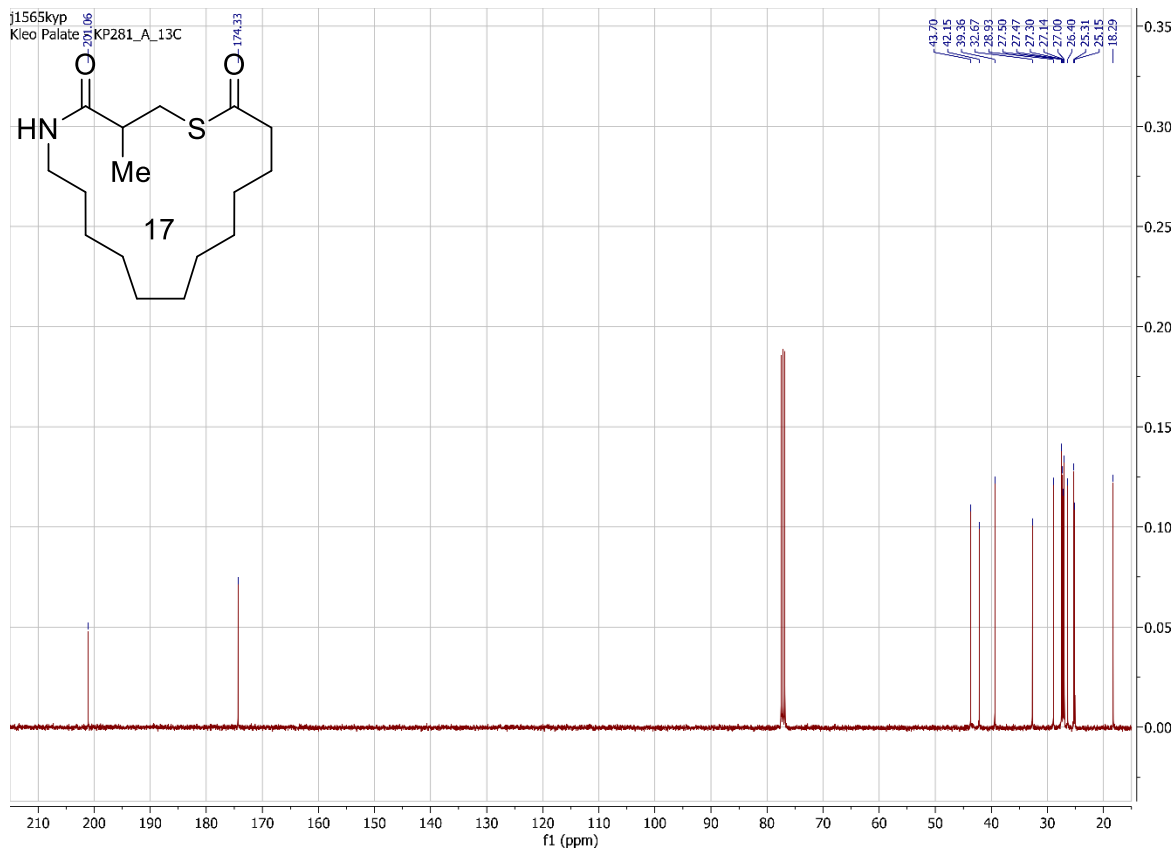
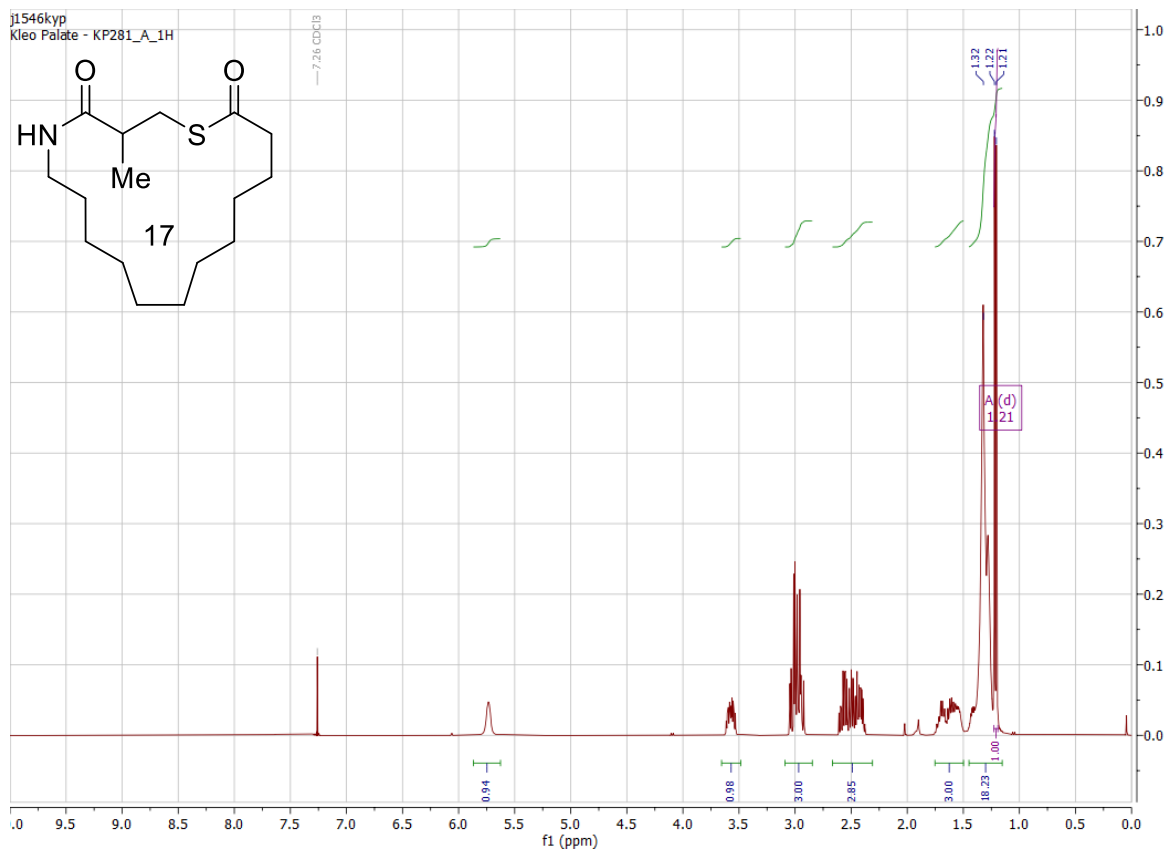




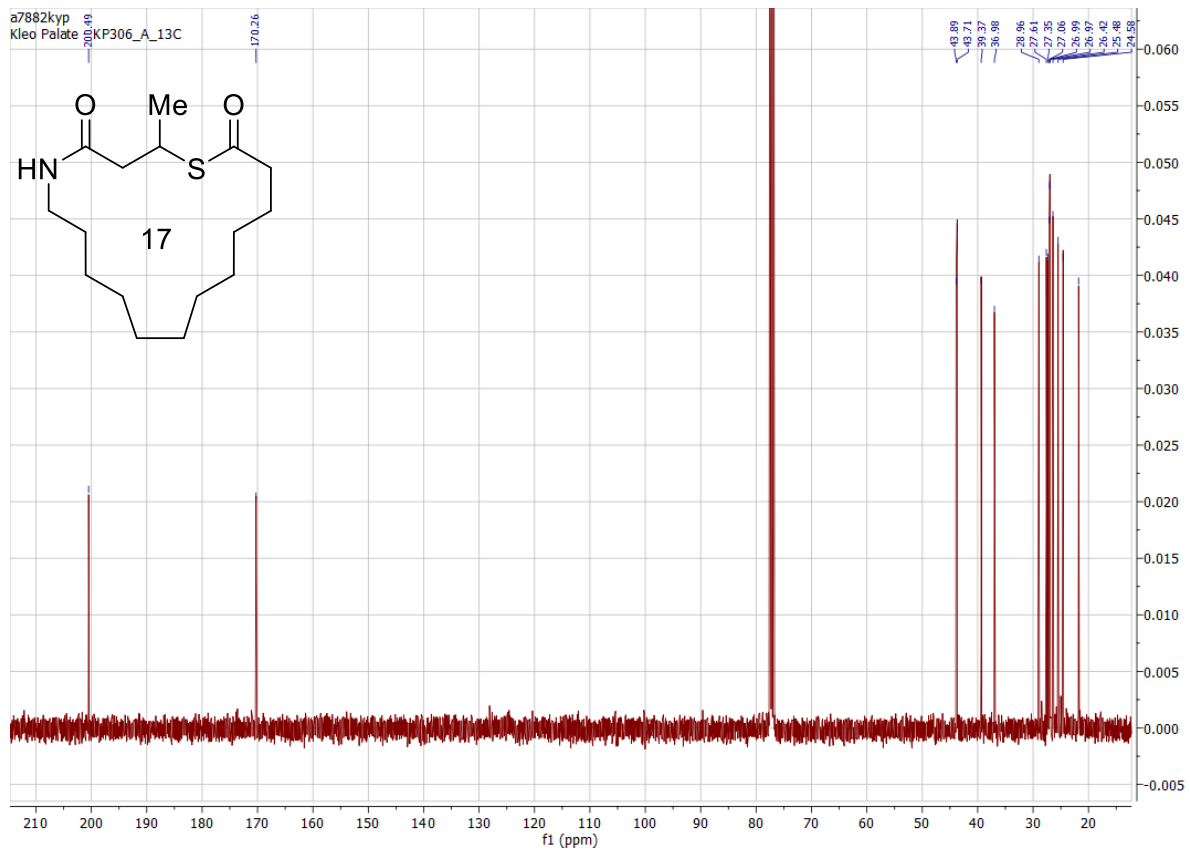
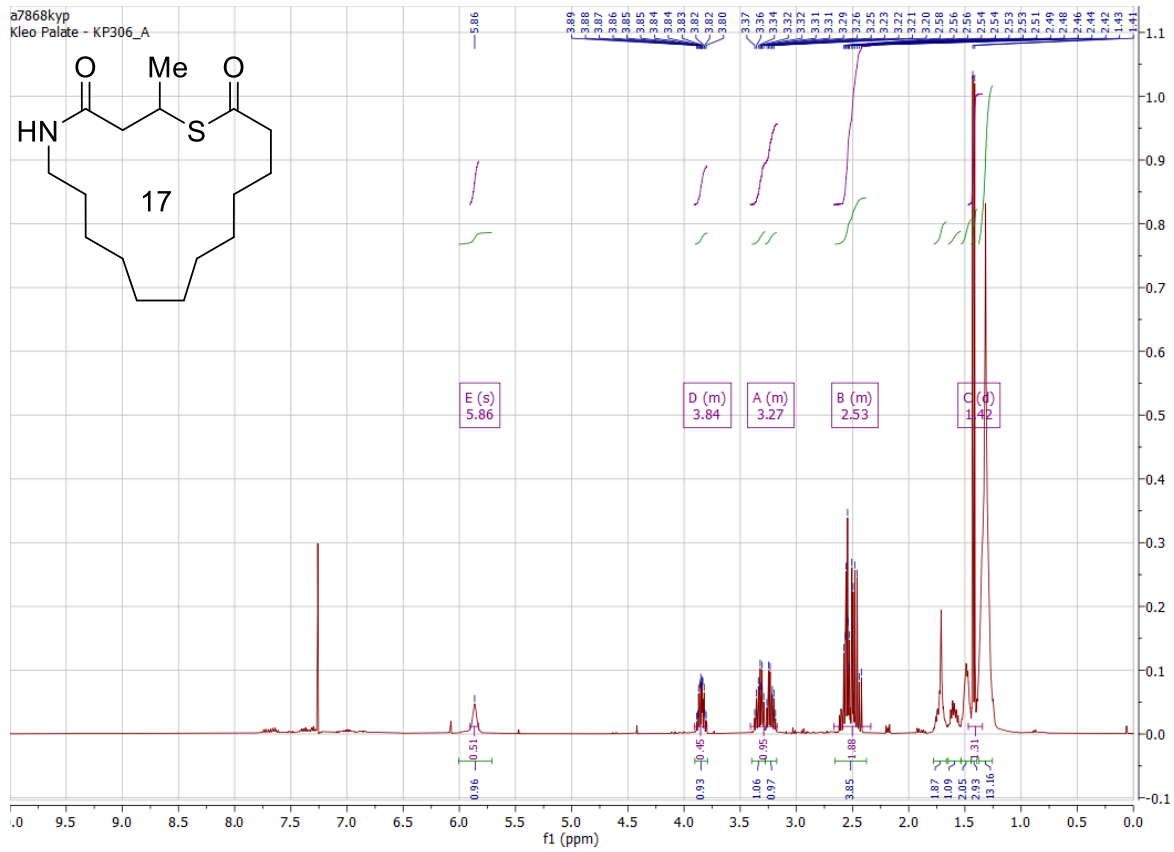
S5

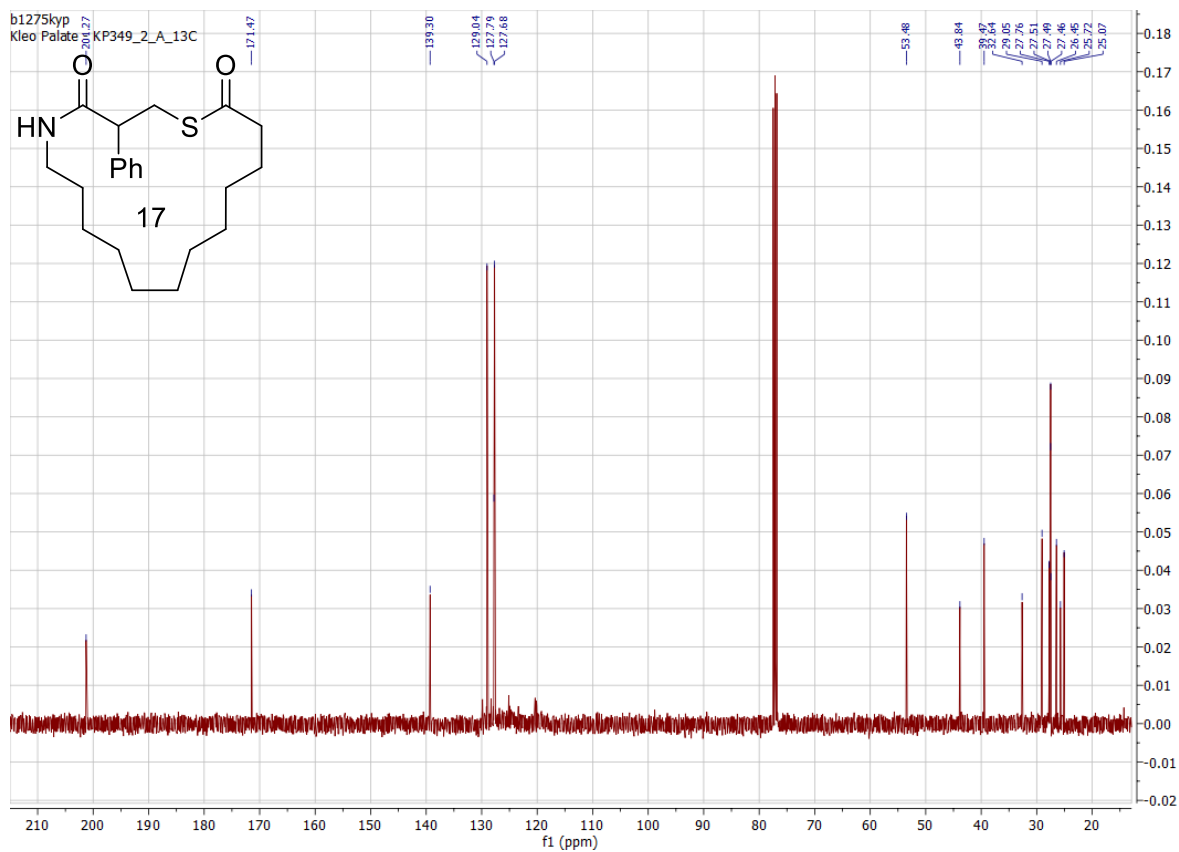
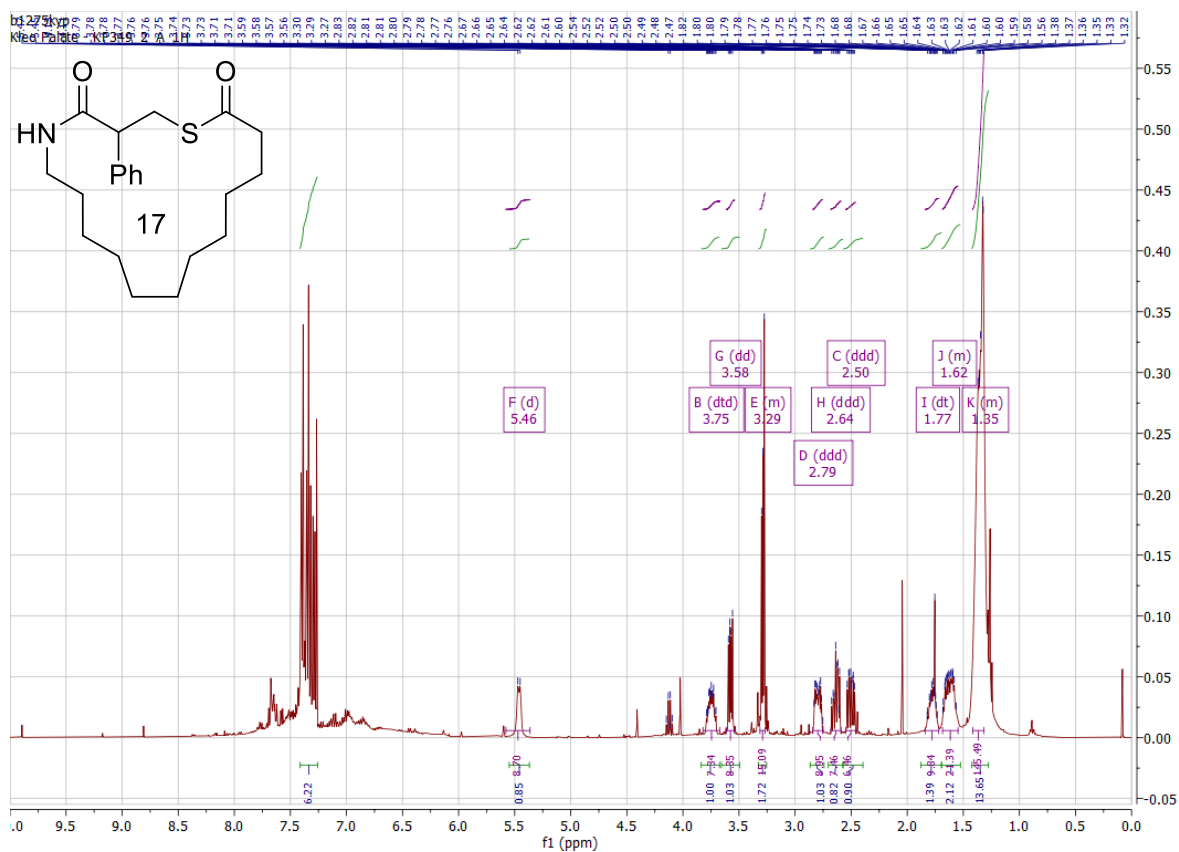


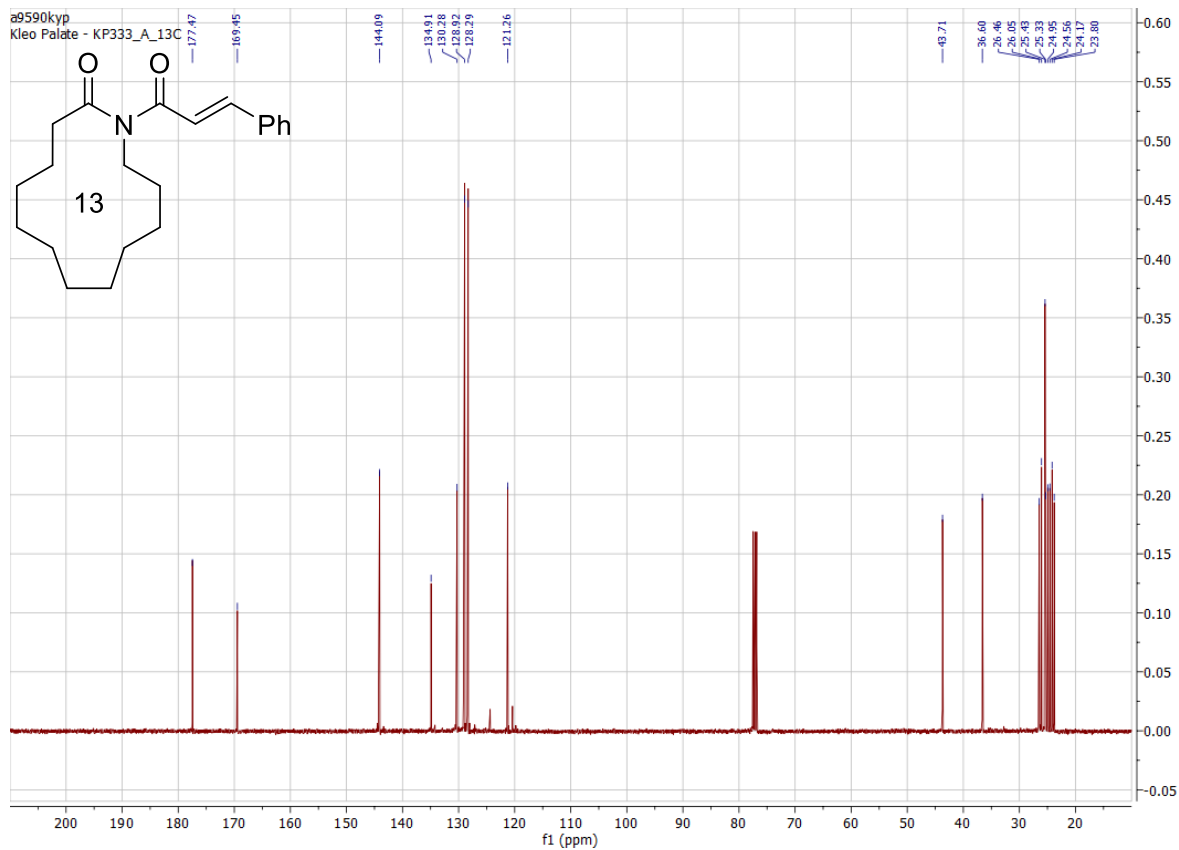
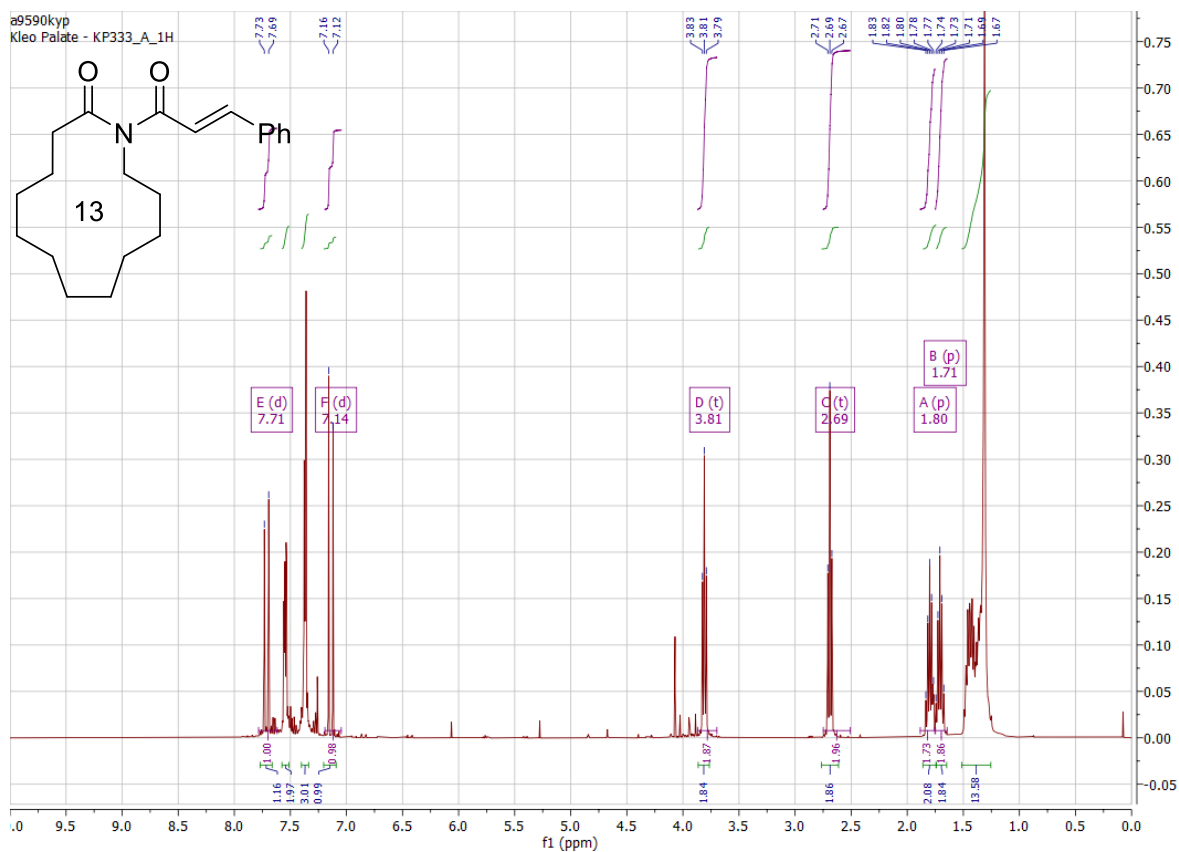
24g



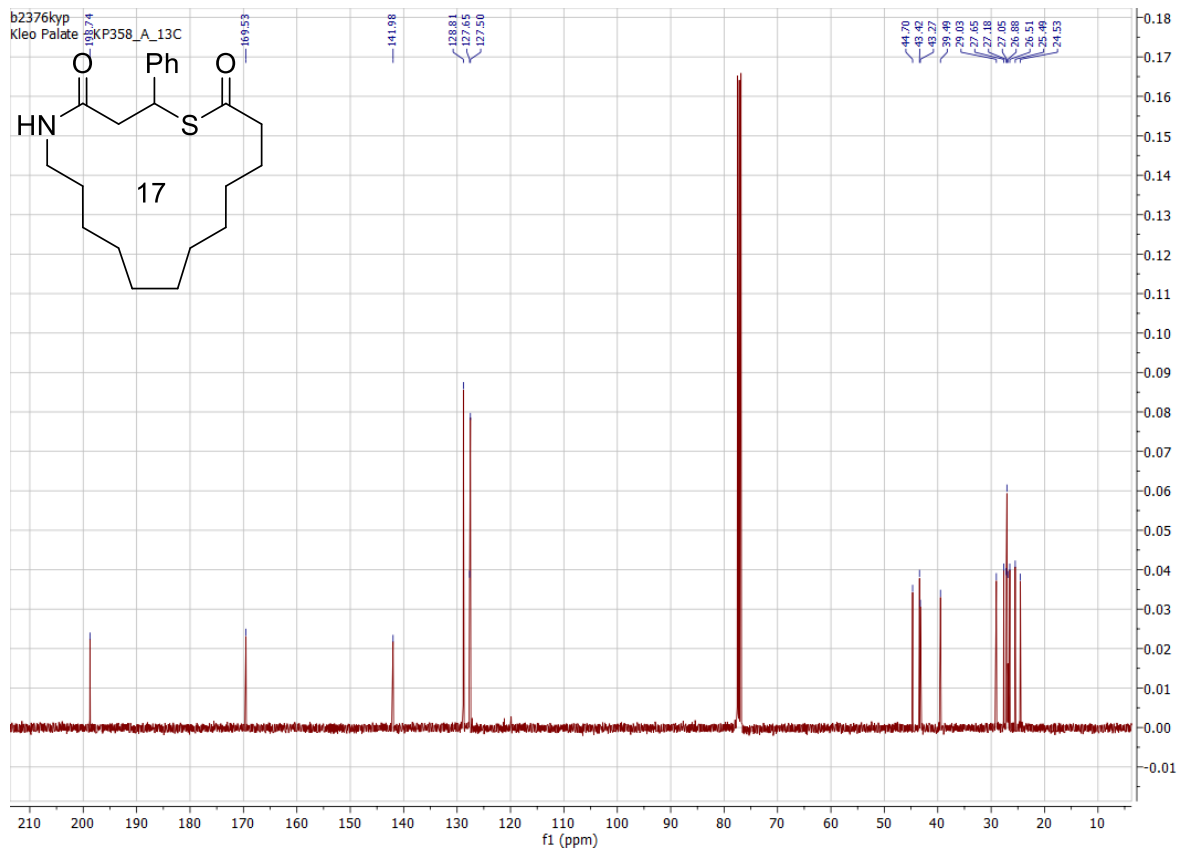
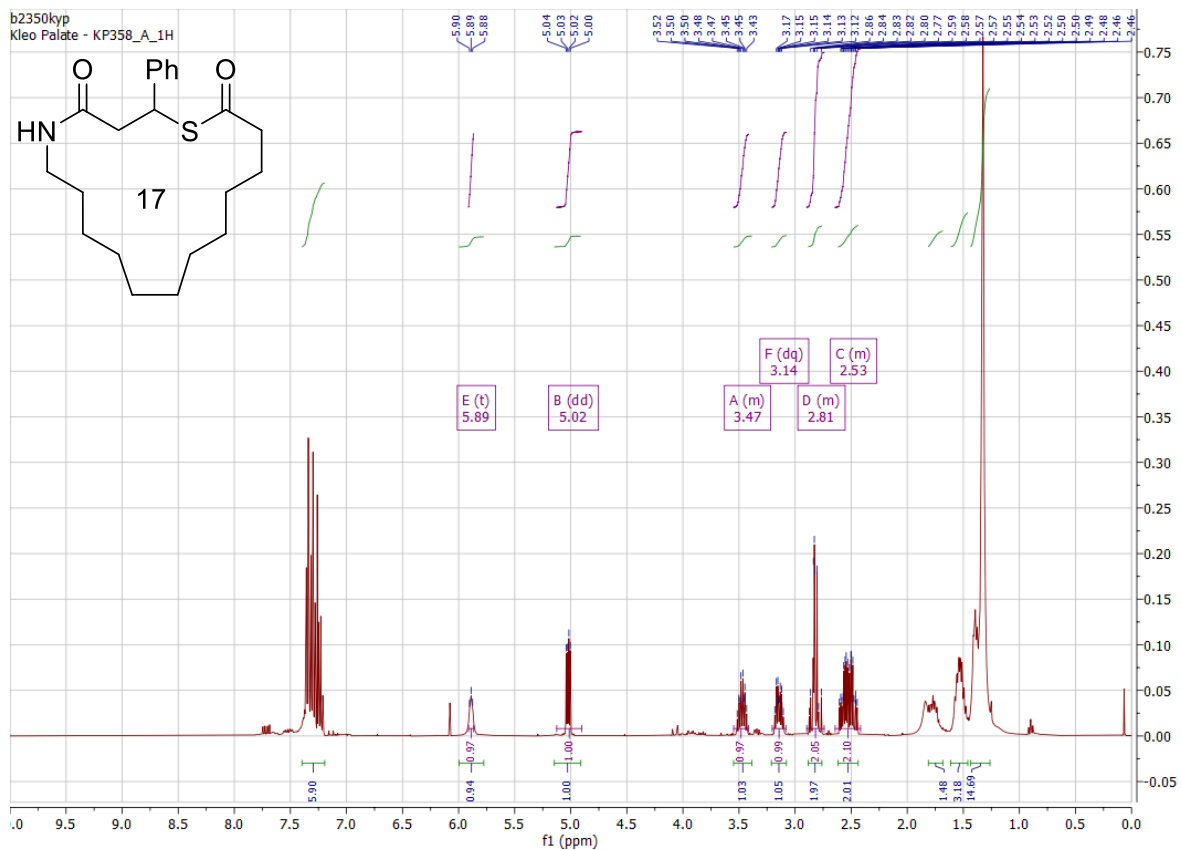
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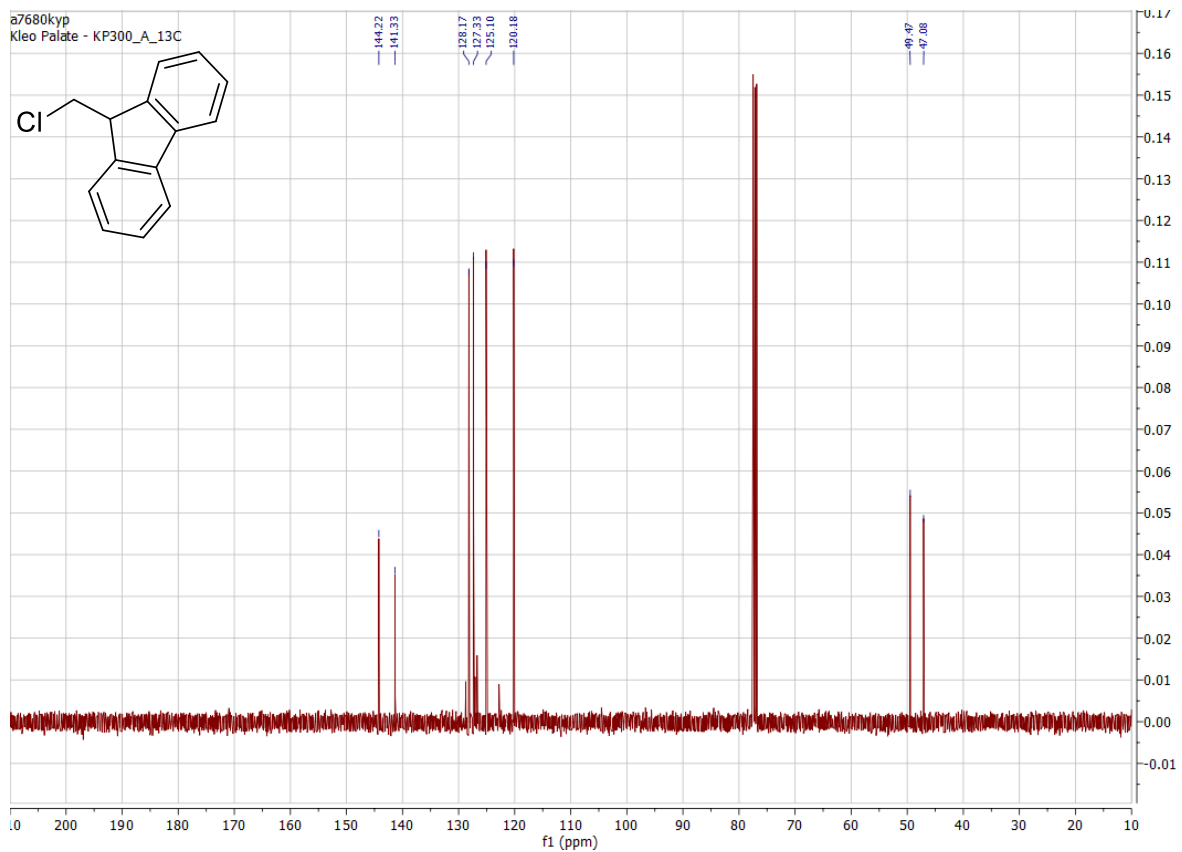
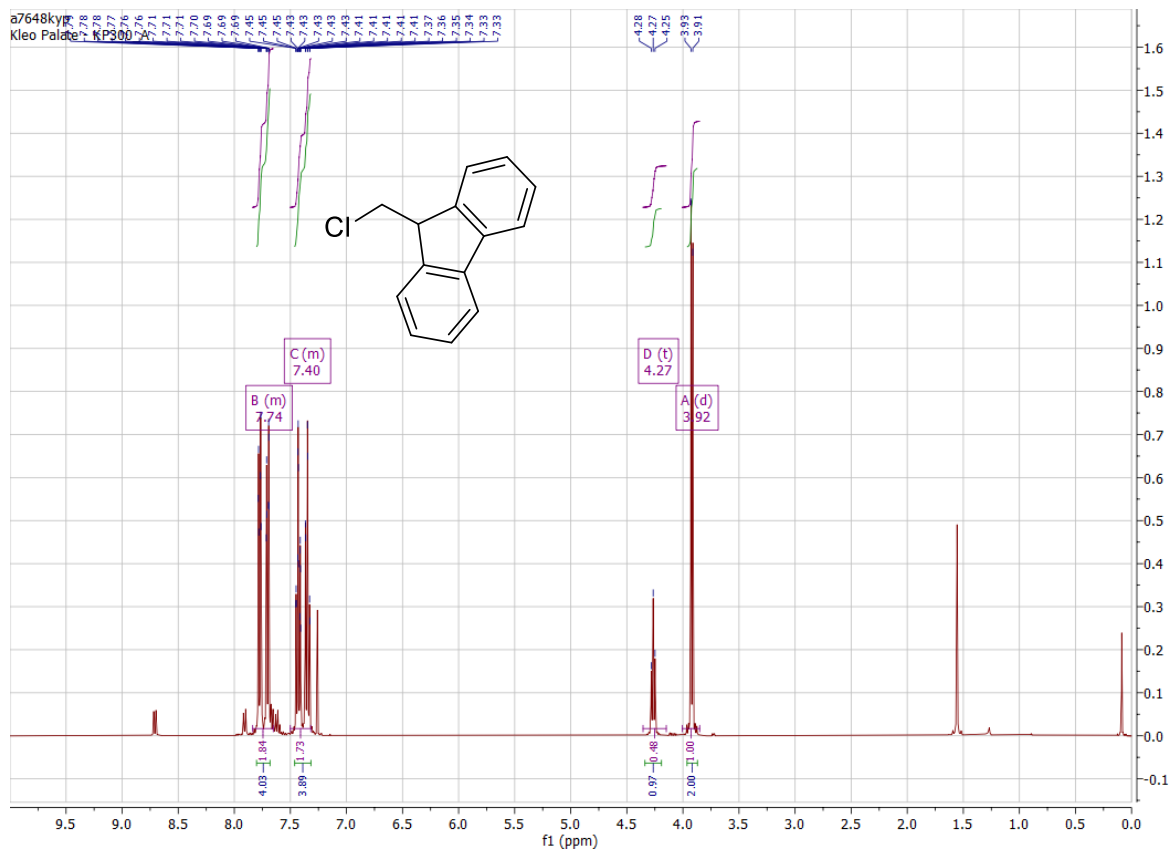




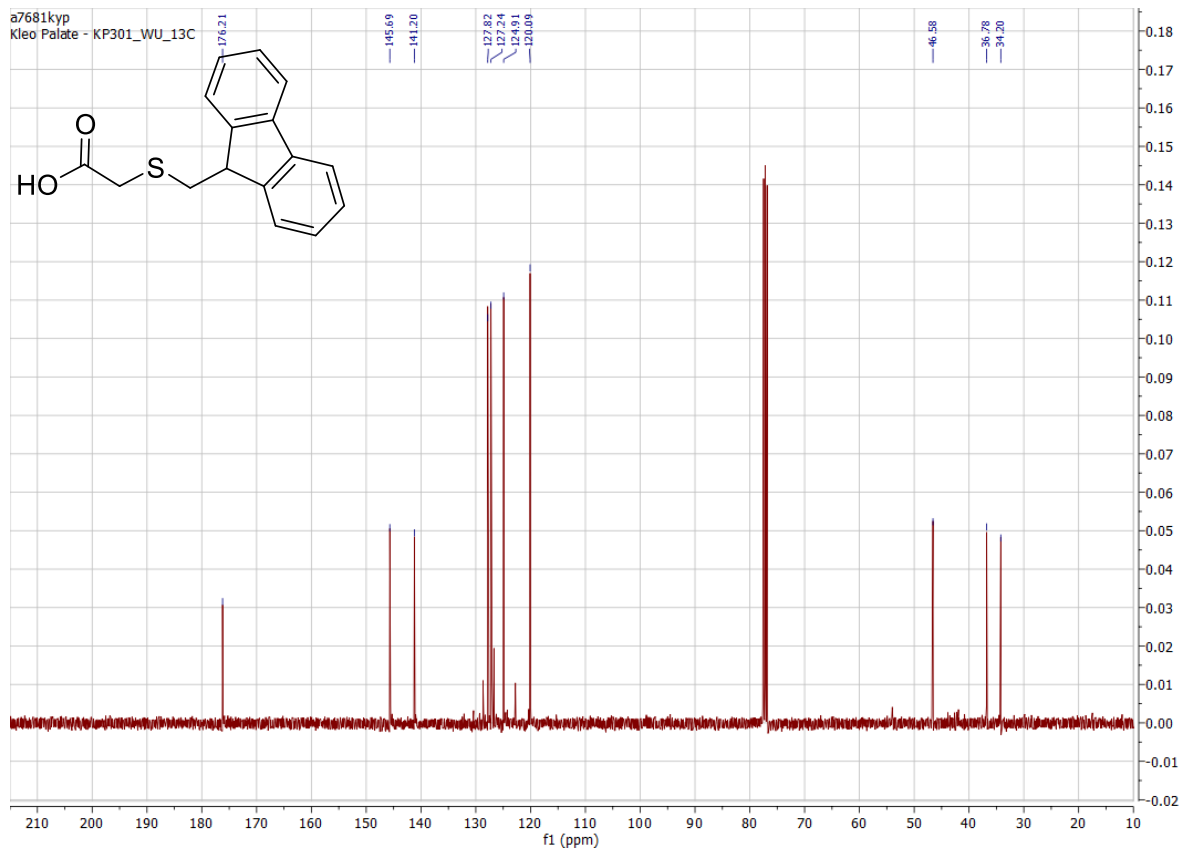
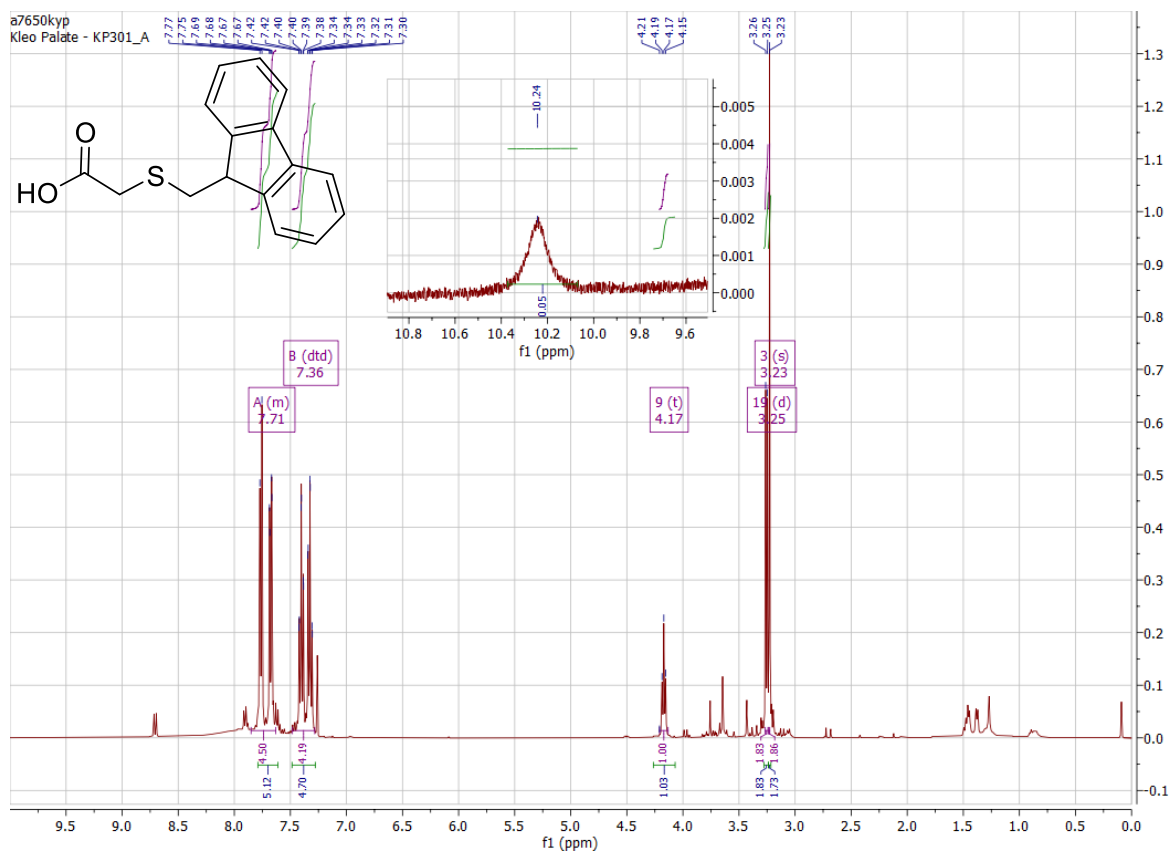
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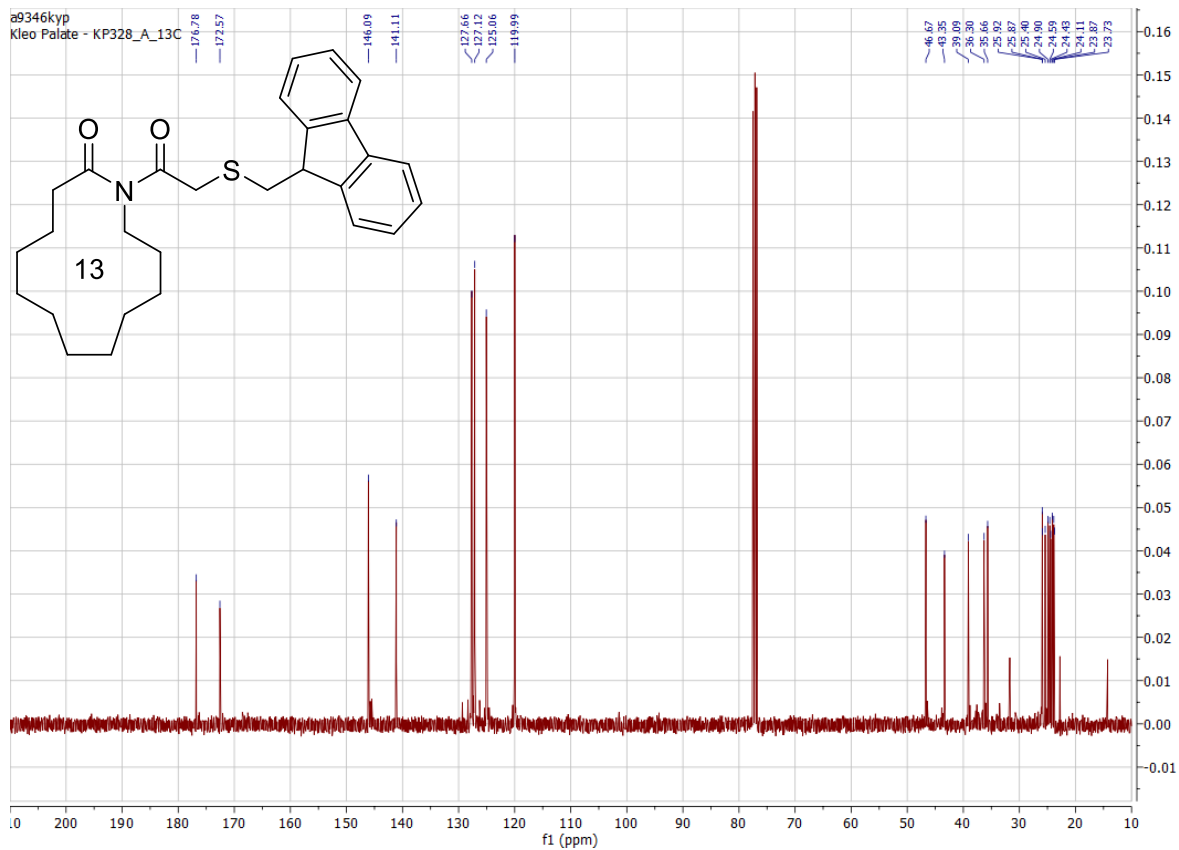
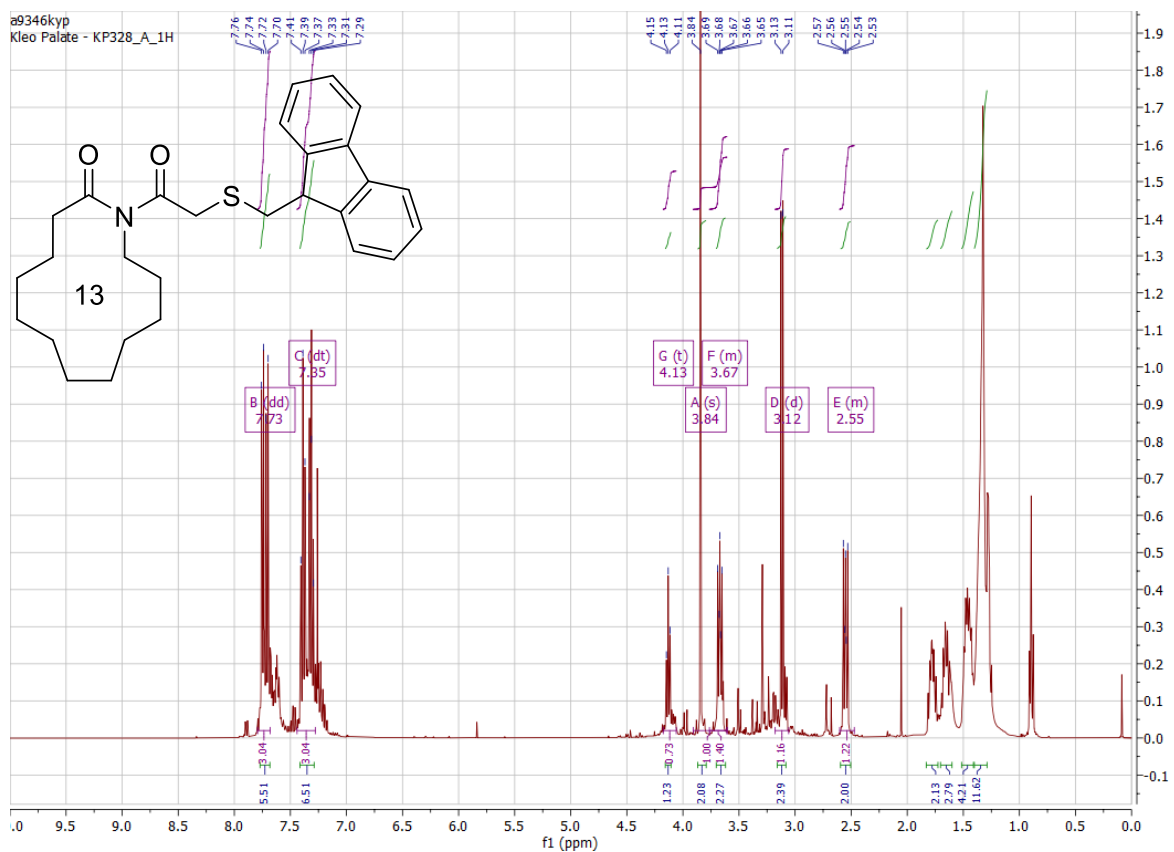


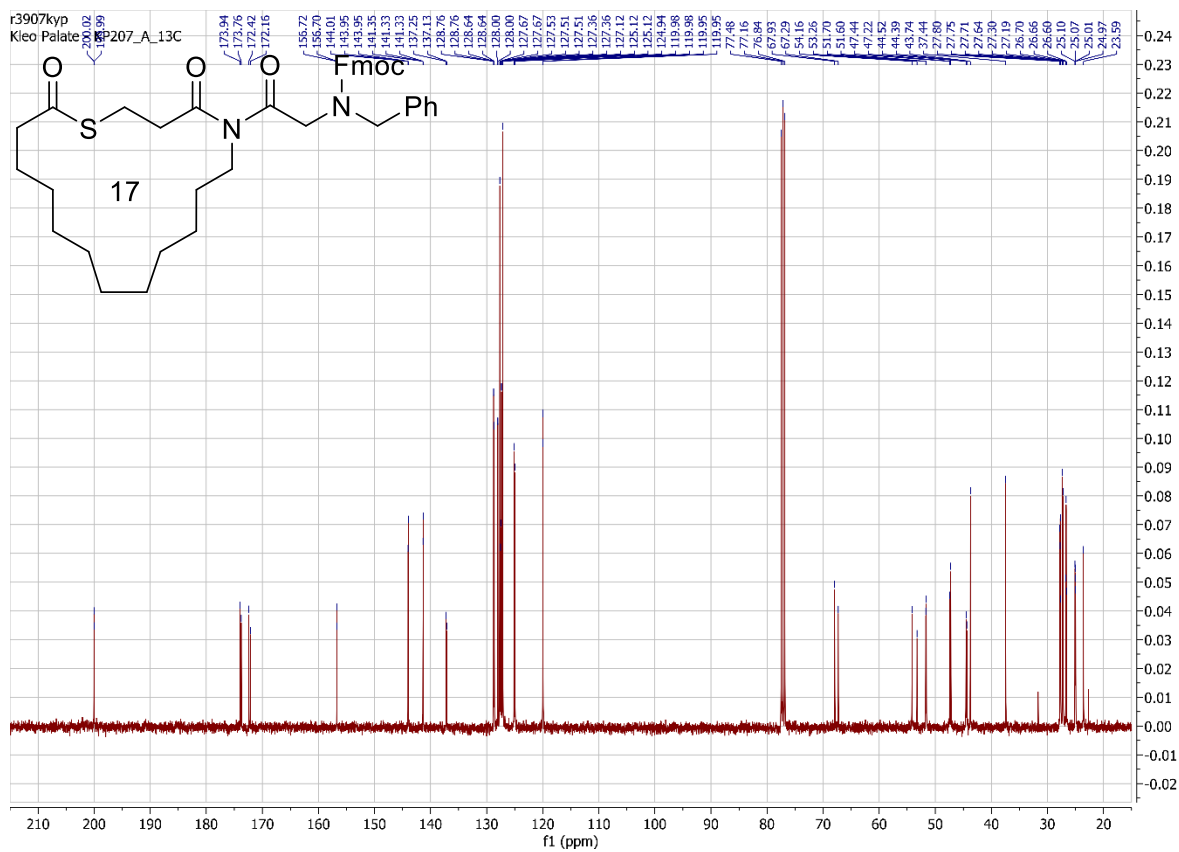
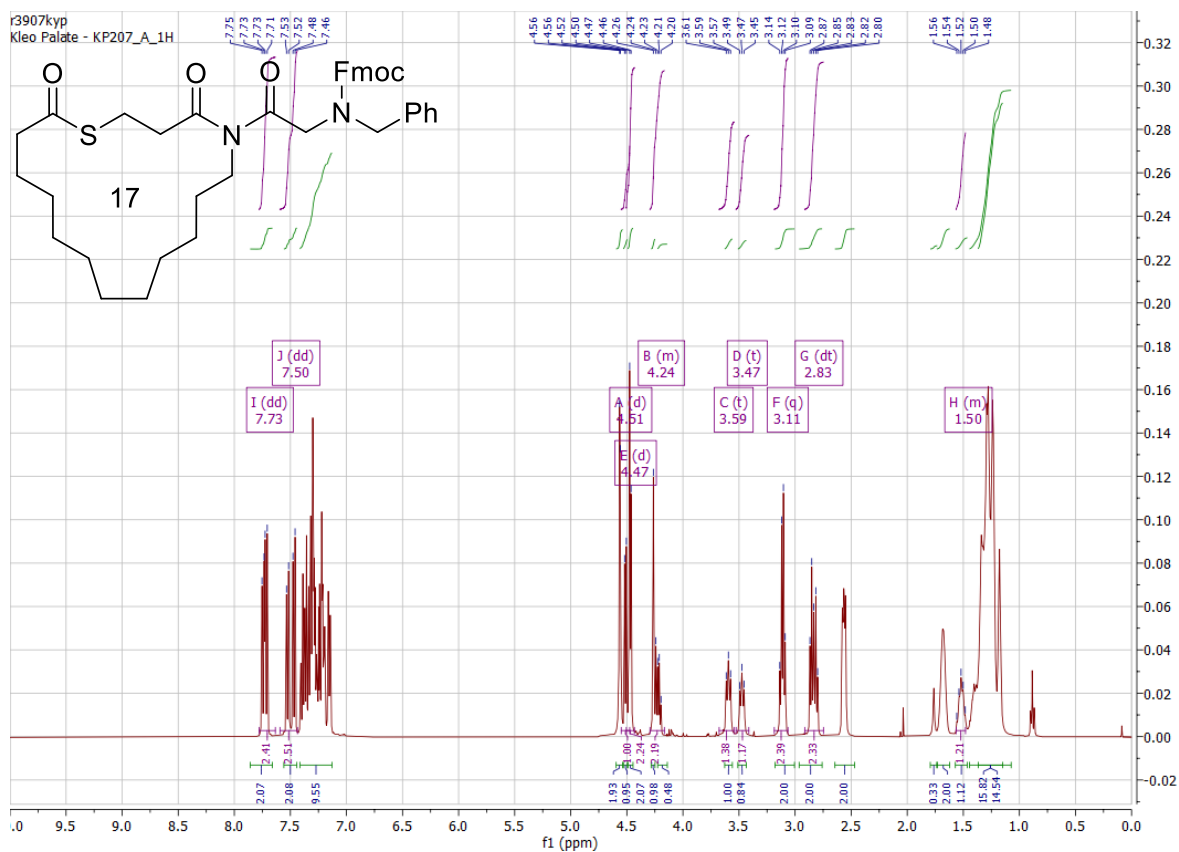
9-Fluorenylmethyl chloride

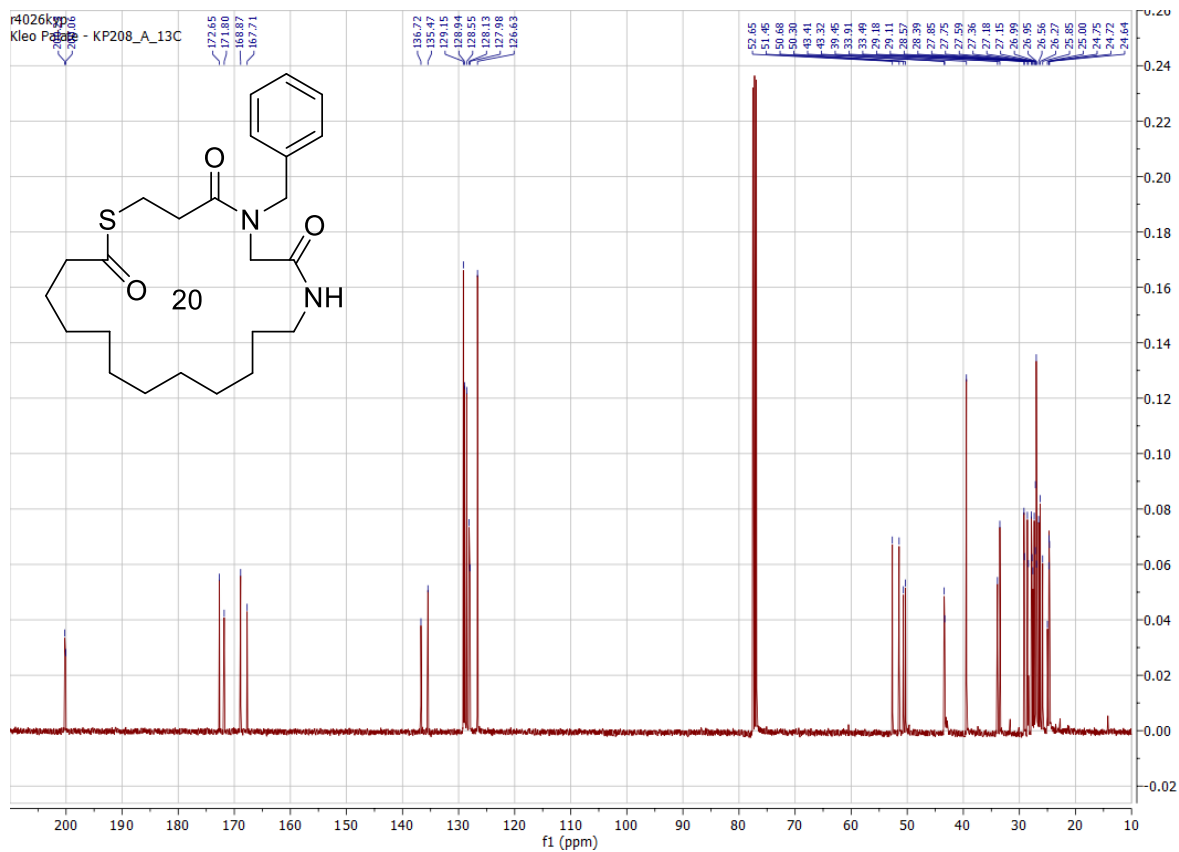
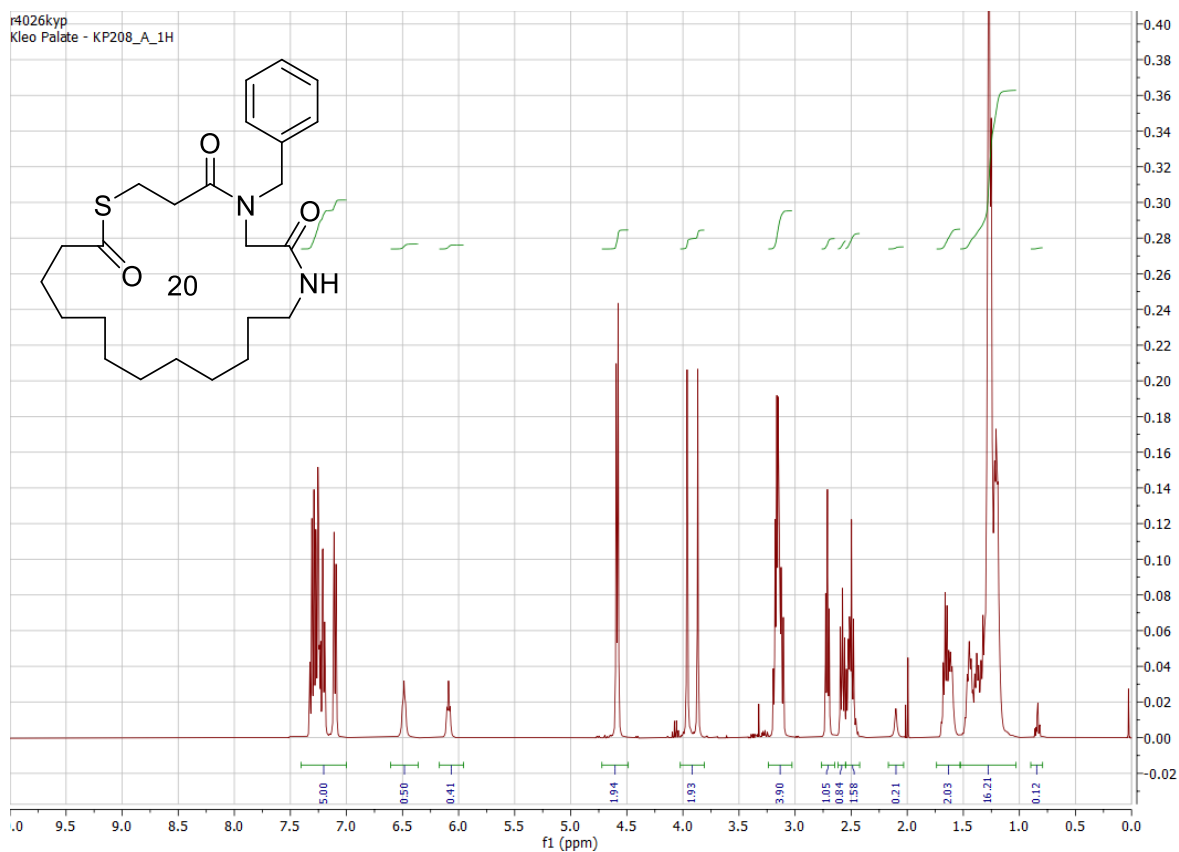


S7

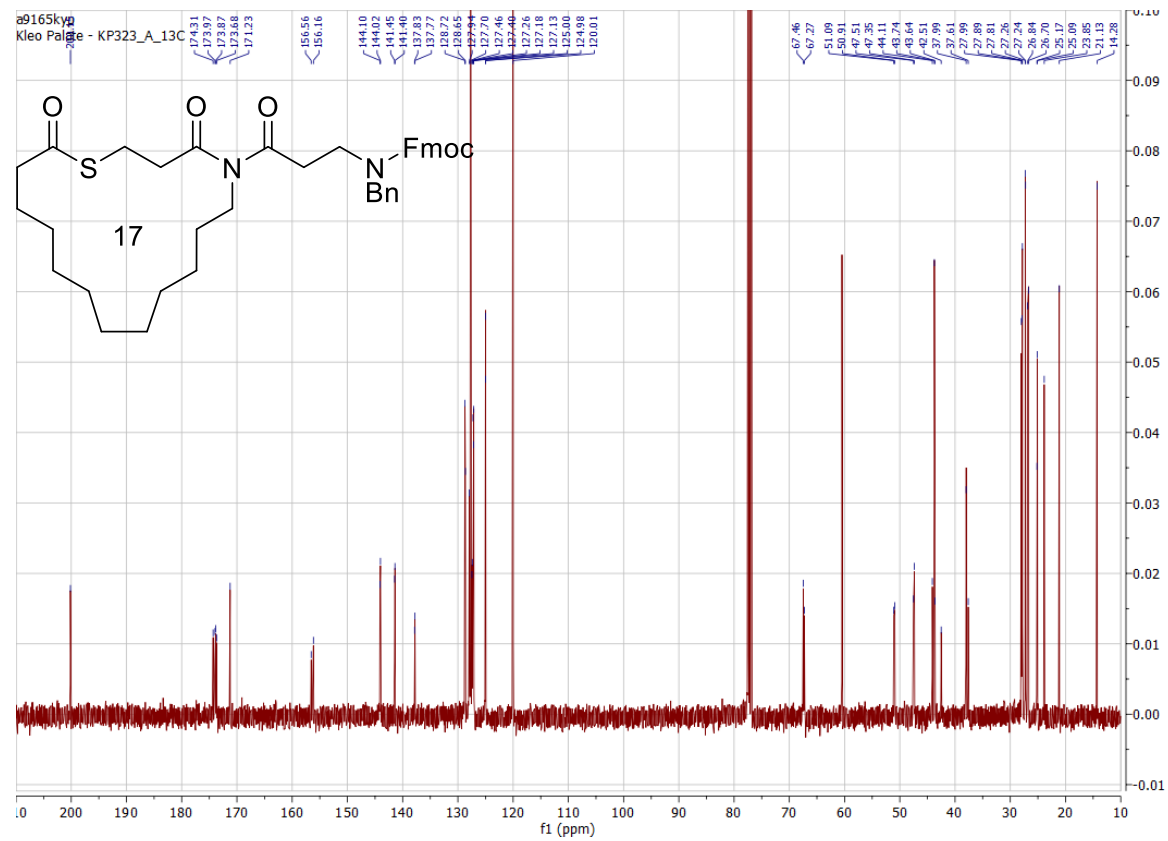
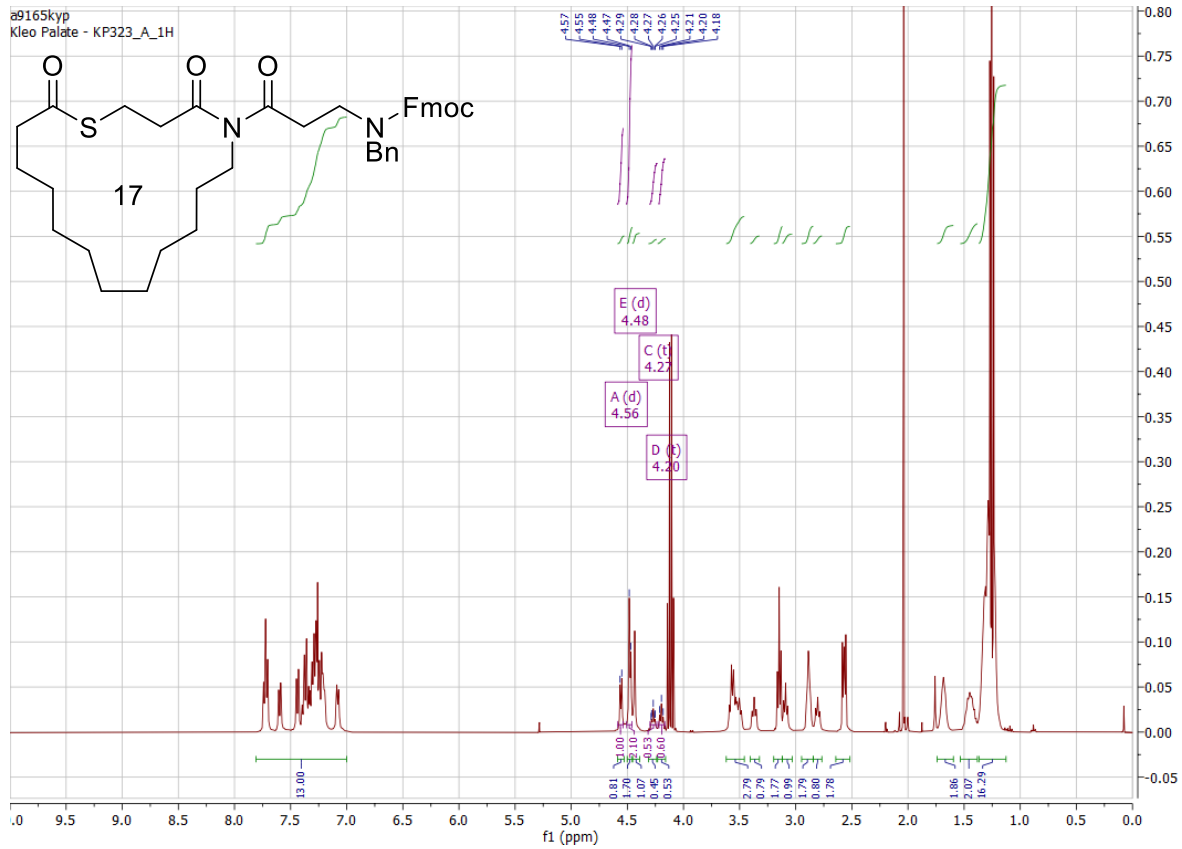




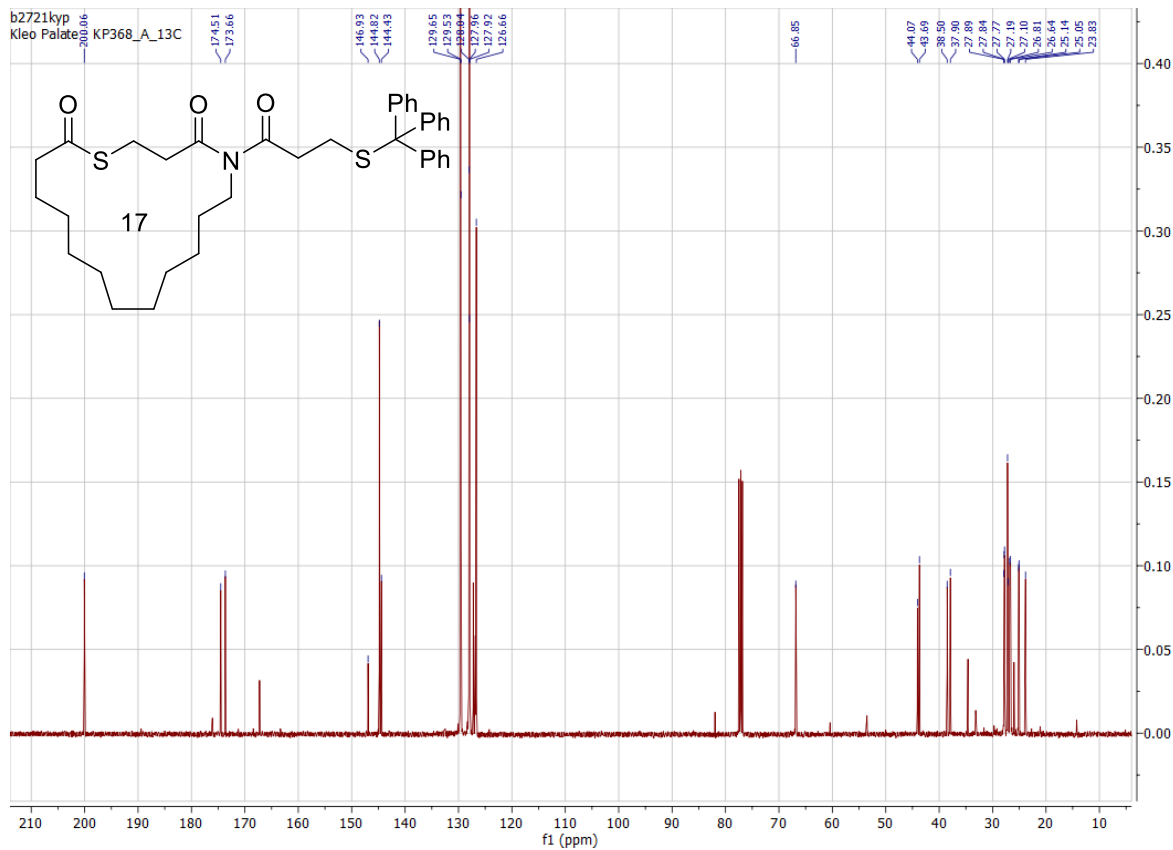
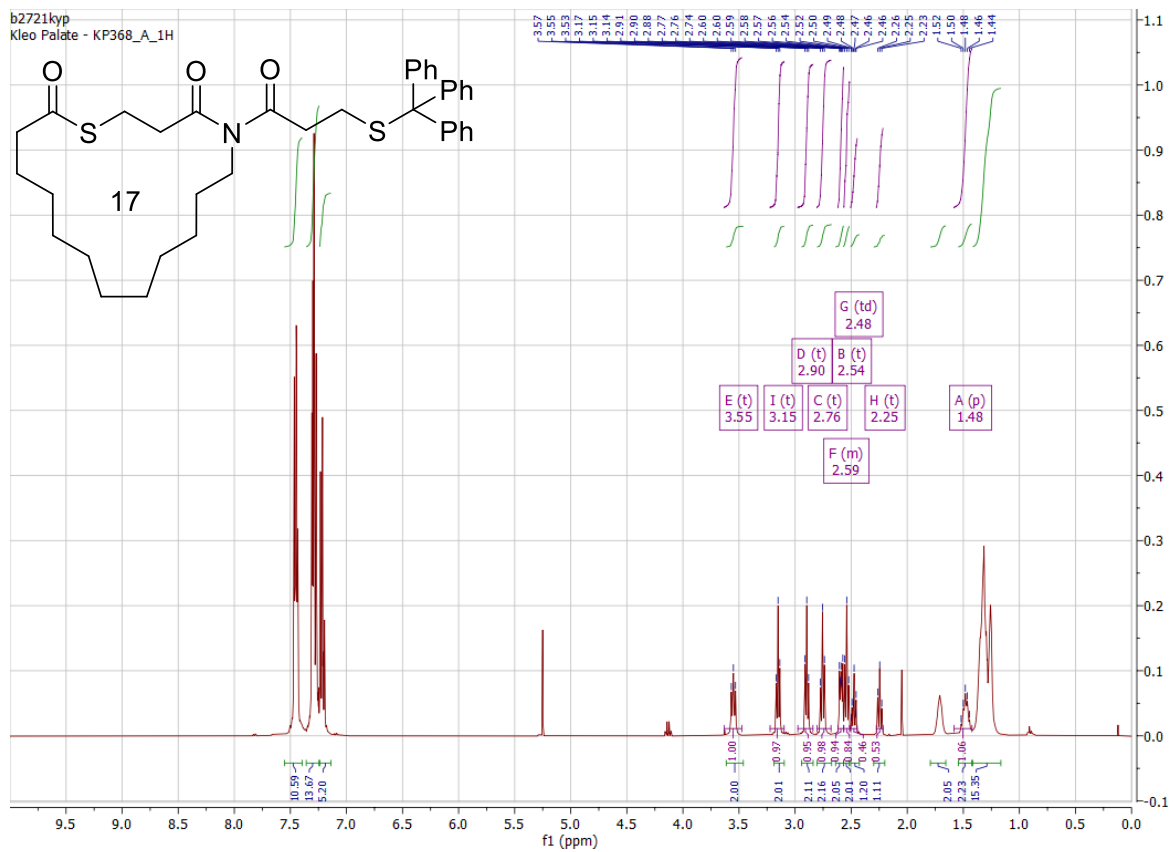


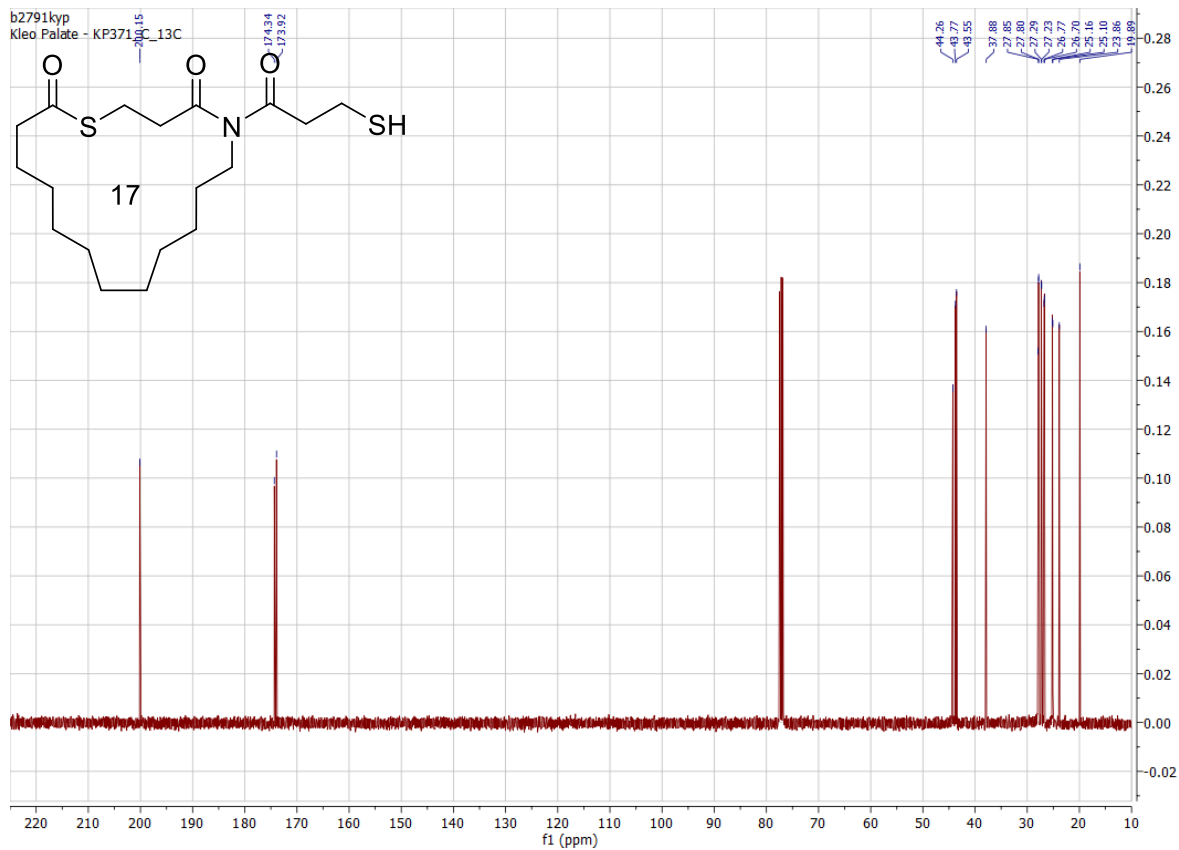
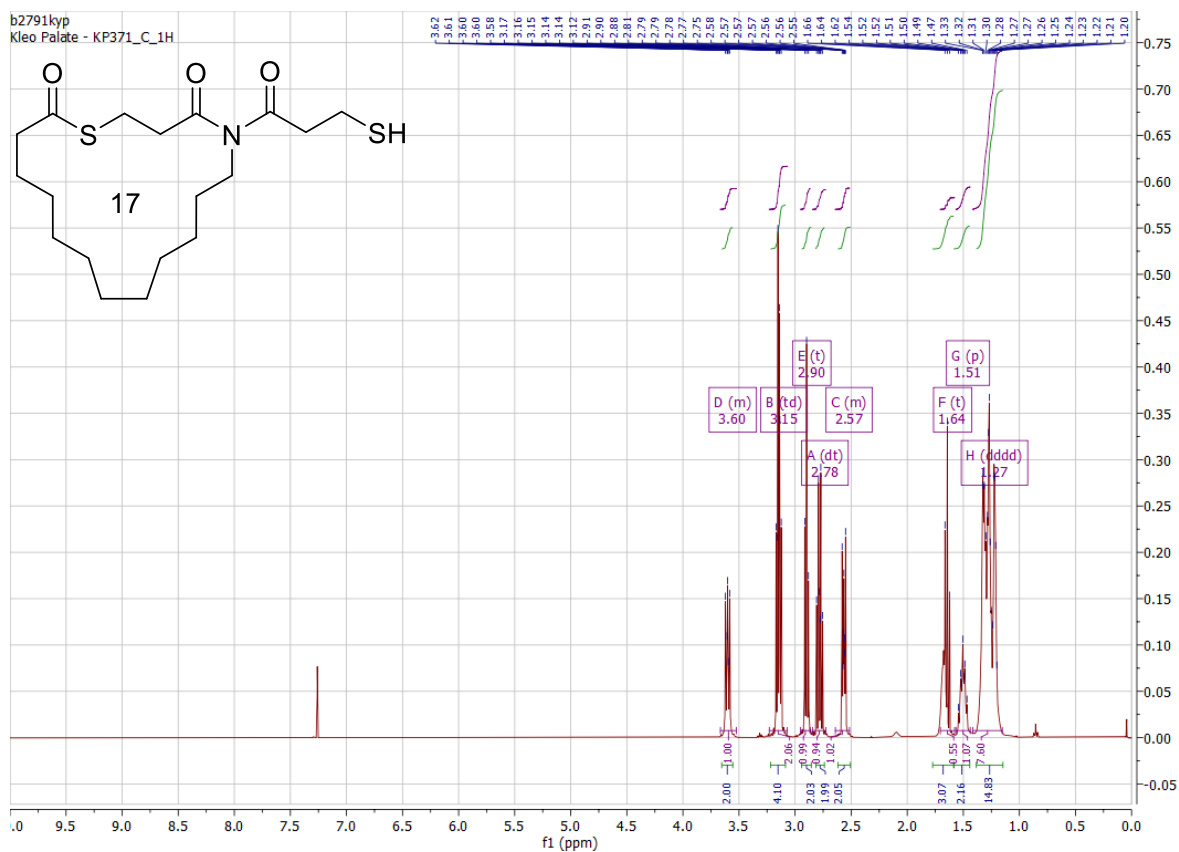


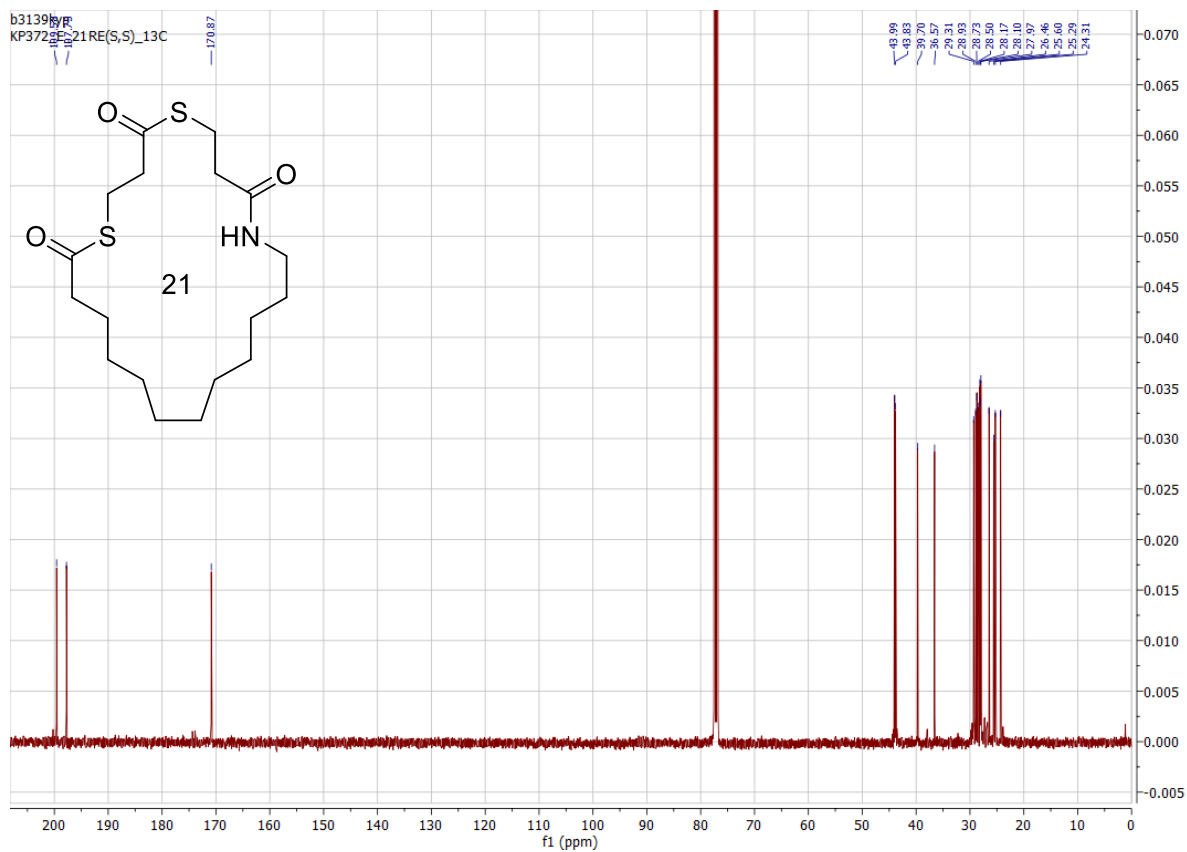
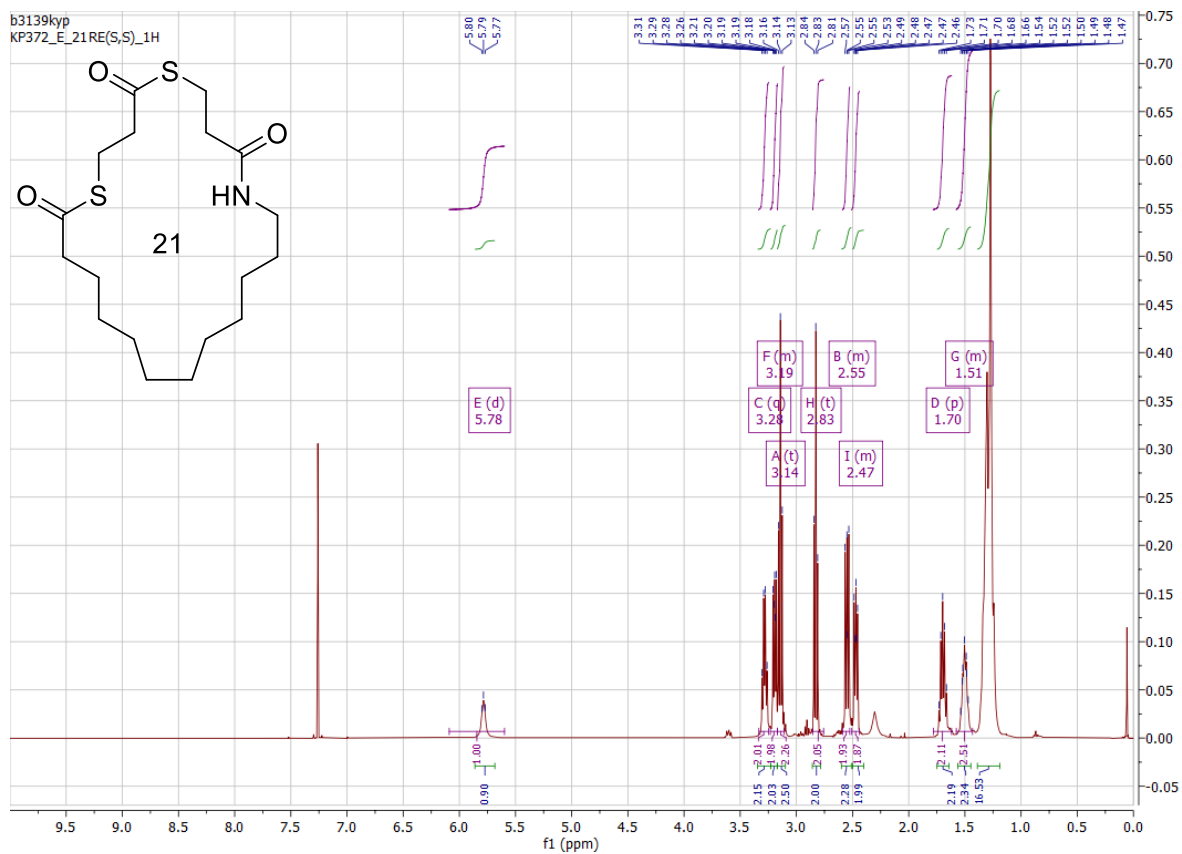
9H-Fluoren-9-yl)methyl benzyl(3-(4,17-dioxo-1-thia-5-azacycloheptadecan-5-yl)-3-oxopropyl)carbamate



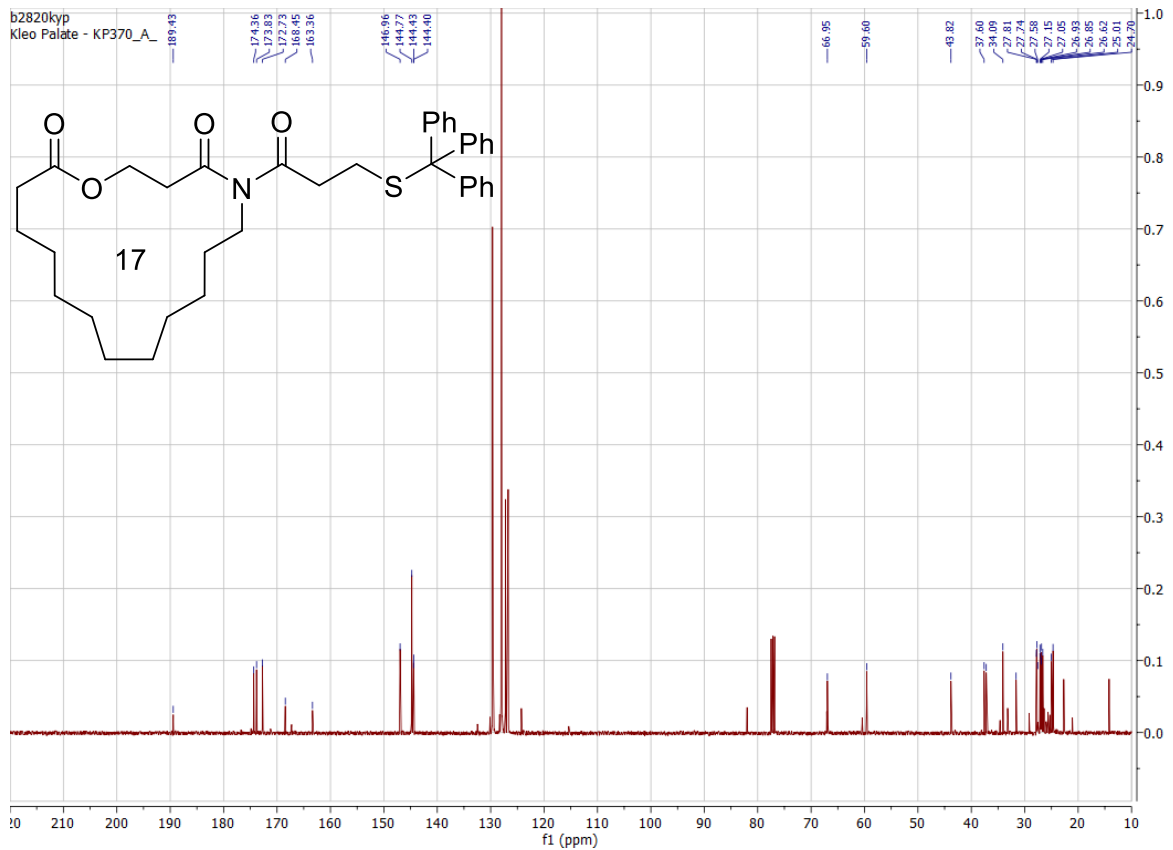
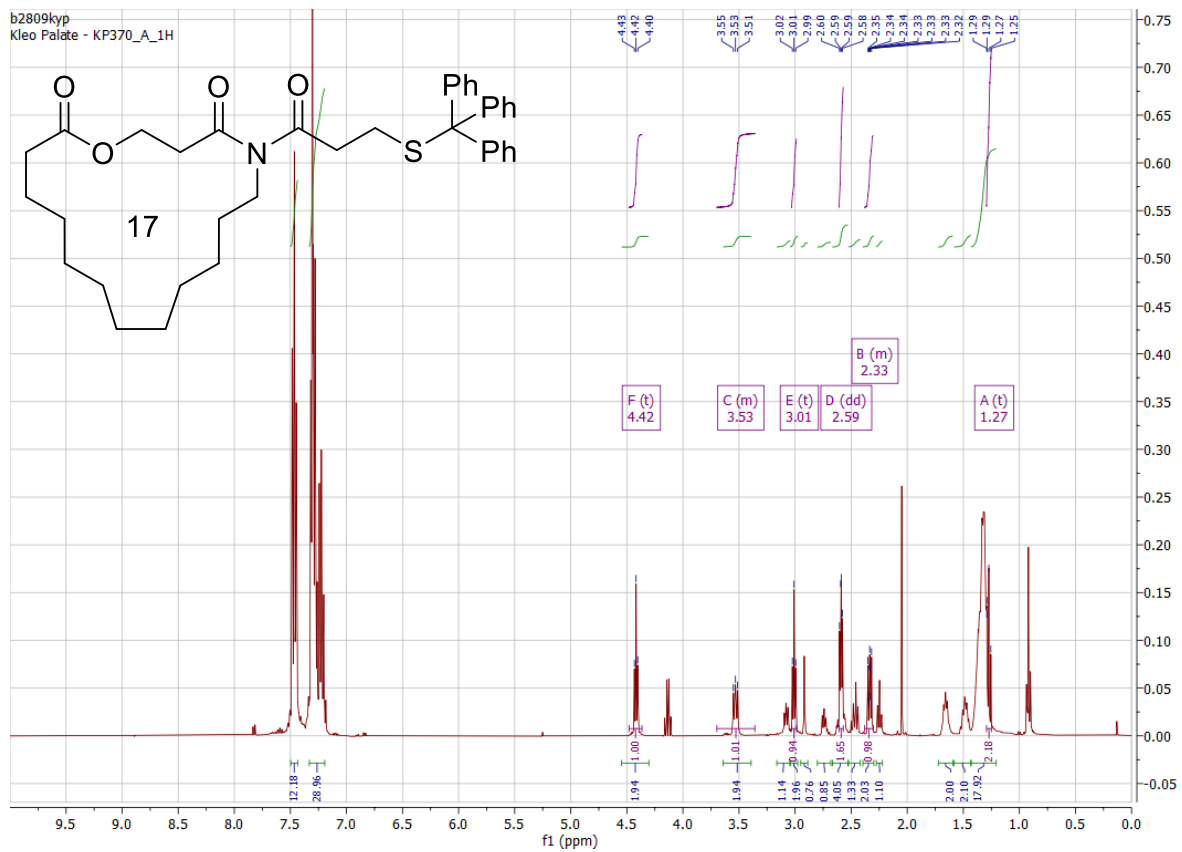
38 (crude)

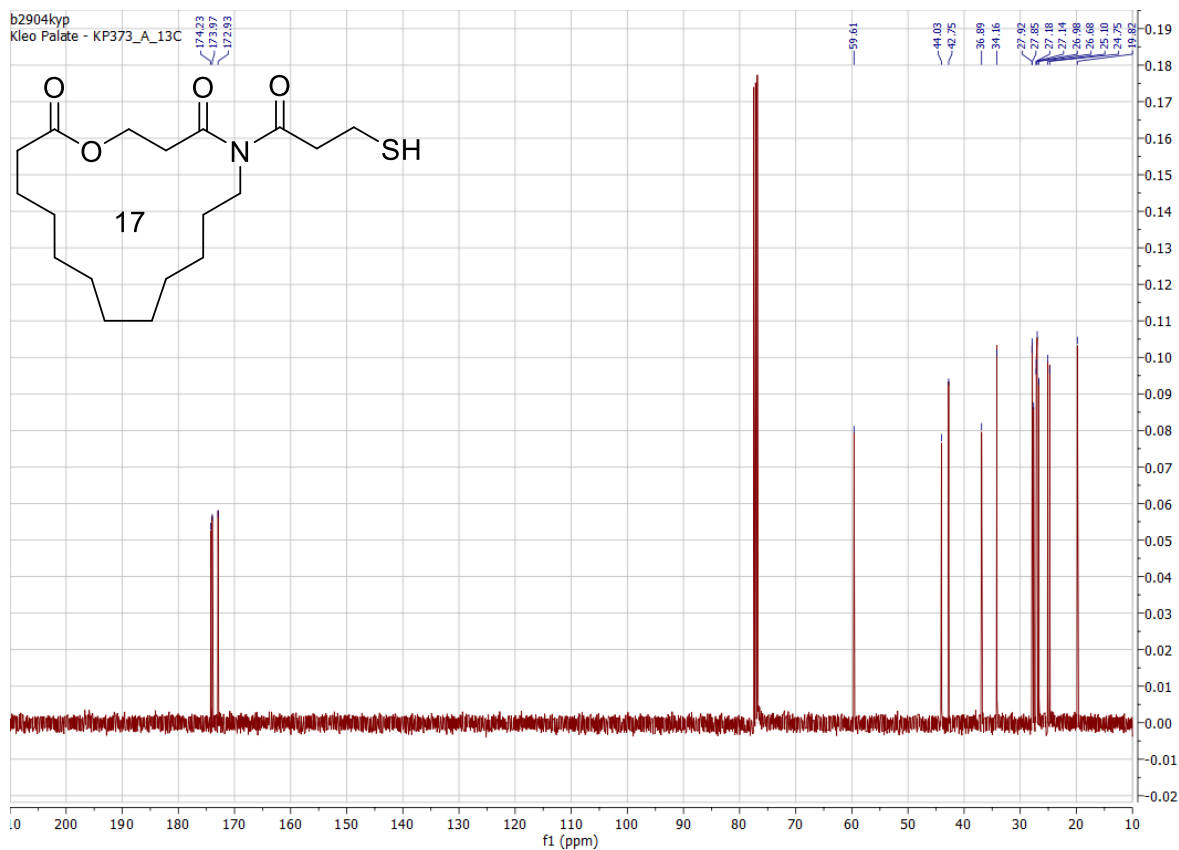
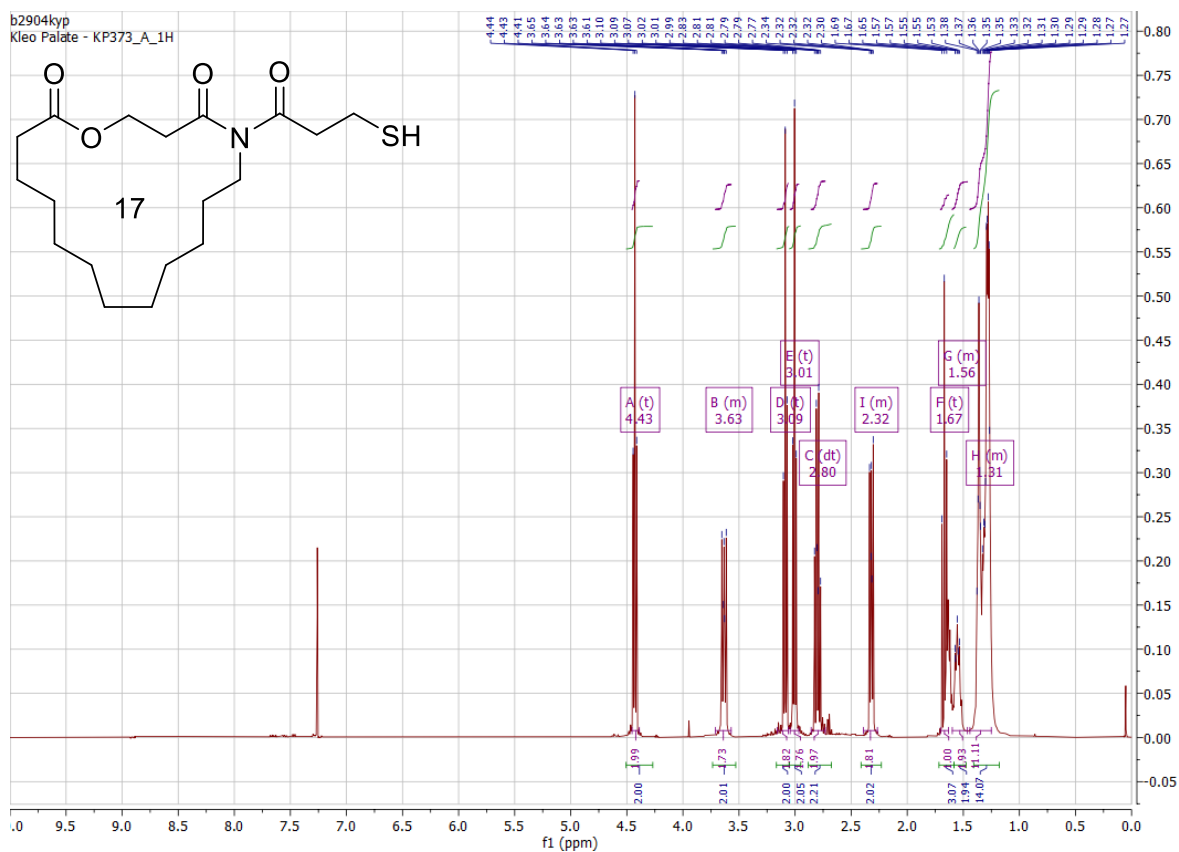


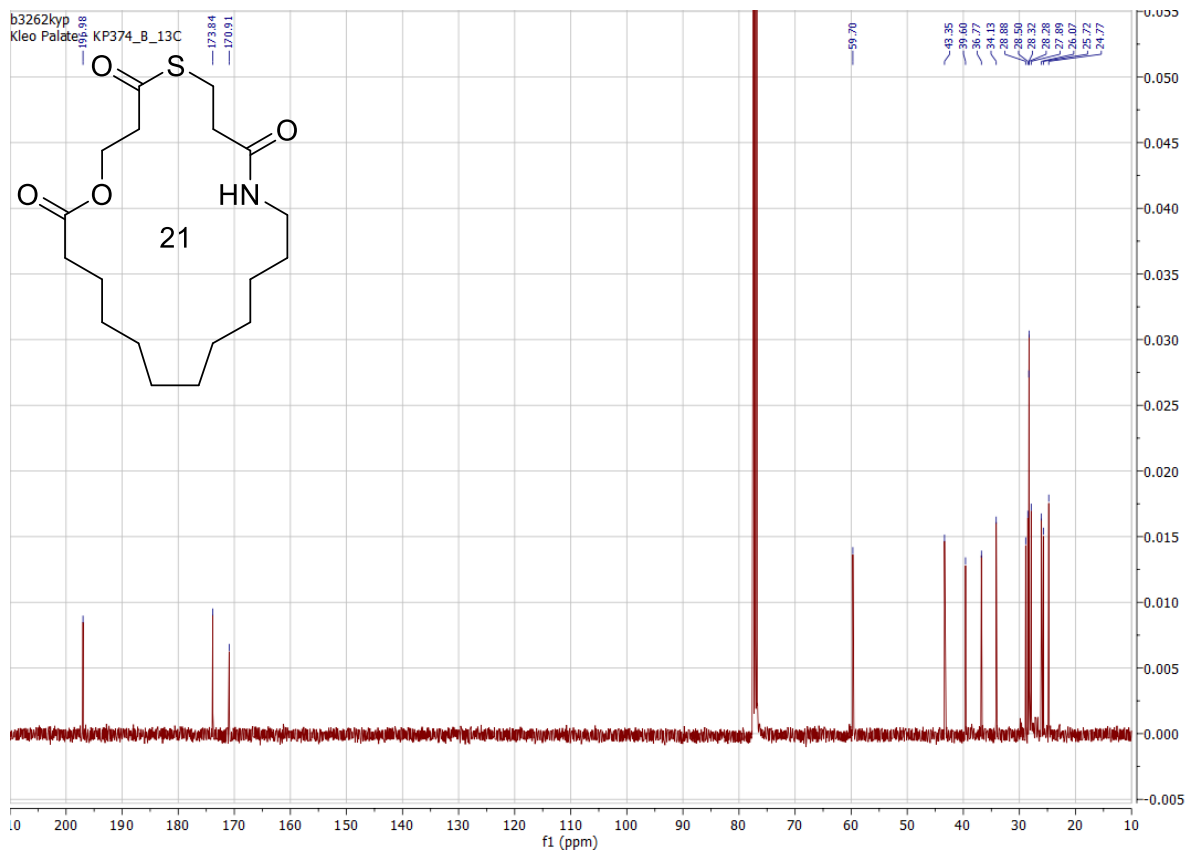
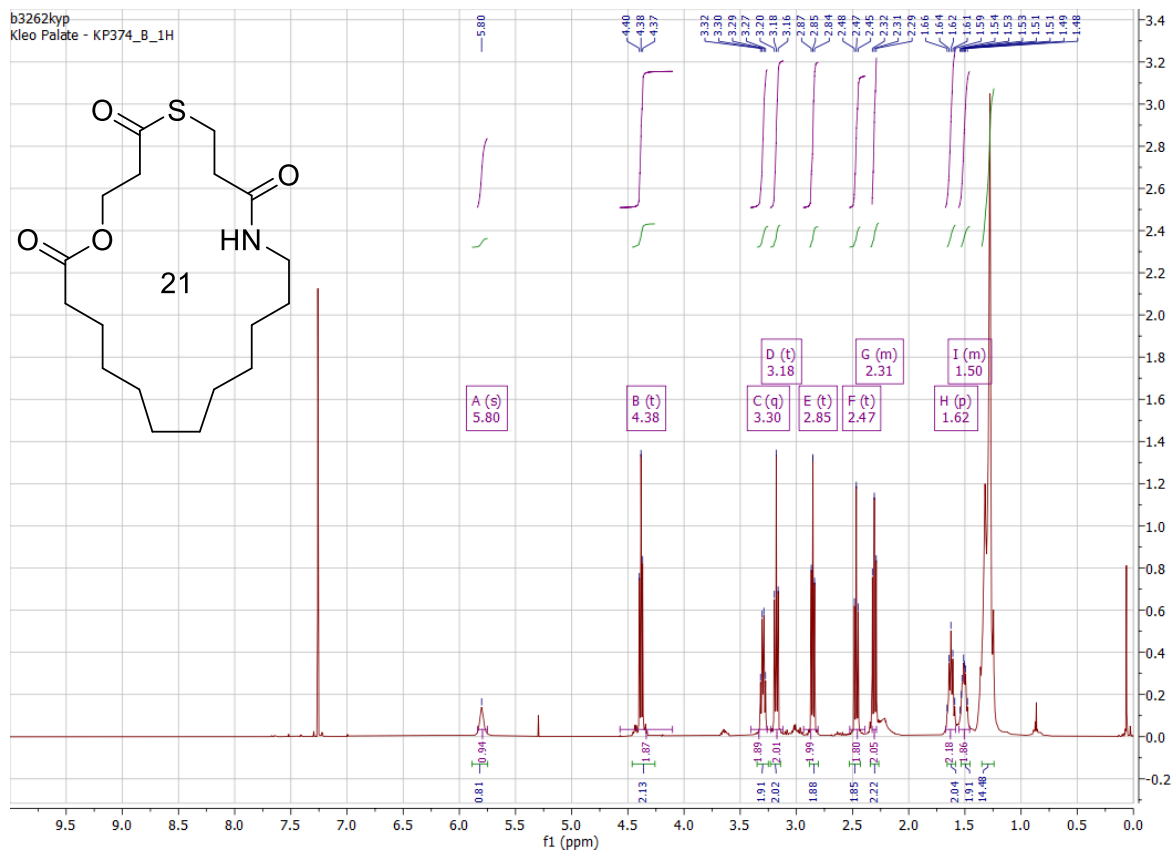


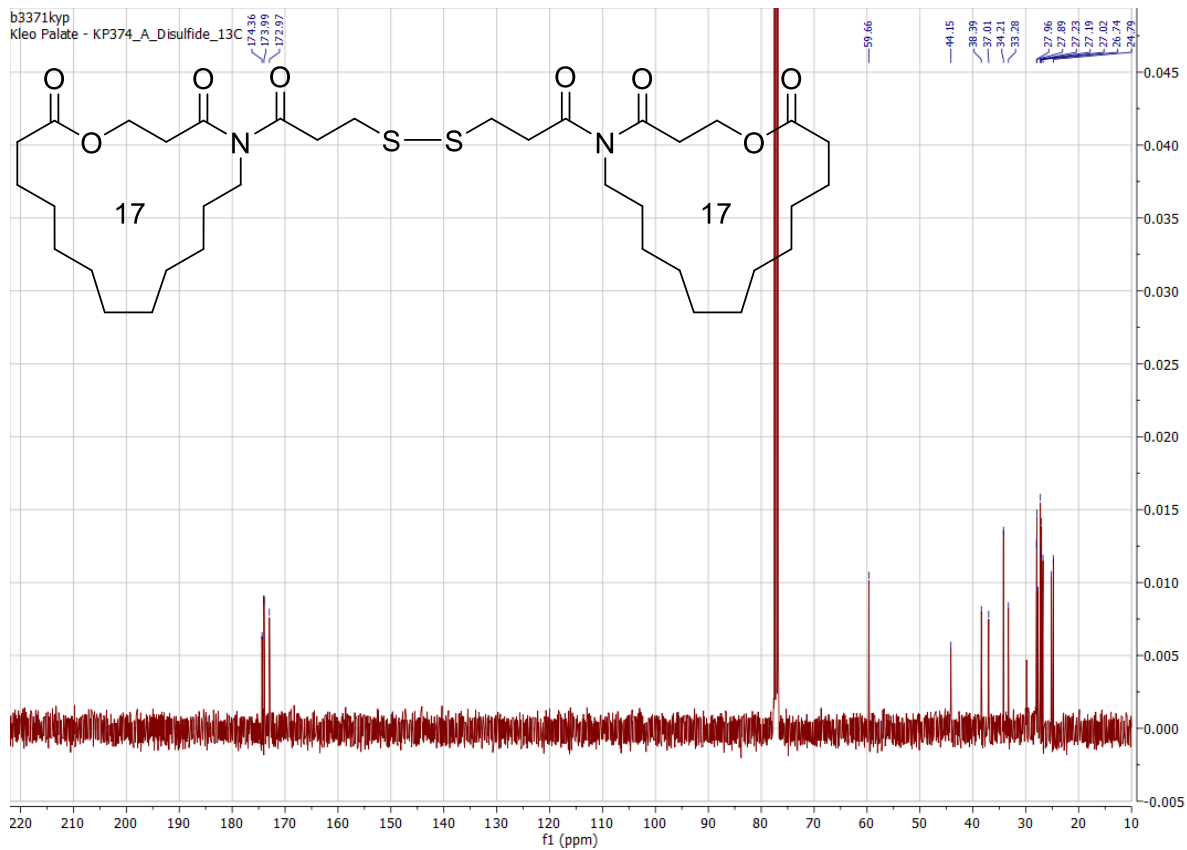
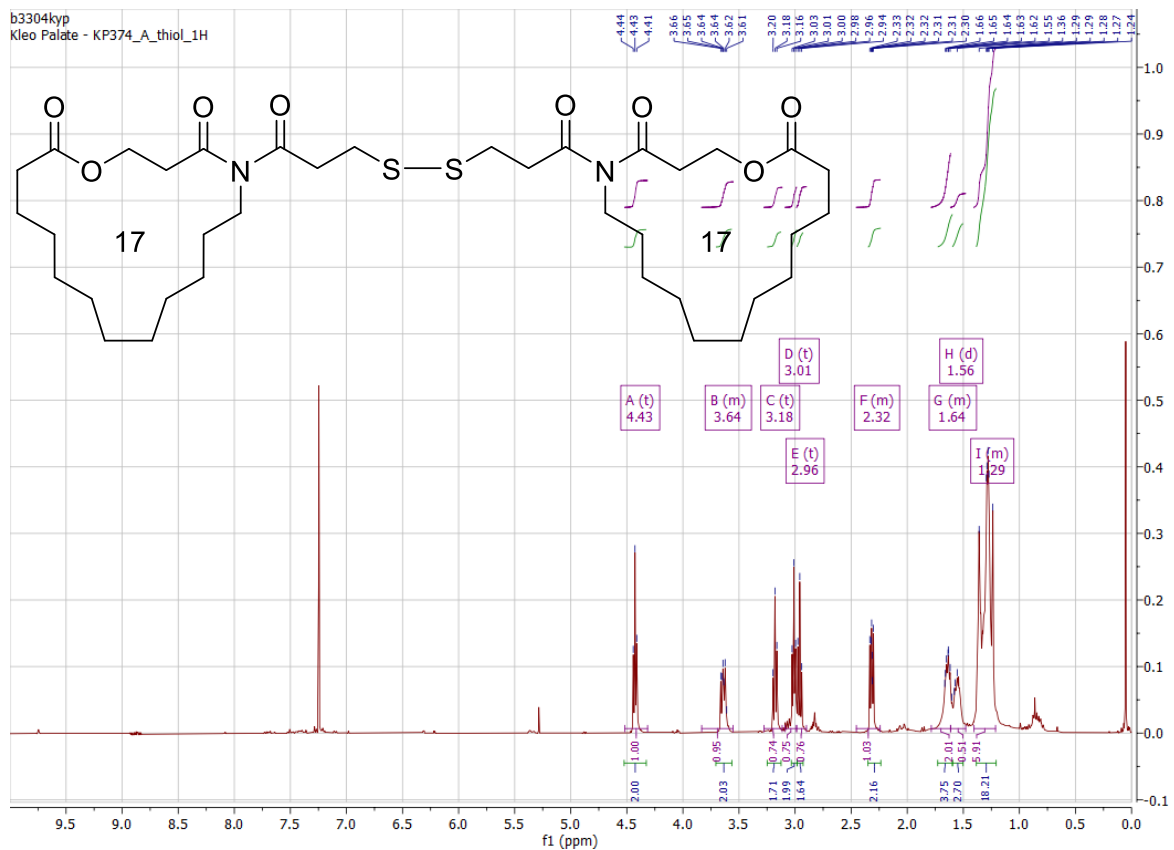


42 (crude)

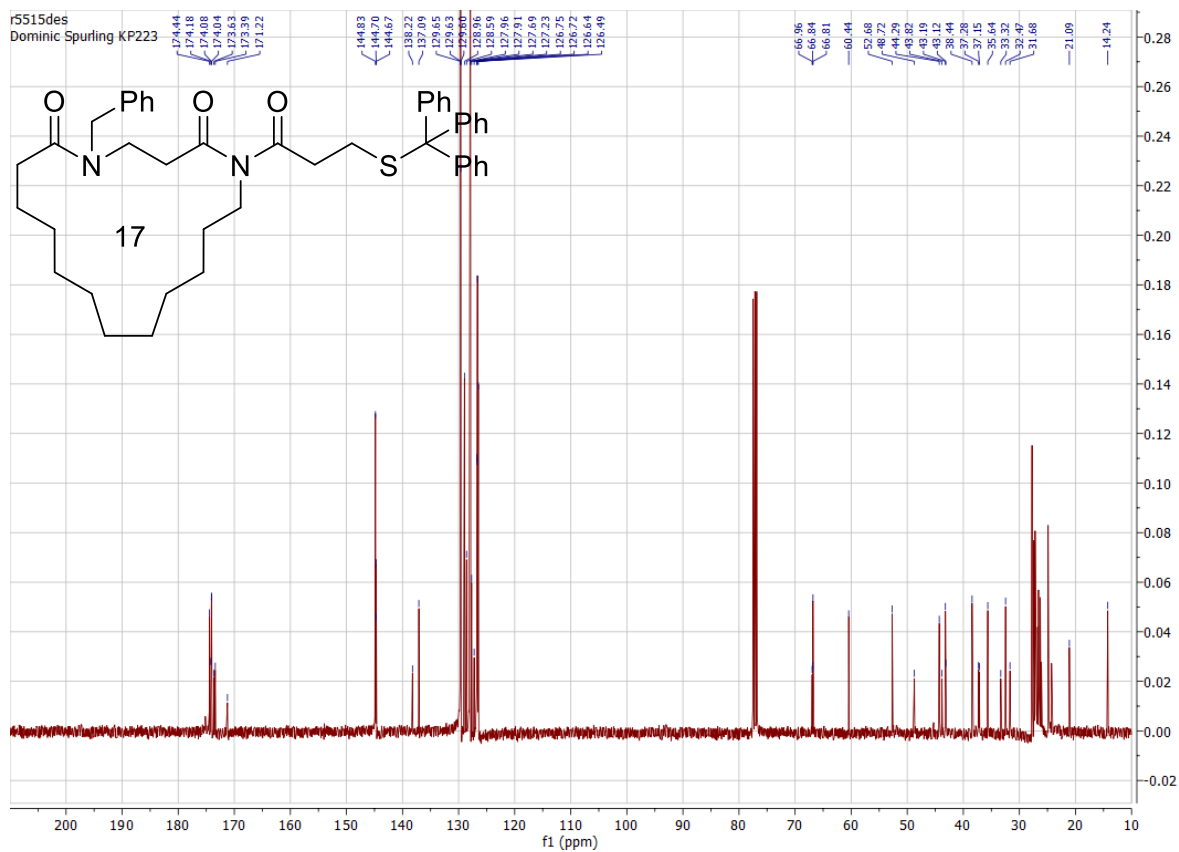
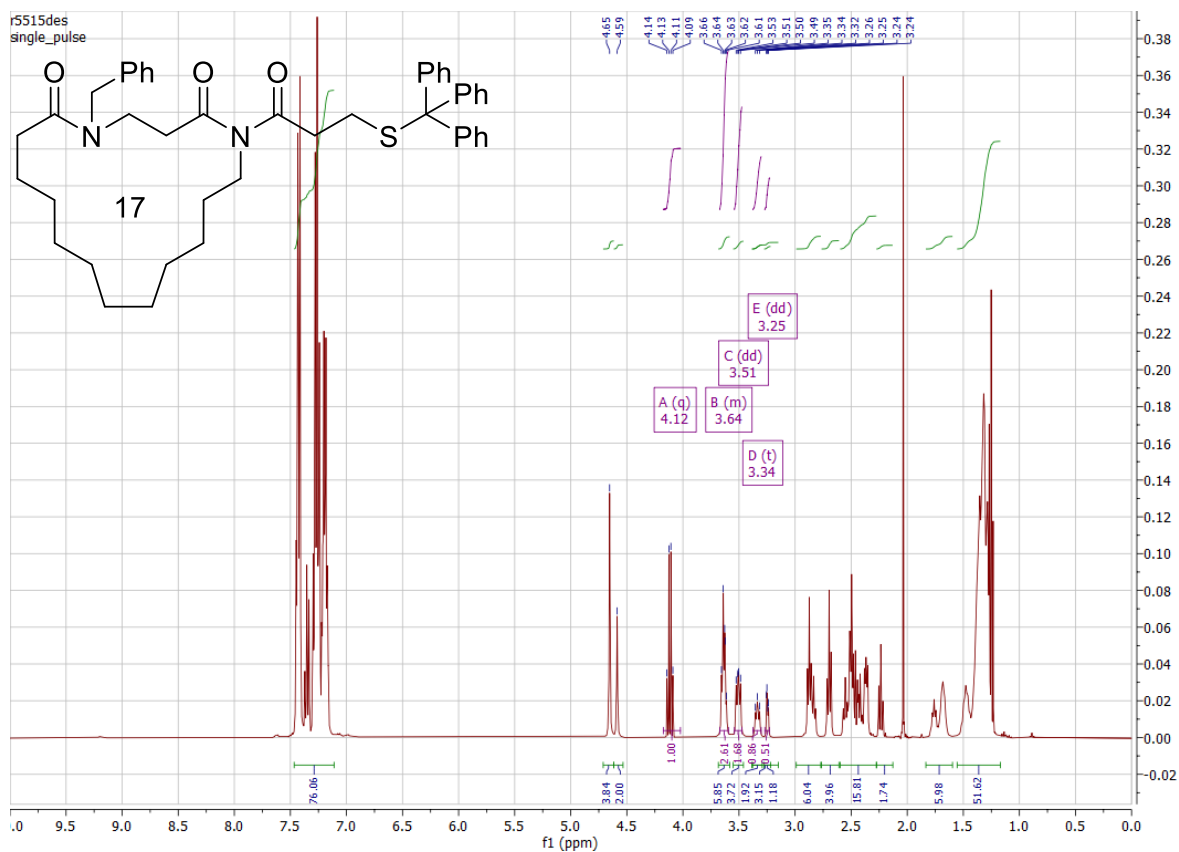


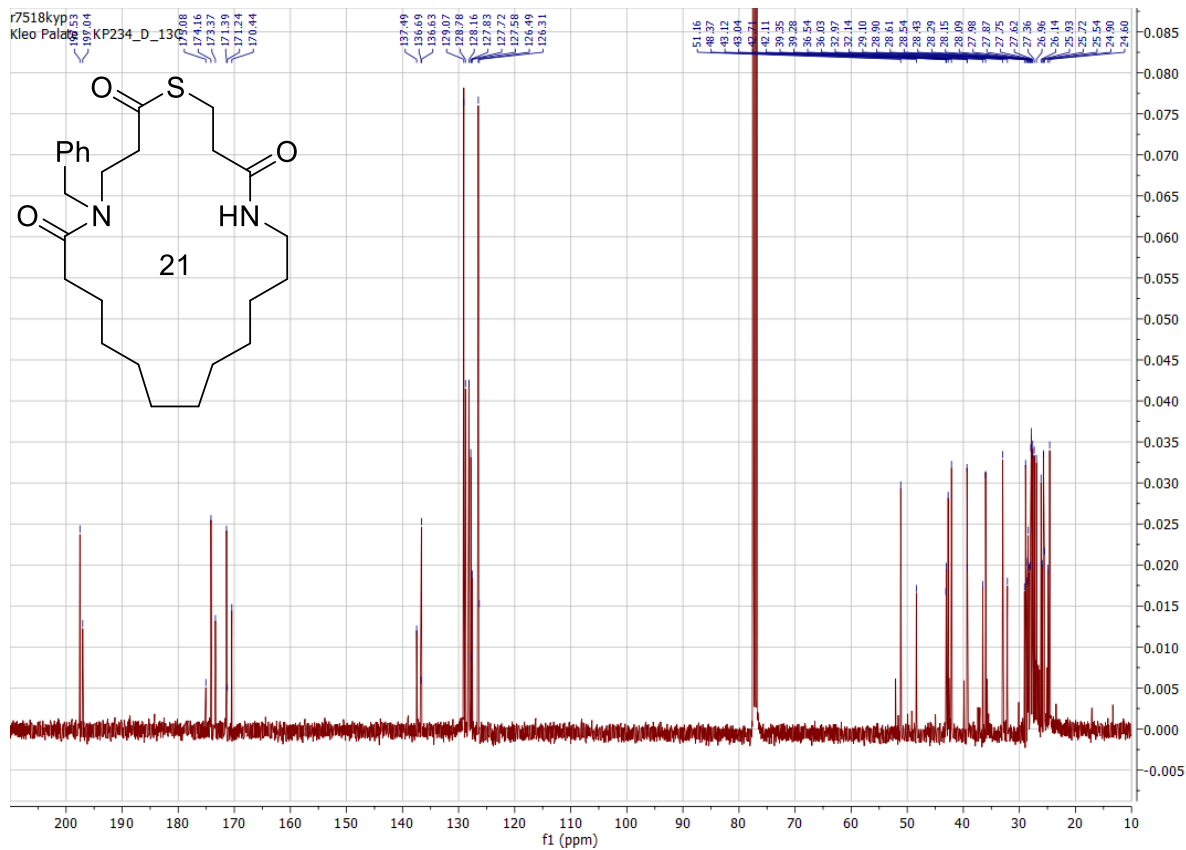
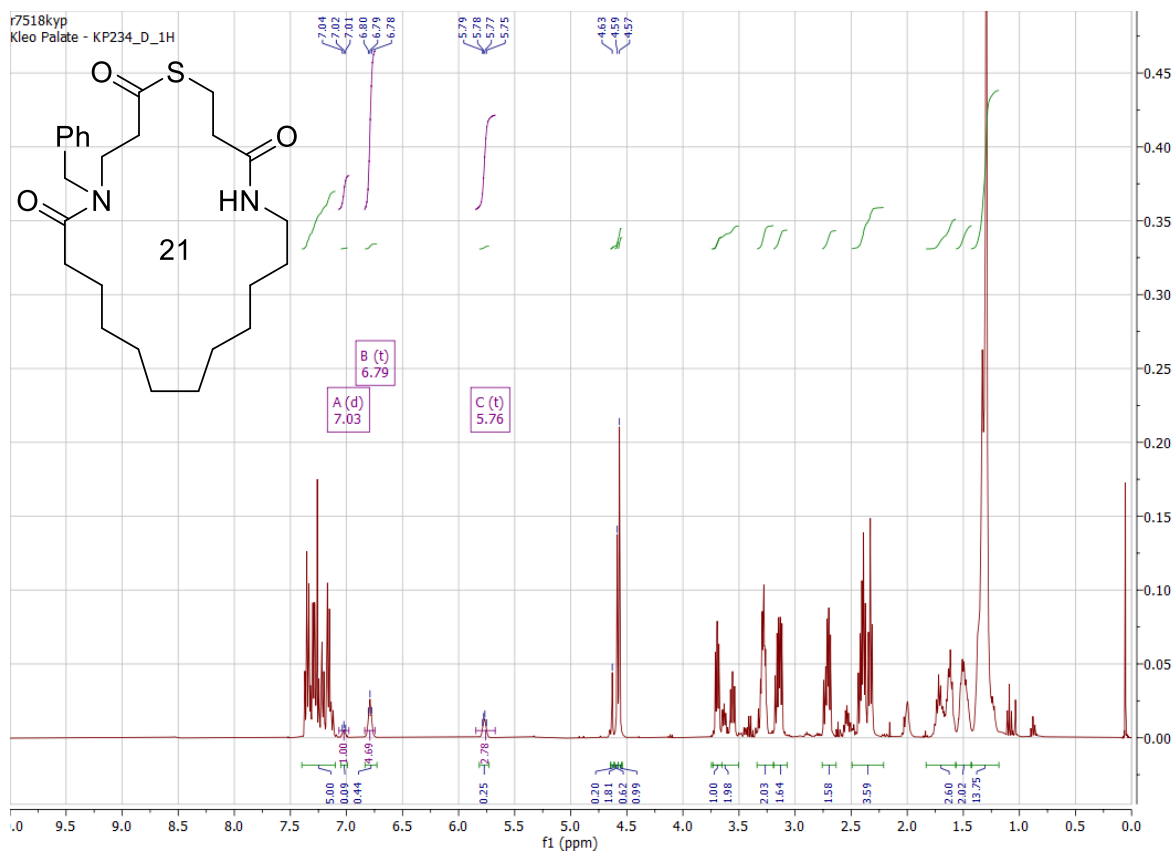






47 (contains trace impurities- used in this form towards the synthesis of **49**)





Computational Studies

The structures were drawn in PCModel,¹⁵ and a conformational analysis was performed using the Molecular Mechanics Force Field (MMFF) level of theory.¹⁶ The structures within 3.5 kcal/mol of the lowest energy conformation were kept and the geometry of each optimised in Gaussian 09, Revision D.01,¹⁷ at the B3LYP/6-31G* level of theory.^{18,19} The structure with the lowest calculated electronic energy was then resubmitted for a frequency calculation, which confirmed that the structures were minima due to the absence of imaginary frequencies. The SCF energies were corrected for their zero-point energies, thermal energies and entropies at 298 K (obtained from the frequency calculations). For compound **20_{RE}**, where x-ray crystallography data was available,²⁰ the crystal structure geometry was optimised at the B3LYP/6-31G* level of theory with subsequent frequency calculation, with no initial conformational search performed. No symmetry constraints were applied. Energies in Hartrees and xyz coordinates are provided.

Energies and xyz Coordinates

15_{RO}

SCF Done: E(RB3LYP) = -955.407990925

Zero-point correction= 0.236721

Thermal correction to Gibbs Free Energy= 0.195657

H	-3.25898800	1.05310000	-0.81456900
C	-2.69732800	1.23711200	0.11129300
H	-2.95655200	2.24358900	0.44748600
C	-3.09798800	0.19821300	1.18358100
H	-2.36922400	0.22505400	2.00501800
H	-4.05416200	0.51779200	1.61516300
C	-1.98851800	-1.83544400	0.03505600
H	-2.22790800	-2.83106800	-0.36027100
H	-1.21373100	-1.98398200	0.79836200
C	-1.39140500	-1.00477200	-1.10959700
H	-0.71427500	-1.61897100	-1.69964100
H	-2.17668600	-0.63931400	-1.77937600
N	-0.57832300	0.14774700	-0.65664600
C	-1.20165800	1.31444500	-0.17733700
O	-0.58895400	2.34842300	0.03095600
C	0.82940600	-0.02009700	-0.74698000
O	1.27571600	-1.04896300	-1.23335100
C	1.76165700	1.05987100	-0.22125900
H	1.45223100	1.37143500	0.77963200
H	1.63994500	1.95307100	-0.84566800
C	3.22418900	0.61306500	-0.22902200
H	3.85656000	1.47023500	0.01939600
H	3.52106700	0.25009500	-1.21492900
H	3.01977200	-1.68260800	0.42238300
C	-3.25431100	-1.23402300	0.65740300
H	-4.05584200	-1.24258400	-0.09646700
H	-3.59744800	-1.88111500	1.47461900
S	3.66157100	-0.66280400	1.02785800

15_{RC}

SCF Done: E(RB3LYP) = -955.387781518

Zero-point correction= 0.240416

Thermal correction to Gibbs Free Energy= 0.202686

H	3.00970800	2.18935200	-0.35144900
C	2.40073800	1.34679900	0.00219200
H	2.15251500	1.55779400	1.04996100
C	2.51302500	-1.20567700	0.36483700
C	1.18762500	-1.51554200	-0.35585500
H	0.94856900	-2.57487300	-0.19646100
H	1.28345700	-1.38923400	-1.43962400
C	-0.04178500	-0.73513300	0.15416300
C	1.10356000	1.33158100	-0.82054000
O	-0.12018900	-0.82129300	1.57545400
H	-0.40415800	-1.72638200	1.78799800
N	-0.04238600	0.67311100	-0.17380500
H	3.18300500	-2.06201500	0.21559100
H	2.31693000	-1.14451800	1.44131500
H	0.76476800	2.35259700	-0.99297600
H	1.27933700	0.86990700	-1.80104000
C	-1.12624100	1.47501700	0.17184700
O	-1.10027200	2.69297600	0.05462800
C	-2.38655300	0.75114500	0.62459300
H	-3.16548700	1.51480300	0.69705300
H	-2.23183600	0.31119700	1.61298200
C	-2.81118300	-0.32805600	-0.37949000
H	-3.72166700	-0.82915800	-0.03932100
H	-3.01698300	0.12352400	-1.35473500
C	3.22896600	0.06269700	-0.11354300
H	4.16171400	0.17863200	0.45366800
H	3.52528700	-0.06953700	-1.16519400
S	-1.52710500	-1.63027000	-0.60193800

15_{RE}

SCF Done: E(RB3LYP) = -955.405834775

Zero-point correction= 0.239231

Thermal correction to Gibbs Free Energy= 0.199612

H	3.00970800	2.18935200	-0.35144900
C	2.40073800	1.34679900	0.00219200
H	2.15251500	1.55779400	1.04996100
C	2.51302500	-1.20567700	0.36483700
C	1.18762500	-1.51554200	-0.35585500
H	0.94856900	-2.57487300	-0.19646100
H	1.28345700	-1.38923400	-1.43962400
C	-0.04178500	-0.73513300	0.15416300
C	1.10356000	1.33158100	-0.82054000
O	-0.12018900	-0.82129300	1.57545400
H	-0.40415800	-1.72638200	1.78799800
N	-0.04238600	0.67311100	-0.17380500
H	3.18300500	-2.06201500	0.21559100
H	2.31693000	-1.14451800	1.44131500
H	0.76476800	2.35259700	-0.99297600
H	1.27933700	0.86990700	-1.80104000
C	-1.12624100	1.47501700	0.17184700
O	-1.10027200	2.69297600	0.05462800
C	-2.38655300	0.75114500	0.62459300
H	-3.16548700	1.51480300	0.69705300
H	-2.23183600	0.31119700	1.61298200
C	-2.81118300	-0.32805600	-0.37949000
H	-3.72166700	-0.82915800	-0.03932100
H	-3.01698300	0.12352400	-1.35473500
C	3.22896600	0.06269700	-0.11354300
H	4.16171400	0.17863200	0.45366800
H	3.52528700	-0.06953700	-1.16519400
S	-1.52710500	-1.63027000	-0.60193800

16_{RO}

SCF Done: E(RB3LYP) = -612.565466747

Zero-point correction= 0.254925

Thermal correction to Gibbs Free Energy= 0.214718

H	2.53071200	0.90028700	-1.53807500
C	2.26923900	1.30122200	-0.55004500
H	2.46632400	2.37529200	-0.57329300
C	3.13936200	0.63018200	0.53761100
H	2.71595400	0.85410900	1.52620500
H	4.12802800	1.10442700	0.51571400
C	2.01427300	-1.69051000	0.35671600
H	1.52205100	-1.64497400	1.33690000
H	2.25628300	-2.74680700	0.18198100
C	1.00593800	-1.25431600	-0.71661700
H	1.51236100	-1.04393500	-1.66458100
H	0.29040900	-2.05401400	-0.89421300
N	0.18881100	-0.07725600	-0.34223000
C	0.76671500	1.20411600	-0.29998900
O	0.12821700	2.21140300	-0.04363300
C	-1.16526300	-0.35568200	0.00275300
O	-1.54087500	-1.52019200	0.00726200
C	-2.11733900	0.77361200	0.35437400
H	-1.70227500	1.34658900	1.18971800
H	-2.16516600	1.47670400	-0.48258800
C	-3.51936100	0.25794300	0.68879600
H	-4.10998700	1.11786500	1.02653400
H	-3.45377600	-0.44305500	1.53816900
H	-3.72942800	-1.19145500	-0.71079800
C	3.31800700	-0.88296600	0.36444300
H	3.97385600	-1.26086500	1.15920400
H	3.84858200	-1.06526500	-0.58216200
N	-4.17522400	-0.30048900	-0.49883700
H	-5.14718600	-0.51198300	-0.27853400

16_{RC}

SCF Done: E(RB3LYP) = -612.550689069

Zero-point correction= 0.256472

Thermal correction to Gibbs Free Energy= 0.219205

H	2.50206700	2.29384900	0.81753400
C	2.02107100	1.32423700	0.63313900
H	1.81141900	0.88311400	1.61298500
C	2.57227000	-1.01134600	-0.31210000
C	1.17105300	-1.21992600	-0.90078400
H	1.04470600	-2.28808700	-1.11517800
H	1.07012600	-0.68948200	-1.85713500
C	-0.02402100	-0.83055200	0.01340600
C	0.70912900	1.64252600	-0.09406200
O	0.26310300	-1.06881400	1.39327400
H	0.31145100	-2.03651700	1.48371600
N	-0.34665400	0.60524500	-0.08687900
H	3.29102400	-1.53096100	-0.95903900
H	2.61767000	-1.50696500	0.66465400
H	0.24656400	2.52157800	0.35553400
H	0.92994600	1.91785200	-1.13660500
C	-1.63940100	1.09403300	-0.12946700
O	-1.87547100	2.29578700	-0.20373900
C	-2.79512100	0.09929400	-0.14813800
H	-3.18169900	0.09166400	-1.17744100
H	-3.58941900	0.52376700	0.47420600
C	-2.39785900	-1.30721600	0.28216200
H	-2.25489000	-1.35174600	1.36574100
H	-3.16344600	-2.04510600	0.02001100
C	3.00219600	0.45018000	-0.15895200
H	3.98605500	0.47761700	0.32761000
H	3.14165700	0.89510300	-1.15588900
N	-1.13171300	-1.70314300	-0.34072500
H	-1.23162500	-1.73355700	-1.35497600

16_{RE}

SCF Done: E(RB3LYP) = -612.581654597

Zero-point correction= 0.256312

Thermal correction to Gibbs Free Energy= 0.218084

H	-3.29285300	-0.09347100	-1.35202900
C	-2.81897800	0.02468800	-0.36731800
H	-3.63639100	0.24043400	0.33438400
C	-1.10993400	1.56648500	0.85891000
C	0.21735000	2.32921300	0.61749700
H	0.63714200	2.64817100	1.57996000
H	0.04257600	3.22312500	0.01156600
C	-2.18830500	-1.32144700	0.05419200
N	-0.90740300	-1.57268800	-0.59799400
H	-1.75926800	2.17782200	1.49858500
H	-0.89129100	0.65701400	1.43153600
H	-1.98123200	-1.35364200	1.12586200
H	-2.89156700	-2.13645800	-0.16084400
C	0.25515600	-1.72818100	0.10226400
O	0.28354600	-1.90184100	1.32017300
C	1.53810600	-1.58603500	-0.71359700
H	2.00880800	-2.56987500	-0.83037600
H	1.32958500	-1.19093500	-1.71216900
C	2.51525800	-0.63903500	0.02424700
H	-0.83337800	-1.36719100	-1.58498800
C	1.22475400	1.46038500	-0.13590700
O	1.41972400	1.56053500	-1.34466700
H	3.01571600	-1.17729800	0.83159300
H	3.27327400	-0.28255100	-0.67716800
C	-1.84409500	1.21309000	-0.44906200
H	-2.39856000	2.09373600	-0.79888800
H	-1.10201200	1.00949000	-1.22886500
N	1.85655000	0.51500300	0.63074100
H	1.47339200	0.34088500	1.55122300

17_{RO}

SCF Done: E(RB3LYP) = -651.874769263

Zero-point correction= 0.283135

Thermal correction to Gibbs Free Energy= 0.240916

C	-1.31942600	1.27356800	-0.19985400
O	-0.72044600	2.31252300	0.02209800
N	-0.67198400	0.08930600	-0.59722500
C	0.74075700	-0.08394100	-0.60981700
C	-1.46330700	-1.09395400	-1.00658500
H	-0.75950700	-1.74632800	-1.51889600
C	-2.11570000	-1.84773300	0.16143500
H	-2.21566500	-0.77787100	-1.73663200
H	-1.38281500	-1.93169200	0.97432400
H	-2.32484400	-2.87216400	-0.17282200
C	-3.41926600	-1.21898600	0.66804200
H	-4.17535400	-1.28752500	-0.12853200
C	-3.30296800	0.24736400	1.10198800
H	-3.80532500	-1.81231300	1.50674100
H	-2.63063900	0.33730800	1.96599700
H	-4.28679000	0.58918700	1.44561600
C	-2.83266200	1.21130300	-0.01136900
H	-3.33303600	0.96234100	-0.95669300
H	-3.11179100	2.23705700	0.23967400
O	1.19609100	-1.16503000	-0.95850500
C	1.65663700	1.04868600	-0.17985000
H	1.38840800	1.36518200	0.83319400
C	3.13463800	0.65474600	-0.23430600
H	1.46468200	1.92052900	-0.81220900
H	3.40357300	0.36059900	-1.26593300
H	3.72174800	1.55211100	0.00089100
N	3.46682700	-0.36706900	0.75442700
C	4.89617500	-0.65000200	0.80990700
H	2.97221200	-1.21552100	0.48621300
H	5.07885300	-1.46889200	1.51405200
H	5.34656700	-0.92689600	-0.16261700
H	5.43139400	0.23297600	1.18092800

17_{RC}

SCF Done: E(RB3LYP) = -651.855610717

Zero-point correction= 0.284632

Thermal correction to Gibbs Free Energy= 0.245582

H	2.71414500	-0.27705500	1.31622800
C	2.64574200	0.49507600	0.54370900
H	3.48983800	1.17791400	0.70905200
C	1.99889900	-1.48158600	-0.93819800
C	0.47000900	-1.35410500	-0.92524800
H	0.05167600	-2.36527700	-0.98154900
H	0.14354500	-0.82348400	-1.82742000
C	-0.18547600	-0.63540100	0.27913600
C	1.38742100	1.34655900	0.74824900
O	0.36838000	-1.18268200	1.45508600
H	-0.16668000	-0.82040700	2.18425500
N	0.09475000	0.82394100	0.24380100
H	2.27288100	-1.99307700	-1.87076500
H	2.30865300	-2.14382500	-0.12016400
H	1.28286800	1.57742900	1.81744700
H	1.50892900	2.30483500	0.24222900
C	-0.81725700	1.79503200	-0.11913300
O	-0.54485400	2.99171100	-0.09368600
C	-2.21831200	1.35873000	-0.51389400
H	-2.49365100	1.91876800	-1.41311600
H	-2.87496400	1.71139600	0.29063000
C	-2.38548000	-0.14019300	-0.70033000
H	-3.44099600	-0.41718000	-0.60480300
H	-2.07290900	-0.45388200	-1.71272600
C	2.78366000	-0.16844900	-0.83295300
H	3.84355600	-0.38870600	-1.01438100
H	2.47345200	0.52812700	-1.62545900
N	-1.64344200	-0.83620000	0.34781200
C	-2.05566500	-2.23575700	0.46608800
H	-2.04330700	-2.78558500	-0.49058800
H	-1.40511700	-2.75437400	1.17171300
H	-3.08053400	-2.26146600	0.85237500

17_{RE}

SCF Done: E(RB3LYP) = -651.885859098

Zero-point correction= 0.283816

Thermal correction to Gibbs Free Energy= 0.243013

C	-1.19404700	1.26559800	0.14484900
O	-1.38142700	2.25012600	-0.56646400
N	-1.98028100	0.13577000	0.01929700
C	-3.06550800	0.15194600	-0.95690500
C	-1.83998600	-1.09629700	0.79094700
H	-2.96372100	-0.67202300	-1.67494800
H	-4.03620800	0.04894600	-0.45442400
H	-3.03122400	1.10110500	-1.48907900
H	-2.84969900	-1.47648000	0.98680500
C	-1.02747700	-2.19928400	0.07048400
H	-1.39108700	-0.89077300	1.76436400
H	-1.40251100	-2.32553700	-0.95244800
H	-1.17393300	-3.14436100	0.60201900
C	0.47166700	-1.91270600	0.09564200
O	1.16834500	-2.23963400	1.05348100
N	0.96957000	-1.23434200	-0.97711200
C	2.36275600	-0.78975400	-1.03494000
H	2.57056200	-0.52383600	-2.07716200
H	2.99414700	-1.64557000	-0.77559200
C	2.68899800	0.38679400	-0.10052000
H	3.76661400	0.57717300	-0.18673700
H	2.52668400	0.04558200	0.92745000
C	1.89285700	1.68644000	-0.38149400
H	2.58530400	2.48044700	-0.68658700
H	1.21523000	1.54703300	-1.23381600
C	1.06680800	2.20488900	0.80940200
C	-0.09831200	1.28792100	1.21519900
H	1.72433000	2.33383000	1.67942000
H	0.65811400	3.18857400	0.55997300
H	0.27397000	0.29132000	1.46013300
H	-0.56216700	1.67639000	2.13374000
H	0.32867900	-0.91903500	-1.69053400

18_{RO}

SCF Done: E(RB3LYP) = -632.432710989

Zero-point correction= 0.242378

Thermal correction to Gibbs Free Energy= 0.202557

C	-0.77979900	1.22843500	-0.35576700
O	-0.12380300	2.24561800	-0.21233700
C	-2.30041700	1.30297300	-0.44985200
H	-2.51655800	2.37327400	-0.42076900
C	-3.05537900	0.57784500	0.68786100
H	-2.64621900	0.93119600	-1.42368600
H	-4.04451600	1.04238800	0.77948700
C	-3.24166200	-0.92898700	0.47111000
H	-2.54199600	0.76555700	1.64075300
H	-3.83309300	-1.34045000	1.29889900
H	-3.84320800	-1.07829200	-0.43802300
C	-1.94000700	-1.72787400	0.33434200
C	-1.00976000	-1.23260800	-0.78206900
H	-1.38171500	-1.72662300	1.27953400
H	-2.18928000	-2.77603500	0.12481700
N	-0.19423400	-0.05243000	-0.41007300
H	-1.57720000	-0.99442000	-1.68753600
H	-0.29208100	-2.00932000	-1.03703500
C	1.16833200	-0.31203100	-0.11907200
O	1.57979300	-1.46506300	-0.20824800
C	2.09991500	0.80612600	0.31248600
H	2.23596900	1.49435800	-0.52863000
H	1.63134300	1.40477600	1.09974900
C	3.45523700	0.25644700	0.77609800
H	3.30934700	-0.39132900	1.65527000
O	4.16596300	-0.41359100	-0.24787300
H	4.08052300	1.09879700	1.08970400
H	3.61395100	-1.18453000	-0.46518500

18_{RC}

SCF Done: E(RB3LYP) = -632.422019516

Zero-point correction= 0.243615

Thermal correction to Gibbs Free Energy= 0.206324

H	2.50586700	2.28772500	0.83064700
C	2.02174800	1.32090500	0.64061000
H	1.85974900	0.85196100	1.61678400
C	2.56087200	-0.99416000	-0.36169300
C	1.14400300	-1.22472200	-0.90038300
H	1.00299000	-2.29528600	-1.08958100
H	1.00154600	-0.72106900	-1.86377600
C	-0.02286100	-0.81812600	0.02881700
C	0.67842900	1.65967300	-0.01405400
O	0.26170100	-1.08397400	1.39903200
H	0.49044200	-2.02788400	1.45637000
N	-0.35971800	0.60535800	-0.04118700
H	3.26334400	-1.49923700	-1.03712900
H	2.65955000	-1.49200200	0.61122700
H	0.22039700	2.49937800	0.51066600
H	0.85290900	2.00758100	-1.04291700
C	-1.65670600	1.07233300	-0.14278500
O	-1.90603800	2.26943700	-0.22649300
C	-2.78127600	0.04727600	-0.19296800
H	-3.12987200	0.00805500	-1.23259800
H	-3.60685400	0.43831300	0.40964900
C	-2.33096600	-1.32749600	0.26144900
H	-2.19221300	-1.36846700	1.34800500
H	-3.02654900	-2.11644600	-0.03561400
C	2.97085100	0.47422800	-0.21844700
H	3.97988200	0.51548900	0.21211300
H	3.04496200	0.93108000	-1.21671300
O	-1.09474800	-1.62498300	-0.39655200

18_{RE}

SCF Done: E(RB3LYP) = -632.445665857

Zero-point correction= 0.243274

Thermal correction to Gibbs Free Energy= 0.204596

H	-0.36715300	3.46379100	-0.31930700
C	-0.16403600	2.38563400	-0.36474600
H	-0.49548500	2.06494000	-1.36299200
C	-2.35379900	1.14526800	0.31062300
C	-2.33484100	-0.03375700	-0.69321700
H	-1.89450100	0.26102400	-1.64977800
H	-3.36353100	-0.36141000	-0.87782200
C	1.35742900	2.16337400	-0.27653300
N	1.73594600	0.81093500	-0.67600600
H	-2.89610800	0.81254500	1.20303400
H	-2.93894100	1.96304100	-0.13056700
H	1.88231300	2.88074100	-0.91924500
H	1.71999700	2.29965700	0.74542900
C	1.99615800	-0.18912000	0.22175900
O	2.18140600	0.00090600	1.41804300
C	1.97375500	-1.59889800	-0.37486500
H	2.73513800	-2.19801800	0.13348900
H	2.20061000	-1.59139700	-1.44756800
C	0.60298700	-2.23649800	-0.13334500
H	1.43299600	0.51774500	-1.59550600
C	-1.56437000	-1.20322500	-0.11250600
O	-1.91535100	-1.85879200	0.84232300
H	0.53836800	-3.23225100	-0.58374300
H	0.38188700	-2.31469400	0.93291700
C	-0.96418300	1.65283700	0.73546200
H	-0.37921700	0.81126800	1.12271800
H	-1.08874400	2.32966200	1.58992100
O	-0.38028700	-1.37922300	-0.75845700

19_{RO}

SCF Done: E(RB3LYP) = -916.097724890

Zero-point correction= 0.207419

Thermal correction to Gibbs Free Energy= 0.167679

C	1.45217600	1.08389100	0.02399900
C	3.67064800	-0.25756800	0.15131200
C	1.50907100	-1.42124800	-0.33863200
C	2.79494000	-1.46452400	0.47691700
N	0.78158300	-0.12852300	-0.21695600
C	2.89974100	1.01453100	0.50466900
H	4.61733900	-0.28784200	0.70232400
H	1.72587900	-1.59701400	-1.40023300
H	3.30894600	-2.40605700	0.25144000
H	3.92433100	-0.26271100	-0.91749700
H	0.81647500	-2.20398900	-0.02962000
H	2.55835300	-1.47627500	1.54952800
O	0.90735600	2.16915400	-0.08885900
C	-0.59461800	-0.20941800	-0.55323000
O	-1.02888000	-1.27481500	-0.96534800
C	-1.50604500	0.99141200	-0.36020000
H	-1.23460900	1.75025700	-1.10387200
H	-1.31295300	1.46091400	0.60778600
C	-2.98257800	0.62189800	-0.51017200
H	-3.16760900	0.11657700	-1.46004500
H	-3.58003900	1.53785500	-0.49320100
H	-3.03603600	-1.54515700	0.50890800
S	-3.67575700	-0.40861200	0.85241700
H	2.84809700	1.12151200	1.59823700
H	3.38504700	1.92081500	0.13194300

19_{RC}

SCF Done: E(RB3LYP) = -916.080235426

Zero-point correction= 0.211240

Thermal correction to Gibbs Free Energy= 0.174785

C	0.22593700	-0.73371100	0.17802100
C	2.76523000	-0.66801200	-0.10134800
C	1.43398700	1.43169500	0.26839500
C	2.65011000	0.82327900	-0.42482300
N	0.18314700	0.70489700	-0.06237300
C	1.46232800	-1.37016100	-0.49228500
H	2.94970900	-0.80245500	0.97192100
H	1.57311100	1.41813500	1.35757900
H	2.56076600	0.96228300	-1.51071900
H	3.60562200	-1.12672300	-0.63545600
H	1.27433700	2.46500600	-0.03395500
H	3.54697700	1.36571500	-0.10186300
O	0.26785800	-0.88521500	1.59514700
H	0.29115500	-1.83848300	1.78401800
C	-2.49855800	-0.58489000	0.25964500
H	-3.47612800	-1.00040900	-0.00037200
C	-0.96845400	1.48566200	-0.08530000
O	-0.90380100	2.70763500	-0.04011700
H	-2.37683600	-0.63654300	1.34548100
C	-2.34099600	0.83723300	-0.25900200
H	-2.56871000	0.86394600	-1.33235700
H	-3.04506400	1.51594600	0.23337200
S	-1.23249400	-1.64216000	-0.52139100
H	1.48845400	-2.43283200	-0.22019700
H	1.32451900	-1.31924600	-1.57863900

19_{RE}

SCF Done: E(RB3LYP) = -916.091242468

Zero-point correction= 0.210632

Thermal correction to Gibbs Free Energy= 0.173111

C	0.50587400	-1.56157100	0.29550300
C	2.14133900	-0.08259800	-0.91455700
C	2.36459500	0.87720500	0.28250200
C	1.77015600	-1.54408400	-0.53151600
H	3.05719800	-0.14472100	-1.51332400
H	1.36519800	0.31677600	-1.57709500
H	3.30772900	1.42039900	0.14230900
O	0.50372600	-1.44818600	1.50584300
H	2.48401000	0.30093300	1.20868000
C	1.26916100	1.94276600	0.48315600
H	1.56257100	2.60481900	1.30859100
H	1.16131700	2.55984700	-0.41196900
N	-0.05518500	1.39351800	0.75111900
C	-2.15188100	-0.79213900	0.50113300
H	-3.10718500	-1.32070700	0.45314300
H	-1.72067900	-0.97675400	1.48905500
C	-2.35846100	0.70551900	0.20219100
H	-2.86499200	1.16071600	1.06561700
H	-3.01374300	0.83299600	-0.66228900
C	-1.09593000	1.51538500	-0.12974500
O	-1.05020300	2.23109800	-1.12304600
H	-0.13241900	0.72549400	1.50638200
H	2.56952200	-1.99109100	0.06924500
H	1.64177700	-2.13485900	-1.44559500
S	-1.01383300	-1.60841600	-0.69281000

20_{RO}

SCF Done: E(RB3LYP) = -994.716587754

Zero-point correction= 0.265962

Thermal correction to Gibbs Free Energy= 0.223991

H	-3.36645000	1.89758900	1.54608000
C	-2.81548500	1.18433200	0.92090400
H	-2.29814700	0.51957400	1.62640200
C	-1.78497600	1.99184600	0.11440500
H	-1.09361200	2.49018800	0.80297300
H	-2.30263100	2.78692500	-0.44086100
C	-0.96476500	1.19610500	-0.90789500
H	-1.60056700	0.83489100	-1.71564300
H	-0.20753000	1.84391400	-1.34931800
N	-0.25224800	0.03960300	-0.32349600
C	-0.89413600	-1.20322400	-0.16881200
C	-3.82164400	0.36126300	0.08405900
H	-4.79959500	0.38901900	0.58071100
H	-3.97553300	0.84092300	-0.89399200
C	-3.47055800	-1.12408800	-0.11358500
C	-2.19703700	-1.45785300	-0.92494300
H	-3.38106900	-1.60813700	0.86796200
H	-4.31148000	-1.61351400	-0.62093100
H	-2.22589100	-0.97083500	-1.90422400
H	-2.18650200	-2.53748900	-1.09986900
O	-0.44600500	-2.07980100	0.55348800
C	1.03425600	0.32973700	0.19674300
O	1.42050600	1.48979800	0.19204500
C	1.92731300	-0.79314500	0.69988100
H	1.50689000	-1.16686500	1.64110500
H	1.89103300	-1.64349200	0.01392500
C	3.36631500	-0.32609600	0.92346600
H	3.39922700	0.54635200	1.57884000
H	3.92942000	-1.13108500	1.40424800
S	4.31601200	0.05120100	-0.61105000
H	3.66027900	1.19236100	-0.90575000

20_{RC}

SCF Done: E(RB3LYP) = -994.691211656

Zero-point correction= 0.269473

Thermal correction to Gibbs Free Energy= 0.230521

H	4.10530800	1.05401500	0.14038200
C	3.18093200	0.56839400	-0.19777900
H	3.43645200	0.08260800	-1.15214900
C	2.15215000	1.68200000	-0.44379900
H	2.59978000	2.41809100	-1.12643700
H	1.94837300	2.21673000	0.49198200
C	0.80738800	1.27966700	-1.06187700
H	0.31249200	2.18857000	-1.40683500
H	0.95539900	0.64024900	-1.93679900
N	-0.16523000	0.63821900	-0.15368400
C	-0.28093900	-0.79439700	0.03009300
C	2.77249600	-0.49588300	0.84062300
H	2.10579000	-0.04764800	1.58601100
H	3.66692900	-0.81901800	1.38909800
C	2.12216200	-1.77035900	0.27949000
C	0.85685200	-1.62997200	-0.59081200
H	2.86107400	-2.31171200	-0.32786800
H	1.88576000	-2.42535000	1.12598000
H	0.45946500	-2.64086400	-0.74862900
H	1.09542600	-1.25816500	-1.58945700
O	-0.33281400	-1.01607400	1.43661500
C	-3.02426700	-0.09209000	-0.24023100
H	-3.26857900	0.49413200	-1.13126800
C	-1.14750100	1.48107600	0.36392500
O	-1.02237000	2.69807100	0.33492700
H	-3.94508200	-0.55946400	0.11926500
C	-2.43278000	0.82312400	0.84520400
H	-3.13081000	1.63838600	1.05395100
H	-2.25899800	0.26309300	1.76591100
S	-1.88459000	-1.45416800	-0.74143900
H	-0.71623400	-1.89983000	1.56431500

20_{RE}

SCF Done: E(RB3LYP) = -994.720705873

Zero-point correction= 0.268135

Thermal correction to Gibbs Free Energy= 0.227369

C	0.27138700	2.82804000	0.48045500
C	1.33785200	1.72199100	0.58558900
C	-0.99384300	2.46297100	-0.33262000
C	1.86731100	1.20945100	-0.76190500
C	2.97257300	0.14454200	-0.65547100
C	2.60838900	-1.12546600	0.13555900
C	-2.14070100	-1.57794000	-0.10372100
C	-0.94688800	-2.54201100	-0.18320800
H	0.70558100	3.72893400	0.02658100
H	-0.04484100	3.10189100	1.49293900
H	0.92488400	0.88928500	1.16672700
H	2.17635400	2.11807200	1.17642000
H	-0.76966600	2.37380400	-1.40014600
H	-1.73401100	3.26536200	-0.21792000
H	2.26187100	2.05381000	-1.34567600
H	1.03846100	0.79337200	-1.34685400
H	3.86460700	0.57516700	-0.17891000
H	3.28319100	-0.14078100	-1.67130000
H	2.44292800	-0.90208100	1.19118300
H	3.44559500	-1.83444500	0.07951100
H	-3.05707400	-2.06090800	-0.45164400
H	-2.28536100	-1.22688700	0.92246100
H	-0.75708400	-2.83737800	-1.22199300
H	-1.20334900	-3.45062000	0.37626700
C	-1.63071300	1.18001700	0.17884200
O	-1.93125800	0.99532800	1.33335800
S	-1.86657400	-0.07447000	-1.12416100
C	0.29209300	-1.93868900	0.48160500
O	0.27431000	-1.61779000	1.66535500
N	1.38639000	-1.77832400	-0.32132100
H	1.29918800	-2.00455600	-1.30227600

21_{RO}

SCF Done: E(RB3LYP) = -1034.02371841

Zero-point correction= 0.294897

Thermal correction to Gibbs Free Energy= 0.251696

C	3.77956600	-0.89927500	0.50808700
C	3.86365600	0.19153000	-0.57674500
C	2.39664500	-1.36636200	0.99407400
C	3.17676900	1.54271400	-0.27302700
C	1.46982400	-2.01456500	-0.04920800
C	1.73718000	1.74832300	-0.81202800
C	0.74164200	-1.05194800	-1.00409100
H	4.33357800	-1.77595400	0.14285400
H	4.33402000	-0.54106900	1.38712000
H	3.50789600	-0.19532100	-1.54098100
H	4.93220700	0.39022200	-0.73138000
H	2.57164800	-2.10708800	1.78524900
H	1.87296500	-0.54050600	1.49320500
H	3.78070200	2.33614500	-0.72847900
H	3.18201200	1.74550100	0.80580500
H	0.70167000	-2.59618800	0.47098200
H	2.03822700	-2.72798200	-0.66308900
H	1.54590700	2.82605600	-0.82672800
H	1.66562900	1.39623000	-1.84590600
H	1.43779800	-0.56630900	-1.68471400
H	0.02358600	-1.61249900	-1.60415000
C	0.60477600	1.21656400	0.06337000
O	0.23233500	1.87301400	1.02245800
N	-0.01337200	-0.00097200	-0.28960000
C	-1.29081200	-0.38530100	0.17611200
O	-1.66842800	-1.53304500	-0.01415800
C	-2.19617100	0.64051000	0.84210400
H	-2.12975100	1.60297400	0.32784000
H	-1.81201100	0.82336600	1.85266500
C	-3.64582900	0.15997700	0.91921700
H	-3.71013900	-0.81401700	1.40781500
H	-4.22670600	0.87394400	1.50997100
H	-3.86679100	-1.01548500	-1.15592500
S	-4.52647400	0.06825100	-0.69803400

21_{RC}

SCF Done: E(RB3LYP) = -1034.00234866

Zero-point correction= 0.298354

Thermal correction to Gibbs Free Energy= 0.258250

C	3.09515400	-0.40813900	-0.98357100
C	1.76135600	-1.04888200	-1.39900300
C	3.14766300	0.41302600	0.31773000
C	1.17823000	-2.11420400	-0.45301200
C	2.16374200	1.59752100	0.43453300
C	0.50423100	-1.64519700	0.85288100
C	0.81850600	1.35029400	1.14074700
H	3.85843800	-1.19768500	-0.91742900
H	3.41477300	0.24745500	-1.80633700
H	1.01428900	-0.27170000	-1.58574600
H	1.93024400	-1.53846100	-2.36779000
H	3.04274200	-0.24398900	1.19183200
H	4.16744200	0.81446000	0.38925800
H	0.45134600	-2.70847500	-1.01899800
H	1.97529200	-2.81549000	-0.16646500
H	2.65373000	2.38283700	1.02602500
H	1.97084300	2.04491300	-0.54669800
H	0.09749400	-2.53531800	1.35235800
H	1.23790700	-1.23034100	1.54704900
H	0.95810400	0.76190300	2.04941300
H	0.41876700	2.31949500	1.44558300
C	-0.66745500	-0.63819800	0.76050100
N	-0.25052900	0.69957100	0.33674300
C	-1.00052500	1.59491900	-0.41620000
O	-0.60553900	2.74415100	-0.57914200
C	-2.30561400	1.17227100	-1.08536900
H	-2.07287600	0.91992600	-2.12765700
H	-2.91972800	2.07888900	-1.10684600
C	-3.04672300	0.01634900	-0.43201000
H	-3.92337300	-0.28258500	-1.01341400
H	-3.36877100	0.25998200	0.58476100
S	-1.92347300	-1.41765700	-0.36814500
O	-1.23797900	-0.44890600	2.05454600
H	-1.52064300	-1.32082500	2.37761500

21_{RE}

SCF Done: E(RB3LYP) = -1034.03746475

Zero-point correction= 0.296886

Thermal correction to Gibbs Free Energy= 0.254096

C	-3.21826300	0.01674000	0.23721600
C	-2.57563000	-1.38015300	0.10586900
C	-2.87634100	0.99903800	-0.89805400
C	-1.41887100	1.48509500	-0.98833900
C	-0.97432400	2.40629100	0.15899300
C	1.56507000	-2.25842100	0.29064000
C	0.49303100	2.88284500	0.03824200
C	2.60776300	-1.32999200	-0.34255300
C	1.50002000	2.13367900	0.92610800
H	-2.94909200	0.43296300	1.21418700
H	-4.30597700	-0.12476600	0.25083200
H	-3.53154100	1.87576900	-0.79428300
H	-3.15246300	0.53041200	-1.85364200
H	-0.73426800	0.63201000	-1.06858700
H	-1.30459200	2.03598300	-1.93231600
H	-1.11764700	1.90302000	1.12490500
H	-1.64255800	3.27831500	0.17360500
H	1.34401100	-2.00644700	1.33204400
H	1.93979400	-3.28576700	0.27586600
H	0.56231300	3.94360300	0.31415300
H	0.82998800	2.81415800	-1.00332000
H	2.72293700	-1.55444000	-1.40737900
H	3.57906000	-1.56470200	0.11570100
H	2.49620700	2.55946700	0.77781600
H	1.22871400	2.26247000	1.98105700
C	2.47104300	0.19729100	-0.24167000
O	3.19349600	0.90693400	-0.93571000
N	1.60616100	0.69846600	0.68092300
H	0.96563200	0.08665200	1.17282500
S	-0.05241900	-2.32214600	-0.58700400
C	-1.12094600	-1.42413700	0.54131200
O	-0.72724500	-0.91601900	1.57669000
H	-2.68150700	-1.76923500	-0.91343900
H	-3.09874400	-2.08136400	0.77114500

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- 20 CCDC 1921223 (**20_{RE}**) contains the crystallographic data for this macrocyclic thiolactone, see: www.ccdc.cam.ac.uk/data_request/cif