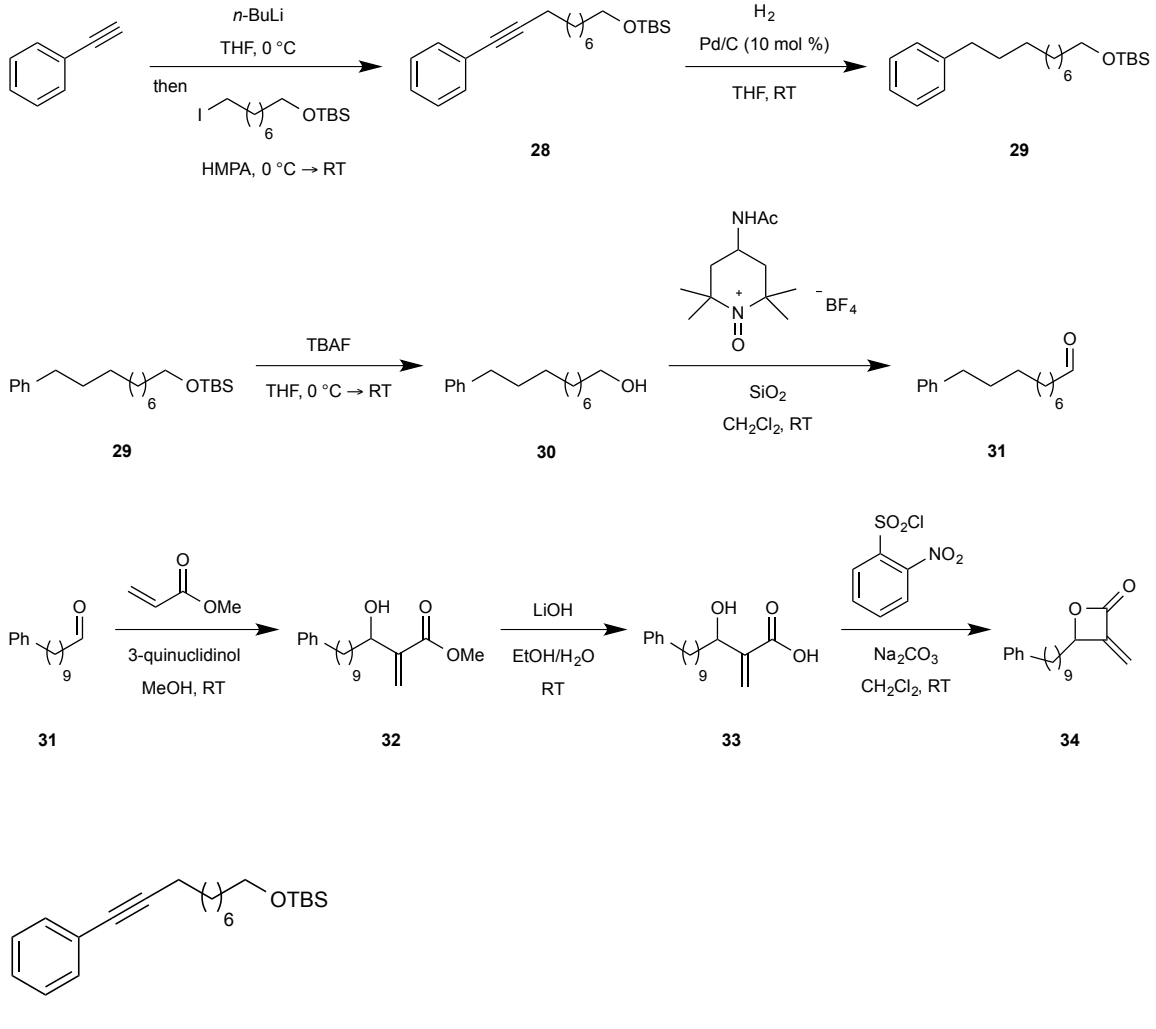
Synthesis of β-lactone probes. General experimental. Tetrahydrofuran (THF) was dried using a solvent dispensing system (SDS) with a column of neutral alumina. Pyridine, toluene, dimethylformamide (DMF), methylene chloride (CH_2Cl_2), deuterated chloroform ($CDCl_3$), methanol (MeOH), deuterated methanol (CD_3OD) and ethanol (EtOH) were dried over 4 Å molecular sieves. All reagents were purchased from Acros, Aldrich or Alfa Aesar and used without further purification. Compounds (**4 – 23**) in **Supplementary Fig. 3** were prepared as described elsewhere[1]. All reactions were conducted under an atmosphere of N_2 in glassware that had been dried overnight in an oven at 120 ^{o}C. Where appropriate, control of the reaction temperature was achieved with a solid CO_2/acetone bath, an ice bath or a heated oil bath. NMR Spectra were obtained on a Bruker Avance DRX-400 (400 MHz ^{1}H, 100 MHz ^{13}C), Bruker Avance (500 MHz ^{1}H, 125 MHz ^{13}C), or Bruker Avance (300 MHz ^{1}H, 75 MHz ^{13}C) spectrometer. ^{1}H and ^{13}C chemical shifts are reported in parts per million (ppm) and calibrated to the residual $CHCl_3$ peak at 7.26 or the $CDCl_3$ signal at 77.23 ppm, respectively. IR spectra were recorded on a Bruker FT-IR spectrometer. GC/MS spectra were obtained on a gas chromatograph equipped with a HP-1 methyl siloxane column and detected on a low-resolution 5970 series mass selective detector. High-resolution mass spectra were obtained on an AccuTOF instrument equipped with a DART ionization source. Melting points were observed in open Pyrex capillary tubes and are uncorrected. Flash chromatography was performed on Silica Gel, 40 micron, 32-63 flash silica. Thin layer chromatography was performed on silica gel. Compounds were visualized by UV, 5% phosphomolybdic acid in ethanol, 0.5% $KMnO_4$ in H_2O or a solution of EtOH/H_2SO_4/AcOH/*p*-anisaldehyde (135:5:1.5:3.7).

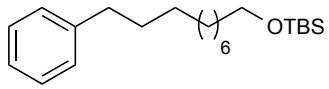
Preparation of 3-methylene-4-(9-phenylnonyl)oxetan-2-one (34)



28

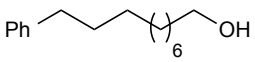
1-*(tert*-Butyldimethylsilyloxy)-10-phenyldec-9-yne (28): *n*-BuLi (2.5 M in THF, 12.5 mL, 31.2 mmol) was added to a solution of phenylacetylene (3.43 mL, 31.2 mmol) in THF (10 mL) at 0 ^{o}C. After 10 min a solution of 1-*(tert*-butyldimethylsilyloxy)-8-iodooctane (5.87 g, 15.6 mmol) and HMPA (10 mL) was added drop-wise. The resultant solution was stirred at 0 ^{o}C for 30 min, then allowed to slowly warm to rt overnight. Saturated aqueous NH_4Cl (60 mL) was added. The layers were separated, followed by extraction of the aqueous layer with Et_2O (3 X 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 99:1) to yield 1-*(tert*-

butyldimethylsilyloxy)-10-phenyldec-9-yne (**28**) (2.56 g, 48%) as a colorless oil: IR (neat) 2927, 2855, 1462, 1253, 1093, 834, 774, 754, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.38 (m, 2H), 7.30–7.23 (m, 3H), 3.61 (t, *J* = 6.6 Hz, 2H), 2.40 (t, *J* = 7.1 Hz, 2H), 1.64–1.57 (m, 2H), 1.53–1.44 (m, 4H) 1.38–1.33 (m, 6H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.8, 128.4, 127.6, 124.3, 90.6, 80.8, 63.5, 33.1, 29.6, 29.4, 29.1, 29.0, 26.2, 26.0, 19.6, 18.6, –5.0; HRMS (ESI) calcd for $C_{22}H_{37}OSi$ $[M + H]^+$ *m/z* 345.2608, found 345.2596.



29

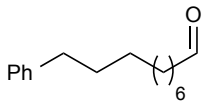
1-*(tert*-Butyldimethylsilyloxy)-10-phenyldecane (29). Pd/C (10 mol%, 0.27 g, 0.26 mmol) was added to a solution of 1-*(tert*-butyldimethylsilyloxy)-10-phenyldec-9-yne (**28**) (2.96 g, 8.59 mmol) in THF (34 mL). The mixture was purged with H_2 for 5 min and then stirred under H_2 for 7.5 h. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated to provide 1-*(tert*-butyldimethylsilyloxy)-10-phenyldecane (**29**) (2.21g, 74%) as a colorless oil, which was clean based on ^1H and ^{13}C NMR and was used without further purification in the next reaction: IR (neat) 2925, 2853, 1462, 1252, 1096, 834, 774, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H), 7.18–7.15 (m, 3H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.65–1.59 (m, 2H), 1.51 (quin, *J* = 6.8 Hz, 2H) 1.34–1.28 (m, 12H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 128.6, 128.4, 125.8, 63.6, 36.2, 33.1, 31.7, 29.8, 29.7, 29.7, 29.7, 29.6, 26.2, 26.0, 18.6, –5.0; HRMS (ESI) calcd for $C_{22}H_{41}OSi$ $[M + H]^+$ *m/z* 349.2921, found 349.2919.



30

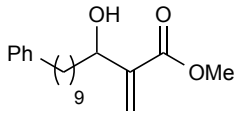
10-Phenyldecane-1-ol (30). TBAF (1 M in THF, 15.0 mL, 15.0 mmol) was added drop-wise to a stirred solution of 1-*(tert*-butyldimethylsilyloxy)-10-phenyldecane (**29**) (2.81 g, 7.5 mmol) in THF (140 mL) at 0 °C. The reaction was allowed to warm to rt and stir overnight. Saturated aqueous NH_4Cl (100 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 X 50 mL). The combined organic

layers were dried ($MgSO_4$) and concentrated. The crude residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10) to give 10-phenyldecane-1-ol (**30**) (1.41 g, 81%) as a colorless oil: IR (neat) 3431, 2919, 2848, 1494, 1453, 1348, 1060, 717, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.20–7.17 (m, 3H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 1,64–1.52 (m, 4H), 1.48 (br. s, 1H), 1.30–1.28 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 128.6, 128.4, 125.7, 63.2, 36.2, 32.9, 31.8, 29.8, 29.7, 29.6, 29.5, 25.9; HRMS (ESI) calcd for $C_{16}H_{27}O$ $[M + H]^+$ *m/z* 235.2056, found 235.2065.



31

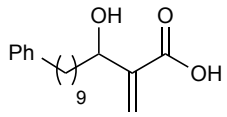
10-Phenyldecanal (31). 4-Acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (2.01 g, 6.68 mmol) and SiO_2 (2.01 g) were added to a solution of 10-phenyldecane-1-ol (**30**) (1.41 g, 6.07 mmol) in CH_2Cl_2 (48 mL). The reaction mixture was stirred at rt overnight. The reaction mixture was then filtered through a pad of SiO_2, and the filtrate was concentrated and used without further purification, as both ^1H and ^{13}C NMR showed clean 10-phenyldecanal (**31**) (1.26 g, 90%) as colorless crystals: mp: 41–42 ^oC; IR (neat) 2913, 2847, 1698, 1411, 1282, 1250, 1218, 942, 744, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.8 Hz, 1H), 7.29–7.25 (m, 2H), 7.18–7.15 (m, 3H), 2.60 (t, *J* = 7.5 Hz, 2H), 2.41 (td, *J* = 7.3, 1.8 Hz, 2H), 1,66–1.57 (m, 4H), 1.30–1.29 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 143.1, 128.6, 128.4, 125.8, 44.1, 36.2, 31.7, 29.6, 29.5, 29.5, 29.3, 22.3; HRMS (ESI) calcd for $C_{16}H_{23}O$ $[M - H]^+$ *m/z* 231.1754, found 231.1734.



32

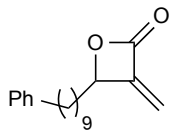
Methyl 3-hydroxy-2-methylene-12-phenyldodecanoate (32). 10-Phenyldecanal (**31**) (1.26 g, 5.45 mmol) and methyl acrylate (0.98 mL, 10.9 mmol) were combined in an empty flask. 3-Hydroxyquinuclidine (0.173 g, 1.36 mmol) was added, followed by

MeOH (0.17 mL). The resulting mixture was stirred for 2 d[2]. MeOH and excess methyl acrylate were removed under reduced pressure. The resulting residue was diluted with a H_2O/saturated aqueous NH_4Cl solution (5:1, 30 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 X 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/-EtOAc, 95:5) gave methyl 3-hydroxy-2-methylene-12-phenyldodecanoate (**32**) (1.06 g, 61%) as a colorless oil: IR (neat) 3350 (br), 2924, 2853, 1717, 1438, 1194, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H), 7.19–7.15 (m, 3H), 6.22 (m, 1H), 5.81 (m, 1H), 4.39 (m, 1H), 3.78 (s, 3H), 2.62–2.56 (m, 3H), 1.69–1.57 (m, 4H), 1.48–1.43 (m, 1H), 1.30–1.28 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 143.1, 142.7, 128.6, 128.4, 125.7, 125.1, 72.0, 52.0, 36.4, 36.2, 31.7, 29.7, 29.7, 29.7, 29.6, 29.5, 26.0; HRMS (ESI) calcd for $C_{20}H_{31}O_3$ $[M + H]^+$ *m/z* 319.2268, found 319.2281.



33

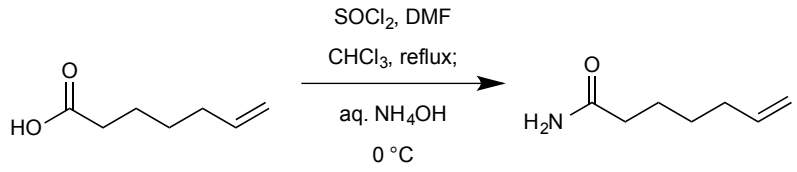
3-Hydroxy-2-methylene-12-phenyldodecanoic acid (33). Methyl 3-hydroxy-2-methyl-ene-12-phenyldodecanoate (**32**) (1.06 g, 3.37 mmol) was dissolved in EtOH/H_2O (2:1, 8 mL). Lithium hydroxide (77 mg, 3.4 mmol) was added; the resulting solution was stirred overnight[3]. The reaction was quenched with 1 M HCl (30 mL), and the solution was extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (30 mL) and dried ($MgSO_4$); CH_2Cl_2 was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc, 85:15) gave 3-hydroxy-2-methylene-12-phenyldodecanoic acid (**33**) (0.396 g, 54%) as a colorless oil: IR (neat) 2919, 2848, 1685, 1622, 1493, 1435, 1284, 1181, 1118, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H), 7.18–7.15 (m, 3H), 6.38 (s, 1H), 5.91 (s, 1H), 4.42 (dd, *J* = 6.3, 6.3 Hz, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.74–1.57 (m, 4H), 1.48–1.43 (m, 1H), 1.30–1.28 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 143.2, 142.0, 128.6, 128.4, 127.6, 125.8, 71.8, 36.4, 36.2, 31.7, 29.7, 29.7, 29.6, 29.5, 26.0; HRMS (ESI) calcd for $C_{19}H_{29}O_3$ $[M + H]^+$ *m/z* 305.2111, found 305.2142.



34

3-Methylene-4-(9-phenylnonyl)oxetan-2-one (34). 3-Hydroxy-2-methylene-12-phenyldodecanoic acid (**33**) (0.40 g, 1.8 mmol) was dissolved in dry CH_2Cl_2 (7 mL). Oven-dried Cs_2CO_3 (0.64 g, 1.8 mmol) was added, and the resulting suspension was stirred for 20 min. *o*-Nosyl chloride (800 mg, 3.6 mmol) was added, and the resulting mixture was stirred for 3 d. The reaction was diluted with CH_2Cl_2 (20 mL), and then 1 M HCl (20 mL) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (3 X 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc, 95:5) gave 3-methylene-4-(9-phenylnonyl)oxetan-2-one (**34**) (0.089 g, 17%) as a colorless oil: IR (neat) 2926, 2854, 1821, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.23 (m, 2H), 7.17–7.13 (m, 3H), 5.87 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.38 (dd, *J* = 1.5, 1.5 Hz, 1H), 4.95–4.91 (m, 1H), 2.59 (t, *J* = 7.6 Hz, 2H), 1.88–1.78 (m, 2H), 1.60 (quin, *J* = 8.0 Hz, 2H), 1.50–1.40 (m, 2H), 1.38–1.29 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 146.6, 143.0, 128.5, 128.4, 125.7, 115.0, 79.8, 36.1, 33.4, 31.6, 29.6, 29.5, 29.5, 29.4, 29.4, 24.7; HRMS (ESI) calcd for $C_{19}H_{27}O_2$ $[M + H]^+$ *m/z* 287.2006, found 287.1999.

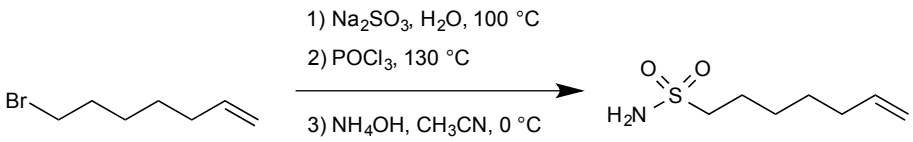
Preparation of alkenes 35 and 36 for cross-metathesis



35

Hept-6-enamide (35). A solution of 6-heptenoic acid (0.50 g, 3.9 mmol), $SOCl_2$ (0.34 mL, 4.7 mmol), and a drop of DMF in $CHCl_3$ (6 mL) was heated at reflux for 2 h[2]. The reaction mixture was cooled to rt and then poured into a mixture of aqueous NH_4OH (28-30%, 6 mL) and ice (6.3 g) and stirred for 2 h. The layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated. Purification by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) gave hept-6-enamide (**35**) (0.42 g, 85%) as a white solid: mp: 84.8–84.9 °C; IR (neat) 3355, 3178, 2938, 1630, 1460,

1410, 1221 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (br s, 1H), 5.84 (br s, 1H), 5.79–5.69 (m, 1H), 4.95 (d, *J* = 17.2 Hz, 1H), 4.88 (d, *J* = 10.2 Hz, 1H), 2.17 (t, *J* = 7.2 Hz, 2H), 2.02 (q, *J* = 6.4 Hz, 2H), 1.60 (quin, *J* = 7.5 Hz, 2H), 1.39 (quin, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 138.5, 114.8, 35.9, 33.5, 28.5, 25.1 MS (EI) *m/z* 127 (M^+), 72, 59 (100); HRMS (ESI) calcd for $C_7H_{14}NO$ $[M + H]^+$ *m/z* 128.1070, found 128.1057.

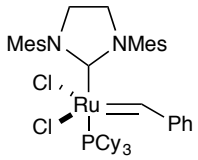


36

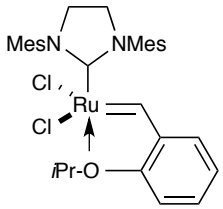
Hept-6-ene-1-sulfonamide (36). A solution of 7-bromo-1-heptene (0.50 g, 4.3 mmol), and sodium sulfite (0.65 g, 5.1 mmol) in H_2O (3.0 mL) was refluxed overnight[4]. After cooling to rt the aqueous solution was washed with Et_2O (2.2 mL) before being evaporated to dryness. The resulting white solid was dried under vacuum at 130 °C for 1 h and then $POCl_3$ (4.3 mL) was added, and the mixture was stirred for 4 h at 130 °C. The reaction mixture was evaporated, and the residue was taken up in CH_3CN (5 mL), and a solution of NH_4OH (28.0–30.0%, 10 mL) in CH_3CN (4 mL) was slowly added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h before being diluted with CH_2Cl_2 (30 mL) and washed with H_2O (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification by flash column chromatography on silica gel (petroleum ether/EtOAc, 80:20) gave hept-6-ene-1-sulfonamide (**36**) (0.29 g, 42%) as a white solid: mp: 52–52.5 °C; IR (neat) 3338, 3253, 2927, 1469, 1294, 1134 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.0, 10.2, 6.4 Hz, 1H), 5.03–4.94 (m, 2H), 4.84 (br s, 2H), 3.13–3.09 (m, 2H), 2.06 (q, *J* = 6.3 Hz, 2H), 1.89–1.81 (m, 2H), 1.45–1.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 114.9, 55.3, 33.4, 28.4, 27.7, 23.8; HRMS (ESI) calcd for $C_7H_{16}NO_2S$ $[M + H]^+$ *m/z* 178.0896, found 178.0913.

Cross-metathesis reactions

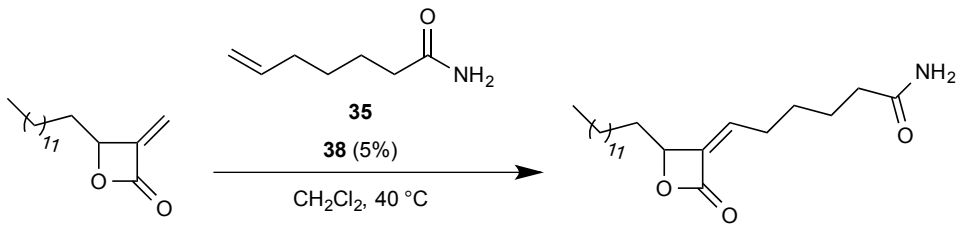
Catalysts used



37

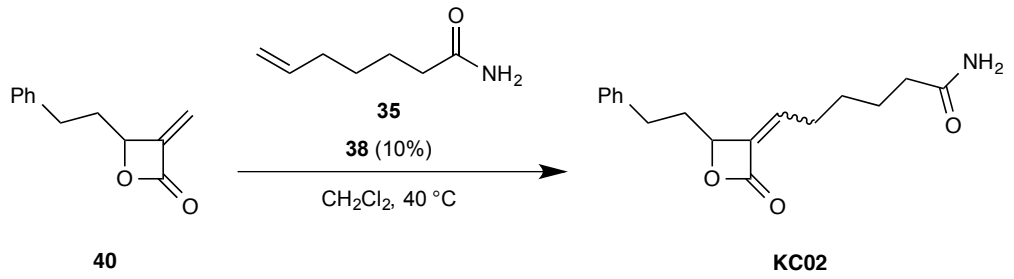


38



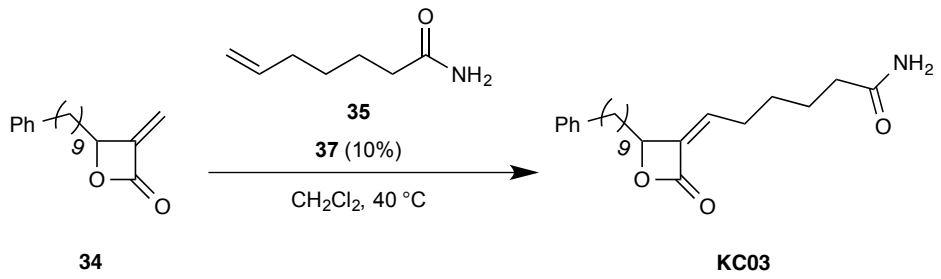
39 **KC01**

***(Z)*-6-(2-Oxo-4-tridecyloxetan-3-ylidene)hexanamide (KC01).** Catalyst **38** (0.03 g, 0.04 mmol) was added to a solution of 3-methylene-4-tridecyloxetan-2-one (**39**) (0.20 g, 0.75 mmol) and hept-6-enamide (**35**) (0.19 g, 1.5 mmol) in dry CH_2Cl_2 (29 mL). The mixture was stirred at 40 °C for 48 h. After cooling to rt, the CH_2Cl_2 was removed under reduced pressure to yield a greenish brown residue. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) gave *(Z/E)*-6-(2-oxo-4-tridecyloxetan-3-ylidene)hexanamide (**KC01**) (*Z/E*, 3.7:1), (0.20 g, 73%) as an off white solid. The *Z*-isomer was separable from the *E*-isomer by careful column chromatography. The *E*-isomer was not obtained as a single compound, but chemical shifts for a number of the protons and carbons were identifiable: ***E*-isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (t, *J* = 7.5 Hz, 1H), 5.35 (br s, 2H) 5.00 (m, 1H), 2.28–2.23 (m, 2H), 2.16 (dt, *J* = 7.4, 7.4 Hz, 2H), the remaining proton signals cannot be readily distinguished from those of the *Z*-isomer; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 164.4, 138.3, 133.2, 79.4, 35.5, 33.5, 32.1, 29.9, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 28.9, 28.2, 28.1, 25.1, 25.0, 24.8, 24.6, 22.9, 14.3. ***Z*-isomer**: mp: 106–107 °C; IR (neat) 3384, 3196, 2915, 2850, 1792, 1656, 1468, 1422, 1180, 1124, 1074, 803 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (t, *J* = 8.0 Hz, 1H), 5.51 (br s, 1H), 5.27 (br s, 1H), 4.87 (dd, *J* = 6.5, 6.5 Hz, 1H), 2.59−2.47 (m, 2H), 2.26 (t, *J* = 7.5 Hz, 2H), 1.82−1.77 (m, 2H), 1.73−1.67 (m, 2H), 1.58-1.52 (m, 2H), 1.47−1.42 (m, 2H), 1.37−1.26 (m, 20H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 164.5, 136.2, 135.5, 79.0, 35.8, 33.9, 32.1, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 28.2, 28.0, 24.8, 24.5, 22.8, 14.3; HRMS (ESI) calcd for $C_{22}H_{40}NO_3$ $[M + H]^+$ *m/z* 366.3003, found 366.3009.



40 **KC02**

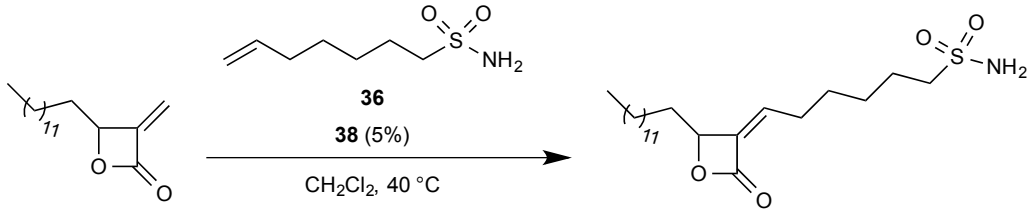
***(Z/E)*-6-(2-Oxo-4-(2-phenethyl)oxetan-3-ylidene)hexanamide (KC02).** Catalyst **38** (0.026 g, 0.041 mmol) was added to a solution of 3-methylene-4-(2-phenethyl)oxetan-2-one (**40**)[5] (0.073 g, 0.41 mmol) and hept-6-enamide (**35**) (0.053 g, 0.41 mmol) in dry CH_2Cl_2 (16 mL). The solution was stirred at 40 ^oC for 24 h. After the reaction was allowed to cool to rt, the CH_2Cl_2 was removed under reduced pressure to yield a greenish brown residue. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH, 99:1) gave *(Z/E)*-6-(2-oxo-4-(2-phenethyl)oxetan-3-ylidene)hexanamide (**KC02**) (*Z/E*, 4:1) (0.050 g, 43%) as an off white solid: IR (neat) 3384, 3182, 2942, 1783, 1644, 1416, 1218, 1179, 1135, 1096, 1014 cm^{-1}; Peak assignment for ***Z*-isomer**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.23–7.18 (m, 3H), 5.74 (td, *J* = 8.0, 1.2 Hz, 1H), 5.35 (br s, 2H) 4.87 (dd, *J* = 6.1, 6.1 Hz, 1H), 2.89–2.70 (m, 2H), 2.56–2.42 (m, 2H), 2.27–2.21 (m, 2H), 2.15–2.08 (m, 2H), 1.70–1.62 (m, 2H), 1.54–1.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 164.3, 140.5, 137.9, 136.1, 128.8, 128.6, 126.6, 78.1, 35.6, 35.1, 31.1, 28.3, 28.1, 24.6; The ***E*-isomer**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.23–7.18 (m, 3H), 6.32 (td, *J* = 7.8, 1.6 Hz, 1H), 5.49 (br s, 2H) 4.99 (m, 1H), the remaining proton signals cannot be readily distinguished from those of the *Z*-isomer; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 164.2, 140.6, 138.0, 133.7, 128.8, 128.6, 126.6, 78.2, 35.4, 35.3, 31.1, 28.8, 28.1, 25.0; HRMS (ESI) calcd for $C_{17}H_{22}NO_3$ $[M + H]^+$ *m/z* 288.1594, found 288.1630.



34 **KC03**

***(Z)*-6-(2-Oxo-4-(9-phenylnonyl)oxetan-3-ylidene)hexanamide (KC03).** Catalyst **37**

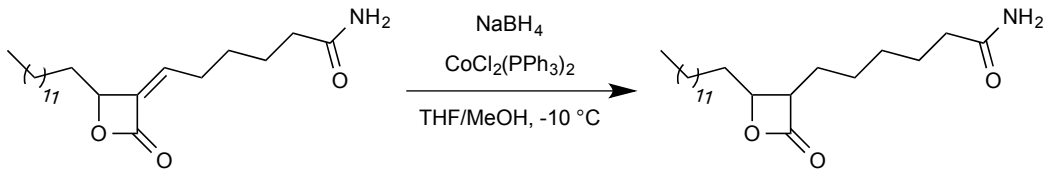
(0.025 g, 0.30 mmol) was added to a solution of 3-methylene-4-(9-phenylnonyl)oxetan-2-one (**34**) (0.085 g, 0.30 mmol) and hept-6-enamide (**35**) (0.038 g, 0.30 mmol) in dry CH_2Cl_2 (11 mL). The solution was stirred at 40 °C for 3 d. After the reaction was allowed to cool to rt, the CH_2Cl_2 was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) gave (*Z/E)*-6-(2-oxo-4-(9-phenylnonyl)oxetan-3-ylidene)hexanamide (**KC03**) (*Z/E*, 3.7:1), (0.068 g, 59%) as an off white solid. Further chromatography using Et_2O gave pure *Z*-isomer: mp: 93–94 °C; IR (neat) 3384, 3194, 2916, 2850, 1791, 1655, 1467, 1421, 1180, 1124, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H), 7.18–7.15 (m, 3H), 5.84 (t, *J* = 8.0 Hz, 1H), 5.50 (br s, 1H), 5.29 (br s, 1H), 4.86 (t, *J* = 6.2 Hz, 1H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.56–2.45 (m, 2H), 2.26 (t, *J* = 7.3 Hz, 2H), 1.84–1.77 (m, 2H), 1.73–1.66 (m, 2H), 1.62–1.53 (m, 4H), 1.49–1.41 (m, 2H), 1.30–1.29 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 164.6, 143.1, 138.3, 135.6, 128.6, 128.4, 125.8, 79.1, 36.2, 35.1, 33.9, 31.7, 29.6, 29.6, 29.6, 29.5, 29.5, 28.3, 28.1, 24.8, 24.6 HRMS (ESI) calcd for $C_{24}H_{36}NO_3$ $[M + H]^+$ *m/z* 386.2690, found 386.2699.



***(Z)*-6-(2-Oxo-4-tridecyloxetan-3-ylidene)hexane-1-sulfonamide (KC04).** Catalyst **38** (0.02 g, 0.03 mmol) was added to a solution of 3-methylene-4-tridecyloxetan-2-one (**39**) (0.16 g, 0.60 mmol) and hept-6-ene-1-sulfonamide (**36**) (0.15 g, 0.90 mmol) in dry CH_2Cl_2 (23 mL). The solution was stirred at 40 °C for 48 h. After the reaction was allowed to cool to rt, the CH_2Cl_2 was removed under reduced pressure to yield a greenish brown residue. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) gave (*Z/E*)-6-(2-oxo-4-tridecyloxetan-3-ylidene)hexane-1-sulfonamide (**KC04**) (*Z/E*, 4:1) (0.19 g, 79%) as an off white solid. The *Z*-isomer, isolated as a white solid, was separable from the *E*-isomer by careful chromatography using the same solvent system. ***Z*-isomer:** mp: 79–80 °C; IR (neat) 2914, 2849, 1791, 1469, 1331, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (t, *J* = 7.6 Hz, 1H), 4.92 (s, 2H), 4.86 (dd, *J* = 6.2, 6.2 Hz, 1H), 3.11 (t, *J* = 7.3 Hz, 2H), 2.58–2.24 (m, 2H),

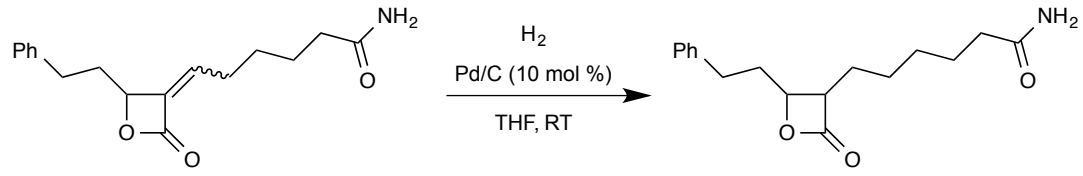
1.91–1.85 (m, 2H), 1.82–1.77 (m, 2H), 1.51 (m, 4H), 1.45–1.39 (m, 2H), 1.34–1.25 (m, 20H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 138.2, 135.6, 79.1, 55.1, 33.9, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 28.3, 28.2, 27.4, 24.8, 23.6, 22.9, 14.3; HRMS (ESI) calcd for $C_{22}H_{42}NO_3$ $[M + H]^+$ *m/z* 416.2829, found 416.2842.

Reduction of α-alkylidene-β-lactones



KC01 **KC05**

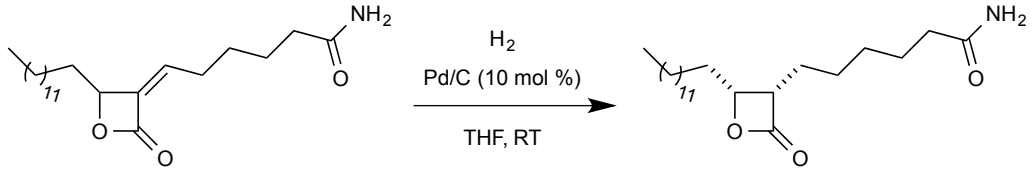
***trans/cis*-6-(2-Oxo-4-tridecyloxetan-3-yl)hexanamide (KC05).** *Z*-6-(2-Oxo-4-tridecyl-oxetan-3-ylidene)hexanamide (**KC01**) (0.050 g, 0.14 mmol) was dissolved in mixture of THF:MeOH (0.9:0.2 mL). This solution was cooled to −10 °C, followed by the addition of $CoCl_2(PPh_3)_2$ (0.01 g, 0.04 mmol) and then portion-wise addition of $NaBH_4$ (13 mg, 0.41 mmol) within 10 min. The mixture was vigorously stirred for 4 h between −10 to −7 °C. The reaction mixture was filtered through a pad of celite, and the celite was then washed with $CHCl_3$ (10 mL). The filtrate was washed with 2M HCl (5 mL), dried ($MgSO_4$) and concentrated. Purification by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) gave an inseparable mixture of *cis/trans*-6-(2-oxo-4-tridecyloxe-tan-3-yl)hexanamide (**KC05**) (*trans/cis*, 1.4:1) (18 mg, 35%) as an off white solid. Peak assignments for *trans*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (br, 2H), 4.21 (ddd, *J* = 6.2, 6.2, 4.0 Hz, 1H), 3.16 (ddd, *J* = 7.8, 7.8, 4.0 Hz, 1H),), 2.23 (t, *J* = 7.4 Hz, 2H), 1.87–1.81 (m, 2H), 1.78–1.65 (m, 4H), 1.55–1.26 (m, 26H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 171.8, 78.3, 56.3, 35.7, 34.6, 32.1, 29.9, 29.9, 29.8, 29.7, 29.6, 29.6, 29.5, 29.0, 27.9, 26.8, 25.2, 22.9, 14.3; HRMS (ESI) calcd for $C_{22}H_{42}NO_3$ $[M + H]^+$ *m/z* 368.3159, found 368.3186.



KC02 **KC06**

***trans/cis*-6-(2-Oxo-4-(2-phenethyl)oxetan-3-yl)hexanamide (KC06).** (*Z/E*)-6-(2-Oxo-4-(2-phenethyl)oxetan-3-ylidene)hexanamide (**KC02**) (0.031 g, 0.011 mmol) was

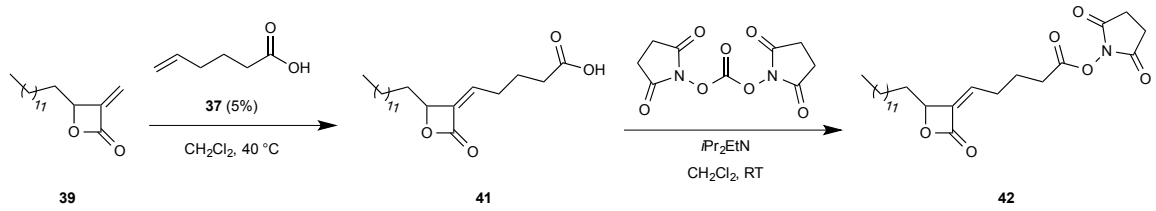
dissolved in THF (1 mL). Pd/C (10 mol%, 1.2 mg, 0.0011 mmol) was added to the solution. The mixture was purged with H_2 gas for 5 min. It was then stirred under H_2 gas for 2 h 15 min. The mixture was filtered through a pad of celite, and the celite was washed with THF (5 mL). The filtrate was concentrated and purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 98:1) to give *trans/cis*-6-(2-oxo-4-(2-phenethyl)oxetan-3-yl)hexanamide (**KC06**) (*trans/cis*, 1:5,) (19 mg, 60%) as an inseparable mixture and off white solid. IR (neat) 3392, 2938, 1796, 1646, 1416, 1135 cm^{-1}; ***cis*-isomer**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.24–7.19 (m, 3H), 5.58–5.50 (br, 2H), 4.54 (ddd, *J* = 10.0, 6.4, 3.4 Hz, 1H), 3.59 (ddd, *J* = 9.2, 6.5, 6.5 Hz, 1H), 2.88 (ddd, *J* = 14.0, 9.4, 5.0 Hz, 1H), 2.69 (ddd, *J* = 13.9, 6,8, 6.8 Hz, 1H), 2.21 (t, *J* = 7.4 Hz, 2H), 2.10–2.01 (m, 1H), 1.98–1.78 (m, 1H), 1.83–1.90 (m, 1H), 1.67–1.50 (m, 4H), 1.43–1.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 172.2, 140.6, 128.8, 128.7, 126.6, 74.7, 52.6, 35.7, 32.4, 31.8, 28.9, 27.3, 25.1, 23.9; ***trans*-isomer**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.54 (ddd, *J* = 8.6, 5.4, 4.1 Hz, 1H), 3.59 (ddd, *J* = 7.6, 7.6, 3.9 Hz, 1H), the remaining proton signals cannot be readily distinguished from those of the *cis*-isomer; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 171.5, 140.3, 128.8, 128.6, 126.6, 77.4, 56.3, 36.2, 32.4, 31.5, 28.9, 27.7, 26.7, 25.1, 23.9; ^1H HRMS (ESI) calcd for $C_{17}H_{24}NO_3$ $[M + H]^+$ *m/z* 290.1751, found 290.1754.



KC01 **KC07**

***cis*-6-(2-Oxo-4-tridecyloxetan-3-yl)hexanamide (KC07).** *Z*-6-(2-Oxo-4-tridecyloxetan-3-ylidene)hexanamide (**KC01**) (50.0 mg, 0.14 mmol) was dissolved in THF (2 mL). Pd/C (10 mol%, 4 mg, 0.004 mmol) was added to the solution. The mixture was purged with H_2 gas for 5 min. It was then stirred under H_2 gas for 2 h. The mixture was filtered through a pad of celite, and the celite was washed with THF (5 mL). The filtrate was concentrated and purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) to give *cis/trans*-6-(2-oxo-4-tridecyloxetan-3-yl)hexanamide (**KC07**) (*trans/cis*, 1:9), (16 mg, 65%) as an off white solid. Careful chromatography under the same conditions provided the *cis*-isomer in >95% purity: mp 98–101 ˚C; IR (neat) 3393, 2918, 2849, 1795, 1649, 1417, 1132, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.40–5.35 (br,

2H), 4.54–4.50 (m, 1H), 3.61–3.55 (m, 1H), 2.23 (t, *J* = 6.1 Hz, 2H), 1.79–1.51 (m, 8H), 1.40–1.26 (m, 24H), 0.89–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 172.5, 75.9, 52.7, 35.8, 32.1, 30.4, 29.9, 29.8, 29.7, 29.6, 29.6, 29.5, 29.0, 27.4, 25.8, 25.2, 23.9, 22.9, 14.3; HRMS (ESI) calcd for $C_{22}H_{42}NO_3$ $[M + H]^+$ *m/z* 368.3159, found 368.3145.



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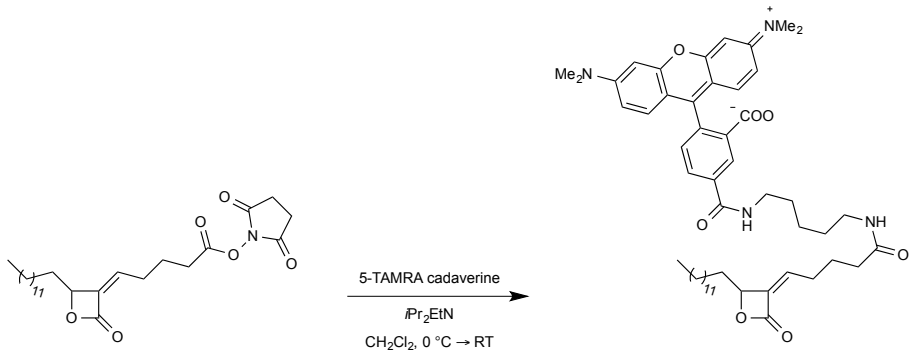
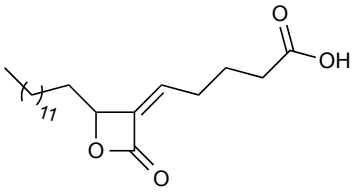


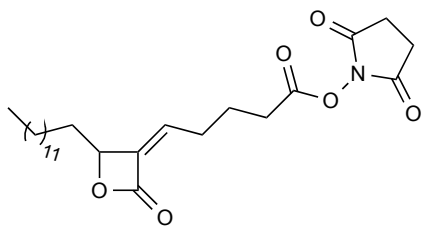
42 WHP01



41

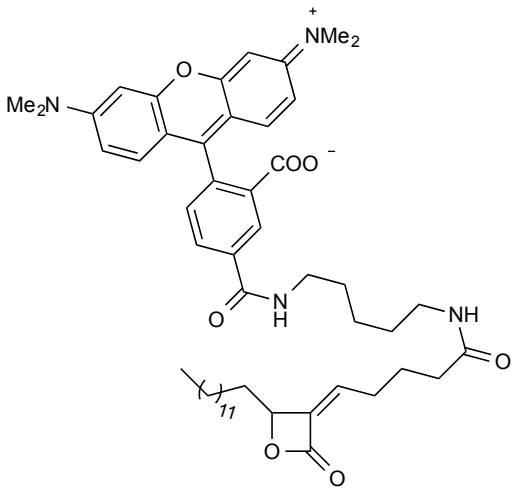
(*Z*)-5-(2-oxo-4-tridecyloxetan-3-ylidene)pentanoic acid (41). Catalyst **37** (8.5 mg, 0.01 mmol, 0.05 equiv) was added to a solution of 3-methylene-4-tridecyloxetan-2-one **(39)** (53 mg, 0.2 mmol, 1.0 equiv) and 6-hexenoic acid (36 µL, 0.3 mmol, 1.5 equiv) in dry CH_2Cl_2 (6 mL). The pale brown solution was then stirred at 40 °C for 48 h. The solution was concentrated under reduced pressure to give a brown residue, which was purified by column chromatography on silica gel (35% EtOAc in hexanes + 1% AcOH) to provide 5-(2-oxo-4-tridecyloxetan-3-ylidene)pentanoic acid (**41**) (*Z*:*E*, 4:1), (28 mg, 40%) as a white powder. The *Z* isomer was separable from the *E*-isomer by careful chromatography. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.84 (td, *J* = 8.0, 1.2 Hz, 1H), 4.86 (dd, *J*

= 6.4, 6.4 Hz, 1H), 2.61-2.51 (m, 2H), 2.41 (t, *J* = 7.0 Hz, 2H), 1.86-1.77 (m, 4H), 1.48-1.26 (m, 22H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm**;** ^{13}C-NMR (125 MHz, $CDCl_3$) δ 178.5, 164.1, 138.8, 134.4, 79.0, 33.8, 33.2, 32.1, 29.8, 29.8, 29.8, 29.6, 29.6, 29.5, 29.4, 28.2, 24.8, 23.9, 22.8, 14.3 ppm**;** HRMS (ESI-TOF$^+$) *m/z* calcd for $C_{21}H_{36}O_4$ $[M+H]^+$: 353.2686, found 353.2689.



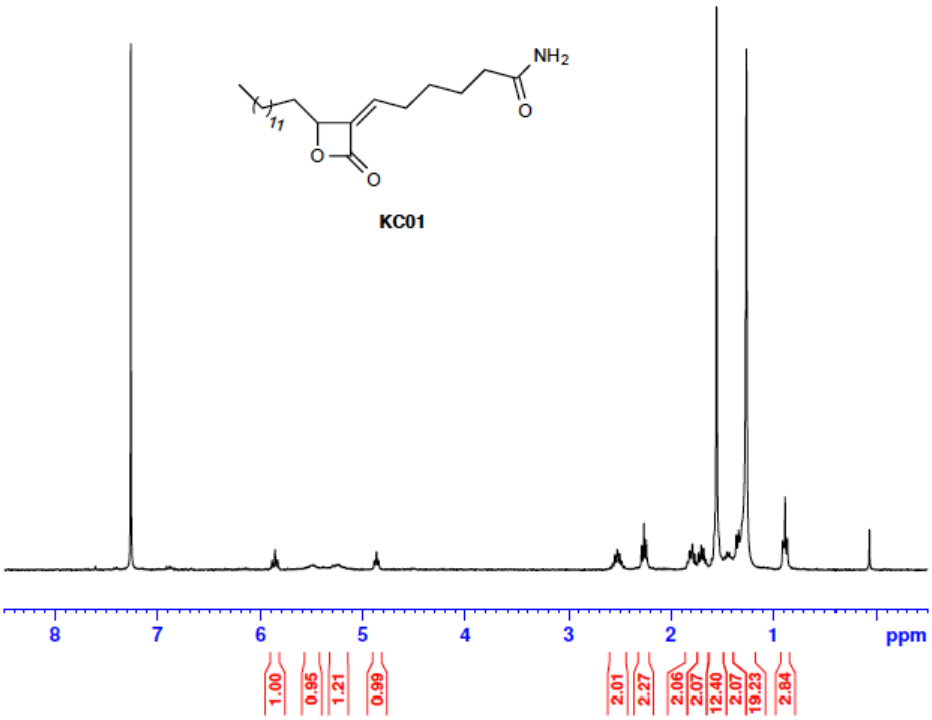
42

2,5-Dioxopyrrolidin-1-yl (*Z*)-5-(2-oxo-4-tridecyloxetan-3-ylidene)pentanoate (42). To a solution of **41** (28 mg, 0.08 mmol, 1.0 equiv) and *i*Pr_2EtN (21 µL, 0.12 mmol, 1.5 equiv) in dry CH_2Cl_2 (1 mL) was added *N*,*N*′-disuccinimidyl carbonate (23 mg, 0.09 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 3 h, eventually forming a white suspension. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (1:2:2 EtOAc/hexanes/CH_2Cl_2) to provide 2,5-dioxopyrrolidin-1-yl (*Z*)-5-(2-oxo-4-tridecyloxetan-3-ylidene)pentanoate (**42**) (29 mg, 80%) as a white powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.85 (td, *J* = 7.6, 0.8 Hz, 1H), 4.88 (dd, *J* = 6.4, 6.4 Hz, 1H), 2.84 (s, 4H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.67-2.54 (m, 2H), 1.98-1.91 (m, 2H), 1.84-1.78 (m, 2H), 1.50-1.39 (m, 2H), 1.36-1.26 (m, 20H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.1, 168.2, 164.0, 139.3, 133.6, 79.0, 33.8, 32.1, 30.4, 29.8, 29.8, 29.8, 29.6, 29.5, 29.5, 29.4, 28.0, 25.7, 24.8, 23.8, 22.8, 14.3 ppm; HRMS (ESI-TOF$^+$) *m/z* calcd for $C_{25}H_{39}NO_6$ $[M+H]^+$: 450.2850, found 450.2851.



WHP01

(*Z*)-2-(6-(dimethylamino)-3-(dimethyliminio)-3*H*-xanthen-9-yl)-5-((5-(5-(2-oxo-4-tridecyloxetan-3-ylidene)pentanamido)pentyl)carbamoyl)benzoate (**WHP01). 42** (4.5 mg, 0.01 mmol, 1.0 equiv), dissolved in dry CH_2Cl_2 (0.5 mL), was slowly added to a solution of 5-TAMRA cadaverine (5.0 mg, 0.01 mmol, 1.0 equiv) and *i*Pr_2EtN (9 µL, 0.05 mmol, 5.0 equiv) in dry CH_2Cl_2 (0.5 mL), chilled on an ice bath. The dark pink solution was allowed to slowly warm to room temperature to stir for 2 h. The reaction mixture was then concentrated under reduced pressure, and the residue purified by column chromatography on silica gel (10% → 15% MeOH/CH_2Cl_2) to yield (*Z*)-2-(6-(dimethylamino)-3-(dimethyliminio)-3*H*-xanthen-9-yl)-5-((5-(5-(2-oxo-4-tridecyloxetan-3-ylidene)pentanamido)pentyl)carbamoyl)benzoate (**WHP01**) (4.6 mg, 54%) as a dark pink solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.39 (s, -NH), 8.19 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 6.85-6.80 (m, 1H), 6.57 (d, *J* = 8.8 Hz, 2H), 6.49 (s, 2H), 6.39 (d, *J* = 8.8 Hz, 2H), 5.86 (t, *J* = 7.6 Hz, 1H), 5.12 (s, -NH), 4.83 (dd, *J* = 6.4, 6.4 Hz, 1H), 3.54-3.49 (m, 2H), 3.32-3.27 (m, 2H), 2.99 (s, 12H), 2.57-2.43 (m, 2H), 2.22 (t, *J* = 6.8 Hz, 2H), 1.86-1.55 (m, 8H), 1.49-1.39 (m, 4H), 1.31-1.25 (m, 20 H), 0.88 (t, *J* = 6.4 Hz, 3H) ppm; HRMS (ESI-TOF$^+$) *m/z* calcd for $C_{51}H_{68}N_4O_7$ $[M+H]^+$: 849.5161, found 849.5164.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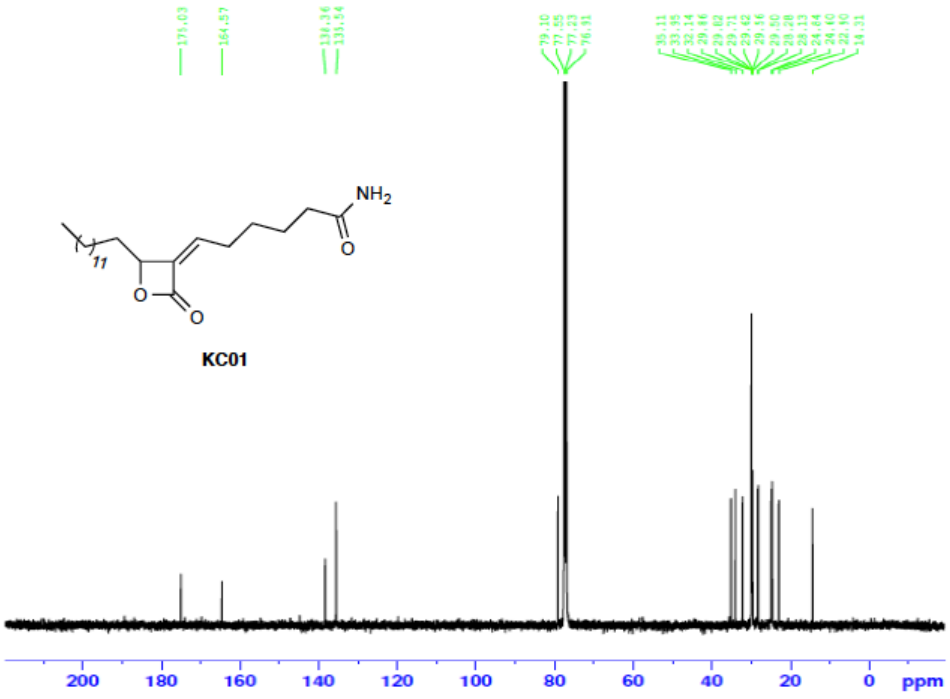
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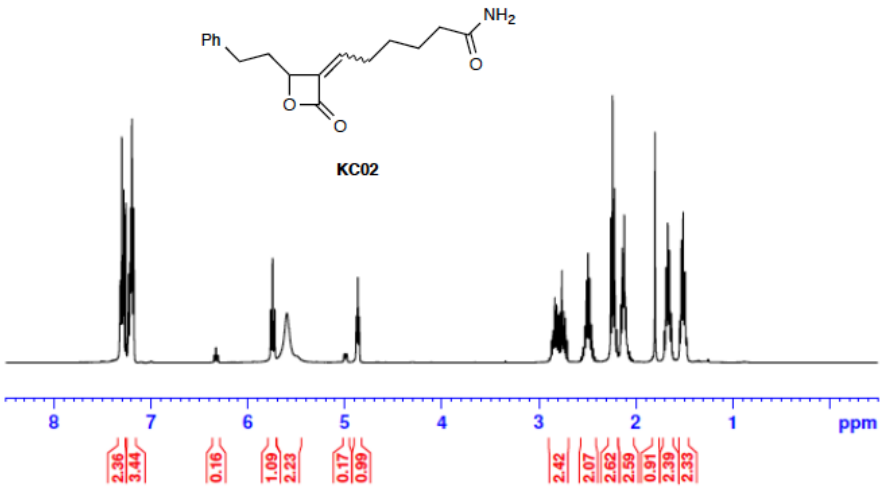
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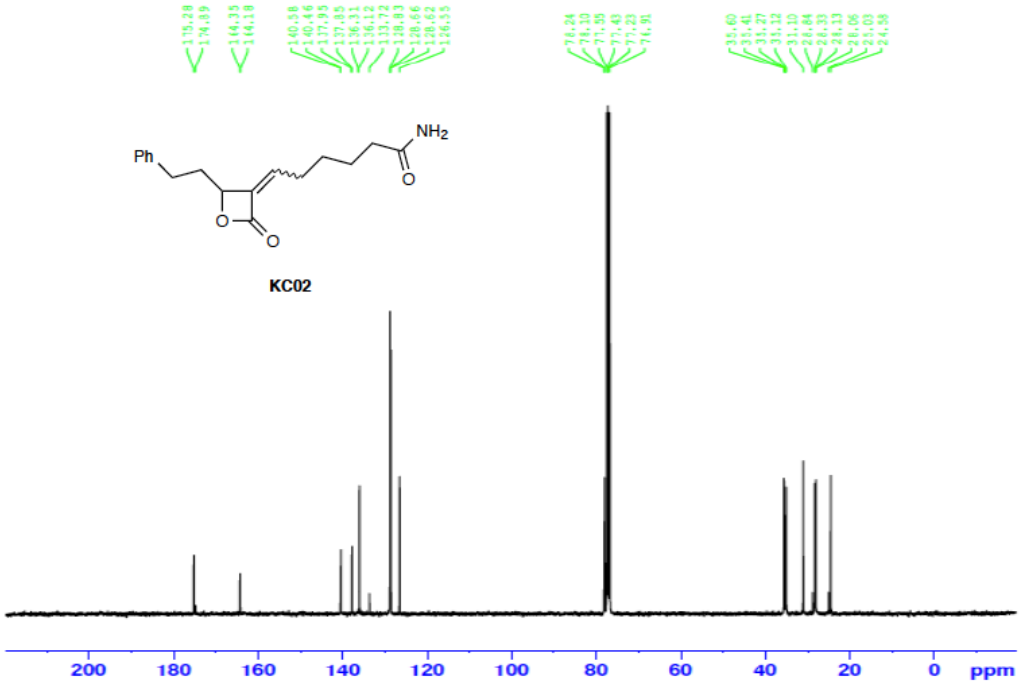
2.33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164.18
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140.46
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137.85
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133.72
128.83
128.66
128.62
126.55
76.24
76.10
75.95
77.43
77.23
76.91
35.60
35.41
35.27
35.12
31.10
28.84
28.33
26.13
26.06
25.03
24.58
Ph
NH2
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O
O
KC02
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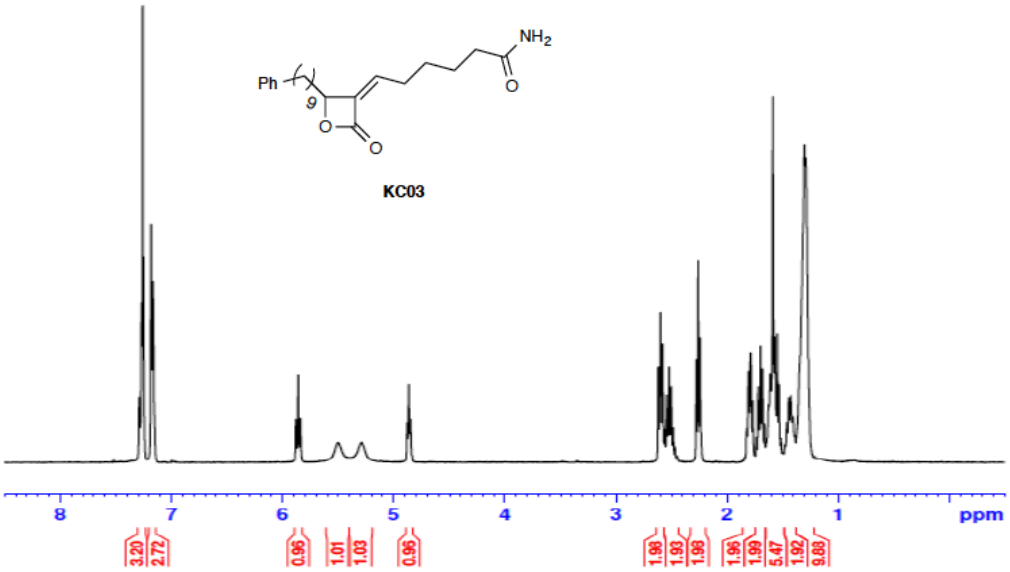
140
120
100
80
60
40
20
0
ppm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O
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4
3
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ppm
3.20
2.72
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0.96
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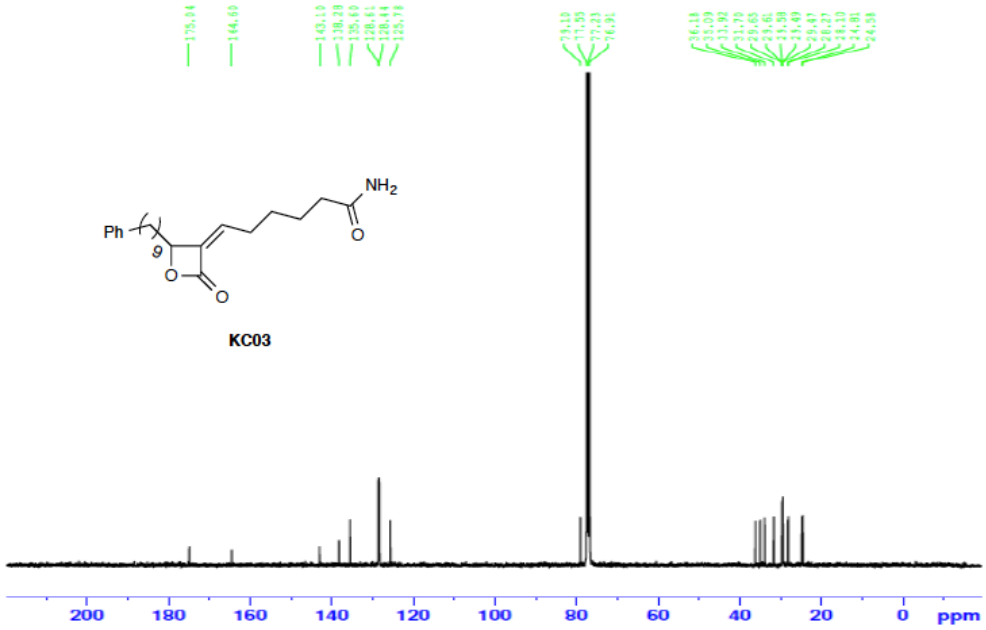
1.93
1.98
1.96
1.99
5.47
1.92
9.68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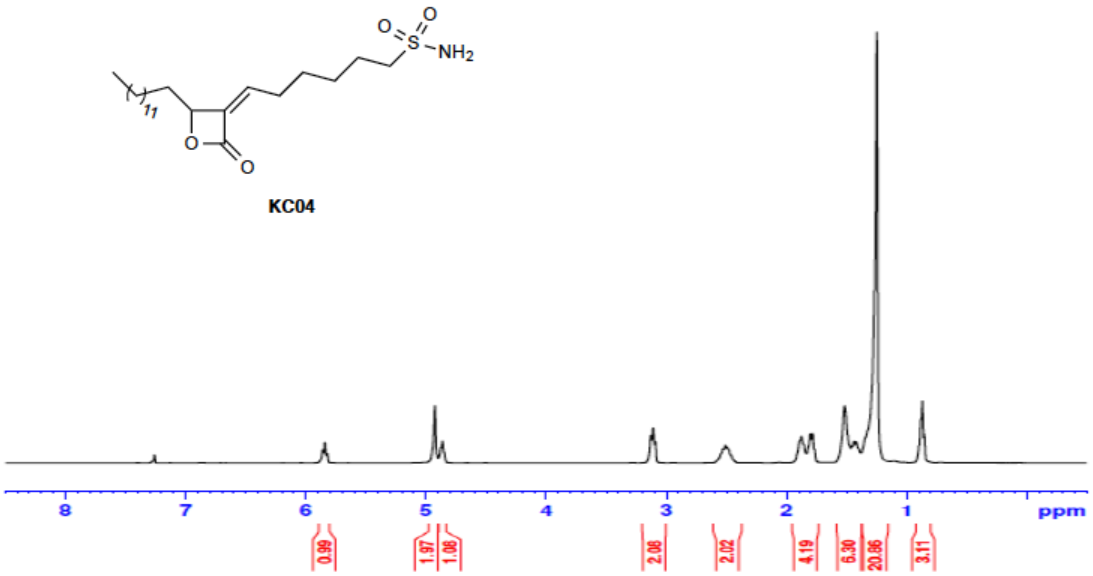
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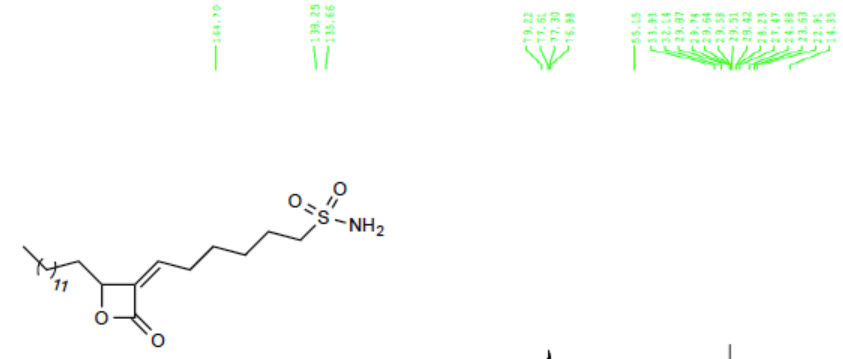
20.86
3.11



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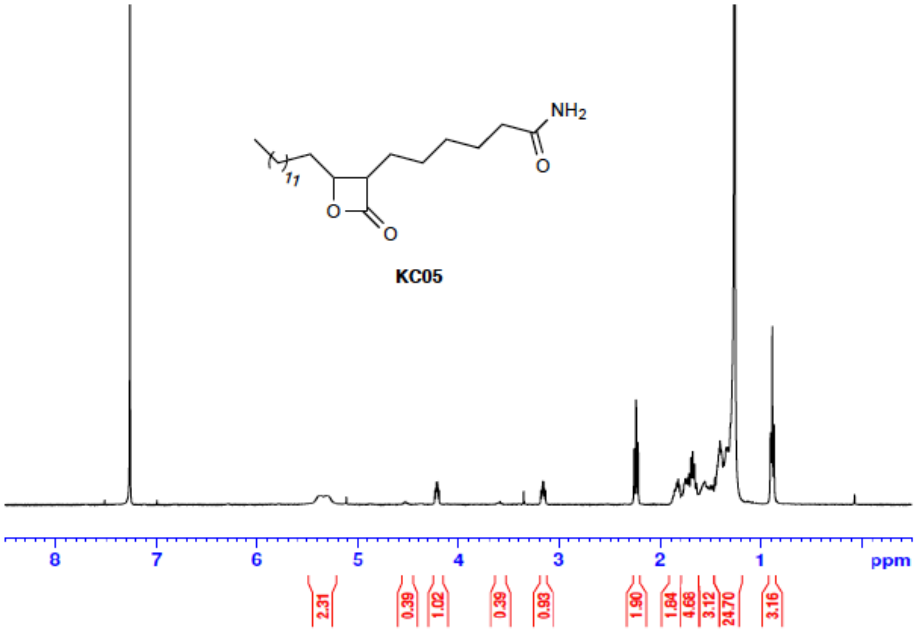
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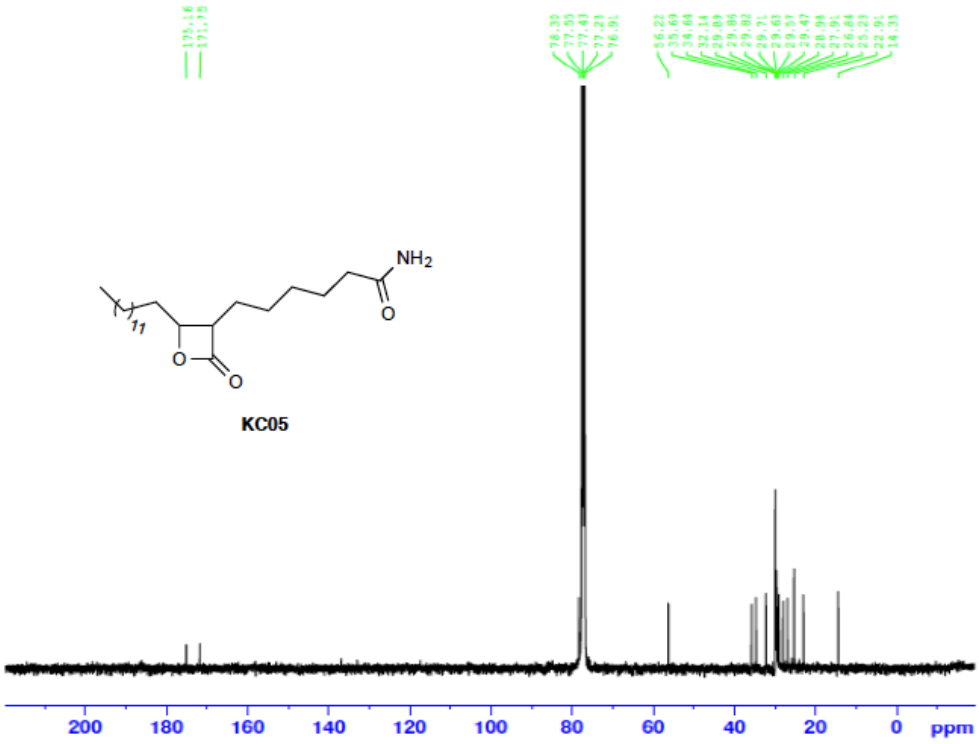
3.16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O
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KC05
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140
120
100
80
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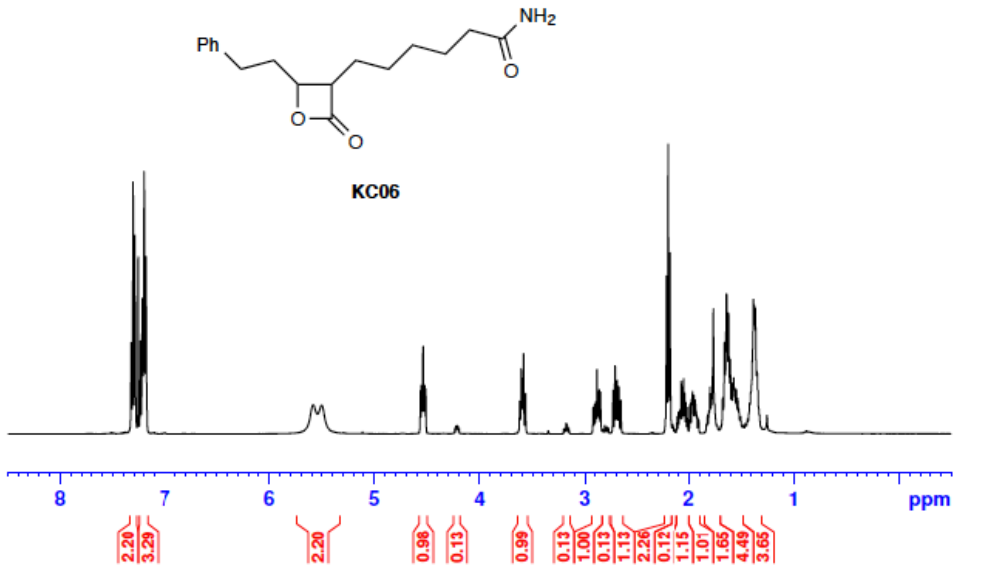
ppm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Ph
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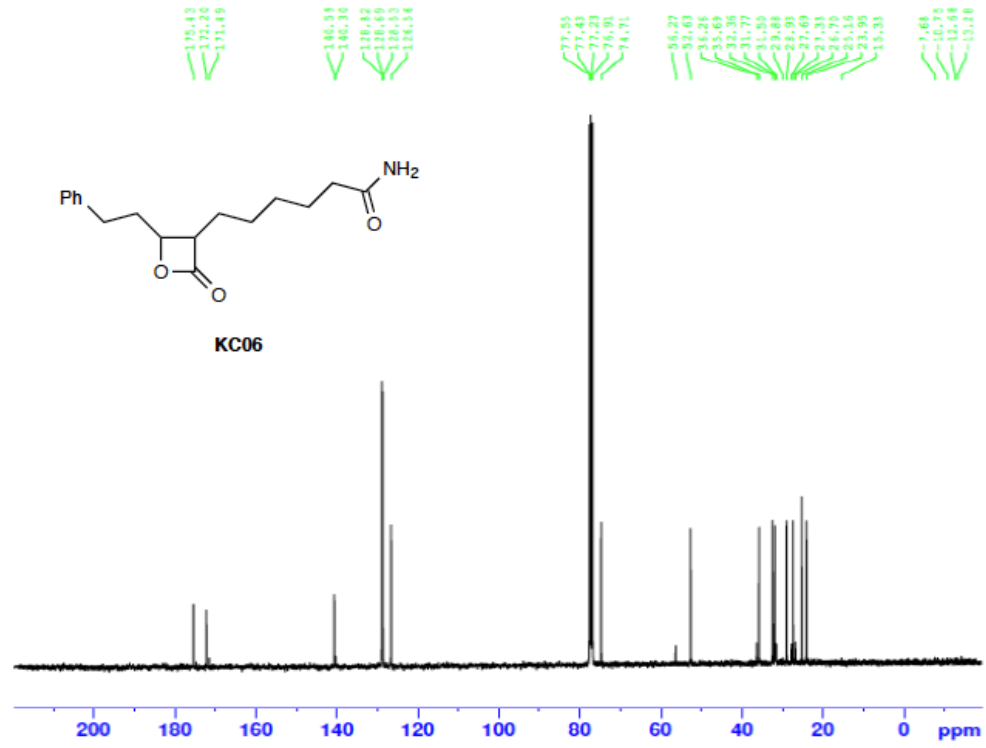
O
O
KC06
8
7
6
5
4
3
2
1
ppm
2.20
3.29
2.20
0.98
0.13
0.99
0.13
1.00
0.13
1.13
2.26
0.12
1.15
1.07
1.65
4.49
3.65


NH2
Ph
O
O
O
KC06
200
180
160
140
120
100
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0
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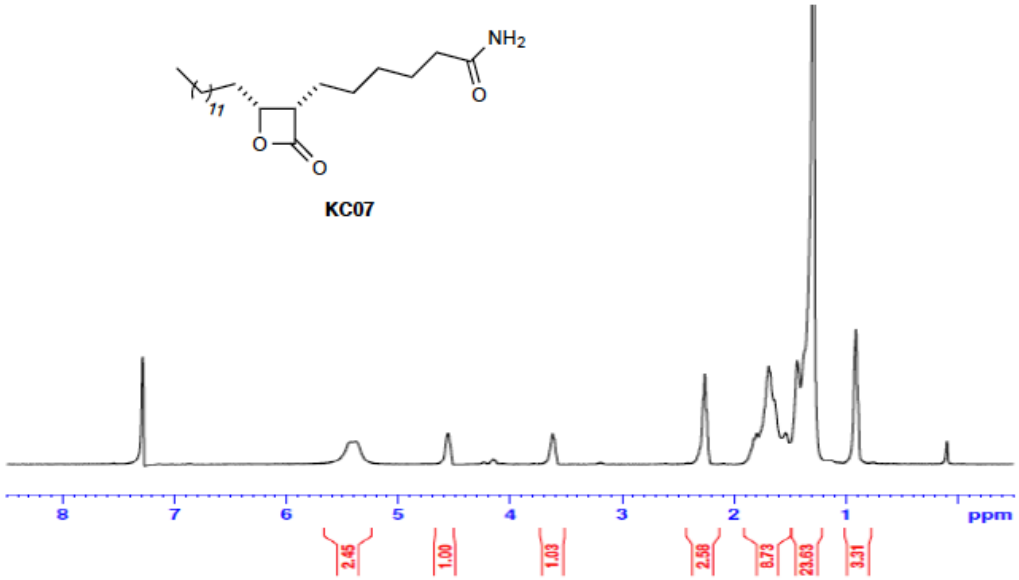
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O
11
O
O
KC07
8
7
6
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4
3
2
1
ppm
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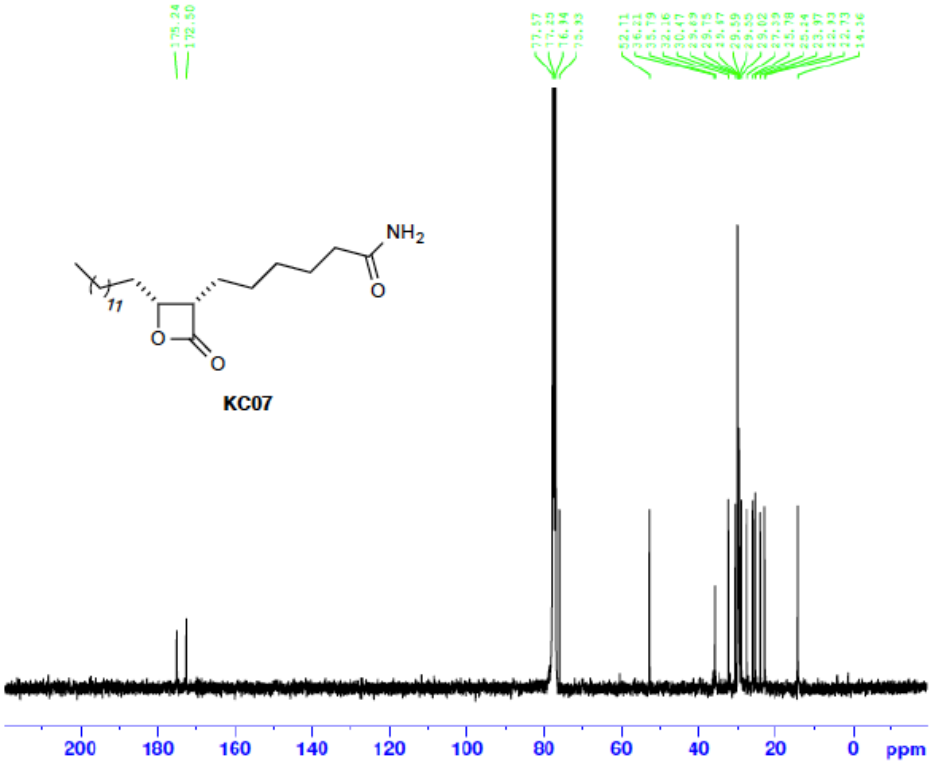
1.00
1.03
2.58
8.73
20.63
3.31


175.24
172.50
NH2
O
11
O
O
KC07
200
180
160
140
120
100
80
60
40
20
0
ppm

References

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