Electronic Supplementary Information for

Incorporation of a Self-Immolative Spacer Enables Mechanically Triggered Dual Payload Release

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Table of Contents

I. General Experimental Details and Methods

Reagents from commercial sources were used without further purification unless otherwise stated. Methyl acrylate was passed through a short plug of basic alumina to remove inhibitor immediately prior to use. Anhydrous DCM, THF, diethyl ether, MeCN, and DMF were obtained from a Pure Process Technology solvent purification system. All reactions were performed under a N_2 atmosphere unless specified otherwise. Freshly cut copper wire was immersed in 1 M HCl for 15 min, rinsed consecutively with deionized water and acetone, and then dried under a flow of N_2 prior to use. Column chromatography was performed on a Biotage Isolera system using SiliCycle SiliaSep HP or SiliaBond C18 cartridges.

NMR spectra were recorded using a 400 MHz Bruker Avance III HD with Prodigy Cryoprobe, a 400 MHz Bruker Avance Neo, or Varian Inova 500 MHz spectrometers. All ^{1}H NMR spectra are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm), dichloromethane (5.32 ppm), methanol (3.31 ppm), acetone (2.05 ppm), toluene (2.08 ppm), or acetonitrile (1.94 ppm) in deuterated solvent. All ^{13}C NMR spectra were measured in deuterated solvents and are reported in ppm relative to the signals for chloroform (77.16 ppm), acetone (29.84 ppm), or acetonitrile (1.32 ppm). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dq = doublet of quartets, ABq = AB quartet, m = multiplet, br s = broad singlet.

High resolution mass spectra (HRMS) were obtained from an Agilent 6230 series time-of-flight mass spectrometer equipped with an Agilent G1958 Jet Stream Electrospray Ionization (ESI) Source or a JEOL JMS-T2000 GC AccuTOF GC-Alpha mass spectrometer interfaced with an Agilent 8890 GC system with samples analyzed by field desorption (FD) or field ionization (FI), which generally resulted in radical cations, $M^{+\bullet}$.

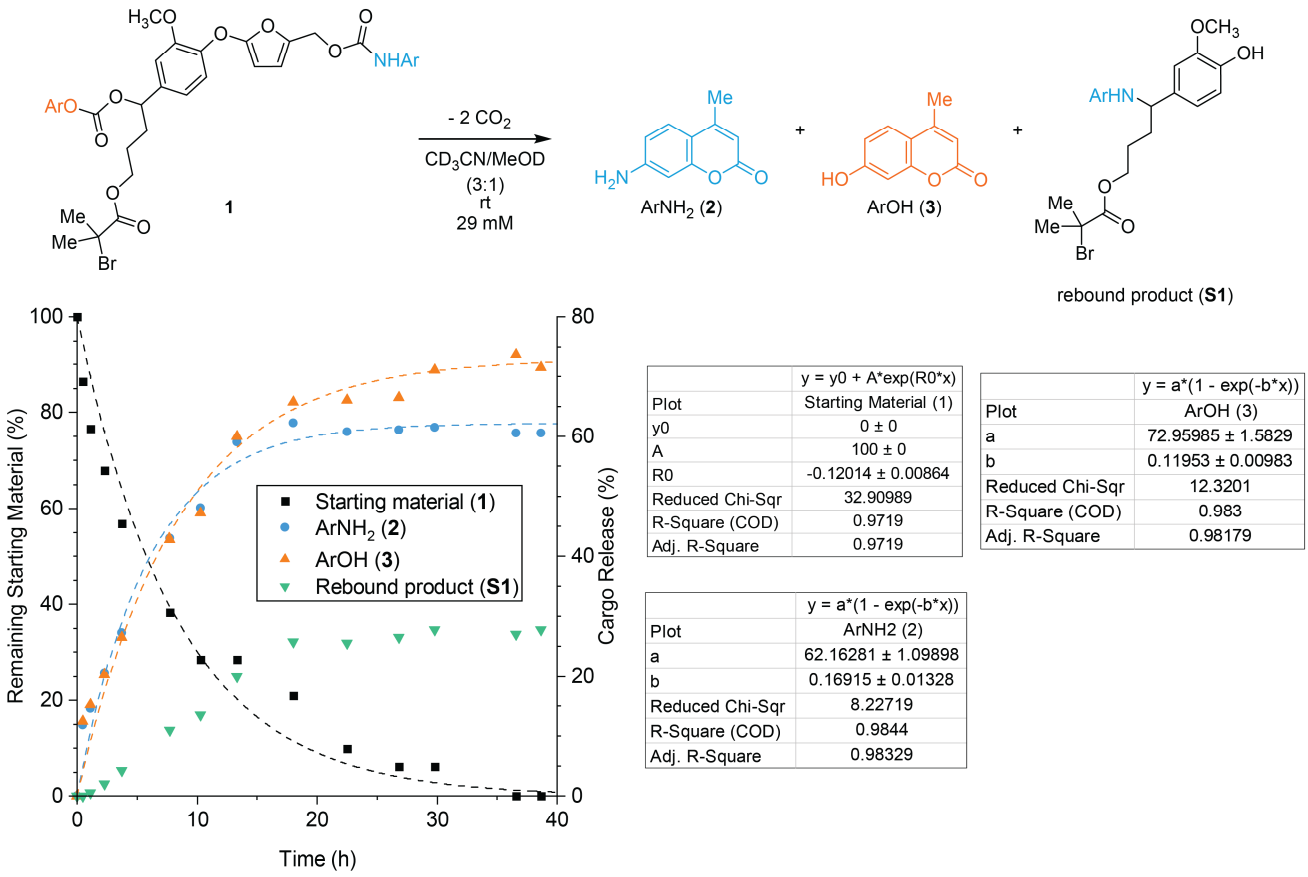
Analytical gel permeation chromatography (GPC) was performed using an Agilent 1260 series pump equipped with two Agilent PLgel MIXED-B columns (7.5 x 300 mm), an Agilent 1200 series diode array detector, a Wyatt 18-angle DAWN HELEOS light scattering detector, and an Optilab rEX differential refractive index detector. The mobile phase was THF at a flow rate of 1 mL/min. Molecular weights and molecular weight distributions were calculated by light scattering using a dn/dc value of 0.062 mL/g (25 °C) for poly(methyl acrylate).

Photoluminescence spectra were recorded on a Shimadzu RF-6000 spectrofluorophotometer using a quartz microcuvette (Starna Cells 18F-Q-10-GL14-C, 10 x 2 mm). Excitation and emission slit widths were 5 nm and 3 nm, respectively.

Analytical high-performance liquid chromatography (HPLC) measurements were performed with an Agilent Eclipse XDB-C18 column (993967-902) using a multi-wavelength UV-vis detector.

Ultrasound experiments were performed inside of a sound abating enclosure using a 500 watt Vibra Cell 505 liquid processor (20 kHz) equipped with a 0.5-inch diameter solid probe (part #630-0217), sonochemical adapter (part #830-00014), and a Suslick reaction vessel made by the Caltech glass shop (analogous to vessel #830-00014 from Sonics and Materials).

II. Supplementary Figures



	y = y0 + A*exp(R0*x)
Plot	Starting Material (1)
y0	0 ± 0
A	100 ± 0
R0	-0.12014 ± 0.00864
Reduced Chi-Sqr	32.90989
R-Square (COD)	0.9719
Adj. R-Square	0.9719

	y = a*(1 - exp(-b*x))
Plot	ArOH (3)
a	72.95985 ± 1.5829
b	0.11953 ± 0.00983
Reduced Chi-Sqr	12.3201
R-Square (COD)	0.983
Adj. R-Square	0.98179

	y = a*(1 - exp(-b*x))
Plot	ArNH2 (2)
a	62.16281 ± 1.09898
b	0.16915 ± 0.01328
Reduced Chi-Sqr	8.22719
R-Square (COD)	0.9844
Adj. R-Square	0.98329

Figure S1. Decomposition of model compound **1** ($[\mathbf{1}]_0$ = 29 mM) in 3:1 CD_3CN/MeOD at room temperature produces $ArNH_2$ **2**, ArOH **3**, and rebound product **S1**. Time-dependent reaction profiles for the conversion of **1** and the generation of **2**, **3** and **S1** were characterized by ^1H NMR spectroscopy using the signal for acetonitrile at 1.94 ppm as an internal standard (see Figure S2). The data were fit to expressions of simple first order kinetics (fitting parameters and statistics shown at right).

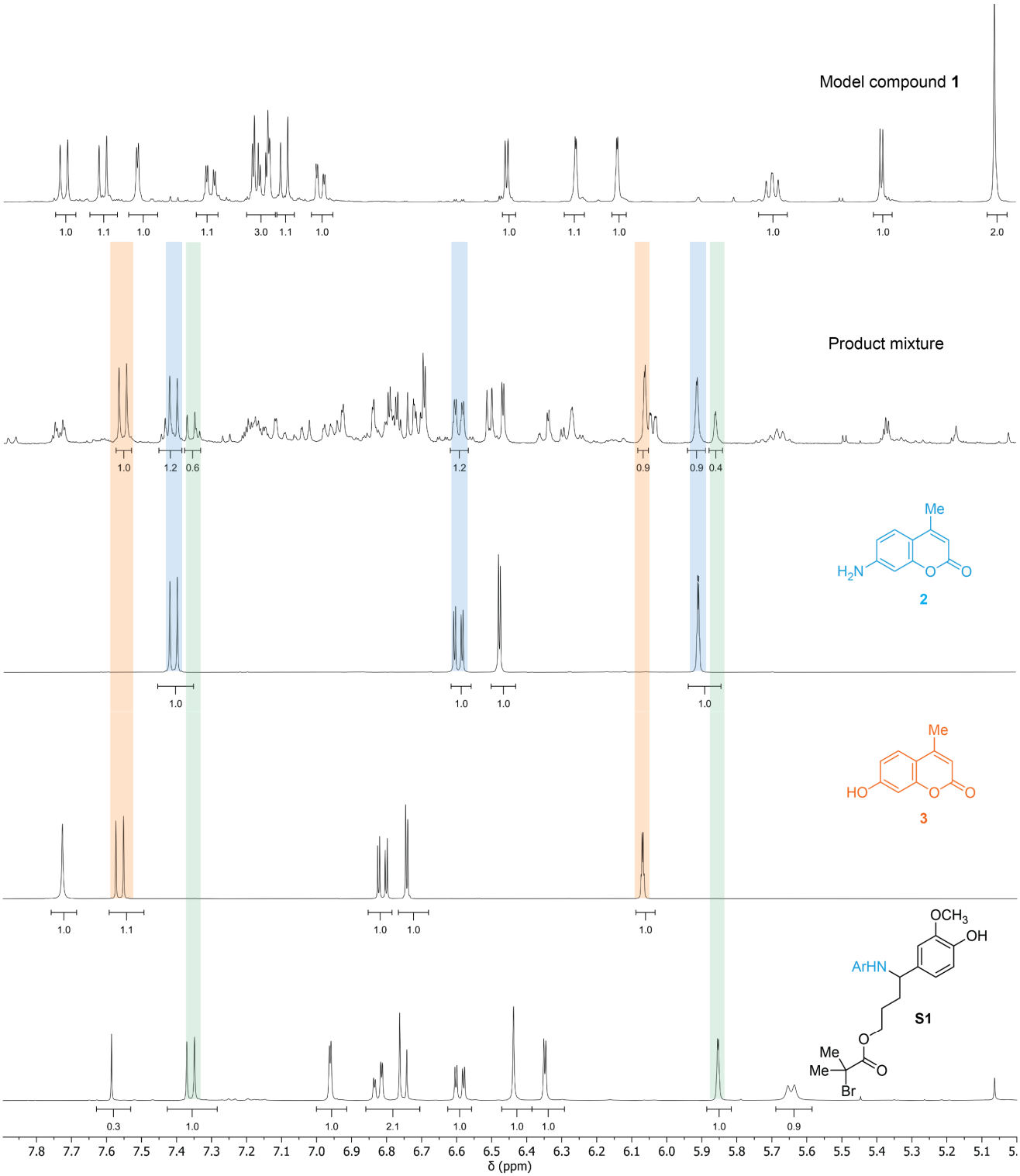


Figure S2. Characterization of the decomposition of model compound **1** by ^{1}H NMR spectroscopy (3:1 CD_3CN/MeOD; [**1**]$_0$ = 29 mM). Partial ^{1}H NMR spectra of starting material **1** in CD_3CN (top) compared to the product mixture after 48 h in 3:1 CD_3CN/MeOD (second from top). ^{1}H NMR spectra of isolated compounds $ArNH_2$ **2**, ArOH **3**, and rebound product **S1** in CD_3CN are shown for comparison.

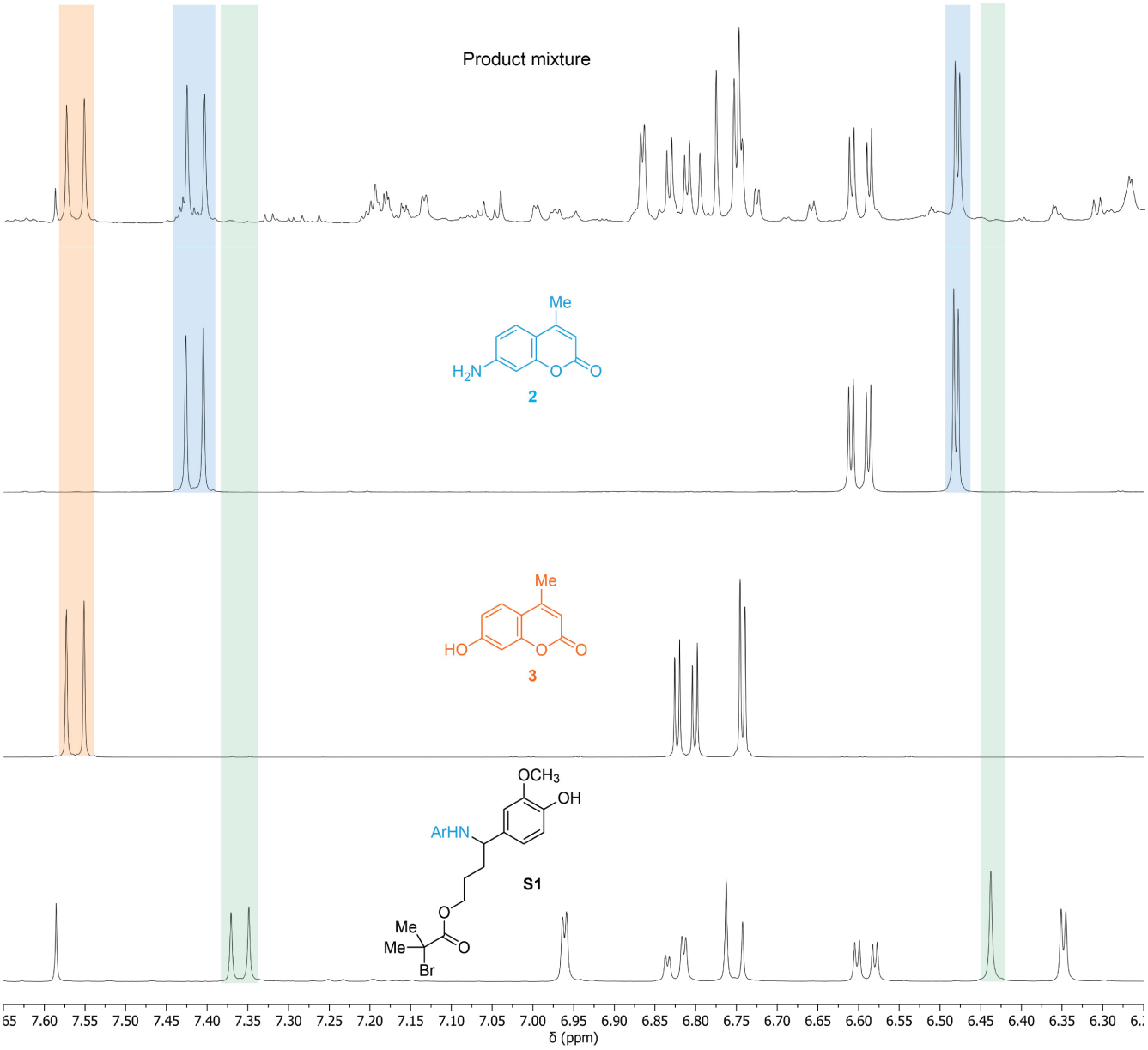


Figure S3. Characterization of the decomposition of model compound **1** and product distribution in 3:1 CD_3CN/MeOD at lower substrate concentration ($[\mathbf{1}]_0$ = 20 µM). Partial ^1H NMR spectra of the product mixture after 48 h compared to isolated compounds in CD_3CN demonstrating the conversion of **1** to $ArNH_2$ **2** and ArOH **3**. The rebound product **S1** is not observed at this lower substrate concentration.

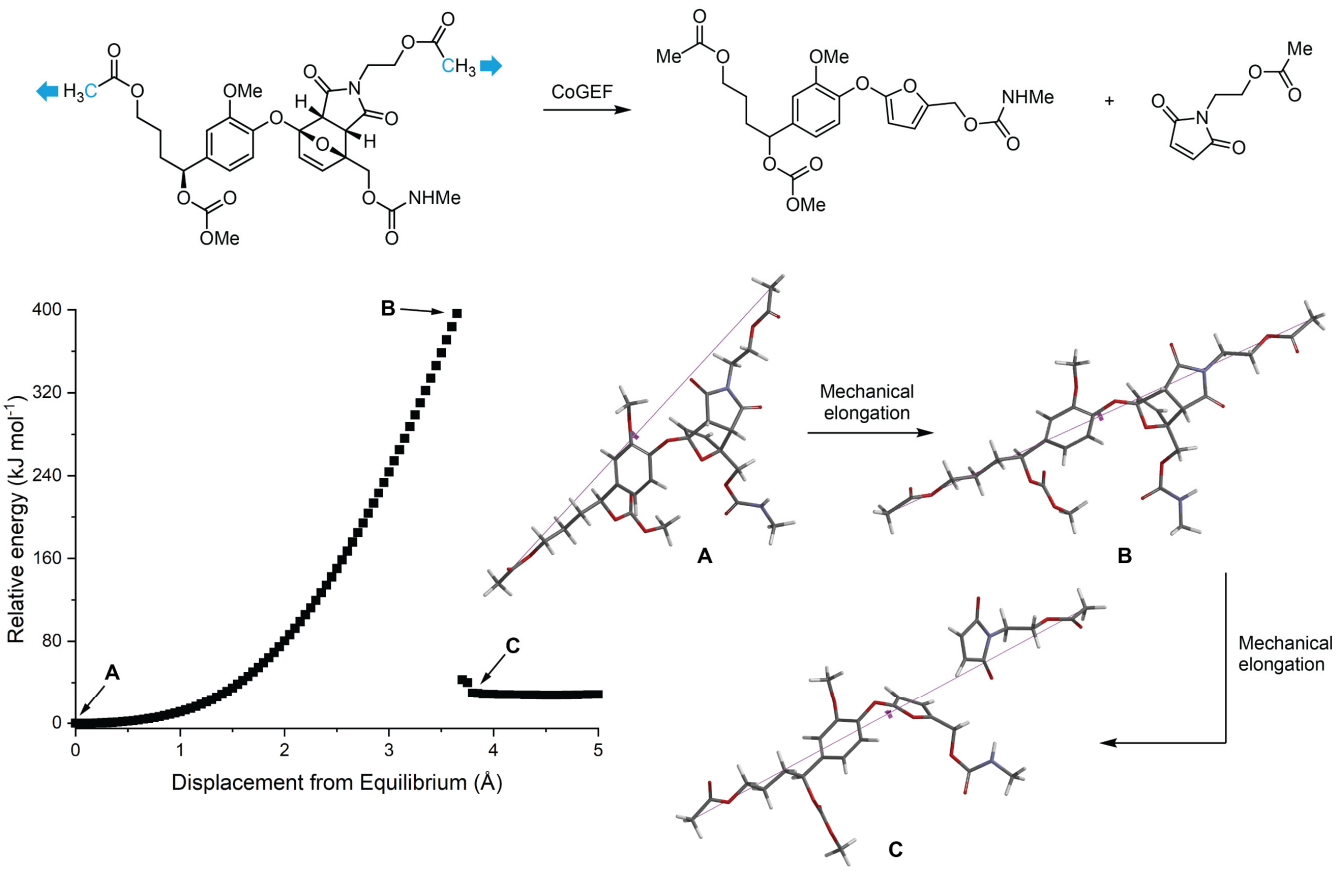


Figure S4. Results of density functional theory calculations performed on a truncated model of the furan–maleimide Diels–Alder adduct in polymer **PMA-1** using the constrained geometries simulate external force (CoGEF) method at the B3LYP/6-31G* level of theory. Pulling points were defined as the carbon atoms in the terminal methyl groups (colored blue) with a step size of 0.05 Å. A formal retro-Diels–Alder reaction is predicted to occur upon mechanical elongation at a maximum rupture force (F_{max}) of 4.2 nN to generate the expected 5-aryloxy-substituted furfuryl carbamate and maleimide products. The corresponding computed structures at various points of elongation indicted in the CoGEF plot are shown at right.

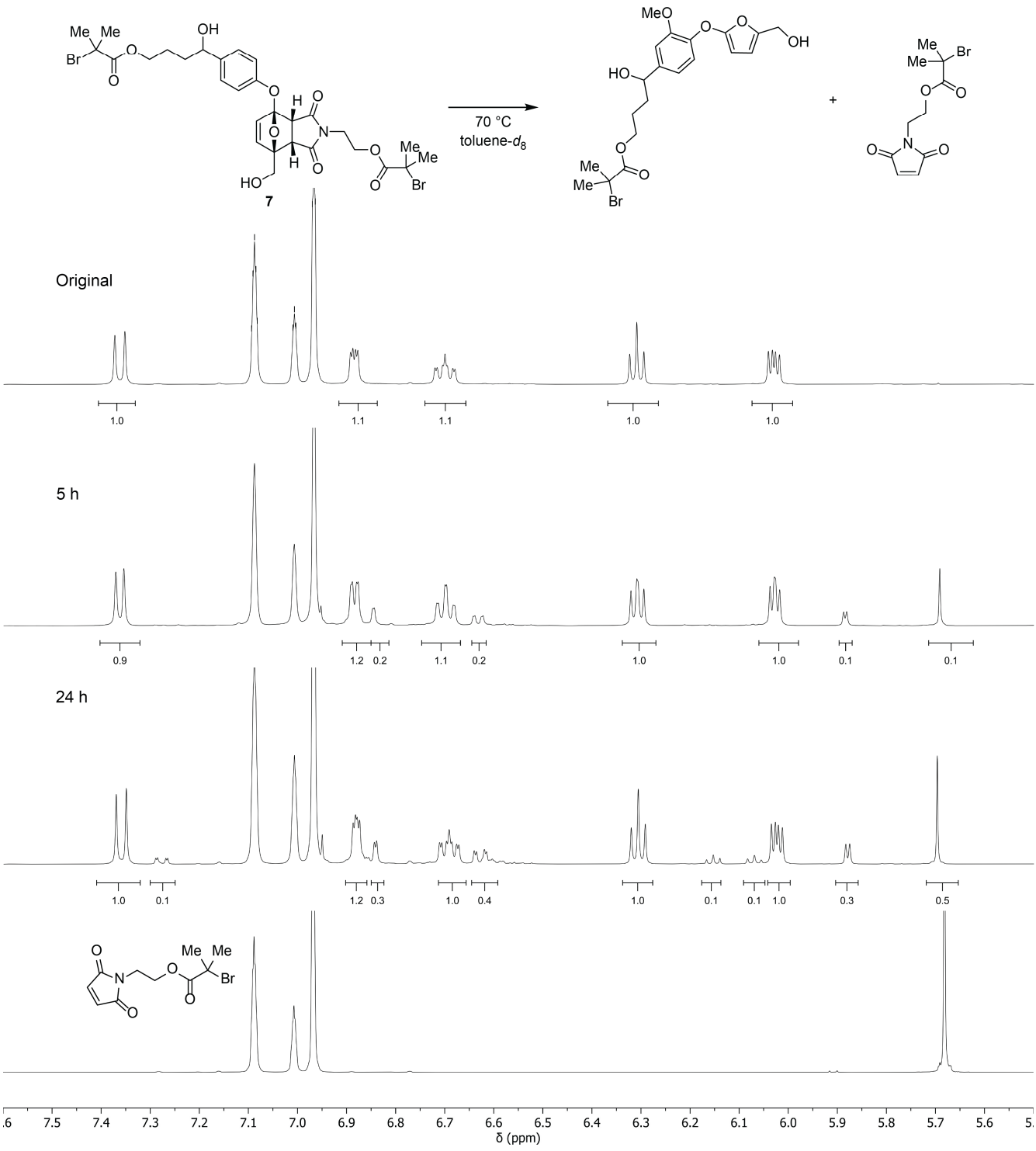


Figure S5. Thermal stability study of Diels–Alder adduct **7** in toluene-d_8 (39 mM) upon heating at 70 °C. Partial ^{1}H NMR spectra of **7** after heating at 70 °C for the indicated amount of time. Compound **7** undergoes a retro-Diels–Alder reaction upon heating at 70 °C with a conversion of ~5% after 5 h and ~25% after 24 h. The partial ^{1}H NMR spectrum of the maleimide fragment in toluene-d_8 is shown at bottom for reference.

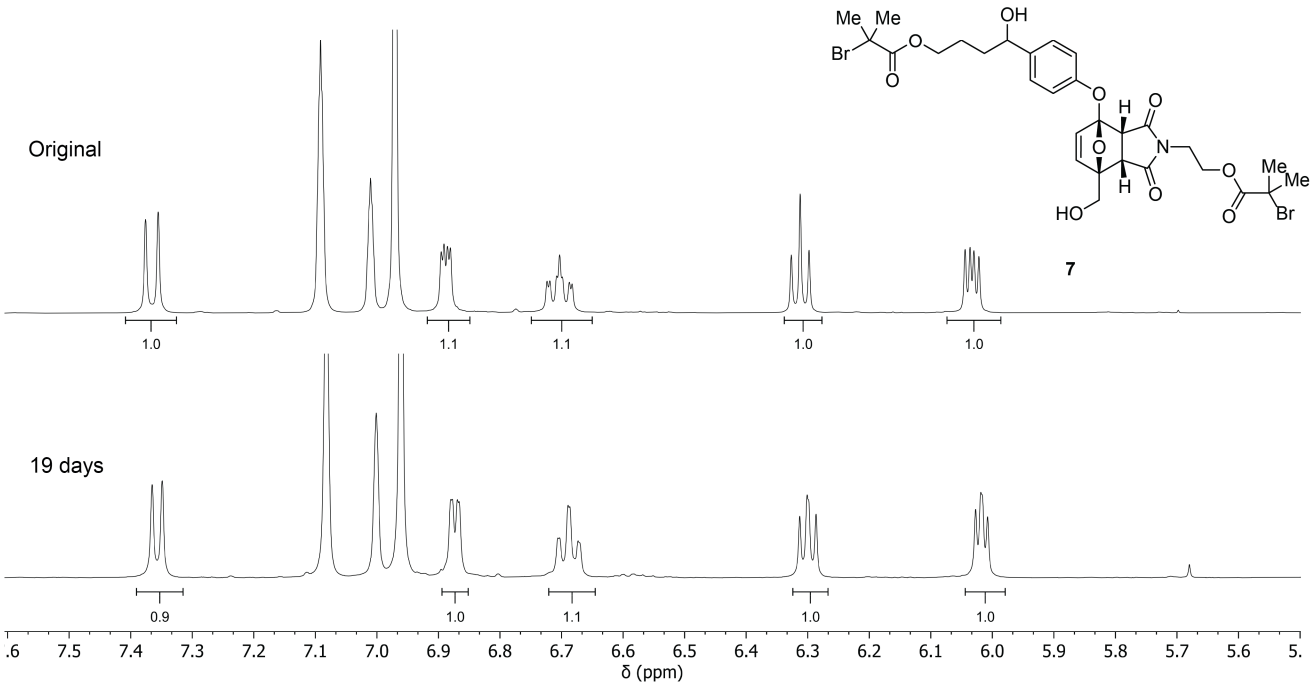


Figure S6. Thermal stability study of Diels–Alder adduct **7** in toluene-d_8 (39 mM) at room temperature. Partial ^{1}H NMR spectra of **7** after being kept at room temperature for 19 days, demonstrating minimal retro-Diels–Alder reaction over this time period. The maleimide signal at 5.68 ppm integrates to 0.04H, indicating a conversion of ~2%.

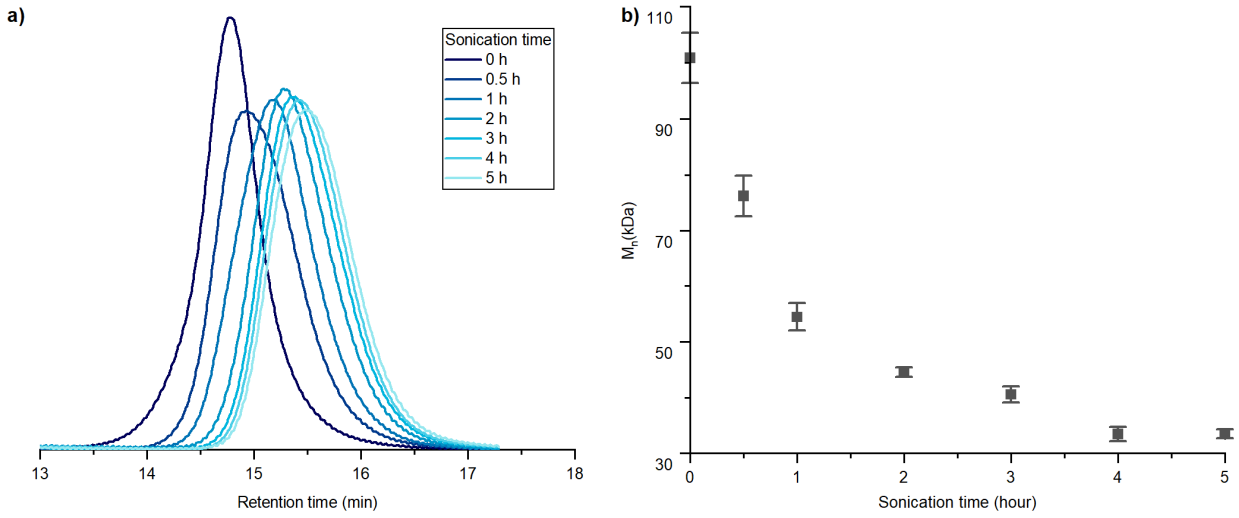


Figure S7. Characterization of **PMA-1** by gel permeation chromatography (GPC) during ultrasonication for 5 h. a) GPC traces as a function of sonication time monitored with a refractive index (RI) detector. b) Number average molar mass (M_n) as a function of sonication time calculated using light scattering showing a steady decrease in M_n as a result of mechanochemical chain scission. Error bars represent standard deviation from three replicate trials.

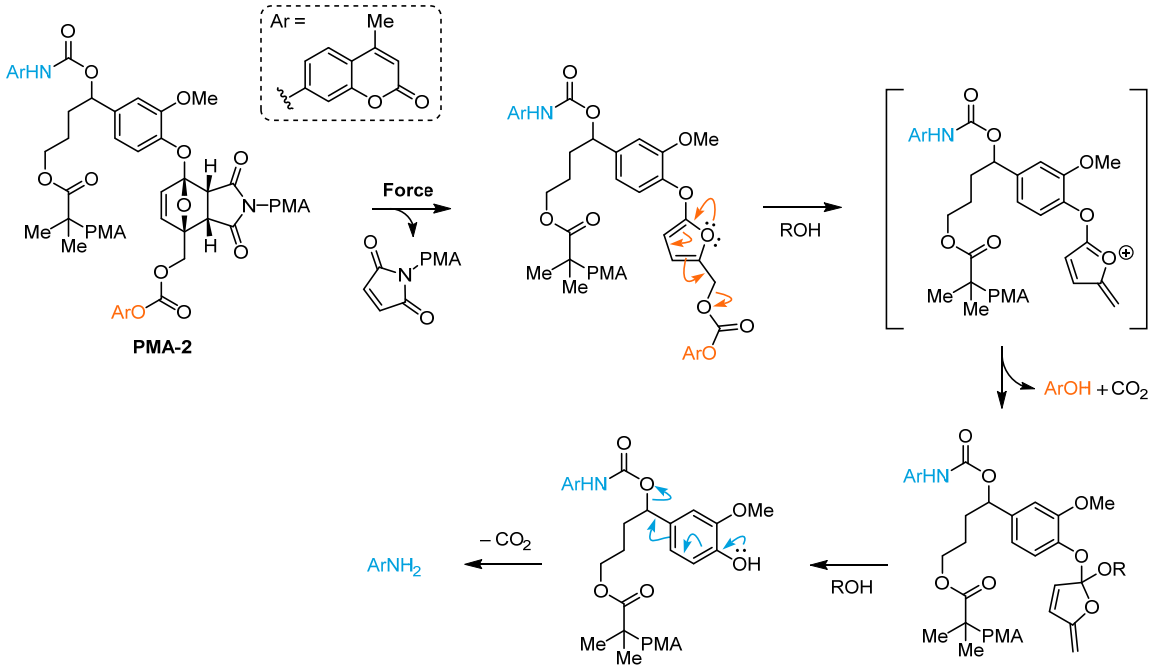


Figure S8. Proposed mechanism for the mechanically triggered release of $ArNH_2$ **2** and ArOH **3** upon ultrasound-induced mechanochemical activation of **PMA-2** in polar protic solvent via a multistep retro-Diels–Alder/fragmentation–decarboxylation cascade.

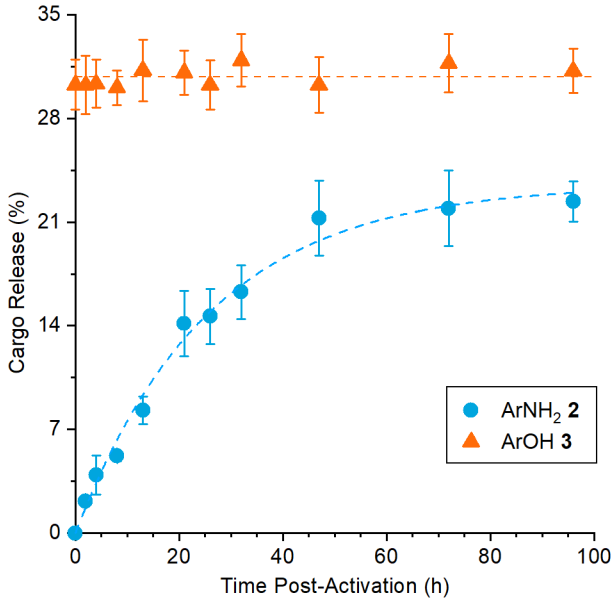


Figure S9. Mechanically triggered release of $ArNH_2$ **2** and ArOH **3** upon ultrasound-induced mechanochemical activation of **PMA-2** (2 mg/mL in 3:1 MeCN/MeOH). Cargo release was measured at room temperature beginning immediately after sonication of **PMA-2** for 60 min and characterized by quantitative HPLC. Error bars represent standard deviation from three replicate experiments. See Section VI for additional details.

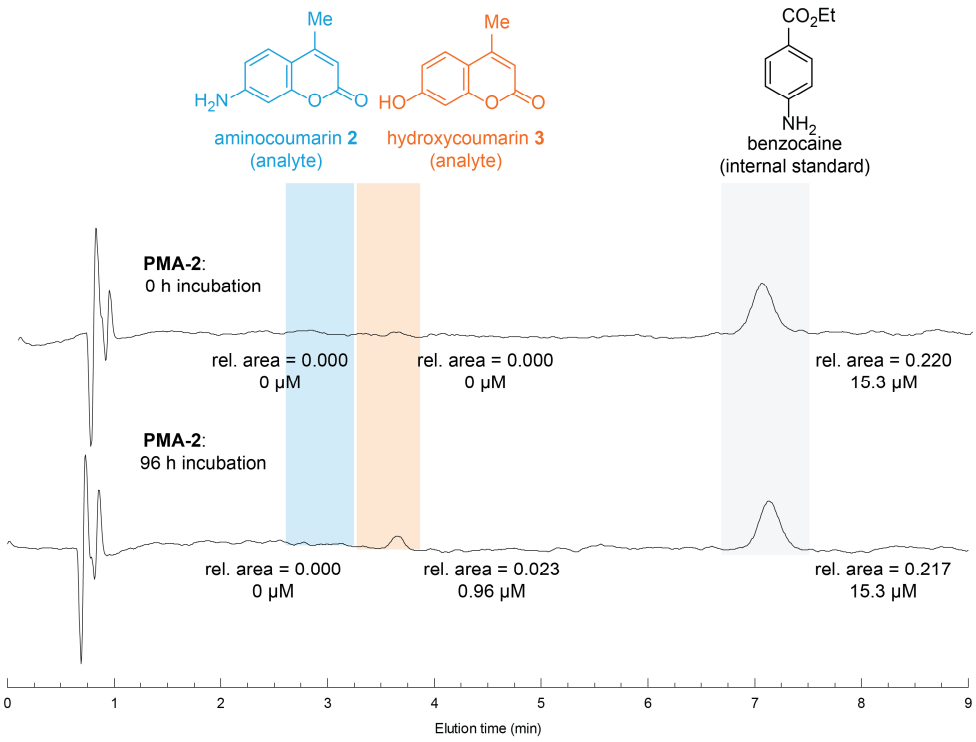
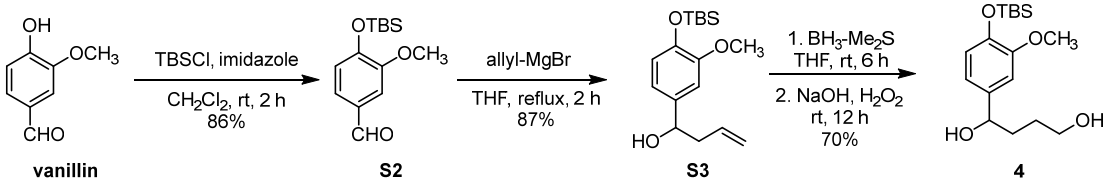


Figure S10. Representative HPLC chromatograms characterizing the release of $ArNH_2$ **2** and ArOH **3** from **PMA-2** (2 mg/mL) upon incubation in acetonitrile/methanol (3:1 v/v) at room temperature. No release of $ArNH_2$ **2** was observed, while < 5% release of ArOH **3** was observed after 96 h, illustrating stability of the payloads in the absence of a mechanical trigger (see Section VI for additional details). HPLC conditions: 22:78 MeCN/water + 0.1% AcOH, isocratic, 2 mL/min, λ = 310 nm.

III. Synthetic Details

Scheme S1. Synthesis of Diol **4**.



4-((tert-butyldimethylsilyl)oxy)-3-methoxybenzaldehyde (S2). A two-neck round bottom flask equipped with a stir bar was charged with vanillin (10.2 g, 66.8 mmol), imidazole (11.4 g, 167 mmol), and DCM (67 mL). To the stirred solution at room temperature was added *tert*-butyldimethylsilyl chloride (TBSCl, 13.1 g, 86.8 mmol) in one portion. After 2 h, 10% NH_4Cl (30 mL) was added, the mixture was extracted with DCM (3 x 150 mL), and the combined organic phase was washed with brine (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (0–10% EtOAc/hexanes) to afford the title compound as a colorless oil (15.3 g, 86% yield).

TLC (25% ethyl acetate/hexane): R_f = 0.67

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.85 (s, 1H), 7.40 (d, *J* = 1.9 Hz, 1H), 7.37 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 3,87 (s, 3H), 1.00 (s, 9H), 0.19 (s, 6H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 191.2, 151.8, 151.5, 131.1, 1264, 120.9, 110.3, 55.6, 25.7, 18.7, −4.4 ppm.

HRMS (ESI, m/z): calcd for $[C_{14}H_{23}O_3Si]^+$ $(M+H)^+$, 267.1411; found, 267.1409.

1-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)but-3-en-1-ol (S3). A flame dried two-neck round bottom flask equipped with a stir bar and a condenser was charged with compound **S2** (313 mg, 1.18 mmol) and THF (12 mL). A solution of allyl magnesium bromide in diethyl ether (0.7 mmol/mL, 2.0 mL, 1.4 mmol) was added dropwise by syringe and then refluxed in an oil bath for 2 h. The reaction was then cooled to 0 °C in an ice bath before deionized water (5 mL) was added. The mixture was then extracted with EtOAc (3 x 40 mL) and the combined organic phase was washed with brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (15–20% EtOAc/hexanes) to afford the title compound as a yellow oil (316 mg, 87% yield).

TLC (13% ethyl acetate/hexane): R_f = 0.38

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.89 (d, *J* = 1.8 Hz, 1H), 6.83 – 6.76 (m, 2H), 5.86 – 5.70 (m, 1H), 5.19 – 5.07 (m, 2H), 4.66 (t, *J* = 6.5 Hz, 1H), 3.81 (s, 3H), 2.55 – 2.46 (m, 2H), 1.98 (br s, 1H), 0.99 (s, 9H), 0.15 (s, 6H) ppm.

^{13}C{^{1}H} NMR (500 MHz, $CDCl_3$) δ: 150.9, 144.3, 137.6, 134.8, 120.6, 118.2, 118.1, 109.7, 73.3, 55.5, 43.9, 25.8, 18.5, −4.6 ppm.

HRMS (FI, m/z): calcd for $[C_{17}H_{28}O_3Si]^{+\bullet}$ $(M)^{+\bullet}$, 308.1808; found, 308.1808.

1-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)butane-1,4-diol (4). A flame dried two-neck round bottom flask equipped with a stir bar was charged with compound **S3** (6.20 g, 20.1 mmol) and THF (67 mL). The solution was cooled to 0 °C in an ice bath and borane dimethyl sulfide complex (2.9 mL, 30.6 mmol) was added dropwise by syringe. After stirring at room temperature for 4 h, the solution was cooled to 0 °C in an ice bath followed by the consecutive dropwise addition of 3N $NaOH_{(aq)}$ (8.0 mL) and then 35% $H_2O_{2\ (aq)}$ (8.0 mL). After stirring at room temperature for 16 h, the mixture was extracted with EtOAc (3 x 400 mL) and the combined organic phase was washed with brine (200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (40–60% EtOAc/hexanes) to afford the title compound as a white solid (4.61 g, 70% yield).

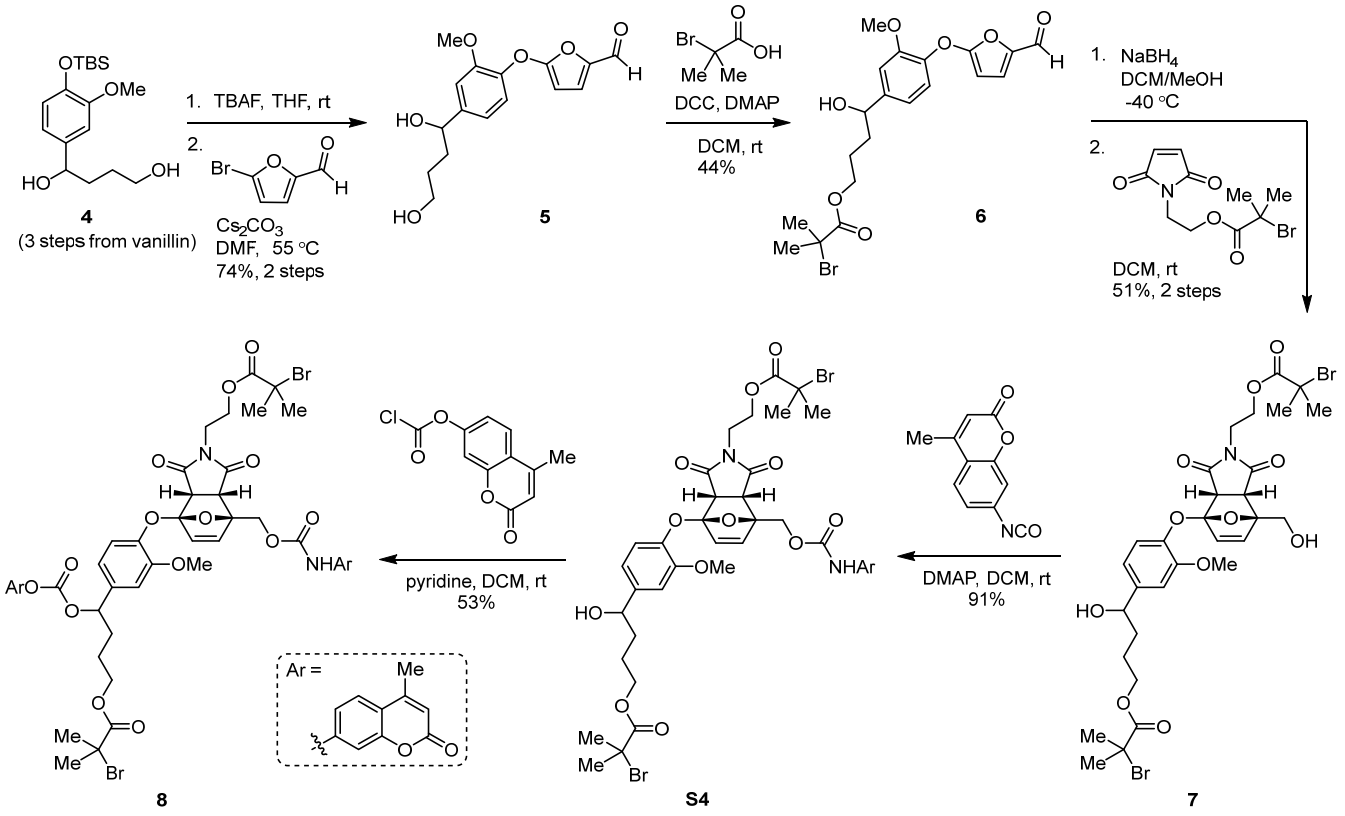
TLC (75% ethyl acetate/hexane): R_f = 0.52

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.87 (d, *J* = 1.9 Hz, 1H), 6.81 – 6.72 (m, 2H), 4.64 (dd, *J* = 7.1, 5.6 Hz, 1H), 3.80 (s, 3H), 3.72 – 3.58 (m, 2H), 2.98 (s, 1H), 1.89 – 1.77 (m, 2H), 1.75 – 1.59 (m, 3H), 0.99 (s, 9H), 0.14 (s, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 151.0, 144.4, 138.4, 120.7, 118.2, 109.7, 74.4, 62.9, 55.6, 36.4, 29.5, 25.8, 18.6, −4.5.

HRMS (FD, m/z): calcd for $[C_{17}H_{30}O_4Si]^{+\bullet}$ $(M)^{+\bullet}$, 326.1913; found, 326.1915.

Scheme S2. Synthesis of Bis-Initiator **8**.



5-(4-(1,4-dihydroxybutyl)-2-methoxyphenoxy)furan-2-carbaldehyde (5). A two-neck round bottom flask equipped with a stir bar was charged with compound **4** (210 mg, 0.644 mmol), a solution of tetrabutylammonium fluoride (TBAF) in THF (1 M, 0.77 mL, 0.77 mmol), and THF (6 mL). After stirring at room temperature for 2 h, the solution was concentrated under reduced pressure. To the flask were added 5-bromo-2-furaldehyde (134 mg, 0.766 mmol), Cs_2CO_3 (312 mg, 0.957 mmol), and DMF (2 mL). The solution was then heated at 55 °C in an oil bath for 4 h. The reaction was cooled to room temperature followed by the addition of 10% NH_4Cl (20 mL). The mixture was then extracted with EtOAc (3 x 50 mL) and the combined organic phase was washed with brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (50−100% EtOAc/hexanes) to afford the title compound as a yellow solid (146 mg, 74% yield over 2 steps).

TLC (100% ethyl acetate): R_f = 0.40

^{1}H NMR (500 MHz, acetone-d_6) δ: 9.33 (s, 1H), 7.39 (d, *J* = 3.8 Hz, 1H), 7.28 – 7.16 (m, 2H), 7.01 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.44 (d, *J* = 3.8 Hz, 1H), 4.72 (dd, *J* = 7.7, 5.0 Hz, 1H), 4.60 (br s, 1H), 3.83 (s, 3H), 3.76 (br s, 1H), 3.57 (t, *J* = 6.3 Hz, 2H), 1.86 – 1.50 (m, 4H) ppm.

^{13}C{^{1}H} NMR (125 MHz, acetone-d_6) δ: 175.8, 164.7, 151.5, 147.2, 145.4, 141.6, 127.6, 121.7, 119.1, 111. 8, 88.4, 73.7, 62.5, 56.3, 37.3 ppm.

HRMS (ESI, m/z): calcd for $[C_{16}H_{19}O_6]^+$ $(M+H)^+$, 307.1176; found, 307.1177.

4-(4-((5-formylfuran-2-yl)oxy)-3-methoxyphenyl)-4-hydroxybutyl 2-bromo-2-methylpropanoate (6). A round bottom flask equipped with a stir bar was charged with compound **5** (99.2 mg, 0.324 mmol), dicyclohexylcarbodiimide (DCC,

89.1 mg, 0.432 mmol), DMAP (8.4 mg, 0.069 mmol), and DCM (8 mL), followed by the addition of α-bromoisobutyric acid (64.3 mg, 0.385 mmol). The solution was stirred at room temperature for 2 h and then the solid precipitate was filtered off and discarded. The filtrate was diluted with EtOAc (300 mL) and washed consecutively with 10% NH_4Cl (50 mL) and brine (50 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (50–70% EtOAc/hexanes) to afford the title compound as a dark orange oil (64.9 mg, 44% yield).

TLC (67% ethyl acetate/hexanes): R_f = 0.47

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.21 (s, 1H), 7.15 (d, *J* = 3.8 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 1.9 Hz, 1H), 6.87 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.34 (d, *J* = 3.8 Hz, 1H), 4.69 (t, *J* = 5.9Hz, 1H), 4.21 – 4.06 (m, 2H), 3.76 (s, 3H), 3.11 (s, 1H), 1.87 (s, 6 H), 1.82 – 1.63 (m, 4H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 175.4, 171.6, 163.8, 150.7, 144.4, 144.2, 141.2, 127.7, 121.0, 118.2, 110.6, 88.5, 73.1, 65.7, 56.1, 56.0, 35.3, 30.7, 24.7 ppm.

HRMS (ESI, m/z): calcd for $[C_{20}H_{24}BrO_7]^+$ $(M+H)^+$, 455.0700; found, 455.0702.

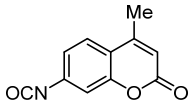
2-(4-(4-(4-((2-bromo-2-methylpropanoyl)oxy)-1-hydroxybutyl)-2-methoxyphenoxy)-7-(hydroxymethyl)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-epoxyisoindol-2-yl)ethyl 2-bromo-2-methylpropanoate (7). A flame-dried two-neck round bottom flask equipped with a stir bar was charged with compound **6** (152 mg, 0.334 mmol), DCM (1.5 mL), and anhydrous methanol (1.5 mL). The solution was cooled to −40 °C in an acetonitrile/dry ice bath before adding $NaBH_4$ (38.1 mg, 1.00 mmol). The mixture was kept at −40 °C for 2 h before being quenched with 10% NH_4Cl (3 mL) and subsequently warmed to room temperature. The solution was then extracted with DCM (3 x 30 mL) and the organic phase was washed with brine (10 mL). The organic layer was dried over Na_2SO_4, and filtered. To the filtrate was added 2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl 2-bromo-2-methylpropanoate (the maleimide ester)[1] (125 mg, 0.43 mmol), which was then concentrated under reduced pressure until ~2 mL of viscous solution remained. The mixture was then allowed to react at room temperature for 12 h. The crude reaction mixture was purified by column chromatography (50–70% EtOAc/hexanes) to afford the title compound (mixture of diastereomers) as a foamy white solid (126 mg, 51% yield).

TLC (67% ethyl acetate/hexanes): R_f = 0.28

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 (d, *J* = 8.2 Hz, 1H), 6.92 (t, *J* = 1.8 Hz, 1H), 6.74 (dt, *J* = 8.2, 1.8 Hz, 1H), 6.37 (d, *J* = 5.8 Hz, 1H), 6.33 (d, *J* = 5.8 Hz, 1H), 4.63 (t, *J* = 5.7 Hz, 1H), 4.22 – 4.03 (m, 6H), 3.86 (d, *J* = 2.0 Hz, 3H), 3.73 – 3.61 (m, 4H), 2.82 (br s, 1H), 2.56 (br s, 1H), 1.88 (s, 6H), 1.86 (s, 6H), 1.82 – 1.63 (m, 4 H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 174.5, 173.1, 171.7, 171.4, 151.60, 151.58, 142.6, 142.52, 142.48, 136.0, 135.9, 135.6, 123.2, 123.1, 117.9, 114.12, 114.09, 110.4, 110.3, 86.5, 73.5, 65.8, 62.5, 61.4, 56.4, 56.1, 55.6, 50.7, 48.81, 48.79, 37.5, 35.1, 30.78, 30.77, 30.7, 24.9 ppm.

HRMS (ESI, m/z): calcd for $[C_{30}H_{38}Br_2NO_{11}]^+$ $(M+H)^+$, 746.0806; found, 746.0804.



7-isocyanato-4-methyl-2*H*-chromen-2-one (4-methylcoumarin-7-isocyanate). The starting material 7-amino-4-methyl-2*H*-chromen-2-one was first purified according to the literature.[2] The substrate (5.52 g, 31.5 mmol) was dissolved in 1N HCl (100 mL) and then the solution was pipetted slowly into a 10% ammonia solution (200 mL) maintained at 0 °C in an ice bath. The precipitate was collected and the solid was recrystallized from hot ethanol to provide a tan crystalline powder (2.79 g, 15.9 mmol).

Following an adapted literature procedure,[3] an oven-dried two-neck round bottom flask equipped with a stir bar, an oven-dried distillation adapter, and a KOH trap was charged with purified 7-amino-4-methyl-2*H*-chromen-2-one (509 mg, 2.91 mmol), triphosgene (287 mg, 0.969 mmol), and DCM (42 mL) under nitrogen. **CAUTION: TRIPHOSGENE IS TOXIC. ALL OPERATIONS ARE CARRIED OUT EXCLUSIVELY INSIDE A FUME HOOD.** The suspension was cooled to 0 °C in an ice bath and then triethylamine (0.81 mL, 5.81 mmol) was added dropwise, which caused the reaction to become homogeneous. The solution was warmed to room temperature and stirred for 1 h, during which time a white precipitate formed. The solid precipitate was removed by vacuum filtration under nitrogen and discarded (see Figure S11). The filtrate was concentrated under reduce pressure, the resulting solid was suspended in anhydrous THF (60 mL), and residual insoluble solid was filtered off and discarded again using a similar apparatus as the one illustrated in Figure S11. The filtrate was concentrated under reduce pressure to afford the title compound as a white solid (527 mg, 90% yield).

TLC (50% ethyl acetate/hexanes): R_f = 0.43

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.55 (*d*, J = 8.3, 1H), 7.10 – 6.96 (m, 2H), 6.27 (s, 1H), 2.43 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 160.4, 154.3, 151.9, 136.9, 125.8, 125.7, 121.3, 118.0, 114.7, 113.1, 18.8 ppm.

HRMS (ESI, m/z): calcd for $[C_{11}H_8NO_3]^+$ $(M+H)^+$, 202.0499; found, 202.0495.

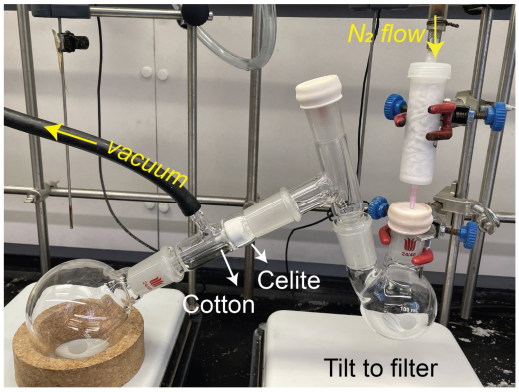


Figure S11. Experimental setup used in the preparation of 7-isocyanato-4-methyl-2*H*-chromen-2-one (i.e., 4-methylcoumarin-7-isocyanate).

2-(4-(4-(4-((2-bromo-2-methylpropanoyl)oxy)-1-hydroxybutyl)-2-methoxyphenoxy)-7-((((4-methyl-2-oxo-2H-chromen-7-yl)carbamoyl)oxy)methyl)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-epoxyisoindol-2-yl)ethyl 2-bromo-2-methylpropanoate (S4). A round bottom flask equipped with a stir bar was charged with compound **7** (166 mg, 0.223 mmol), 4-methylcoumarin-7-isocyanate (44.8 mg, 0.223 mmol), and DCM (5 mL). The solution was cooled to 0 °C in an

ice bath before adding DMAP (0.272 mg, 0.0022 mmol). The mixture was warmed to room temperature and stirred for 1 h. The mixture was then diluted with DCM (100 mL), washed with 10% NH_4Cl (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (40–60% EtOAc/hexanes) to afford the title compound (mixture of diastereomers) as a white foamy solid (193 mg, 91% yield).

TLC (75% ethyl acetate/hexanes): R_f = 0.34

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (s, 1H), 7.50 (d, *J* = 10.3 Hz, 3H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.94 (dd, *J* = 4.9, 1.9 Hz, 1H), 6.80 – 6.67 (m, 1H), 6.45 (dd, *J* = 5.8, 3.6 Hz, 1H), 6.36 (d, *J* = 5.8 Hz, 1H), 6.15 (s, 1H), 4.74 (ABq, $\Delta\nu_{AB}$ = 33.5 Hz, J_{AB} = 10 Hz, 2H), 4.65 (t, *J* = 6.0 Hz, 1H), 4.25 – 4.09 (m, 4H), 3.91 (d, *J* = 7.9 Hz, 1H), 3.84 – 3.79 (m, 4H), 3.77 – 3.60 (m, 2H), 2.53 (br s, 1H), 2.39 (s, 3H), 1.89 (s, 6H), 1.85 (d, *J* = 3 Hz, 6H), 1.83 – 1.66 (m, 4H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 173.8, 173.3, 171.8, 171.5, 161.3, 154.3, 152.6, 152.5, 151.54, 151.48, 142.82, 142.75, 142.4, 141.7, 135.8, 135.6, 135.5, 125.4, 123.2, 123.0, 118.0, 117.9, 115.6, 114.2, 114.1, 113.1, 110.21, 110.16, 106.3, 83.98, 83.96, 73.5, 65.8, 62.9, 62.5, 56.2, 56.1, 55.6, 50.5, 49.1, 37.6, 35.24, 35.23, 30.8, 30.7, 24.9, 18.7 ppm.

HRMS (FD, m/z): calcd for $[C_{41}H_{44}Br_2N_2O_{14}]^{+\bullet}$ $(M)^{+\bullet}$, 946.1159; found, 946.1162.

2-(4-(4-(4-((2-bromo-2-methylpropanoyl)oxy)-1-((((4-methyl-2-oxo-2H-chromen-7-yl)oxy)carbonyl)oxy)butyl)-2-methoxy phenoxy)-7-((((4-methyl-2-oxo-2H-chromen-7-yl)carbamoyl)oxy)methyl)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-epoxyisoindol-2-yl)ethyl 2-bromo-2-methylpropanoate (8). A two-neck round bottom flask equipped with a stir bar was charged with compound **S4** (98.0 mg, 0.104 mmol), DCM (2 mL), and pyridine (17 µL, 0.21 mmol) were added. The solution was cooled to 0 °C in an ice bath before adding a solution of 4-methylcoumarin-7-chloroformate[4] (29.6 mg, 0.124 mmol) in DCM (1 mL) dropwise. The mixture was then warmed to room temperature, and stirred for 1 h. The mixture was then diluted with DCM (100 mL), washed with 10% NH_4Cl (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (0–10% MeOH/DCM) followed by a reverse-phase chromatographic separation on a C18 column (65–85% acetonitrile/H_2O) to afford the title compound (mixture of diastereomers) as a white foamy solid (63 mg, 53% yield).

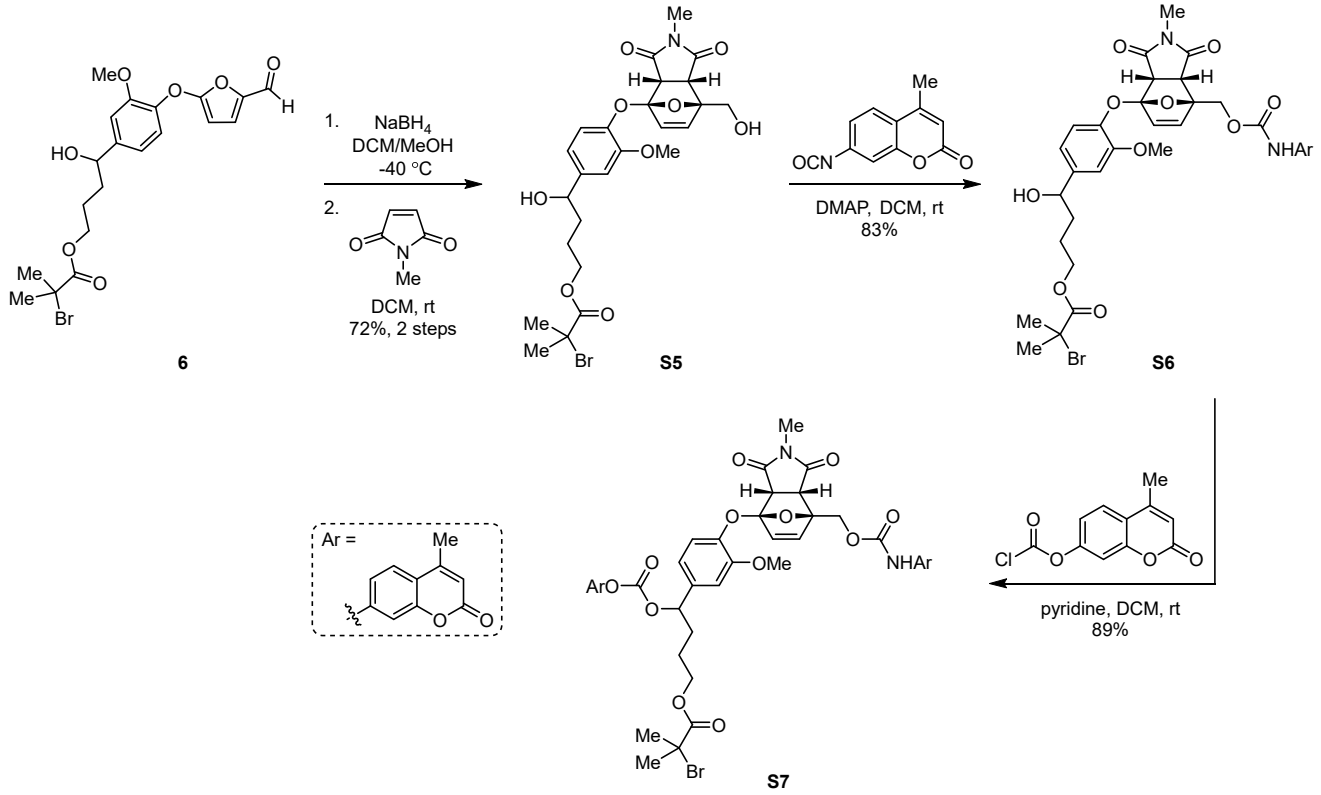
TLC (86% ethyl acetate/hexanes): R_f = 0.25

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.49 (m, 4H), 7.22 (dd, *J* = 8.3, 2.7 Hz, 1H), 7.16 – 7.06 (m, 2H), 6.94 (dd, *J* = 4.7, 2.0 Hz, 1H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.50 – 6.38 (m, 2H), 6.24 (s, 1H), 6.16 (s, 1H), 5.64 (t, *J* = 6.8 Hz, 1H), 4.79 (ABq, $\Delta\nu_{AB}$ = 38.7 Hz, J_{AB} = 12.5 Hz, 2H), 4.27 – 4.13 (m, 4H), 3.95 (d, *J* = 7.9 Hz, 1H), 3.89 – 3.82 (m, 4H), 3.75 – 3.62 (m, 2H), 2.40 (d, *J* = 4.1 Hz, 6H), 2.19 – 2.09 (m, 1H), 2.04 – 1.95 (m, 1H), 1.91 (s, 6H), 1.86 (d, *J* = 2.9 Hz, 6H), 1.82 – 1.77 (m, 1H), 1.74 – 1.67 (m, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 173.6, 173.3, 171.7, 171.4, 161.2, 160.4, 154.4, 154.1, 153.2, 152.50, 152.46, 152.2, 152.0, 151.7, 151.6, 143.50, 143.46, 141.6, 136.54, 136.52, 135.8, 135.6, 125.6, 125.5, 123.24, 123.21, 118.9, 118.7, 118.1, 117.3, 115.7, 114.7, 114.0, 113.2, 111.0, 110.9, 109.8, 106.3, 84.1, 80.81, 80.79, 65.1, 62.9, 62.5, 56.4, 56.0, 55.6, 50.6, 49.1, 37.7, 32.6, 30.8, 30.68, 30.67, 24.6, 18.8, 18.7 ppm.

HRMS (FD, m/z): calcd for $[C_{52}H_{50}Br_2N_2O_{18}]^{+\bullet}$ $(M)^{+\bullet}$, 1148.1425; found, 1148.1425.

Scheme S3. Synthesis of Chain-End Control Initiator **S7**.



4-hydroxy-4-(4-((7-(hydroxymethyl)-2-methyl-1,3-dioxo-1,2,3,3a,7,7a-hexahydro-4H-4,7-epoxyisoindol-4-yl)oxy)-3-methoxyphenyl)butyl 2-bromo-2-methylpropanoate (S5). A flame-dried two-neck round bottom flask equipped with a stir bar was charged with compound **6** (664 mg, 1.46 mmol), DCM (7 mL), and anhydrous methanol (7 mL). The solution was cooled to −40 °C in an acetonitrile/dry ice bath before adding $NaBH_4$ (166 mg, 4.37 mmol). The mixture was kept at −40 °C for 2 h before being quenched with 10% NH_4Cl (10 mL) and subsequently warmed to room temperature. The solution was then extracted with DCM (3 x 50 mL) and the organic phase was washed with brine (20 mL). The organic layer was dried over Na_2SO_4, and filtered. *N*-methylmaleimide (211 mg, 1.90 mmol) was then added to the filtrate, which was concentrated under reduced pressure until ~2 mL of viscous solution remained. The mixture was then allowed to react at room temperature for 12 h. The crude reaction mixture was purified by column chromatography (0–10% MeOH/DCM) to afford the title compound (mixture of diastereomers) as a foamy pink solid (598 mg, 72% yield).

TLC (67% ethyl acetate/hexanes): R_f = 0.23

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.15 (d, *J* = 8.1 Hz, 1H), 6.95 (s, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.34 (d, *J* = 5.8 Hz, 1H), 6.30 (d, *J* = 5.8 Hz, 1H), 4.66 (t, *J* = 5.8 Hz, 1H), 4.25 – 4.05 (m, 4H), 3.90 (s, 3H), 3.73 (d, *J* = 7.7 Hz, 1H), 3.66 (d, *J* = 7.7 Hz, 1H), 2.84 (s, 3H), 2.65 (br s, 1H), 2.39 (br s, 1H), 1.91 (s, 6H), 1.86 – 1.68 (m, 4H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 175.0, 173.6, 171.8, 151.73, 151.70, 142.8, 142.51, 142.47, 136.0, 135.9, 135.6, 123.3 123.2, 118.0, 117.9, 114.2, 114.1, 110.4, 86.4, 73.7, 65.8, 61.7, 56.4, 56.1, 50.9, 49.11, 49.09, 35.2, 30.9, 24.9 ppm.

HRMS (ESI, m/z): calcd for $[C_{25}H_{31}BrNO_9]^+$ $(M+H)^+$, 568.1177; found, 568.1177.

4-hydroxy-4-(3-methoxy-4-((2-methyl-7-((((4-methyl-2-oxo-2H-chromen-7-yl)carbamoyl)oxy)methyl)-1,3-dioxo-1,2,3,3a,7,7a-hexahydro-4H-4,7-epoxyisoindol-4-yl)oxy)phenyl)butyl 2-bromo-2-methylpropanoate (S6). A round bottom flask equipped with a stir bar was charged with compound **S5** (338 mg, 0.596 mmol), 4-methylcoumarin-7-isocyanate (120 mg, 0.597 mmol), and DCM (12 mL). After cooling the solution to 0 °C in an ice bath, DMAP (0.728 mg, 0.006 mmol) was added and then the mixture was warmed to room temperature and stirred for 1 h. The mixture was diluted with DCM (100 mL) and washed consecutively with 10% NH_4Cl (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (0–10% MeOH/DCM) followed by a reverse-phase chromatographic separation on a C18 column (40–60% acetonitrile/H_2O) to afford the title compound (mixture of diastereomers) as a foamy pink solid (381 mg, 83% yield).

TLC (80% ethyl acetate/hexanes): R_f = 0.27

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.25 (s, 1H), 7.56 – 7.38 (m, 3H), 7.11 – 7.04 (m, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.72 (t, *J* = 8.6 Hz, 1H), 6.35 (t, *J* = 5.5 Hz, 1H), 6.30 – 6.25 (m, 1H), 6.10 (s, 1H), 4.72 (ABq, $\Delta\nu_{AB}$ = 30.0 Hz, J_{AB} = 12.5 Hz, 2H), 4.62 (s, 1H), 4.20 – 4.04 (m, 2H), 3.88 – 3.71 (m, 5H), 2.87 – 2.74 (m, 4H), 2.36 (s, 3H), 1.86 (s, 6H), 1.83 – 1.63 (m, 4H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 174.3, 173.8, 171.7, 161.3, 154.2, 152.7, 152.6, 151.44, 151.36, 142.8, 142.7, 142.4, 141.7, 135.6, 135.5, 135.4, 125.4, 122.8, 122.7, 117.9, 117.8, 115.4, 114.7, 114.01, 113.98, 112.9, 110.3, 110.2, 106.1, 83.89, 83.88, 73.3, 65.7, 62.8, 56.15, 56.11, 50.4, 49.1, 35.2, 30.7, 24.9, 24.8, 18.6 ppm.

HRMS (ESI, m/z): calcd for $[C_{36}H_{37}BrN_2NaO_{12}]^+$ $(M+Na)^+$, 791.1422; found, 791.1418.

4-(3-methoxy-4-((2-methyl-7-((((4-methyl-2-oxo-2H-chromen-7-yl)carbamoyl)oxy)methyl)-1,3-dioxo-1,2,3,3a,7,7a-hexahydro-4H-4,7-epoxyisoindol-4-yl)oxy)phenyl)-4-((((4-methyl-2-oxo-2H-chromen-7-yl)oxy)carbonyl)oxy)butyl 2-bromo-2-methylpropanoate (S7). A two-neck round bottom flask equipped with a stir bar was charged with compound **S6** (230 mg, 0.299 mmol), DCM (4 mL), and pyridine (48 µL, 0.60 mmol). The solution was cooled to 0 °C in an ice bath before adding a solution of 4-methylcoumarin-7-chloroformate[4] (85.5 mg, 0.359 mmol) in DCM (2 mL) dropwise. The mixture was then warmed to room temperature and stirred for 1 h. The mixture was then diluted with DCM (100 mL), washed with 10% NH_4Cl (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (70–90% EtOAc/hexanes) to afford the title compound (mixture of diastereomers) as a foamy white solid (259 mg, 89% yield).

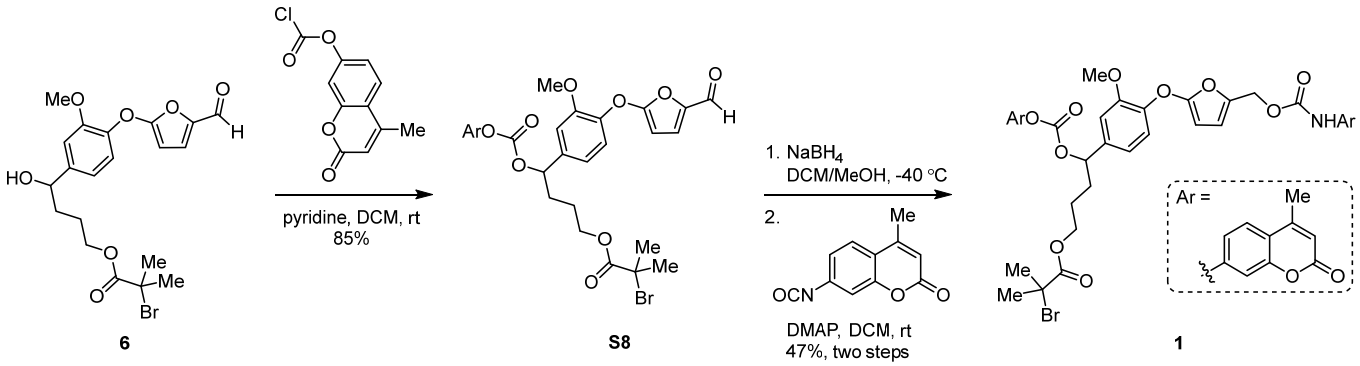
TLC (86% ethyl acetate/hexanes): R_f = 0.21

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 7.0 Hz, 1H), 7.58 – 7.46 (m, 4H), 7.19 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.12 (t, *J* = 2.2 Hz, 1H), 7.08 (dt, *J* = 8.7, 2.6 Hz, 1H), 6.96 – 6.89 (m, 1H), 6.88 – 6.79 (m, 1H), 6.42 (dd, *J* = 5.8, 2.2 Hz, 1H), 6.37 (dd, *J* = 5.8, 1.1 Hz, 1H), 6.22 (s, 1H), 6.14 (s, 1H), 5.62 (t, *J* = 6.8 Hz, 1H), 4.79 (ABq, $\Delta\nu_{AB}$ = 16.0 Hz, J_{AB} = 12.0 Hz, 2H), 4.22 – 4.10 (m, 2H), 3.97 – 3.79 (m, 5H), 2.84 (s, 3H), 2.38 (d, *J* = 5.2 Hz, 6H), 2.16 – 2.05 (m, 1H), 2.03 – 1.93 (m, 1H), 1.89 (s, 6H), 1.82 – 1.63 (m, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 174.0, 173.8, 171.5, 161.2, 160.3, 154.2, 153.9, 153.0, 152.6, 152.5, 152.08, 152.07, 152.0, 151.42, 151.38, 143.5, 143.4, 141.7, 136.23, 136.21, 135.5, 135.4, 125.6, 125.3, 122.6, 122.5, 118.7, 118.5, 117.9, 117.2, 115.4, 114.7, 114.5, 113.8, 112.9, 110.9, 110.7, 109.6, 106.0, 84.1, 80.7, 65.0, 62.7, 56.23, 56.22, 55.9, 50.5, 48.8, 32.5, 30.6, 24.9, 24.4, 18.7, 18.5 ppm.

HRMS (FD, m/z): calcd for $[C_{47}H_{43}BrN_2O_{16}]^{+\bullet}$ $(M)^{+\bullet}$, 970.1796; found, 970.1794.

Scheme S4. Synthesis of Model Compound **1**.



4-(4-((5-formylfuran-2-yl)oxy)-3-methoxyphenyl)-4-((((4-methyl-2-oxo-2H-chromen-7-yl)oxy)carbonyl)oxy) butyl 2-bromo-2-methylpropanoate (S8). A two-neck round bottom flask equipped with a stir bar was charged with furaldehyde **6** (295 mg, 0.647 mmol), DCM (8 mL), and pyridine (131 µL, 1.63 mmol). The solution was cooled to 0 °C in an ice bath before adding a solution of 4-methylcoumarin-7-chloroformate[4] (308 mg, 1.29 mmol) in DCM (5 mL) dropwise. The mixture was then warmed to room temperature, and stirred for 1 h. Afterward, the mixture was diluted with DCM (100 mL) and washed consecutively with 10% NH_4Cl (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (35–50% EtOAc/hexanes) to afford the title compound as a foamy pink solid (364 mg, 85% yield).

TLC (50% ethyl acetate/hexanes): R_f = 0.20

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.35 (s, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.23 – 7.16 (m, 3H), 7.14 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.26 (s, 1H), 5.70 (t, *J* = 6.8 Hz, 1H), 5.48 (d, *J* = 3.8 Hz, 1H), 4.33 – 4.16 (m, 2H), 3.84 (s, 3H), 2.43 (s, 3H), 2.23 – 2.13 (m, 1H), 2.07 – 2.00 (m, 1H), 1.92 – 1.82 (m, 7H), 1.78 – 1.72 (m, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 175.6, 171.6, 163.1, 160.3, 154.1, 153.1, 152.1, 151.9, 151.0, 144.6, 142.6, 138.0, 125.9, 125.6, 121.4, 119.1, 118.0, 117.3, 114.6, 111.4, 109.7, 89.0, 80.5, 65.0, 56.2, 56.0, 32.6, 30.7, 24.5, 18.7 ppm.

HRMS (ESI, m/z): calcd for $[C_{31}H_{30}BrO_{11}]^+$ $(M+H)^+$, 657.0966; found, 657.0971.

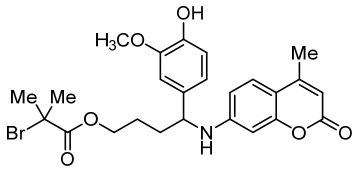
4-(3-methoxy-4-((5-((((4-methyl-2-oxo-2H-chromen-7-yl)carbamoyl)oxy)methyl)furan-2-yl)oxy)phenyl)-4-((((4-methyl-2-oxo-2H-chromen-7-yl)oxy)carbonyl)oxy)butyl 2-bromo-2-methylpropanoate (1). A flame-dried two-neck round bottom flask equipped with a stir bar was charged with furaldehyde **S8** (38.0 mg, 0.0578 mmol), DCM (0.5 mL), and anhydrous methanol (0.5 mL). The solution was cooled to −40 °C in an acetonitrile/dry ice bath before adding $NaBH_4$ (6.6 mg, 0.17 mmol). The mixture was kept at −40 °C for 2 h before being quenched with 10% NH_4Cl (5 mL) and subsequently warmed to room temperature. The solution was then extracted with DCM (3 x 50 mL) and the organic phase was washed with brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was then combined with 4-methylcoumarin-7-isocyanate (12.0 mg, 0.060 mmol) and DCM (1 mL). The solution was cooled to 0 °C in an ice bath before adding DMAP (0.35 mg, 0.00286 mmol). The mixture was warmed to room temperature and stirred for 1 h. The mixture was then diluted with DCM (3 mL) and filtered through celite to remove insoluble 7-amino-4-methylcoumarin. The filtrate was concentrated, dissolved in a small amount of DCM (0.3 mL), and then added into a mixture of diethyl ether (3 mL) and hexanes (6 mL) causing a white precipitate to form. The white solid was isolated using a pipette, washed with hexanes, and finally dried under high vacuum to afford the title compound (23 mg, 47% yield).

TLC (60% ethyl acetate/hexanes): R_f = 0.33

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 8.7 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.35 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.13 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.09 (s, 1H), 7.06 – 7.00 (m, 2H), 6.95 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.42 (d, *J* = 3.3 Hz, 1H), 6.27 (s, 1H), 6.18 (s, 1H), 5.68 (t, *J* = 6.8 Hz, 1H), 5.44 (d, *J* = 3.3 Hz, 1H), 5.08 (s, 2H), 4.29 – 4.16 (m, 2H), 3.91 (s, 3H), 2.41 (d, *J* = 10.1 Hz, 6H), 2.23 – 2.11 (m, 1H), 2.07 – 1.98 (m, 1H), 1.93 (s, 6H), 1.87 – 1.81 (m, 1H), 1.78 – 1.70 (m, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 171.7, 161.3, 160.5, 157.3, 154.4, 154.1, 153.2, 152.8, 152.5, 152.3, 152.0, 150.3, 145.1, 141.6, 141.2, 136.0, 125.6, 125.4, 119.1, 118.8, 118.1, 117.4, 115.5, 114.7, 114.6, 113.11, 113.07, 111.2, 109.9, 106.0, 88.6, 80.8, 65.2, 59.2, 56.3, 56.0, 32.6, 30.8, 24.6, 18.8, 18.7 ppm.

HRMS (ESI, m/z): calcd for $[C_{42}H_{38}BrNNaO_{14}]^+$ $(M+Na)^+$, 882.1368; found, 882.1366.



S1

4-(4-hydroxy-3-methoxyphenyl)-4-((4-methyl-2-oxo-2H-chromen-7-yl)amino)butyl 2-bromo-2-methylpropanoate (S1). Compound **1** (133.0 mg, 0.155 mmol) was dissolved in a 3:1 (v/v) mixture of acetonitrile/methanol (1 mL) and stirred at room temperature. After 48 h, the reaction mixture was concentrated under reduced pressure and the crude mixture was purified by flash chromatography (40–50% EtOAc/hexanes) followed by a reverse-phase chromatographic separation on a C18 column (55–65% acetonitrile/H_2O) to afford the title compound as a yellow solid (5.1 mg, 6% yield).

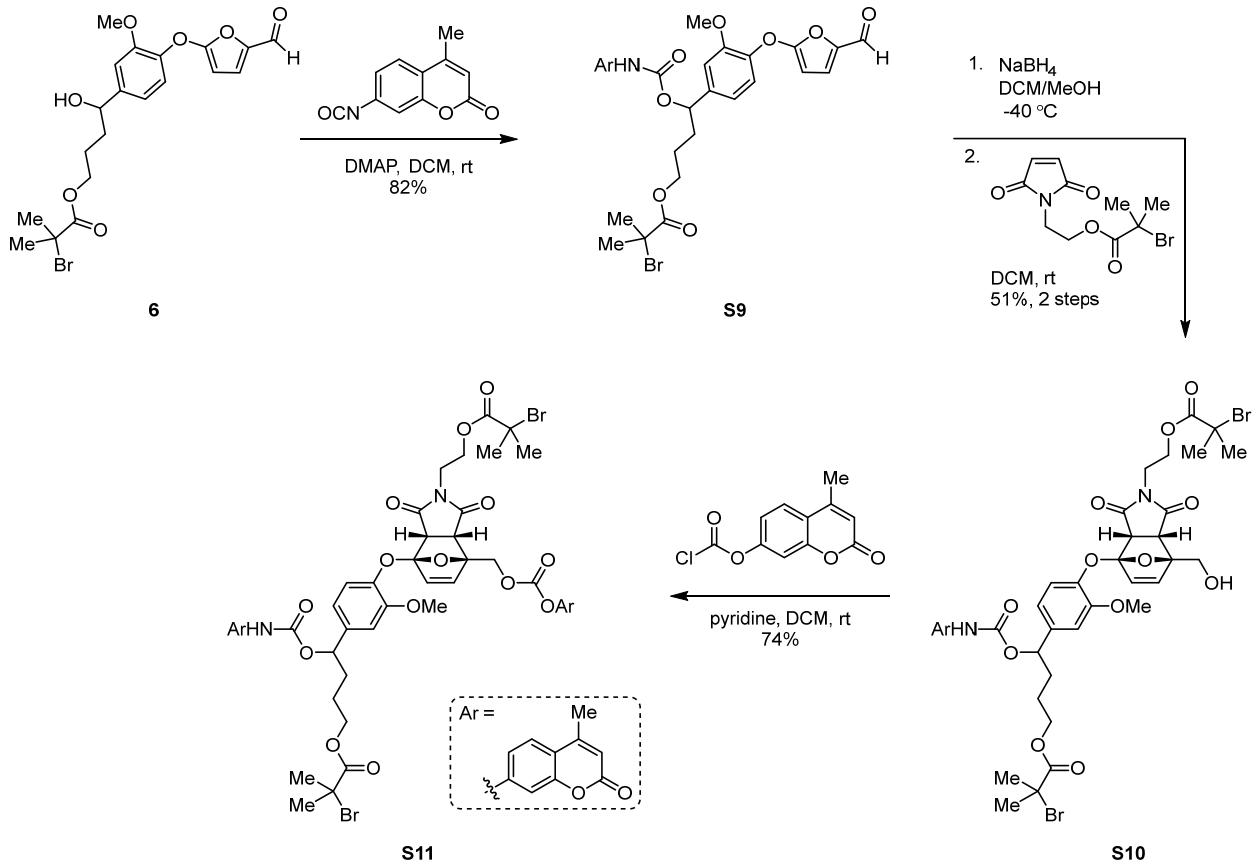
TLC (50% ethyl acetate/hexane): R_f = 0.33

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (d, *J* = 8.7 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.77 – 6.70 (m, 2H), 6.42 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 5.88 (d, *J* = 1.2 Hz, 1H), 5.49 (s, 1H), 4.55 (br s, 1H), 4.25 (t, *J* = 7.2 Hz, 1H), 4.14 (t, *J* = 6.1 Hz, 2H), 3.80 (s, 3H), 2.23 (d, *J* = 1.2 Hz, 3H), 1.96 – 1.59 (m, 10H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 171.8, 162.1, 155.8, 153.1, 150.6, 147.1, 145.1, 134.1, 125.5, 119.1, 114.8, 111.0, 110.9, 109.8, 108.6, 99.4, 65.4, 57.7, 56.1, 34.7, 30.9, 29.8, 25.5, 18.7 ppm.

HRMS (ESI, m/z): calcd for $[C_{25}H_{29}BrNO_6]^+$ $(M+H)^+$, 518.1173; found, 518.1176.

Scheme S5. Synthesis of Bis-Initiator **S11** with Opposite Positions of Cargo Loading.



4-(4-((5-formylfuran-2-yl)oxy)-3-methoxyphenyl)-4-(((4-methyl-2-oxo-2H-chromen-7-yl)carbamoyl)oxy) butyl 2-bromo-2-methylpropanoate (S9). A round bottom flask equipped with a stir bar was charged with compound **6** (400 mg, 0.881 mmol), 4-methylcoumarin-7-isocyanate (265 mg, 1.318 mmol), and DCM (18 mL). The solution was cooled to 0 °C in an ice bath before adding DMAP (1.1 mg, 0.0090 mmol). The mixture was warmed to room temperature and stirred for 1 h. The mixture was then diluted with DCM (150 mL), washed with 10% NH_4Cl (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (30–50% EtOAc/hexanes) to afford the title compound as a foamy white solid (474 mg, 82% yield).

TLC (60% ethyl acetate/hexanes): R_f = 0.38

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.30 (s, 1H), 8.05 (s, 1H), 7.54 – 7.46 (m, 3H), 7.17 (d, *J* = 3.8 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 1.9 Hz, 1H), 6.95 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.14 (s, 1H), 5.76 (t, *J* = 5.4 Hz, 1H), 5.41 (d *J*= 3.8 Hz, 1H), 4.26 – 4.09 (m, 2H), 3.80 (s, 3H), 2.38 (s, 3H), 2.09 – 1.94 (m, 1H), 1.98 – 1.88 (m, 7H), 1.86 – 1.68 (m, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 175.5, 171.7, 163.5, 161.4, 154.3, 152.8, 152.5, 150.8, 144.5, 142.0, 141.9, 139.7, 125.4, 121.3, 118.7, 115.4, 114.6, 112.8, 111.3, 105.9, 88.8, 76.1, 65.2, 56.1, 32.8, 30.7, 24.6, 18.6.ppm.

HRMS(FD, m/z): calcd for $[C_{31}H_{30}BrNO_{10}]^{+\bullet}$ $(M)^{+\bullet}$, 655.1053; found, 655.1075.

2-(4-(4-(4-((2-bromo-2-methylpropanoyl)oxy)-1-(((4-methyl-2-oxo-2H-chromen-7-yl)carbamoyl)oxy)butyl)-2-methoxyphenoxy)-7-(hydroxymethyl)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-epoxyisoindol-2-yl)ethyl 2-bromo-2-methylpropanoate (S10). A flame-dried two-neck round bottom flask equipped with a stir bar was charged with compound **S9** (76.1 mg, 0.116 mmol), DCM (1.6 mL), and anhydrous methanol (1.6 mL). The solution was cooled to −40 °C in an acetonitrile/dry ice bath before adding $NaBH_4$ (13.2 mg, 0.347 mmol). The mixture was kept at −40 °C for 2 h before being quenched with 10% NH_4Cl (5 mL) and subsequently warmed to room temperature. The solution was then extracted with DCM (3 x 50 mL) and the organic phase was washed with brine (20 mL). The organic layer was dried over Na_2SO_4, and filtered. To the filtrate was then added 2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl 2-bromo-2-methylpropanoate[1] (the maleimide ester) (50.2 mg, 0.174 mmol), which was concentrated under reduced pressure until ~2 mL of viscous solution remained. The mixture was then allowed to react at room temperature for 12 h. The crude mixture was purified by column chromatography (60–80% EtOAc/hexanes) to afford the title compound (mixture of diastereomers) as a colorless liquid (56 mg, 51% yield).

TLC (67% ethyl acetate/hexanes): R_f = 0.36

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 2.8 Hz, 1H), 7.53 – 7.39 (m, 3H), 7.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.94 (t, *J* = 1.7 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.41 – 6.33 (m, 2H), 6.14 (d, *J* = 1.4 Hz, 1H), 5.72 (t, *J* = 6.7 Hz, 1H), 4.24 – 4.08 (m, 6H), 3.89 (s, 3H), 3.74 – 3.61 (m, 4H), 2.70 (br s, 1H), 2.36 (s, 3H), 2.07 − 1.95 (m, 2H), 1.90 (s, 6H), 1.87 (s, 6H), 1.80 – 1.64 (m, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 174.4, 173.2, 171.8, 171.5, 161.4, 154.4, 152.7, 152.5, 151.6, 151.5, 143.2, 141.7, 137.70, 137.68, 136.02, 135.97, 135.6, 125.5, 123.3, 123.2, 118.5, 115.5, 114.6, 114.1, 114.0, 113.0, 111.23, 111.19, 105.9, 86.6, 86.5, 65.3, 62.5, 61.58, 61.56, 56.5, 56.1, 55.6, 50.8, 48.93, 48.87, 37.6, 32.63, 32.59, 30.79, 30.75, 30.7, 24.7, 18.7 ppm.

HRMS (FD, m/z): calcd for $[C_{41}H_{45}Br_2N_2O_{14}]^+$ $(M+H)^+$,947.1237; found, 947.1230.

2-(4-(4-(4-((2-bromo-2-methylpropanoyl)oxy)-1-(((4-methyl-2-oxo-2H-chromen-7-yl)carbamoyl)oxy)butyl)-2-methoxyphenoxy)-7-(((((4-methyl-2-oxo-2H-chromen-7-yl)oxy)carbonyl)oxy)methyl)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-epoxyisoindol-2-yl)ethyl 2-bromo-2-methylpropanoate (S11). A two-neck round bottom flask equipped with a stir bar was charged with compound **S10** (112 mg, 0.118 mmol), DCM (1.0 mL), and pyridine (20 µL, 0.25 mmol). The solution was cooled to 0 °C in an ice bath before adding a solution of 4-methylcoumarin-7-chloroformate[4] (36.5 mg, 0.153 mmol) in DCM (1.5 mL) dropwise. The mixture was then warmed to room temperature, and stirred for 1 h. The mixture was then diluted with DCM (100 mL), washed with 10% NH_4Cl (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (50–70% EtOAc/hexanes) to afford the title compound (mixture of diastereomers) as a foamy white solid (100 mg, 74% yield).

TLC (75% ethyl acetate/hexanes): R_f = 0.39

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (br s, 0.5H), 7.93 (br s, 0.5H), 7.61 (t, *J* = 8.2 Hz, 1H), 7.51 – 7.36 (m, 3H), 7.22 – 7.11 (m, 3H), 7.04 – 6.84 (m, 2H), 6.50 – 6.37 (m, 2H), 6.28 (dd, *J* = 10.7, 1.4 Hz, 1H), 6.11 (s, 1H), 5.77 (q, *J* = 6.8 Hz, 1H), 4.97 – 4.69 (m, 2H), 4.22 (t, *J* = 5.2 Hz, 2H), 4.18 – 4.10 (m, 2H), 3.90 (s, 3H), 3.85 – 3.63 (m, 4H), 2.48 – 2.28 (m, 6H), 2.05 – 1.85 (m, 14H), 1.81 – 1.67 (m, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 173.5, 172.6, 171.7, 171.6, 171.4, 161.32, 161.25, 160.7, 160.6, 154.3, 154.0, 153.1, 152.63, 152.58, 152.57, 152.55, 152.5, 152.4, 152.3, 151.64, 151.59, 142.91, 142.88, 142.0, 141.9, 138.6, 138.3, 136.2, 136.1, 135.3, 135.19, 135.18, 125.9, 125.8, 125.33, 125.30, 123.8, 123.5, 118.3, 118.2, 118.07, 118.06, 117.9, 117.63,

117.59, 115.31, 115.26, 114.74, 114.68, 114.51, 114.48, 114.14, 114,10, 112.9, 112.8, 111.2, 111.0, 110.1, 109.92, 109.90, 105.9, 105.8, 83.7, 83.5, 76.2, 76.0, 66.2, 66.13, 66.11, 65.3, 62.50, 62.47, 56.43, 56.39, 56.1, 56.0, 55.6, 50.5, 50.3, 49.8, 49.7, 37. 7, 37.64, 37.62, 33.1, 32.9, 30.73, 30.70, 30.67, 24.61, 24.58, 18.83, 18.82, 18.6 ppm.

HRMS (FD, m/z): calcd for $[C_{52}H_{50}Br_2N_2O_{18}]^{+\bullet}$ $(M)^{+\bullet}$, 1148.1425; found, 1148.1436.

General Procedure A for the Synthesis of Poly(Methyl Acrylate) (PMA) Polymers. Polymers were synthesized by controlled radical polymerization following an adapted procedure by Nguyen *et al.*[5] A flame-dried Schlenk flask equipped with a stir bar was charged with the initiator, DMSO, Me_6TREN, and methyl acrylate. The flask was sealed, the solution was deoxygenated with three freeze-pump-thaw cycles, and then backfilled with nitrogen. The flask was opened briefly under a flow of N_2, and freshly cut copper wire (1.0 cm length, 20 gauge) was added on top of the frozen mixture. The flask was resealed, evacuated for an additional 15 min, warmed to room temperature, and then backfilled with nitrogen. The mixture was stirred at room temperature until the solution became sufficiently viscous, indicating that the desired monomer conversion was reached. Following completion of the polymerization, the flask was then opened to air and the solution was diluted with a minimal amount of DCM. The polymer was precipitated 3× into methanol cooled with dry ice and then dried under vacuum to afford the polymer. GPC traces for each polymer used in this study are shown in Figure S12.

PMA-1. Synthesized using general procedure A with initiator **8** (10.6 mg, 9.23 µmol), DMSO (1.35 mL), Me_6TREN (4.9 µL, 18 µmol), and methyl acrylate (1.35 mL, 14.9 mmol). Polymerization for 3.5 h provided the title polymer as a white solid (633 mg, 49% yield). M_n = 106 kDa, $Đ$ = 1.13.

PMA-Control. Synthesized using general procedure A with initiator **S9** (10.0 mg, 10.3 µmol), DMSO (1.19 mL), Me_6TREN (5.5 µL, 21 µmol), and methyl acrylate (1.19 mL, 13.1 mmol). Polymerization for 3 h provided the title polymer as a white solid (683 mg, 60% yield). M_n = 98 kDa, $Đ$ = 1.15.

PMA-2. Synthesized using general procedure A with initiator **S13** (10.8 mg, 9.41 µmol), DMSO (1.16 mL), Me_6TREN (5.0 µL, 19 µmol), and methyl acrylate (1.16 mL, 12.8 mmol). Polymerization for 1.75 h provided the title polymer as a white solid (570 mg, 52% yield). M_n = 120 kDa, $Đ$ = 1.35.

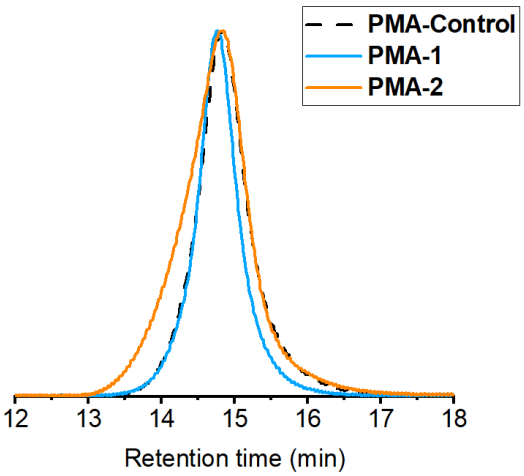


Figure S12. GPC traces (RI response) for the three polymers used in this study: **PMA-control** (M_n = 98 kDa, Đ = 1.15), **PMA-1** (M_n = 106 kDa, Đ = 1.13), and **PMA-2** (M_n = 120 kDa, Đ = 1.35).

IV. General Procedure for Ultrasonication Experiments

An oven-dried sonication vessel was fitted with rubber septa, placed onto the sonication probe, and allowed to cool under a stream of dry argon. The vessel was charged with a solution of the polymer in acetonitrile/methanol (3:1 v/v, 2.0 mg/mL, 20 mL) and submerged in an ice bath. The solution was sparged continuously with argon beginning 15 min prior to sonication and for the duration of the sonication experiment. Pulsed ultrasound (1 s on/1 s off, 30% amplitude, 20 kHz, 16.4 W/cm^2) was then applied to the system. The solution temperature during sonication was measured to be approximately 12–13 °C. Sonicated solutions were filtered through a 0.45 µm syringe filter prior to analysis. Ultrasonic intensity was calibrated using the method described by Berkowski *et al.*[6]

V. Characterization of Aminocoumarin Release Using Photoluminescence Spectroscopy

Aliquots from the sonication experiments were added to a quartz microcuvette. The samples were then monitored with fluorescence spectroscopy at room temperature. Emission spectra were recorded using an excitation wavelength of 365 nm, which selectively excited aminocoumarin **2** in the presence of hydroxycoumarin **3**. A standard calibration curve was constructed to determine the concentration of aminocoumarin **2** (Figure S13).

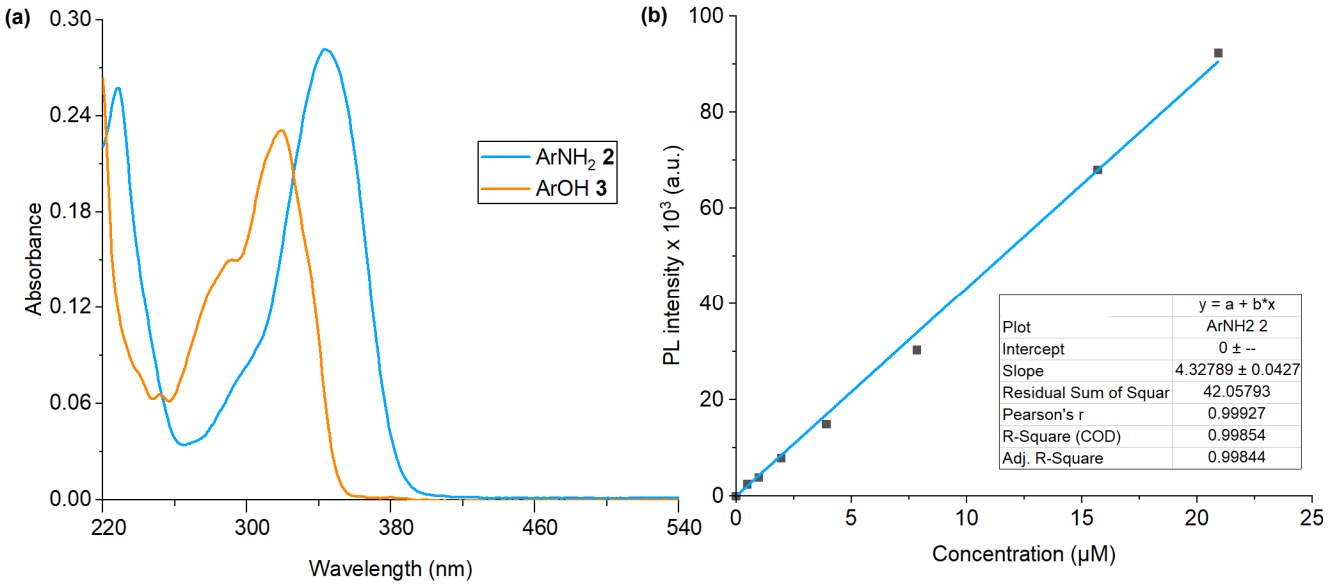


Figure S13. a) UV-vis absorption spectra of $ArNH_2$ **2** and ArOH **3** in acetonitrile/methanol (3:1 v/v). b) Calibration curve for experimental determination of the concentration of $ArNH_2$ **2** (λ_{ex} = 365 nm, λ_{em} = 424 nm) in acetonitrile/methanol (3:1 v/v). A linear regression of the data gives the calibration function: Y = 4328X.

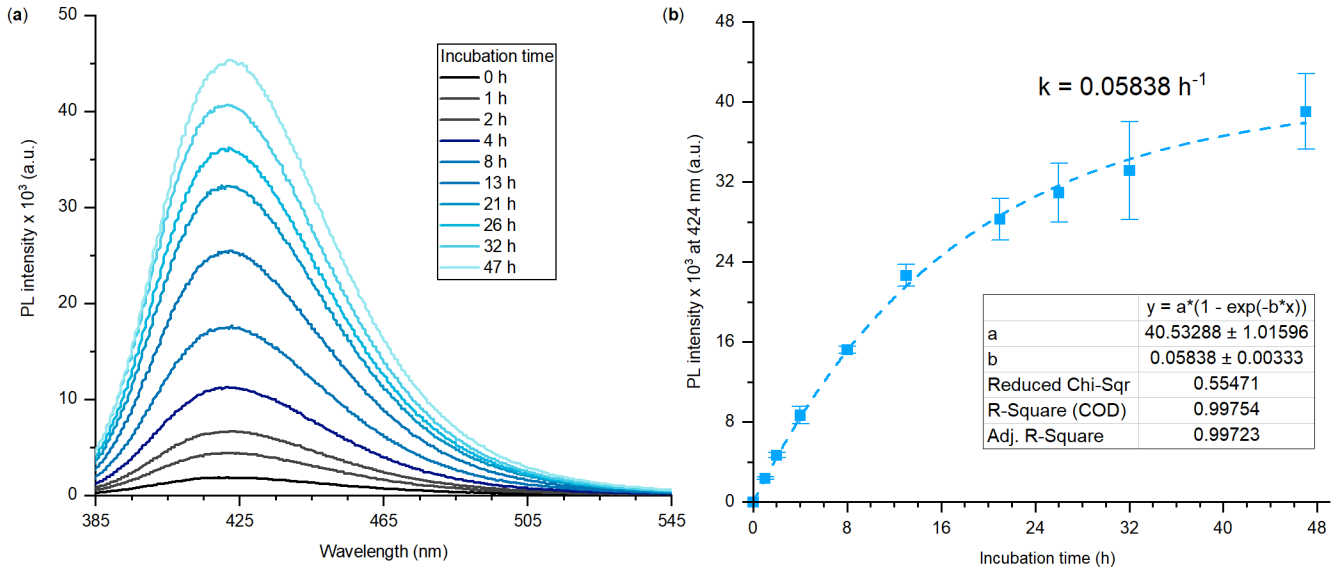


Figure S14. Characterization of the release of $ArNH_2$ **2** from a 2.0 mg/mL solution of **PMA-1** in acetonitrile/methanol (3:1 v/v) by PL spectroscopy immediately after ultrasonication for 60 min (sonication "on" time). a) Representative PL spectra of the sonicated solution at room temperature recorded at the indicated times post-sonication. b) Fluorescence intensity at 424 nm as a function of time. The background fluorescence at the start of monitoring experiment (resulting from the release of $ArNH_2$ **2** during ultrasonication) was subtracted from each measurement. Error bars represent standard deviation from three replicate experiments.

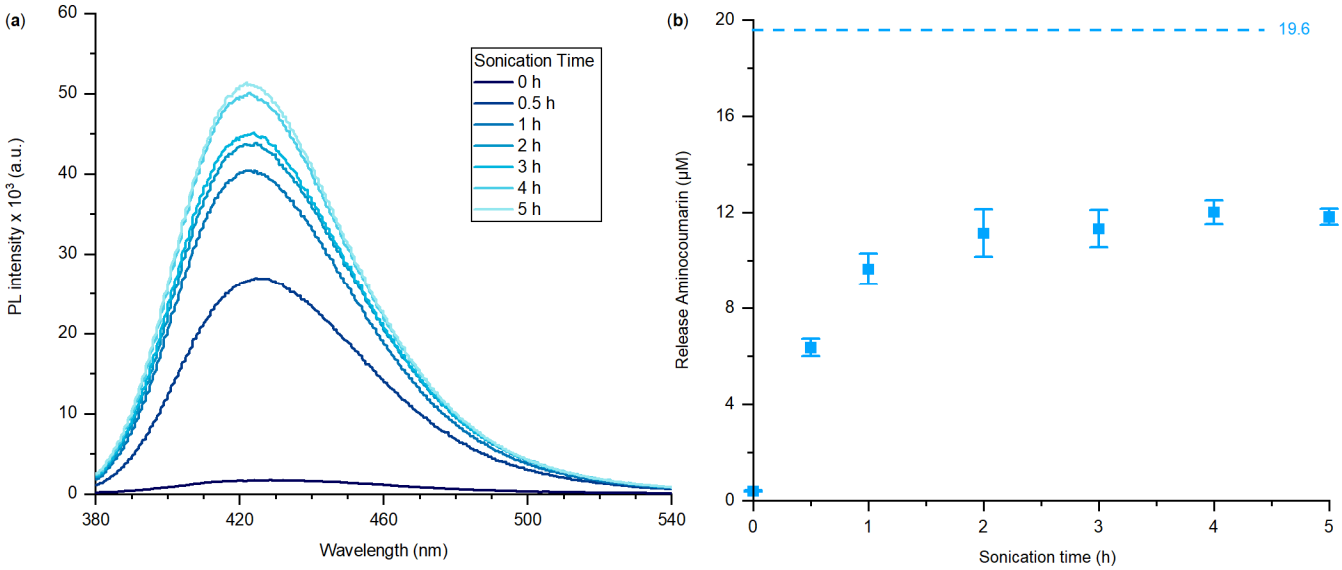


Figure S15. a) Representative PL spectra characterizing the release of $ArNH_2$ **2** from **PMA-1** (2.0 mg/mL in 3:1 MeCN/MeOH) as a function of sonication time. Aliquots were kept at room temperature for 48 h prior to analysis. λ_{ex} = 365 nm. b) Measured concentration of $ArNH_2$ **2** released from **PMA-1** as a function of ultrasonication time calculated from the fluorescence intensity at 424 nm using a standard calibration curve. The theoretical concentration of $ArNH_2$ **2** based on 100% release from the mechanophore is 19.6 μM. Error bars represent standard deviation from three replicate experiments.

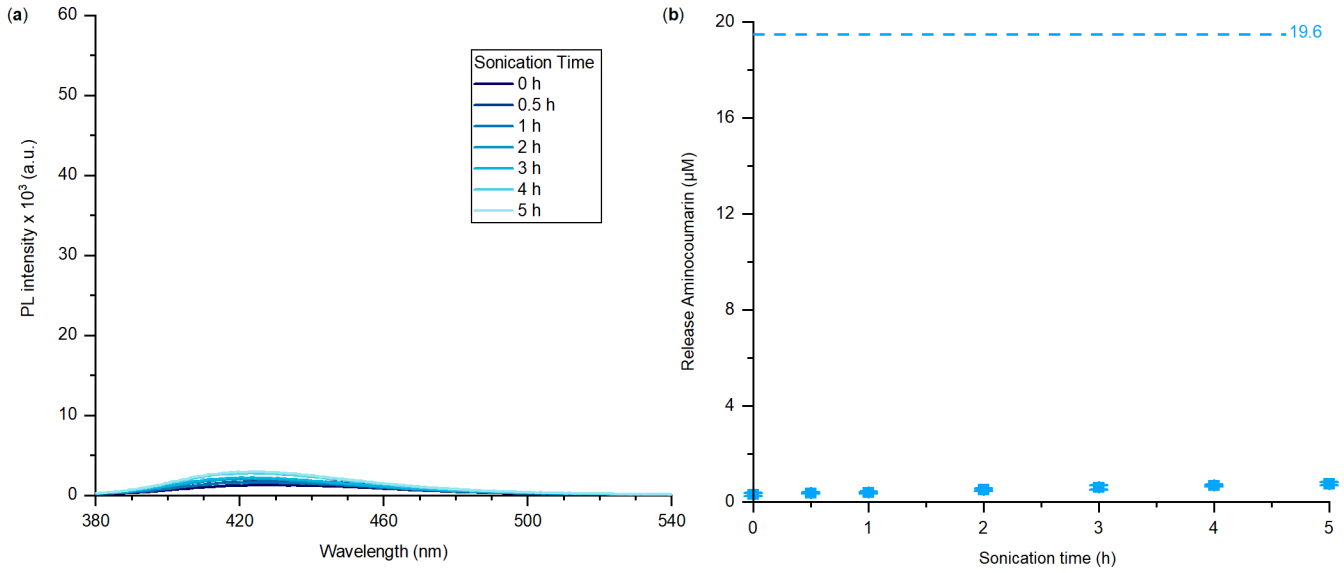


Figure S16. a) Representative PL spectra characterizing the release of $ArNH_2$ **2** from **PMA-Control** (2.0 mg/mL in 3:1 MeCN/MeOH) as a function of sonication time. Aliquots were kept at room temperature for 48 h prior to analysis. λ_{ex} = 365 nm. b) Measured concentration of $ArNH_2$ **2** released from **PMA-Control** as a function of ultrasonication time calculated from the fluorescence intensity at 424 nm using a standard calibration curve. The theoretical concentration of $ArNH_2$ **2** based on 100% release from the mechanophore is 19.6 μM. Error bars represent standard deviation from three replicate experiments.

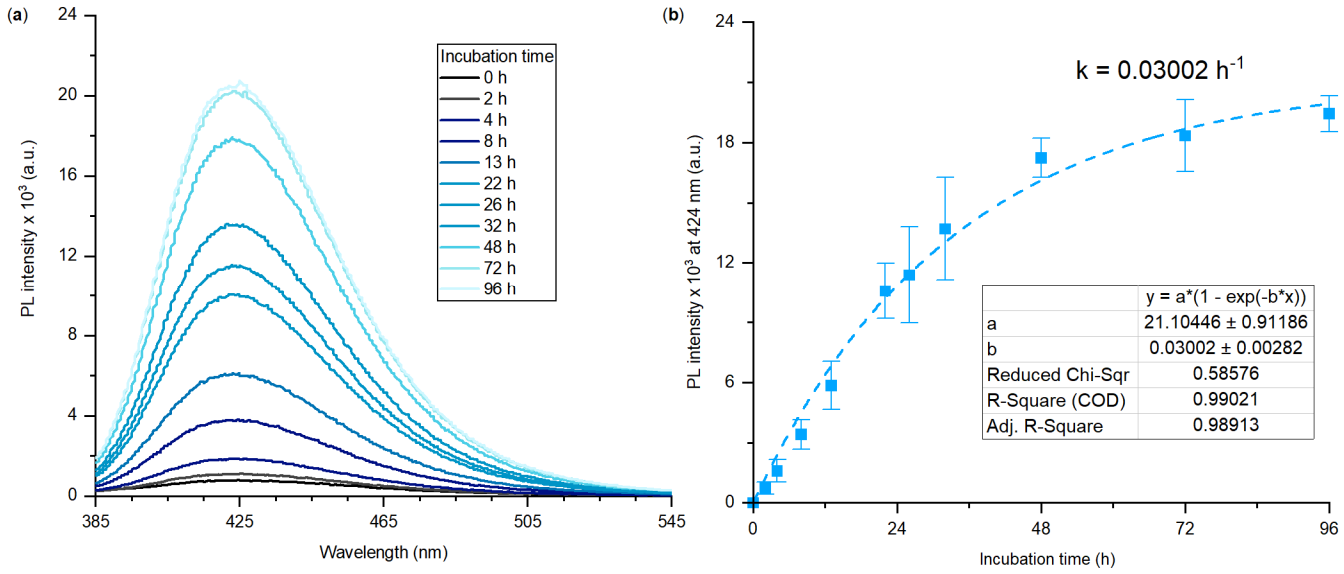


Figure S17. Characterization of the release of $ArNH_2$ **2** from a 2.0 mg/mL solution of **PMA-2** in acetonitrile/methanol (3:1 v/v) by PL spectroscopy immediately after ultrasonication for 60 min (sonication "on" time). a) Representative PL spectra of the sonicated solution at room temperature recorded at the indicated times post-sonication. b) Fluorescence intensity at 424 nm as a function of time. The background fluorescence at the start of monitoring experiment (resulting from the release of $ArNH_2$ **2** during ultrasonication) was subtracted from each measurement. Error bars represent standard deviation from three replicate experiments.

VI. Characterization of Molecular Release Using HPLC

Calculation of relative response factors (RRF). A standard solution with known concentrations of an internal standard (IS, benzocaine) and small molecule analytes ($ArNH_2$ **2** and ArOH **3**) was prepared and analyzed by HPLC equipped with a UV detector (λ = 310 nm). The RRF is calculated from the HPLC results of the standard solution using eq. S1 and was determined to be 0.72 and 1.76, for $ArNH_2$ **2** and ArOH **3**, respectively.

$$\mathrm{RRF} = \frac{\text{response factor of the analyte}}{\text{response factor of the IS}} = \left(\frac{\text{peak area of analyte}}{\text{concentration of analyte}}\right)/\left(\frac{\text{peak area of IS}}{\text{concentration of IS}}\right) \quad \text{(S1)}$$

Determination of the concentration of $ArNH_2$ 2 and ArOH 3 released from polymers after ultrasound-induced mechanochemical activation. Aliquots were removed during ultrasonication experiments and benzocaine (15.28 µM) was added as the internal standard. The solution was then kept at room temperature and analyzed by HPLC at various time intervals (HPLC conditions: 22:78 MeCN/water + 0.1% AcOH, 2 mL/min, λ = 310 nm). The concentration of $ArNH_2$ **2** and ArOH **3** (analytes) in the solution was calculated using eq. S2. A representative HPLC chromatogram is shown below in Figure S18. Data are provided below in Tables S1–S8.

$$\text{concentration of analyte} = \frac{\text{peak area of analyte}}{\text{peak area of IS}} * \frac{1}{\mathrm{RRF}} * \text{concentration of IS} \quad \text{(S2)}$$

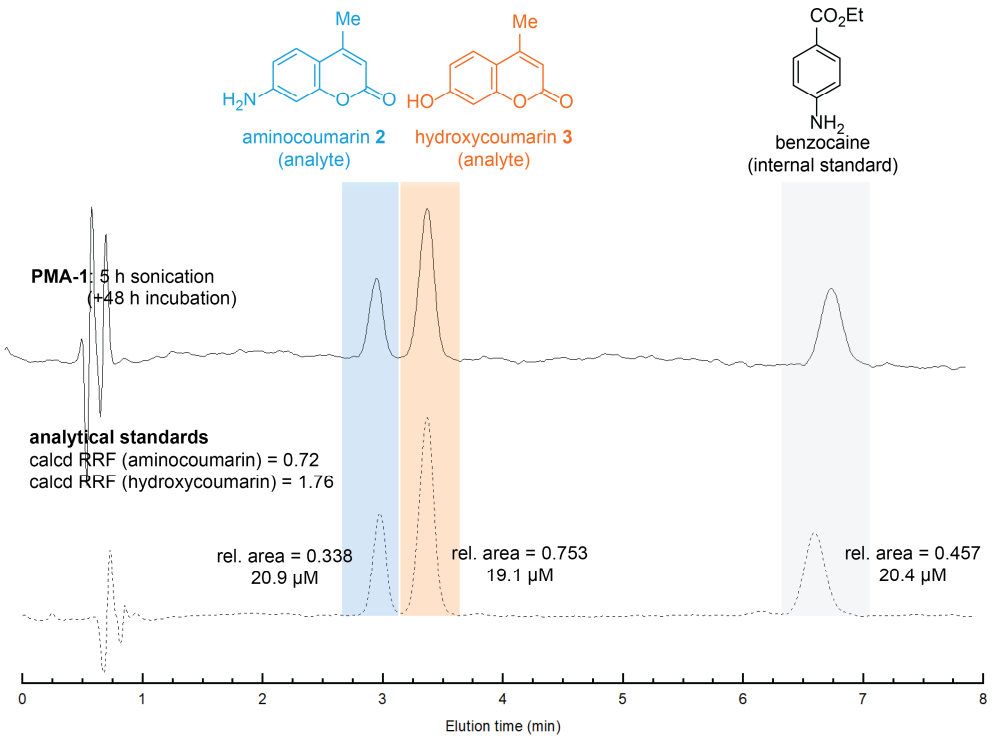


Figure S18. Representative HPLC chromatograms for the analysis of mechanically triggered release of $ArNH_2$ (**2**) and ArOH (**3**) from **PMA-1** containing a chain-centered mechanophore. HPLC conditions: 22:78 MeCN/water + 0.1% AcOH, isocratic, 2 mL/min, λ = 310 nm.

Table S1. Release of $ArNH_2$ 2 from PMA-1 after 60 min of ultrasonication monitored by HPLC.

	Trial 1			Trial 2			Trial 3		
Time Post-Activation (h)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)
0	0.003	0.179	0.4	0.003	0.184	0.3	0.003	0.190	0.4
1	0.006	0.178	0.7	0.009	0.190	1.1	0.009	0.192	1.0
2	0.009	0.182	1.0	0.013	0.173	1.6	0.013	0.182	1.5
4	0.016	0.165	2.0	0.016	0.174	2.0	0.020	0.193	2.2
8	0.018	0.172	2.2	0.038	0.186	4.4	0.037	0.196	4.0
13	0.040	0.179	4.7	0.046	0.170	5.7	0.048	0.193	5.2
21	0.050	0.178	6.0	0.055	0.173	6.7	0.057	0.185	6.6
26	0.061	0.190	6.8	0.058	0.173	7.1	0.065	0.175	7.8
32	0.070	0.188	7.9	0.065	0.180	7.7	0.069	0.170	8.5
47	0.073	0.174	8.8	0.075	0.175	9.1	0.072	0.170	9.0

Table S2. Release of ArOH 3 from PMA-1 after 60 min of ultrasonication monitored by HPLC.

	Trial 1			Trial 2			Trial 3		
Time Post-Activation (h)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)
0	0.008	0.179	0.4	0.014	0.184	0.6	0.010	0.190	0.5
1	0.011	0.178	0.5	0.022	0.190	1.0	0.023	0.192	1.0
2	0.031	0.182	1.5	0.023	0.173	1.1	0.036	0.182	1.7
4	0.039	0.165	2.0	0.035	0.174	1.8	0.041	0.193	1.9
8	0.034	0.172	1.7	0.059	0.186	2.8	0.056	0.196	2.5
13	0.070	0.179	3.4	0.068	0.170	3.4	0.086	0.193	3.9
21	0.091	0.178	4.4	0.102	0.173	5.1	0.103	0.185	4.9
26	0.108	0.190	4.9	0.106	0.173	5.3	0.110	0.175	5.5
32	0.134	0.188	6.2	0.116	0.180	5.6	0.116	0.170	5.9
47	0.133	0.174	6.6	0.130	0.175	6.4	0.134	0.170	6.9

Table S3. Release of $ArNH_2$ 2 from PMA-1 as a function of sonication time monitored by HPLC.[a]

	Trial 1			Trial 2			Trial 3		
Sonication time (h)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)
0	0.001	0.218	0.1	0.001	0.179	0.1	0.001	0.179	0.1
0.5	0.062	0.198	6.7	0.044	0.172	5.4	0.050	0.180	5.9
1	0.074	0.175	9.0	0.075	0.175	9.1	0.072	0.170	9.0
2	0.094	0.196	10.1	0.093	0.181	10.9	0.097	0.177	11.6
3	0.097	0.184	11.2	0.091	0.173	11.2	0.103	0.184	11.9
4	0.115	0.190	12.9	0.095	0.173	11.7	0.103	0.177	12.3
5	0.119	0.191	13.1	0.090	0.158	12.0	0.096	0.162	12.5

[a]Each sample was incubated at rt for 48 h prior to characterization

Table S4. Release of ArOH 3 from PMA-1 as a function of sonication time monitored by HPLC.[a]

	Trial 1			Trial 2			Trial 3		
Sonication time (h)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)
0	0.026	0.218	1.0	0.008	0.179	0.4	0.007	0.179	0.4
0.5	0.106	0.198	4.7	0.093	0.172	4.7	0.105	0.180	0.5
1	0.142	0.175	7.1	0.130	0.175	6.4	0.134	0.170	0.3
2	0.182	0.196	8.1	0.195	0.181	9.4	0.194	0.177	0.8
3	0.197	0.184	9.3	0.188	0.173	9.4	0.209	0.184	1.1
4	0.238	0.190	10.9	0.194	0.173	9.8	0.213	0.177	0.3
5	0.254	0.191	11.5	0.188	0.158	10.3	0.196	0.162	1.0

[a]Each sample incubated at rt for 48 h prior to characterization

Table S5. Release of $ArNH_2$ 2 from PMA-Control as a function of sonication time monitored by HPLC.[a]

	Trial 1			Trial 2			Trial 3		
Sonication time (h)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)
0	0.002	0.167	0.2	0.003	0.180	0.3	0.003	0.189	0.4
0.5	0.005	0.187	0.6	0.003	0.178	0.3	0.004	0.189	0.5
1	0.005	0.182	0.6	0.002	0.169	0.2	0.003	0.207	0.3
2	0.006	0.180	0.7	0.001	0.199	0.1	0.007	0.173	0.8
3	0.005	0.192	0.6	0.002	0.190	0.2	0.009	0.184	1.1
4	0.004	0.177	0.5	0.003	0.190	0.4	0.002	0.182	0.3
5	0.006	0.192	0.7	0.004	0.182	0.4	0.009	0.196	1.0

[a]Each sample incubated at rt for 48 h prior to characterization

Table S6. Release of ArOH 3 from PMA-Control as a function of sonication time monitored by HPLC.[a]

	Trial 1			Trial 2			Trial 3		
Sonication time (h)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)
0	0.019	0.167	1.0	0.013	0.180	0.6	0.015	0.189	0.7
0.5	0.009	0.187	0.4	0.011	0.178	0.5	0.029	0.189	1.3
1	0.014	0.182	0.7	0.021	0.169	1.1	0.014	0.207	0.6
2	0.020	0.180	1.0	0.016	0.199	0.7	0.026	0.173	1.3
3	0.026	0.192	1.2	0.023	0.190	1.1	0.021	0.184	1.0
4	0.013	0.177	0.6	0.018	0.190	0.8	0.016	0.182	0.8
5	0.014	0.192	0.7	0.017	0.182	0.8	0.031	0.196	1.4

[a]Each sample incubated at rt for 48 h prior to characterization

Table S7. Release of $ArNH_2$ 2 from PMA-2 after 60 min of ultrasonication monitored by HPLC.

	Trial 1			**Trial 2**			**Trial 3**		
Time Post-Activation (h)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)
0	0.002	0.225	0.2	0.003	0.235	0.3	0.000	0.173	0.0
2	0.005	0.207	0.5	0.009	0.252	0.8	0.004	0.175	0.4
4	0.007	0.213	0.7	0.011	0.226	1.0	0.009	0.183	1.1
8	0.012	0.214	1.2	0.013	0.215	1.3	0.010	0.185	1.1
13	0.018	0.228	1.7	0.022	0.258	1.8	0.016	0.185	1.8
22	0.028	0.224	2.7	0.030	0.224	2.9	0.029	0.186	3.3
26	0.032	0.233	2.9	0.032	0.239	2.9	0.029	0.185	3.3
32	0.034	0.215	3.3	0.036	0.240	3.1	0.031	0.183	3.6
48	0.044	0.226	4.1	0.048	0.246	4.1	0.042	0.189	4.7
72	0.048	0.243	4.2	0.049	0.241	4.3	0.043	0.188	4.9
96	0.054	0.239	4.7	0.046	0.223	4.4	0.040	0.188	4.5

Table S8. Release of ArOH 3 payload from PMA-2 after 60 min of ultrasonication monitored by HPLC.

	Trial 1			**Trial 2**			**Trial 3**		
Time Post-Activation (h)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)	Payload peak area	IS peak area	Released payload, calcd (μM)
0	0.144	0.225	5.6	0.169	0.235	6.2	0.120	0.173	6.0
2	0.131	0.207	5.5	0.178	0.252	6.2	0.124	0.175	6.2
4	0.141	0.213	5.8	0.164	0.226	6.3	0.122	0.183	5.8
8	0.140	0.214	5.7	0.151	0.215	6.1	0.126	0.185	5.9
13	0.154	0.228	5.9	0.196	0.258	6.6	0.126	0.185	5.9
22	0.152	0.224	5.9	0.166	0.224	6.4	0.128	0.186	6.0
26	0.150	0.233	5.6	0.172	0.239	6.3	0.126	0.185	5.9
32	0.147	0.215	5.9	0.184	0.240	6.6	0.131	0.183	6.2
48	0.144	0.226	5.5	0.178	0.246	6.3	0.131	0.189	6.0
72	0.164	0.243	5.9	0.183	0.241	6.6	0.134	0.188	6.2
96	0.160	0.239	5.8	0.165	0.223	6.4	0.133	0.188	6.1

VII. DFT (CoGEF) Calculations

CoGEF calculations were performed using Spartan '18 Parallel Suite according to previously reported methods.[7,8] Ground state energies were calculated using DFT at the B3LYP/6-31G* level of theory. Starting from the equilibrium geometry of the unconstrained molecule (relative energy = 0 kJ/mol), the distance between the carbon atoms in the terminal methyl groups of the truncated structure was increased in increments of 0.05 Å and the energy was minimized at each step. The maximum force associated with the retro-Diels–Alder reaction was calculated from the slope of the curve immediately prior to bond cleavage.

VIII. References

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(4) Hu, X.; Zeng, T.; Husic, C. C.; Robb, M. J. Mechanically Triggered Small Molecule Release from a Masked Furfuryl Carbonate. *J. Am. Chem. Soc.* **2019**, *141*, 15018–15023.

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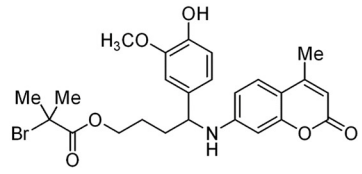
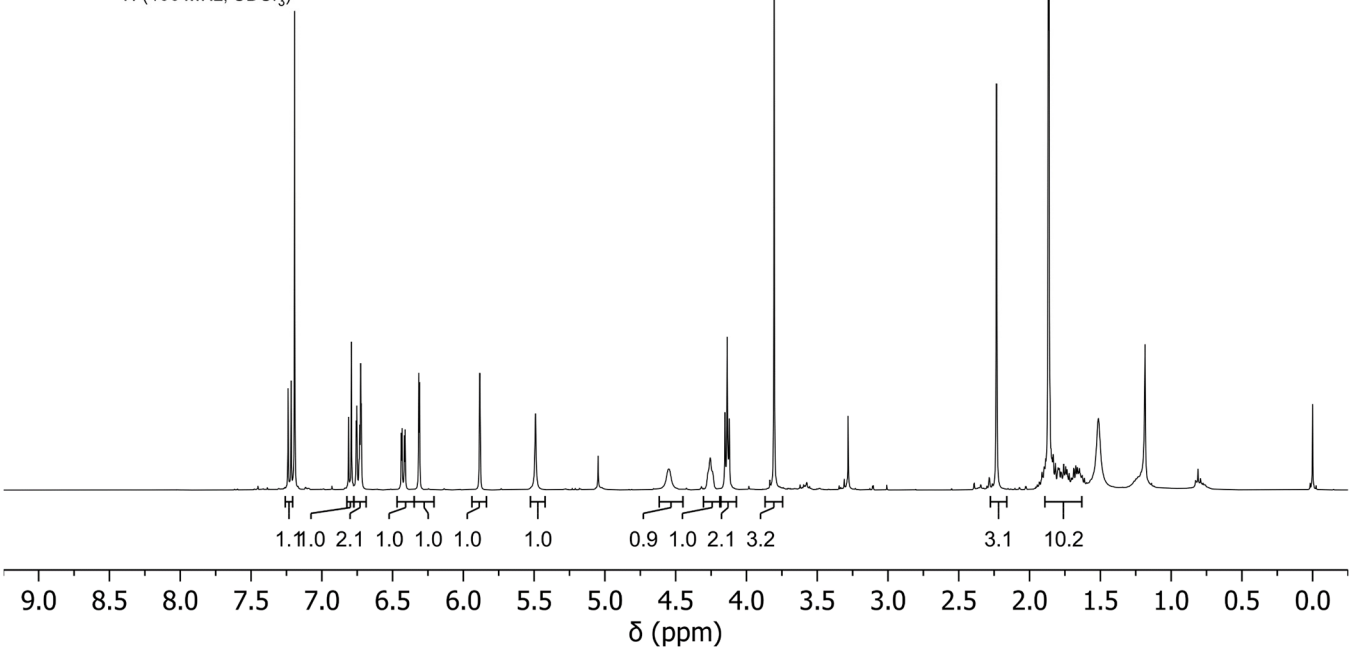
(8) Klein, I. M.; Husic, C. C.; Kovács, D. P.; Choquette, N. J.; Robb, M. J. Validation of the CoGEF Method as a Predictive Tool for Polymer Mechanochemistry. *J. Am. Chem. Soc.* **2020**, *142*, 16364–16381.

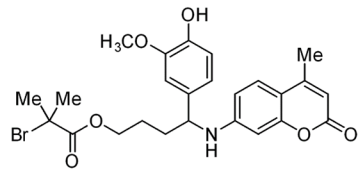
IX. ^{1}H and ^{13}C NMR Spectra



S1

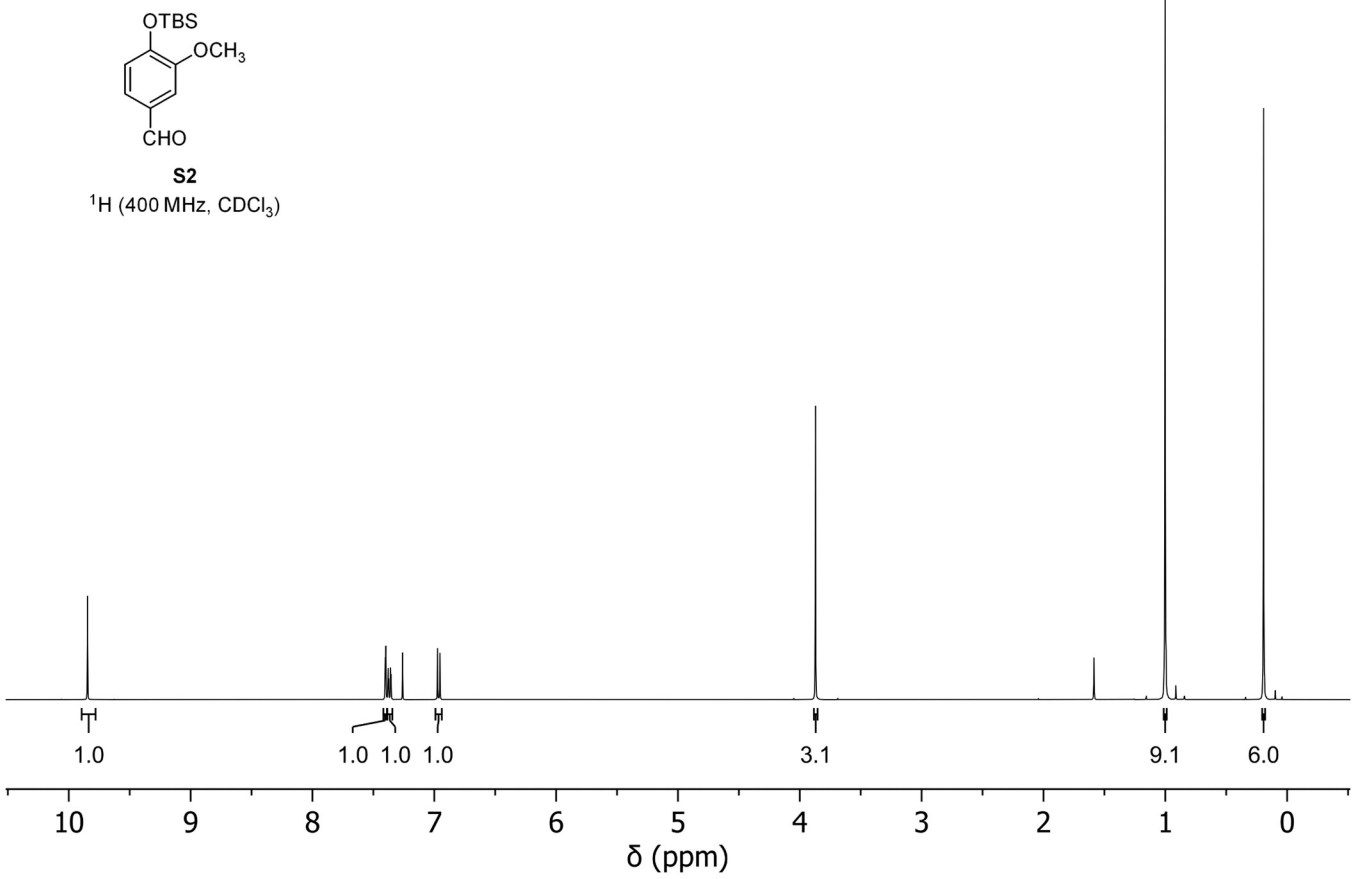
^{1}H (400 MHz, $CDCl_3$)





S1

^{13}C (100 MHz, $CDCl_3$)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OCH3
CHO
S2
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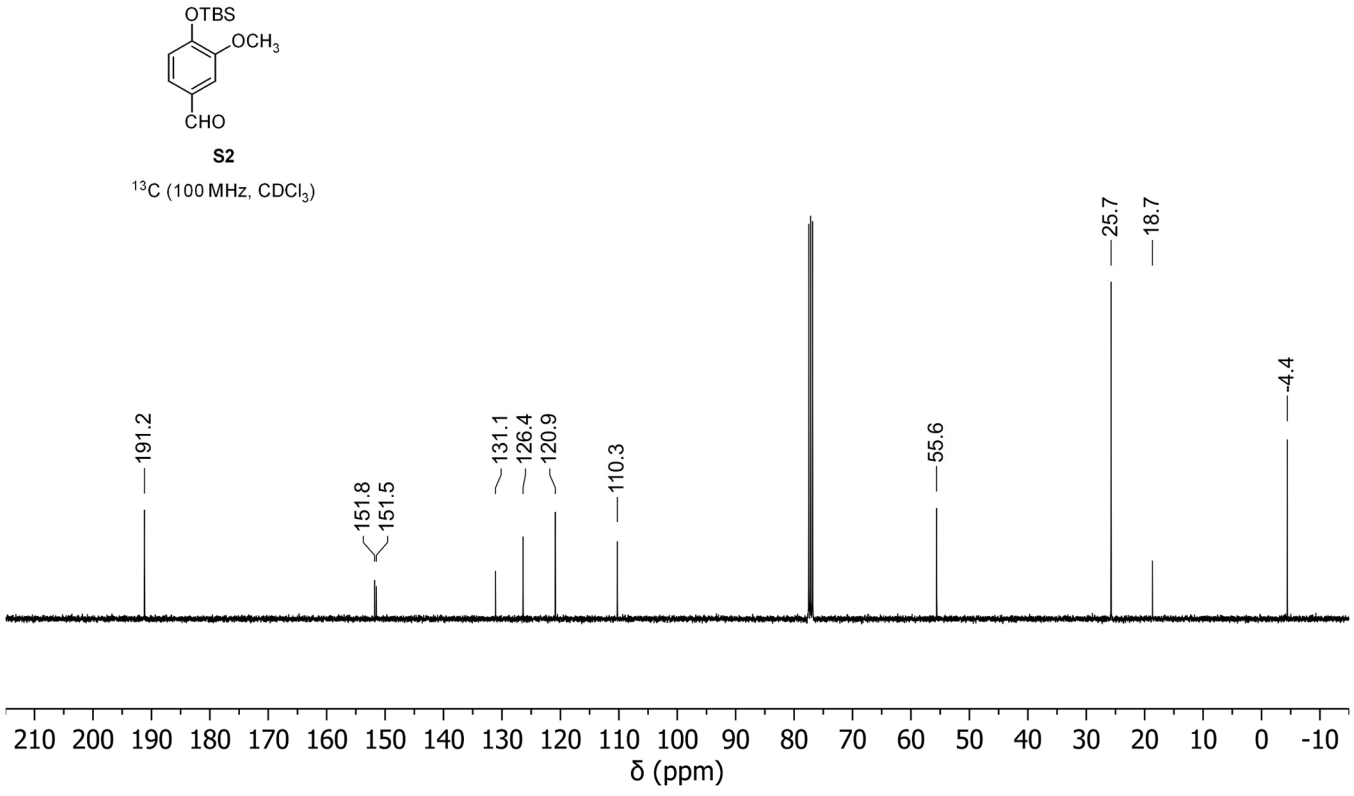
3.1
9.1
6.0
10 9 8 7 6 5 4 3 2 1 0
δ (ppm)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OCH3
CHO
S2
13C (100 MHz, CDCl3)
191.2
151.8
151.5
131.1
126.4
120.9
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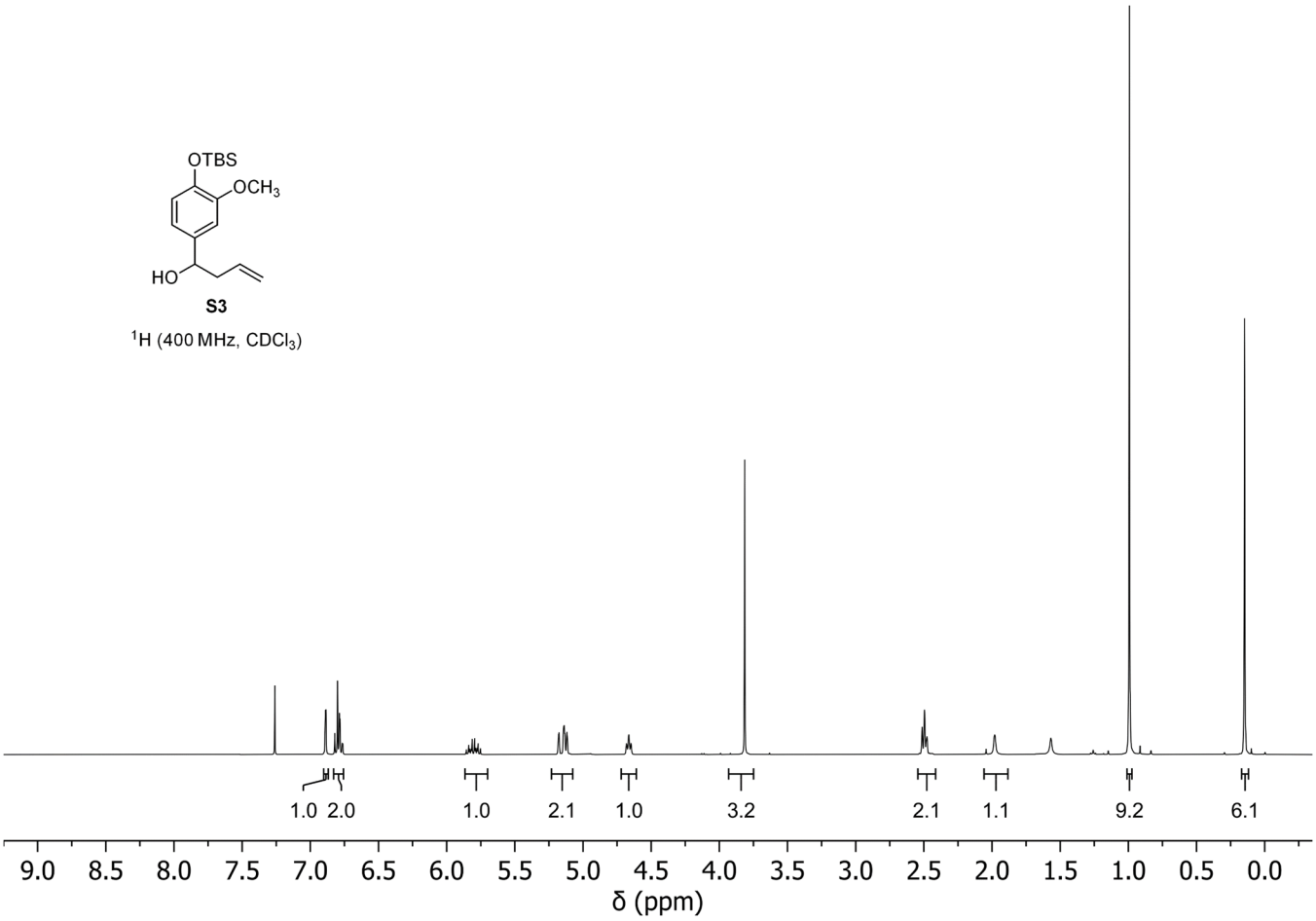
δ (ppm)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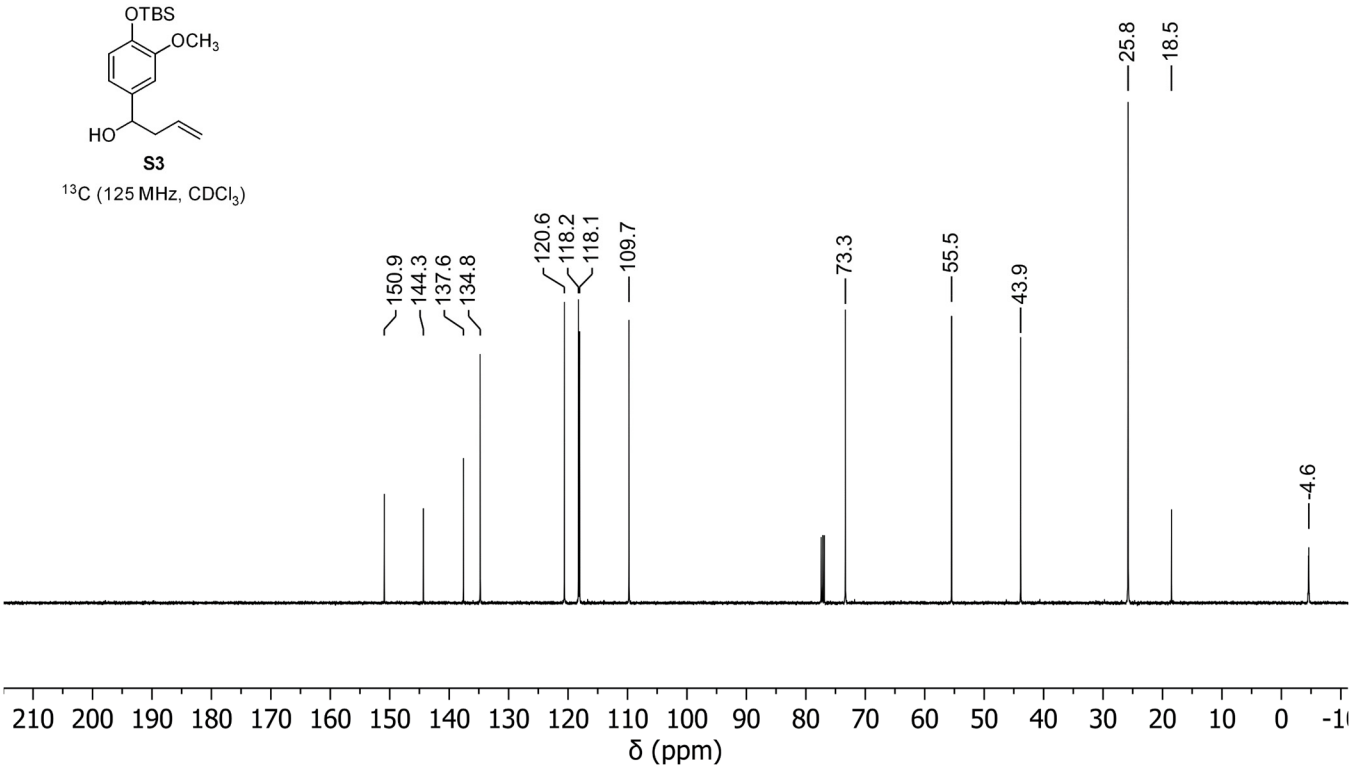
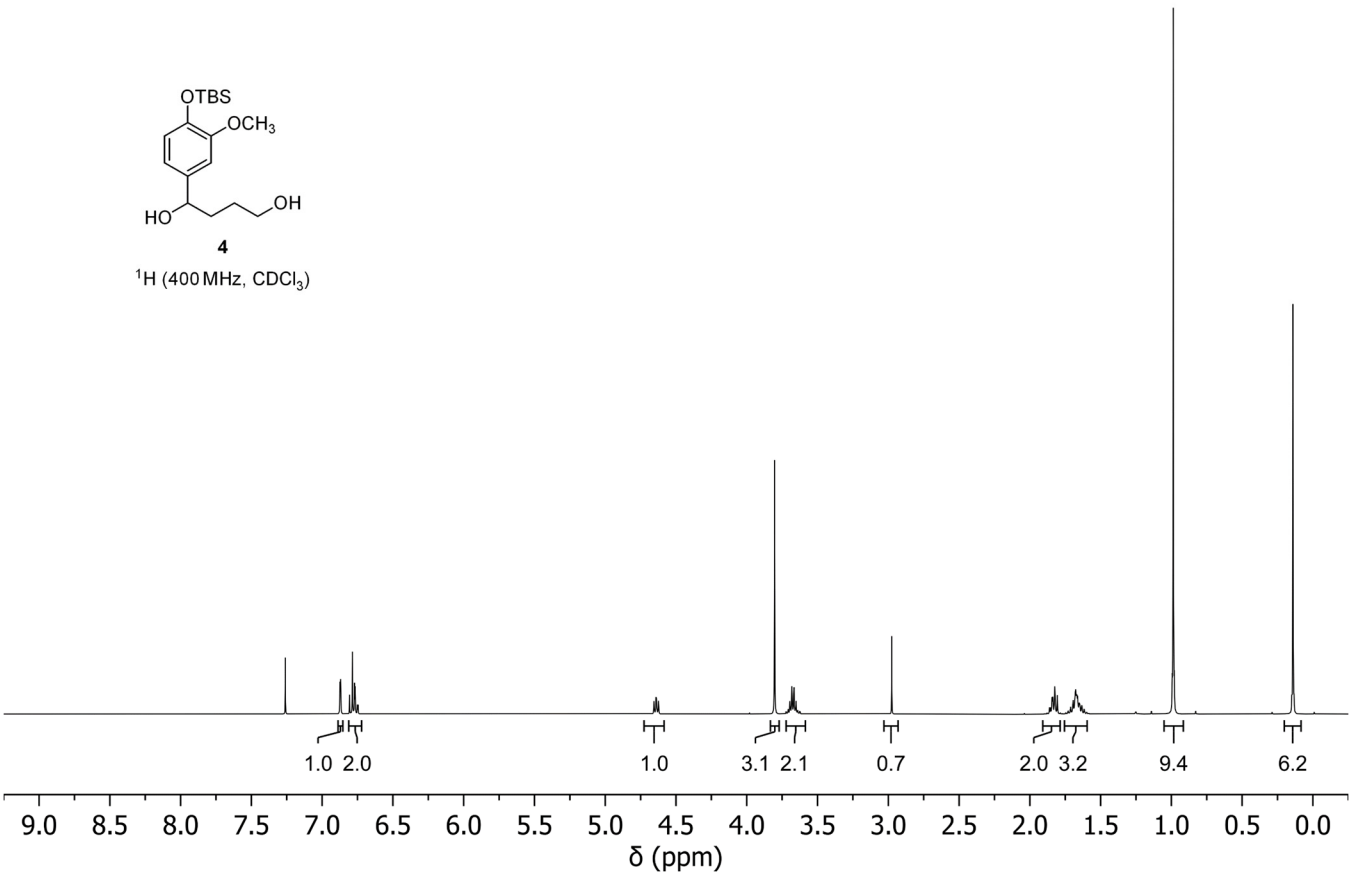
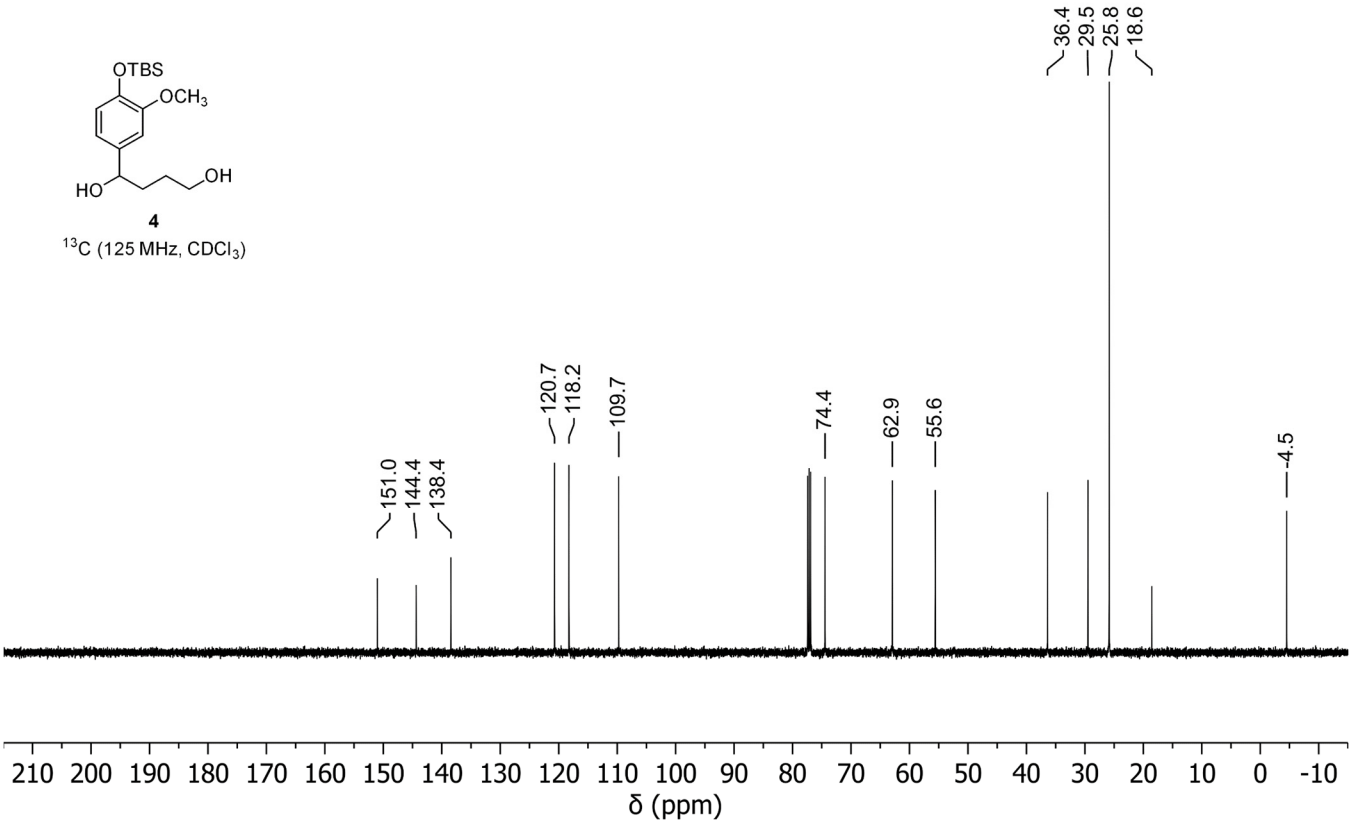
OCH3
HO
S3
1H (400 MHz, CDCl3)
1.0 2.0 1.0 2.1 1.0 3.2 2.1 1.1 9.2 6.1
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)


OTBS
OCH3
HO
S3
13C (125 MHz, CDCl3)
150.9
144.3
137.6
134.8
120.6
118.2
118.1
109.7
73.3
55.5
43.9
25.8
18.5
-4.6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
δ (ppm)


OTBS
OCH3
HO
OH
4
1H (400 MHz, CDCl3)
1.0 2.0
1.0
3.1 2.1
0.7
2.0 3.2
9.4
6.2
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)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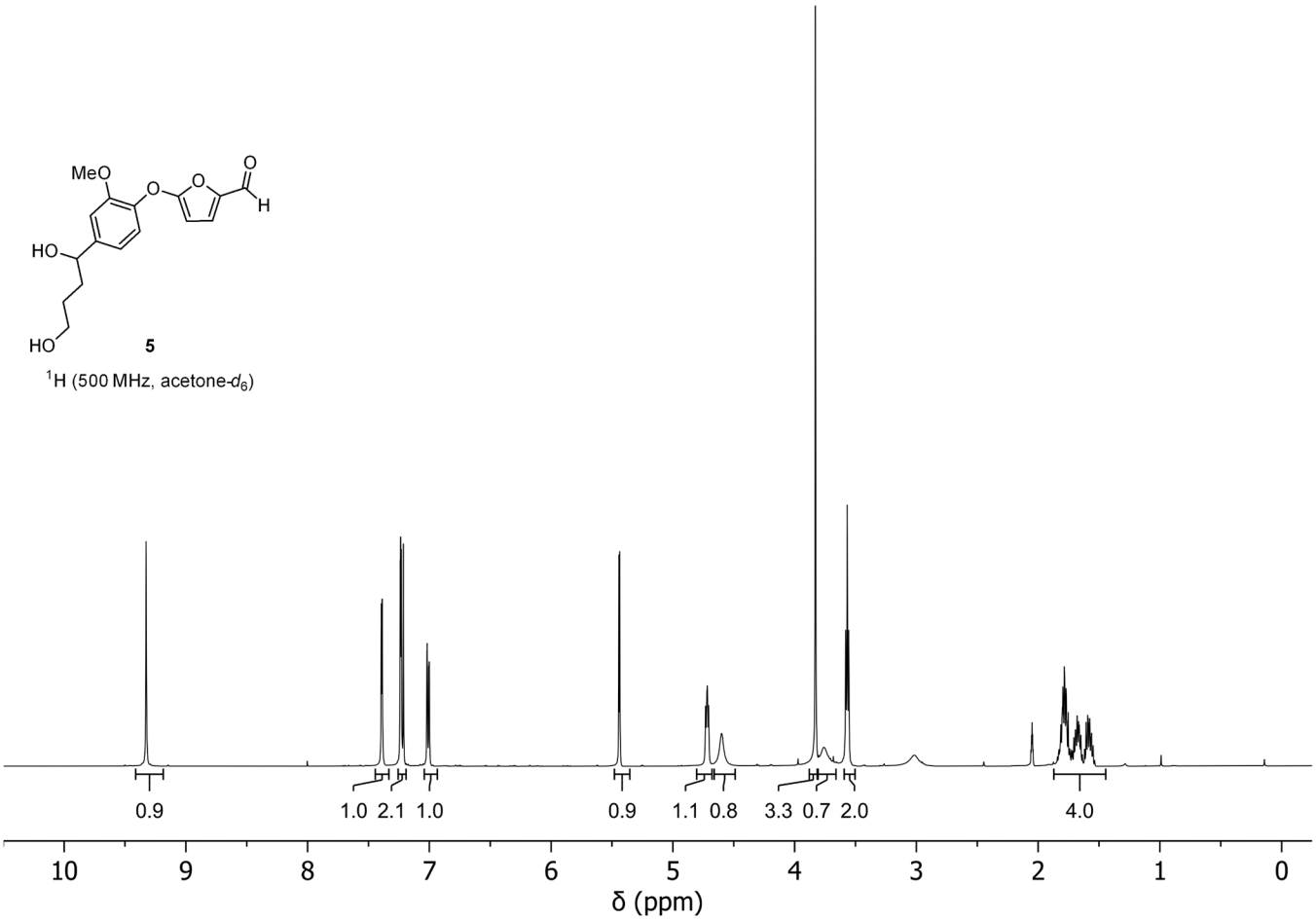
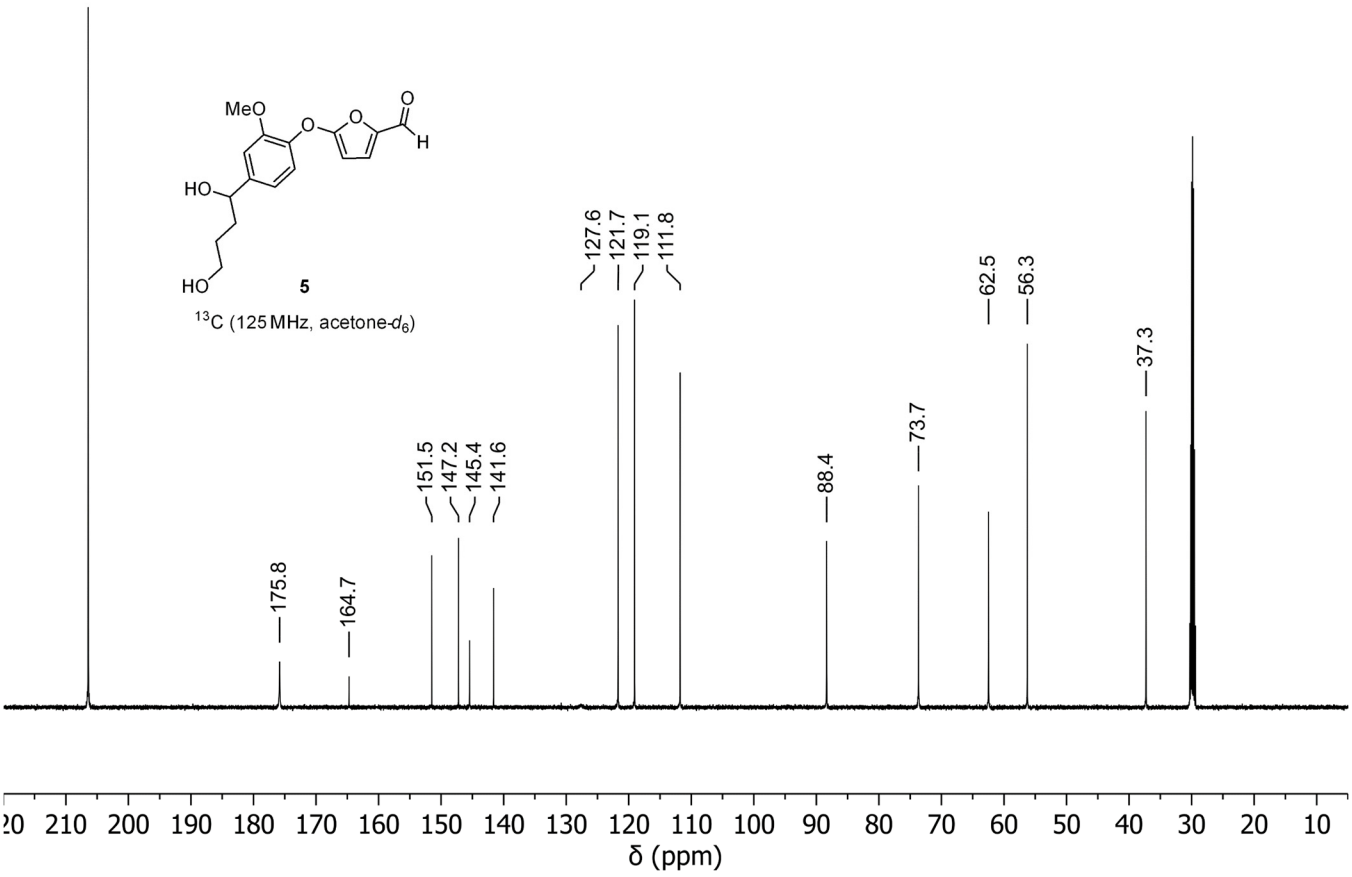
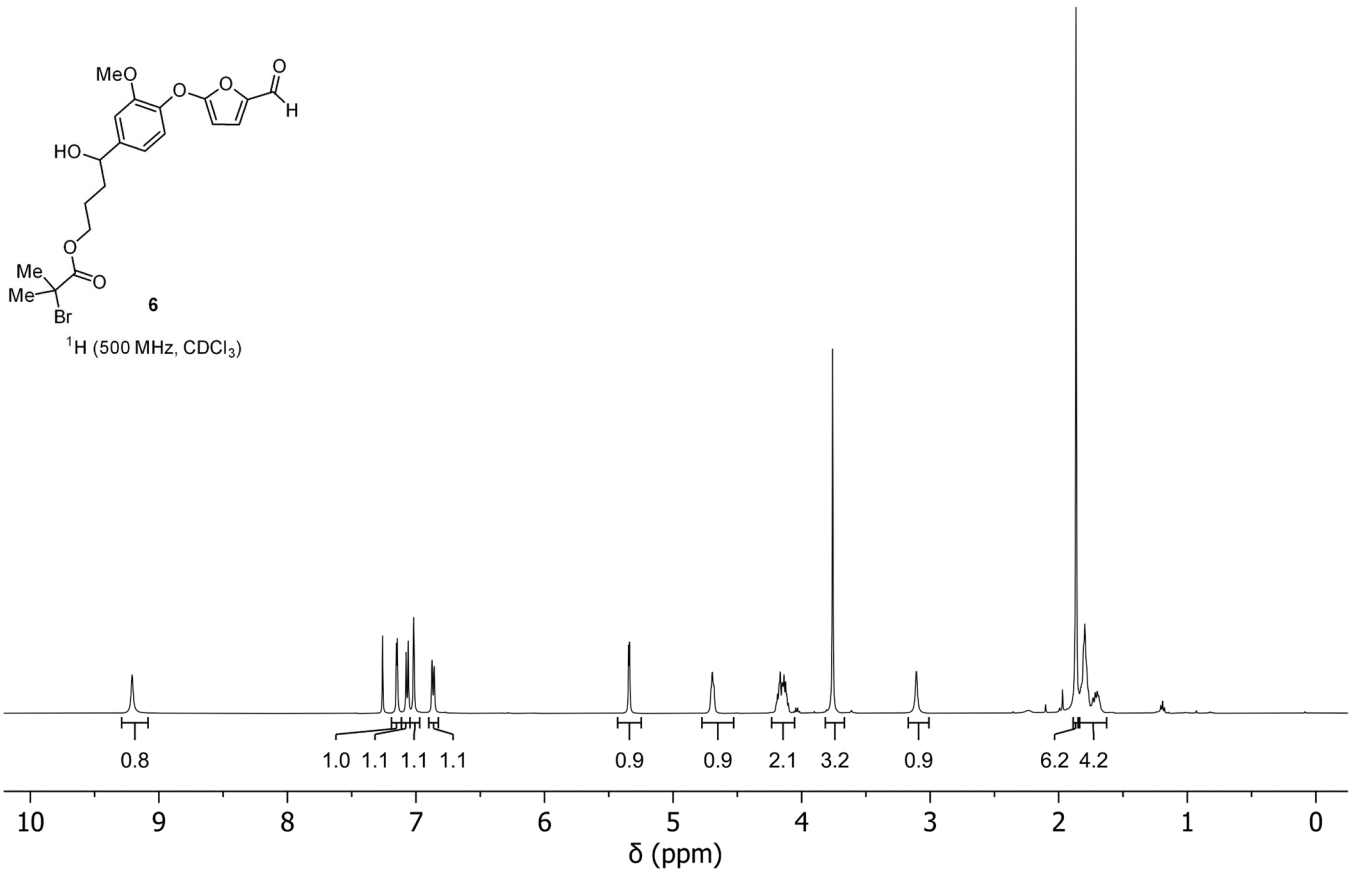
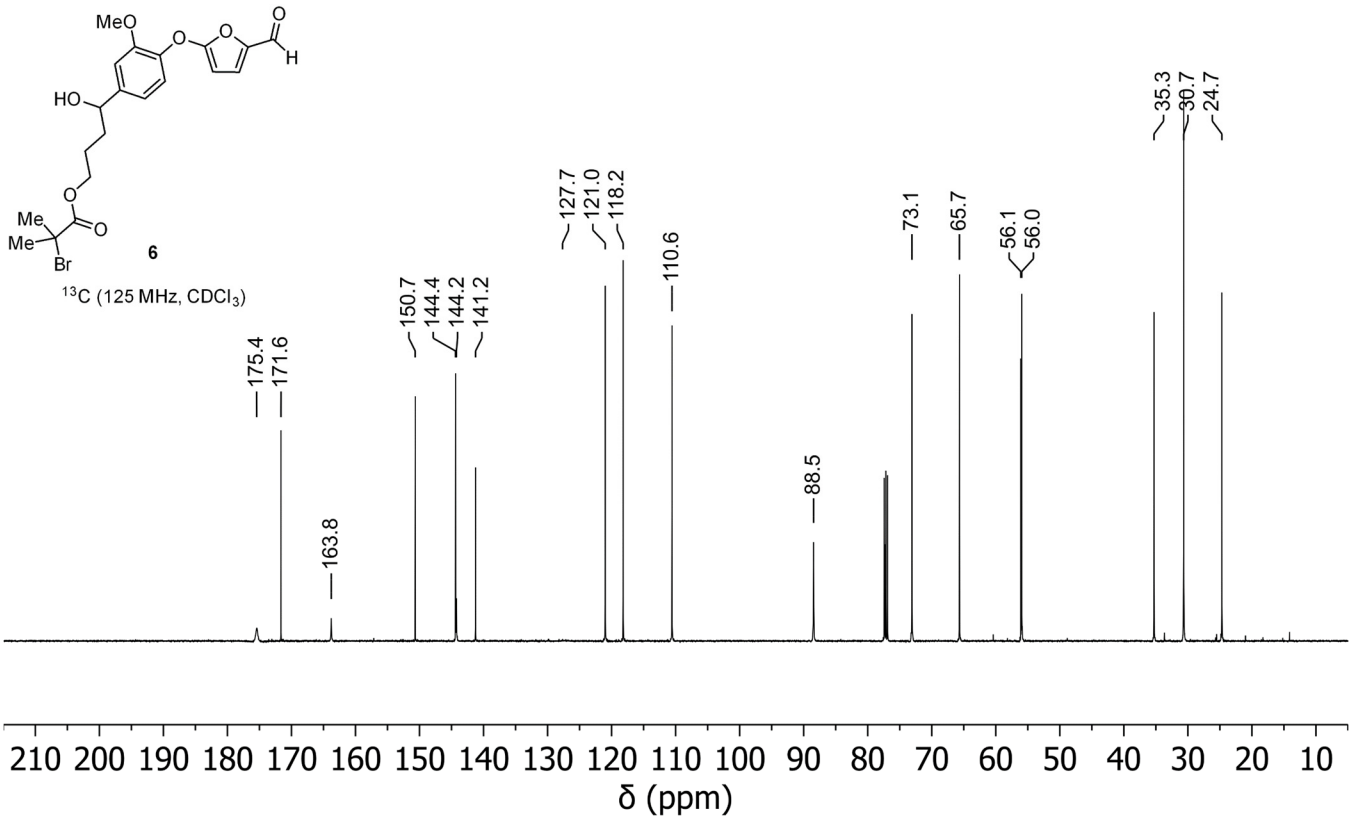
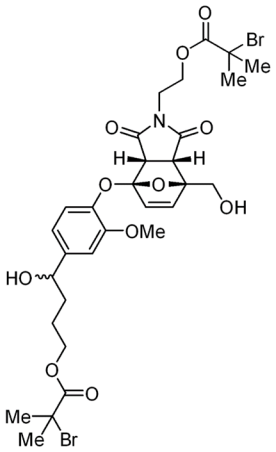
OCH3
HO
OH
4
13C (125 MHz, CDCl3)
36.4
29.5
25.8
18.6
151.0
144.4
138.4
120.7
118.2
109.7
74.4
62.9
55.6
-4.5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)


MeO
O
O
O
H
HO
HO
5
^{1}H (500 MHz, acetone-d_6)
0.9
1.0
2.1
1.0
0.9
1.1
0.8
3.3
0.7
2.0
4.0
10
9
8
7
6
5
4
3
2
1
0
δ (ppm)


MeO
O
O
O
H
HO
HO
5
^{13}C (125 MHz, acetone-d_6)
175.8
164.7
151.5
147.2
145.4
141.6
127.6
121.7
119.1
111.8
88.4
73.7
62.5
56.3
37.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
δ (ppm)

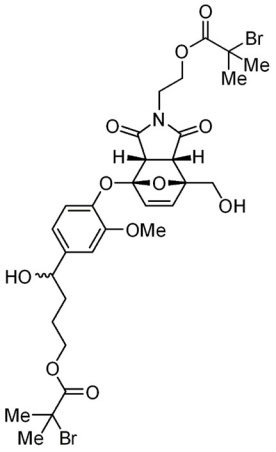

MeO
O
O
H
HO
O
Me
Me
Br
O
6
^{1}H (500 MHz, CDCl$_3$)
0.8
1.0 1.1 1.1 1.1
0.9
0.9
2.1
3.2
0.9
6.2 4.2
10 9 8 7 6 5 4 3 2 1 0
δ (ppm)


MeO
O
O
H
HO
O
Me
Me
Br
O
6
^{13}C (125 MHz, CDCl$_3$)
175.4
171.6
163.8
150.7
144.4
144.2
141.2
127.7
121.0
118.2
110.6
88.5
73.1
65.7
56.1
56.0
35.3
30.7
24.7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
δ (ppm)



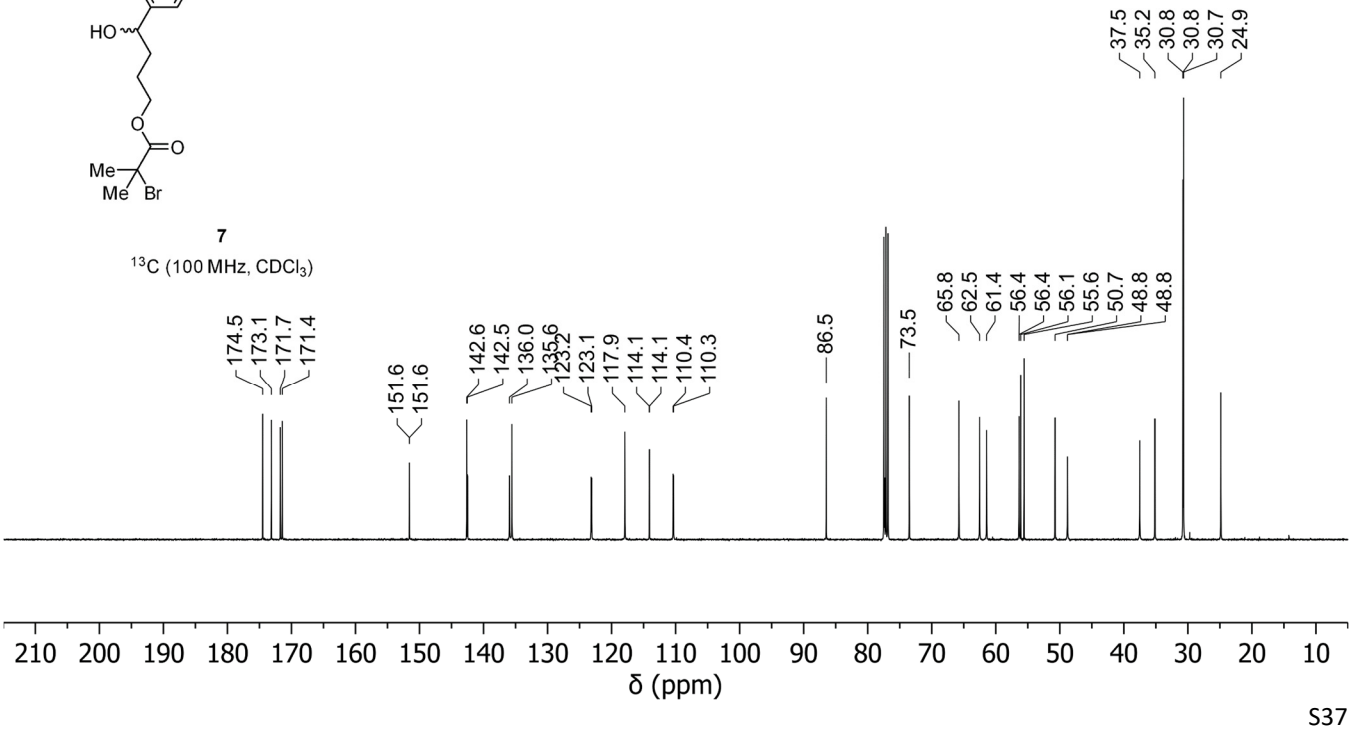
7

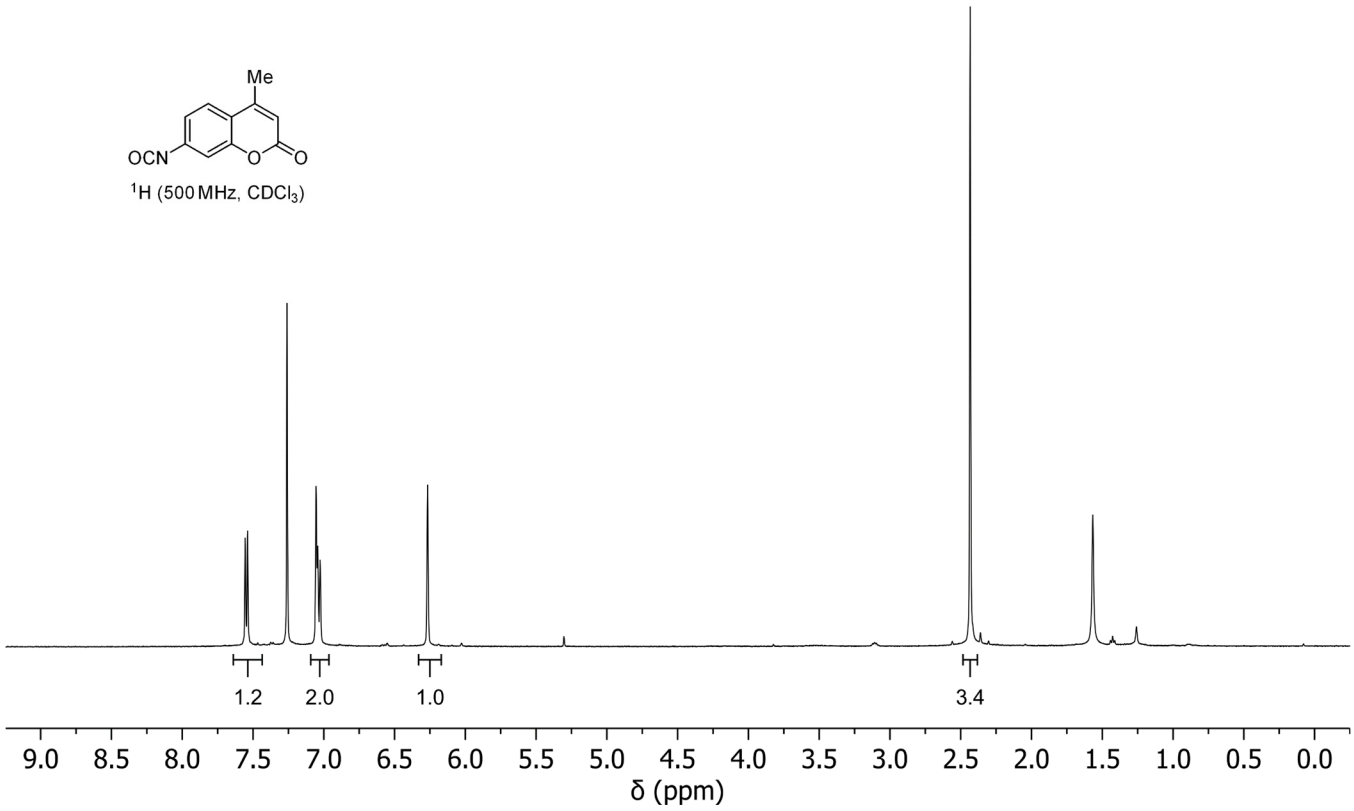
^{1}H (400 MHz, $CDCl_3$)

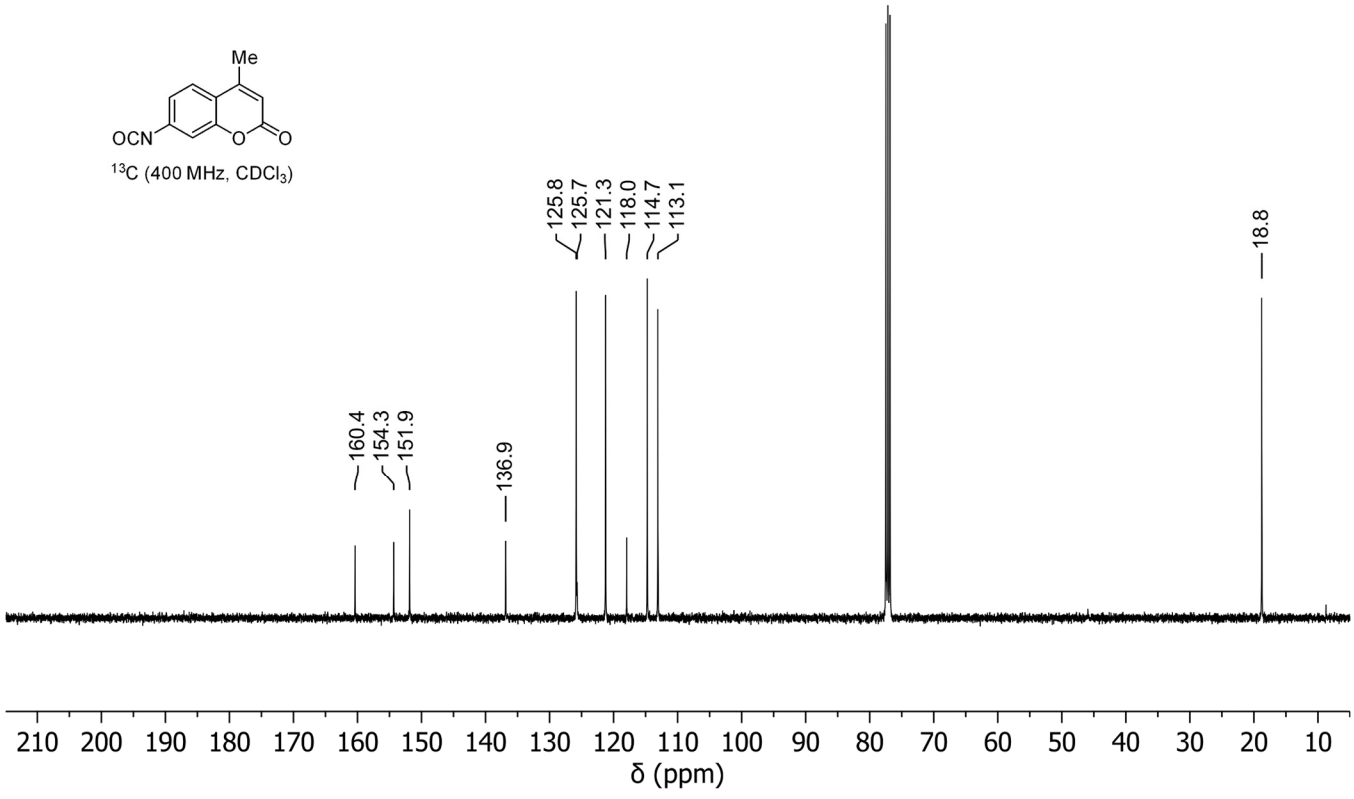


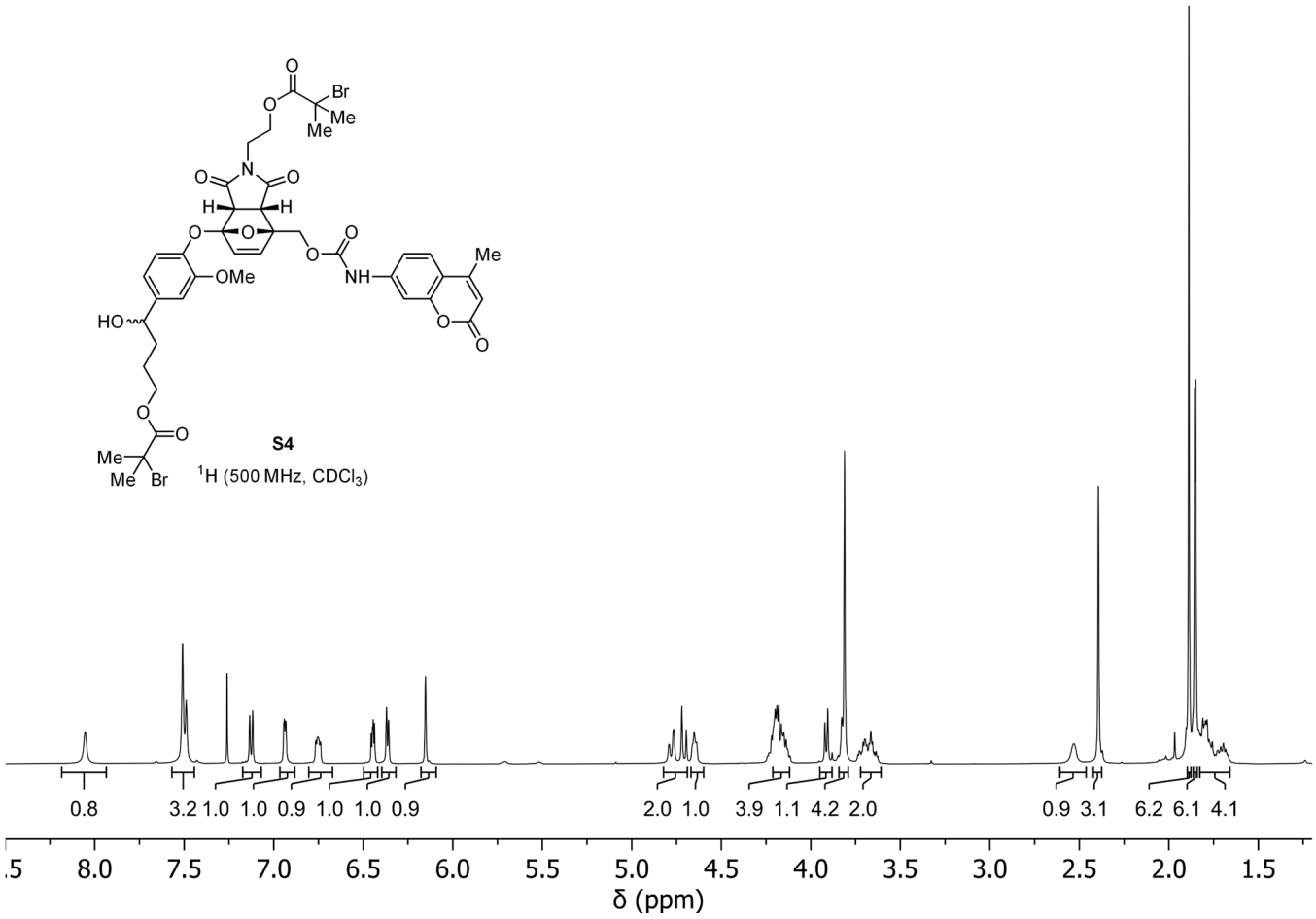
7

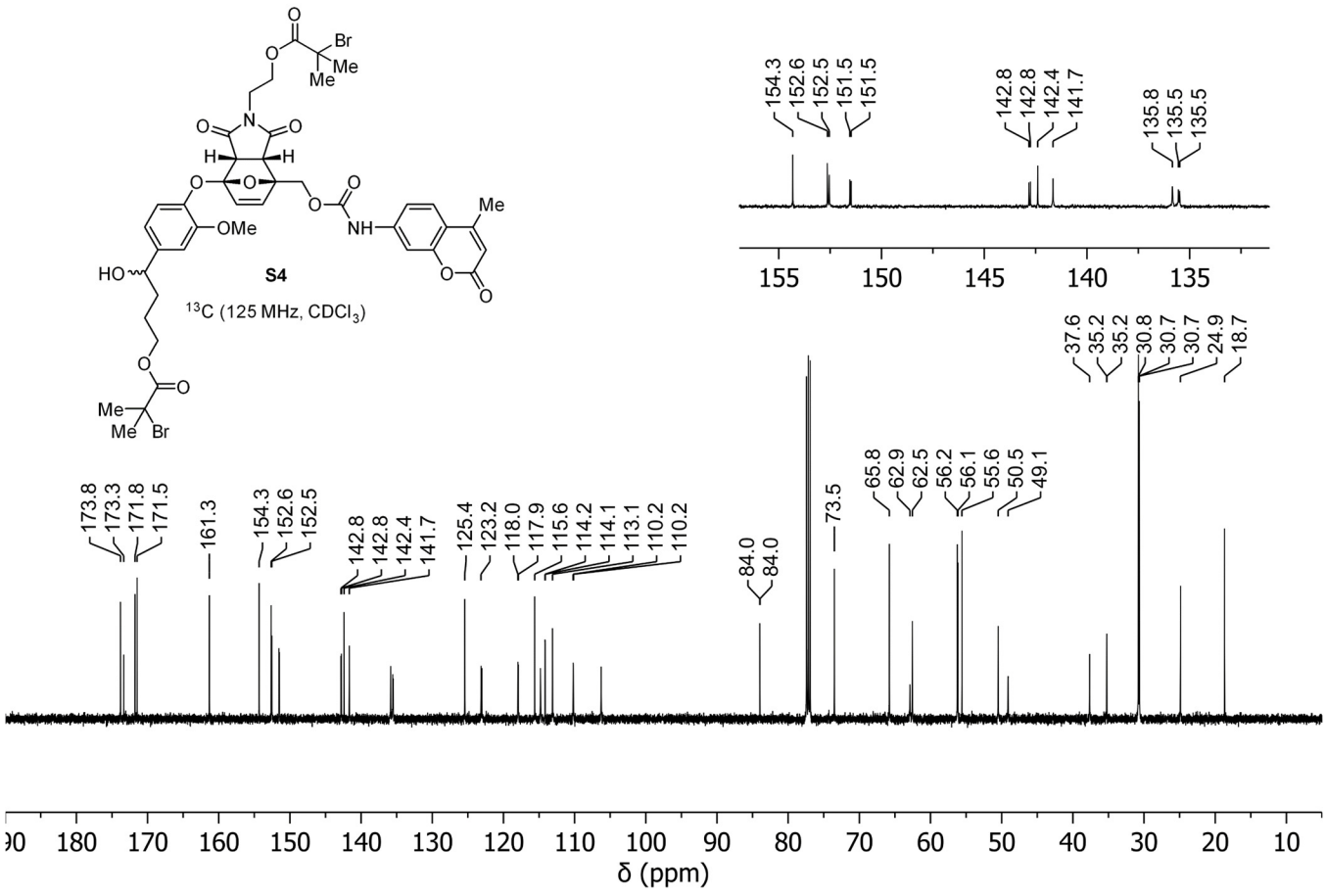
^{13}C (100 MHz, $CDCl_3$)

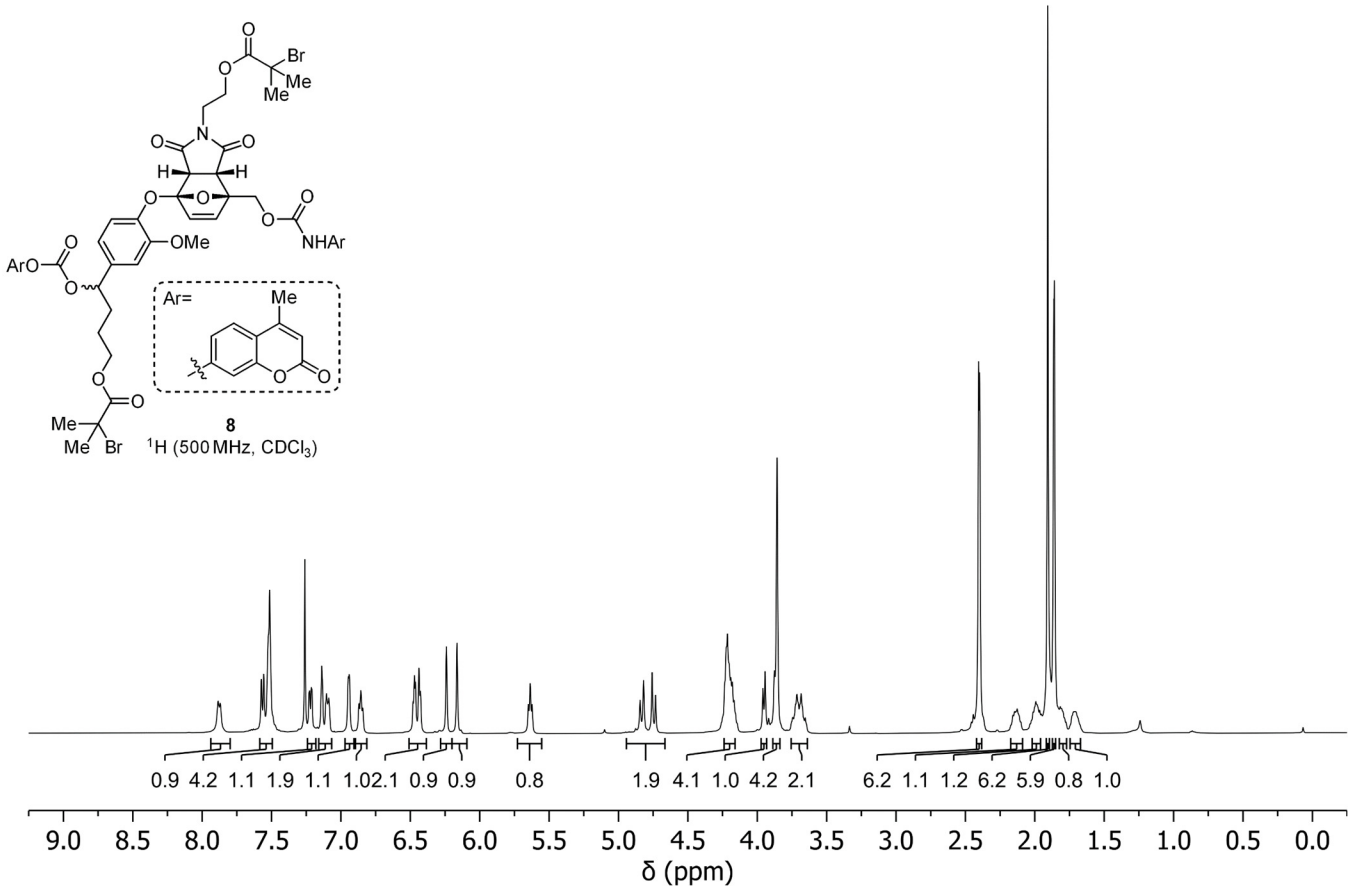


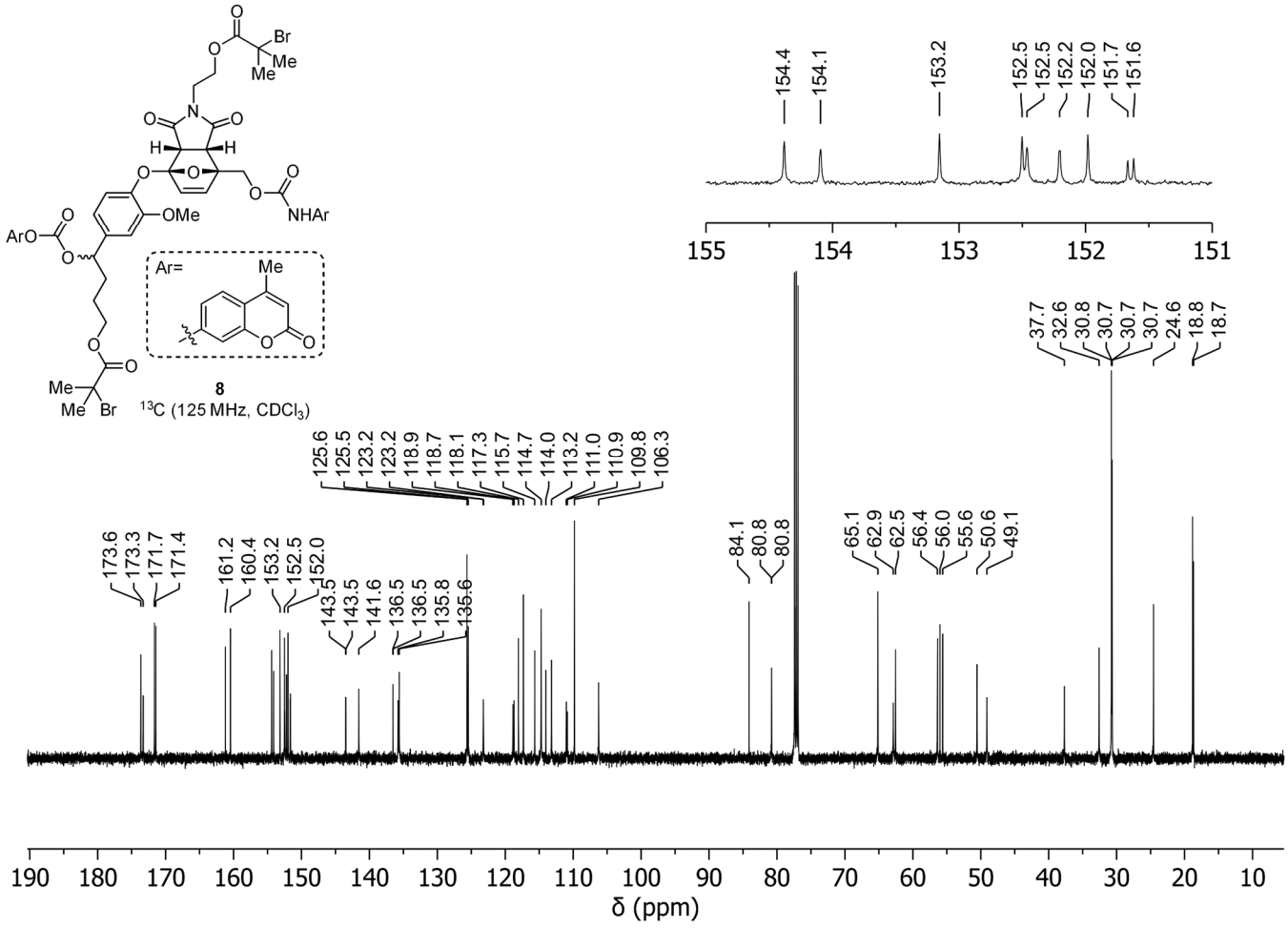

Me
OCN
O
O
1H (500 MHz, CDCl3)
1.2
2.0
1.0
3.4
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

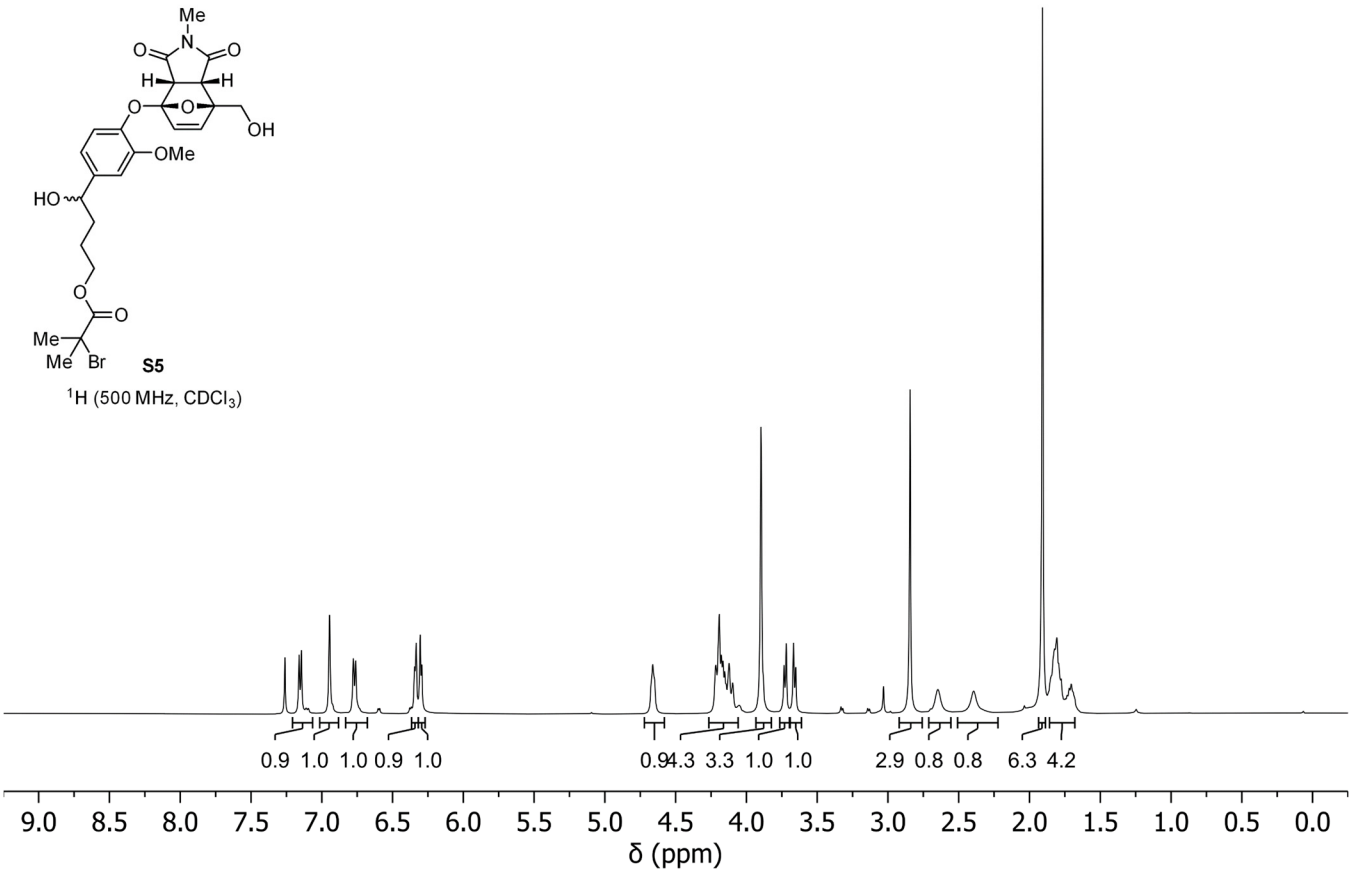

Me
OCN
O
O
13C (400 MHz, CDCl3)
160.4
154.3
151.9
136.9
125.8
125.7
121.3
118.0
114.7
113.1
18.8
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
δ (ppm)

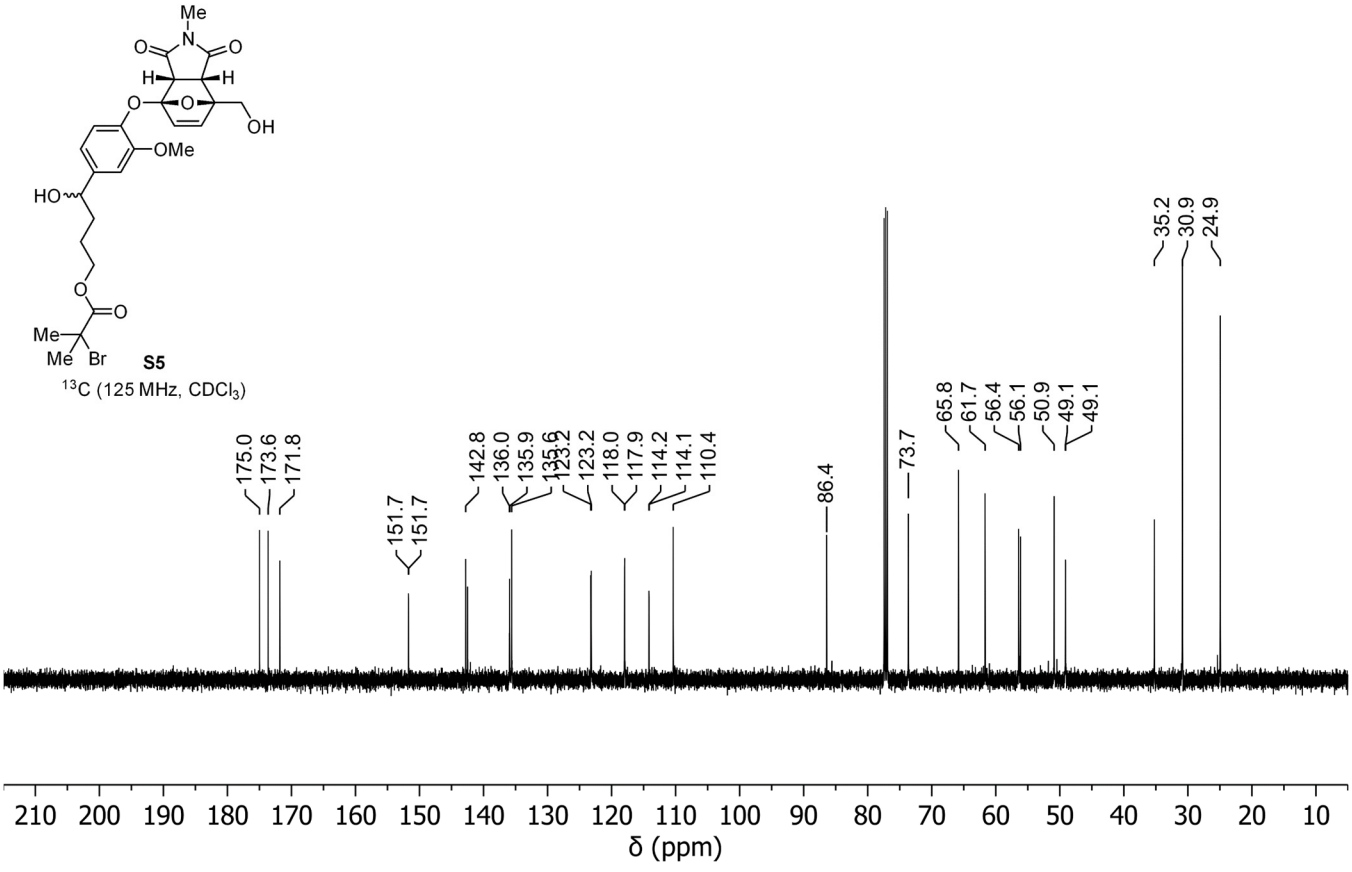

S4
^{1}H (500 MHz, $CDCl_3$)
0.8
3.2 1.0 1.0 0.9 1.0 1.0 0.9
2.0 1.0
3.9 1.1 4.2 2.0
0.9 3.1
6.2 6.1 4.1
δ (ppm)

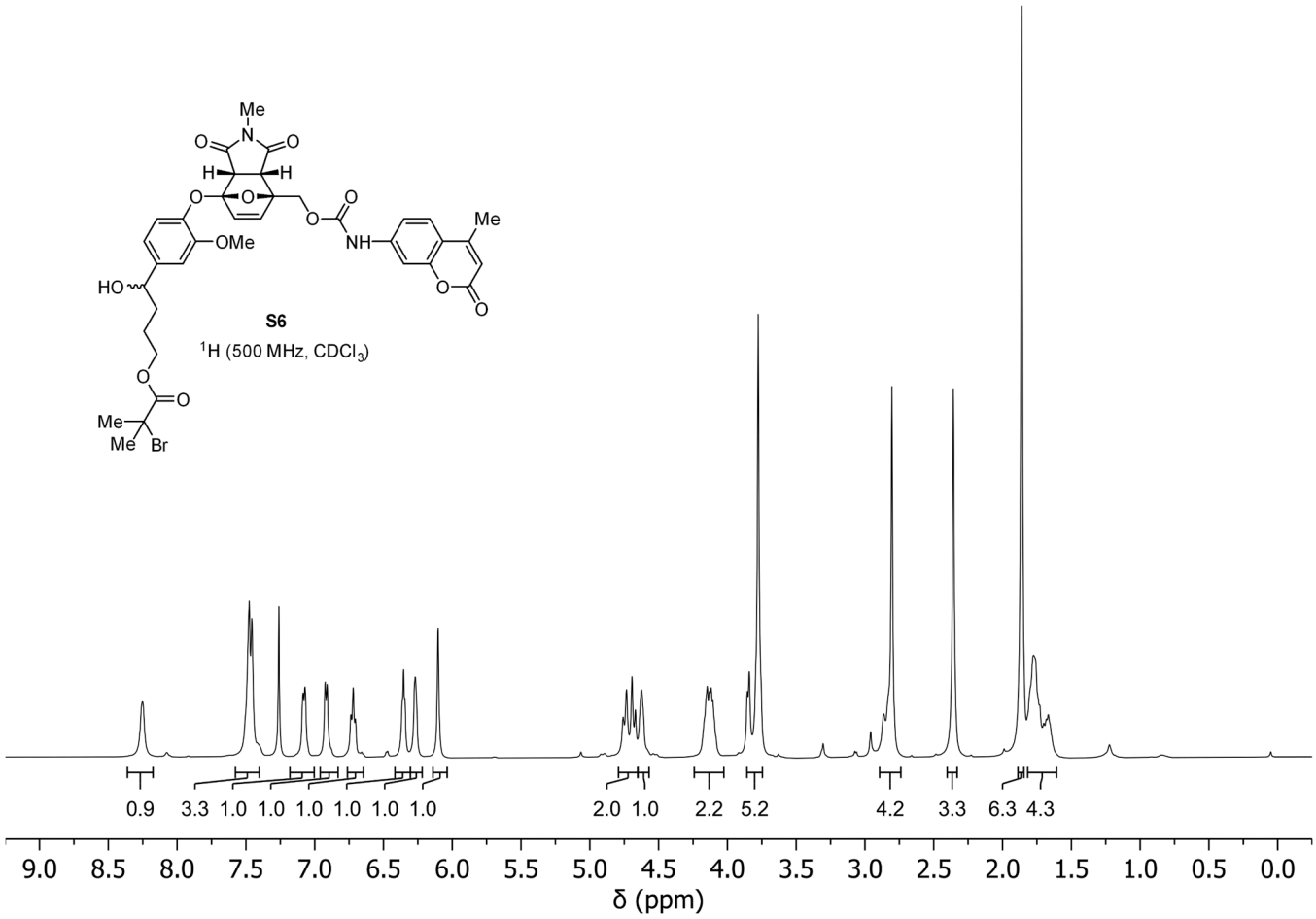

S4
^{13}C (125 MHz, $CDCl_3$)
154.3
152.6
152.5
151.5
151.5
142.8
142.8
142.4
141.7
135.8
135.5
135.5
155
150
145
140
135
37.6
35.2
35.2
30.8
30.7
30.7
24.9
18.7
65.8
62.9
62.5
56.2
56.1
55.6
50.5
49.1
173.8
173.3
171.8
171.5
161.3
154.3
152.6
152.5
142.8
142.8
142.4
141.7
125.4
123.2
118.0
117.9
115.6
114.2
114.1
113.1
110.2
110.2
84.0
84.0
73.5
δ (ppm)

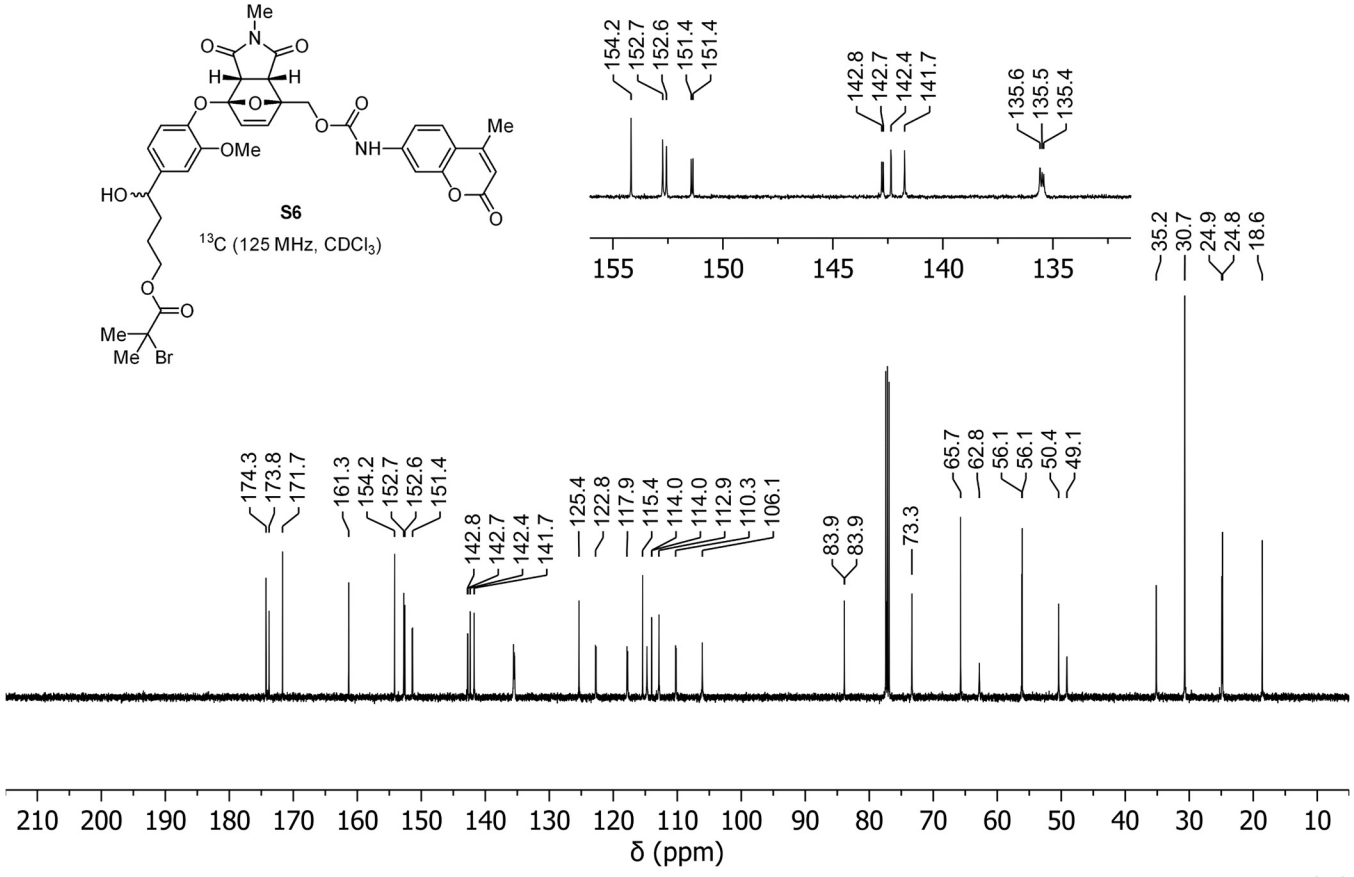

Br
Me
Me
N
O
H
H
OMe
NHAr
ArO
Ar=
Me
Me
Me
Br
8
^{1}H (500 MHz, CDCl$_3$)
0.9 4.2 1.1 1.9 1.1 1.02.1 0.9 0.9 0.8 1.9 4.1 1.0 4.2 2.1 6.2 1.1 1.2 6.2 5.9 0.8 1.0
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

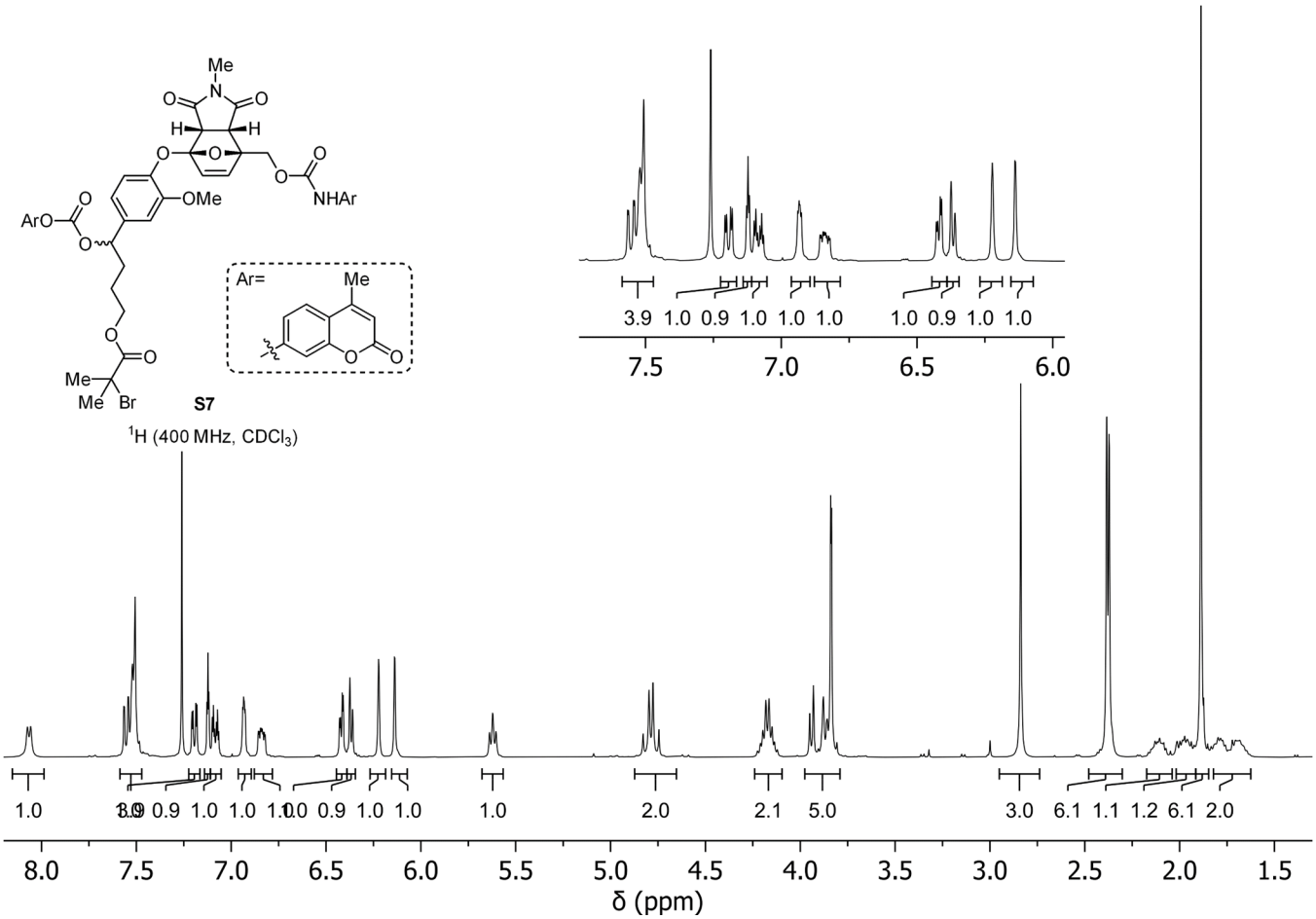

Br
Me
Me
N
O
H
H
OMe
NHAr
ArO
Ar=
Me
Me
Me
Br
8
^{13}C (125 MHz, CDCl$_3$)
154.4
154.1
153.2
152.5
152.5
152.2
152.0
151.7
151.6
155 154 153 152 151
37.7
32.6
30.8
30.7
30.7
30.7
24.6
18.8
18.7
125.6
125.5
123.2
123.2
118.9
118.7
118.1
117.3
115.7
114.7
114.0
113.2
111.0
110.9
109.8
106.3
173.6
173.3
171.7
171.4
161.2
160.4
153.2
152.5
152.0
143.5
143.5
141.6
136.5
136.5
135.8
135.6
84.1
80.8
80.8
65.1
62.9
62.5
56.4
56.0
55.6
50.6
49.1
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
δ (ppm)

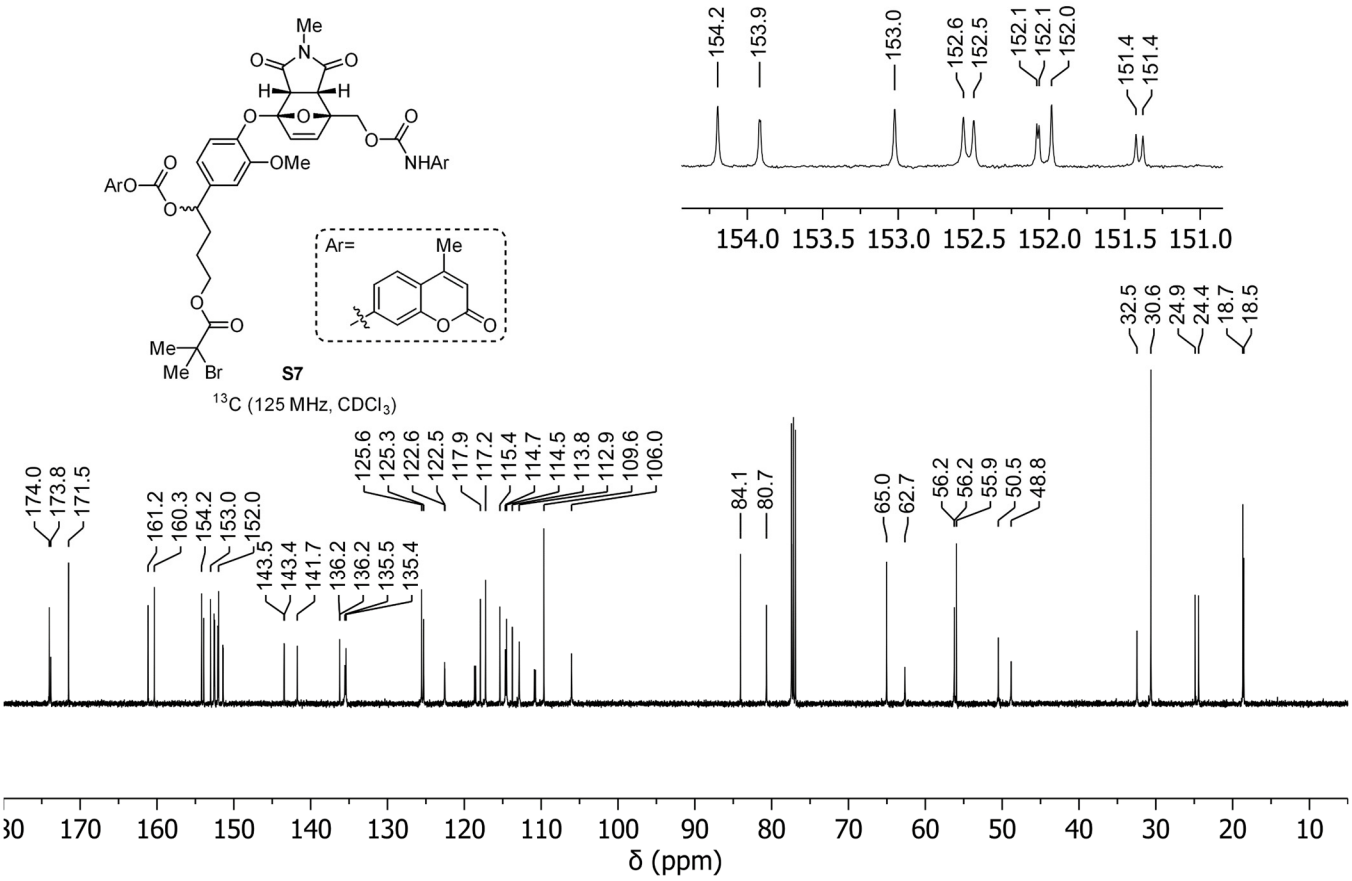

Me
N
O
O
H
H
O
O
OH
OMe
HO
O
O
Me
Me
Br
S5
^{1}H (500 MHz, CDCl$_3$)
0.9 1.0 1.0 0.9 1.0
0.9 4.3 3.3 1.0 1.0
2.9 0.8 0.8 6.3 4.2
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

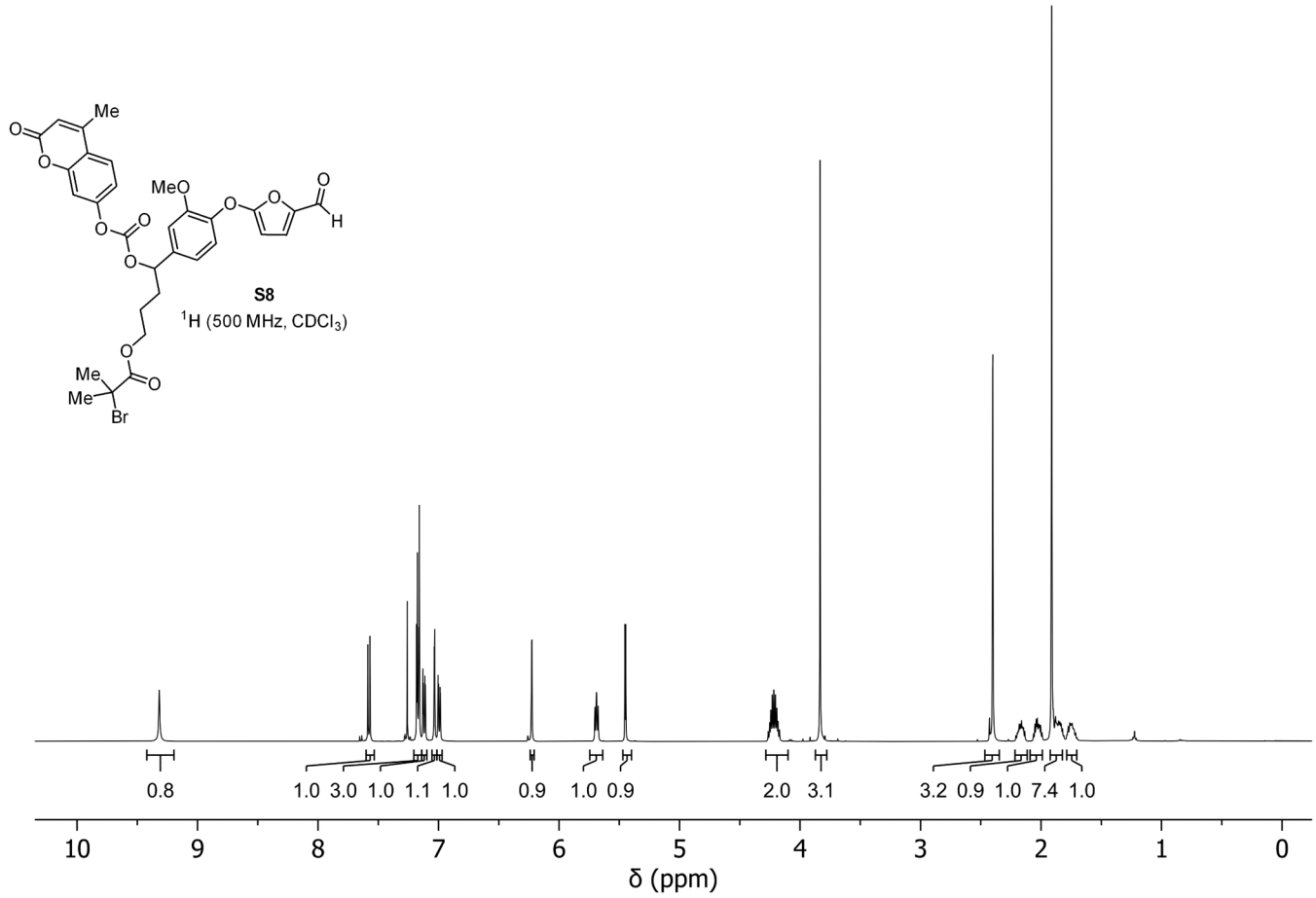

Me
N
O
O
H
H
O
O
OH
OMe
HO
O
O
Me
Me
Br
S5
^{13}C (125 MHz, CDCl$_3$)
175.0
173.6
171.8
151.7
151.7
142.8
136.0
135.9
123.2
118.0
117.9
114.2
114.1
110.4
86.4
73.7
65.8
61.7
56.4
56.1
50.9
49.1
49.1
35.2
30.9
24.9
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
δ (ppm)

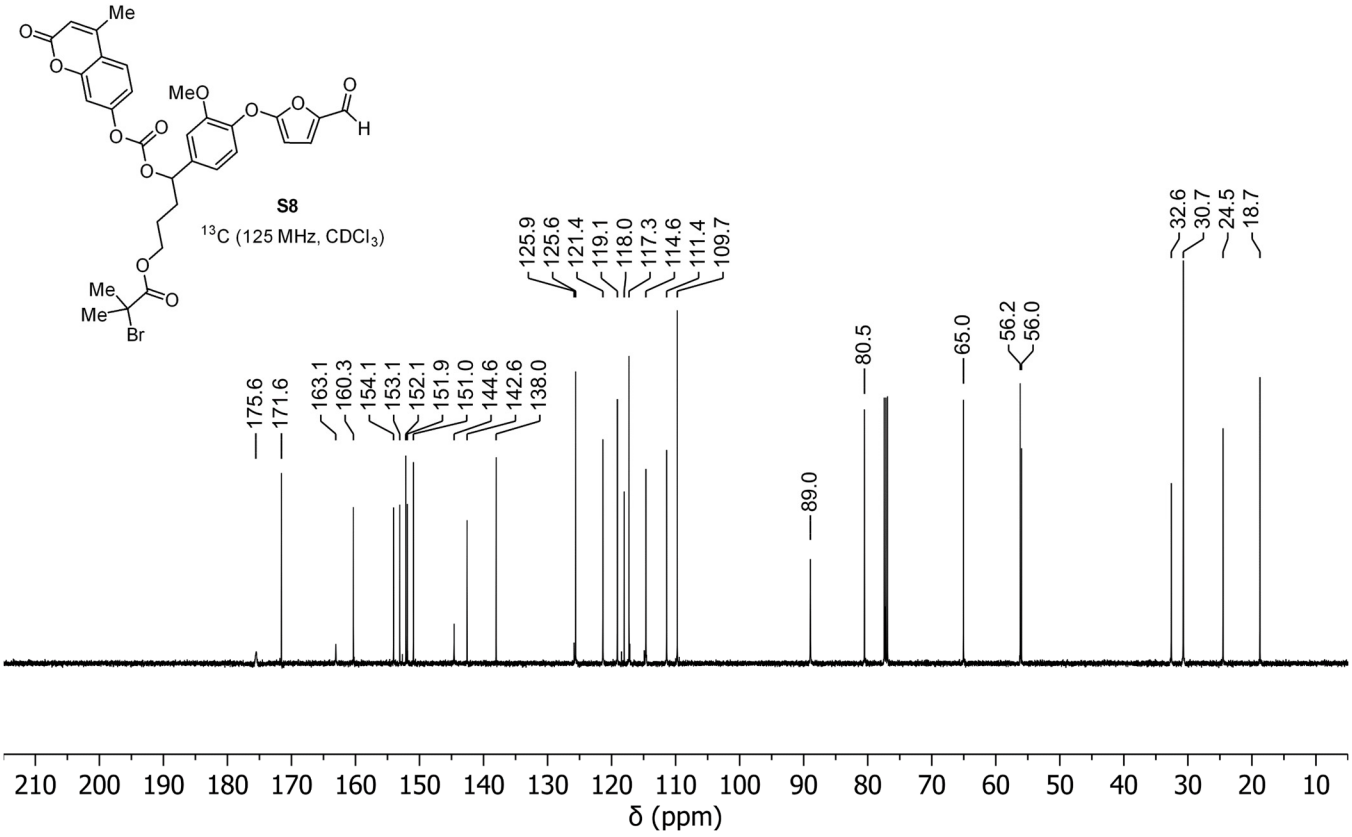

S6
^{1}H (500 MHz, CDCl$_3$)
0.9 3.3 1.0 1.0 1.0 1.0 1.0 1.0
2.0 1.0 2.2 5.2 4.2 3.3 6.3 4.3
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

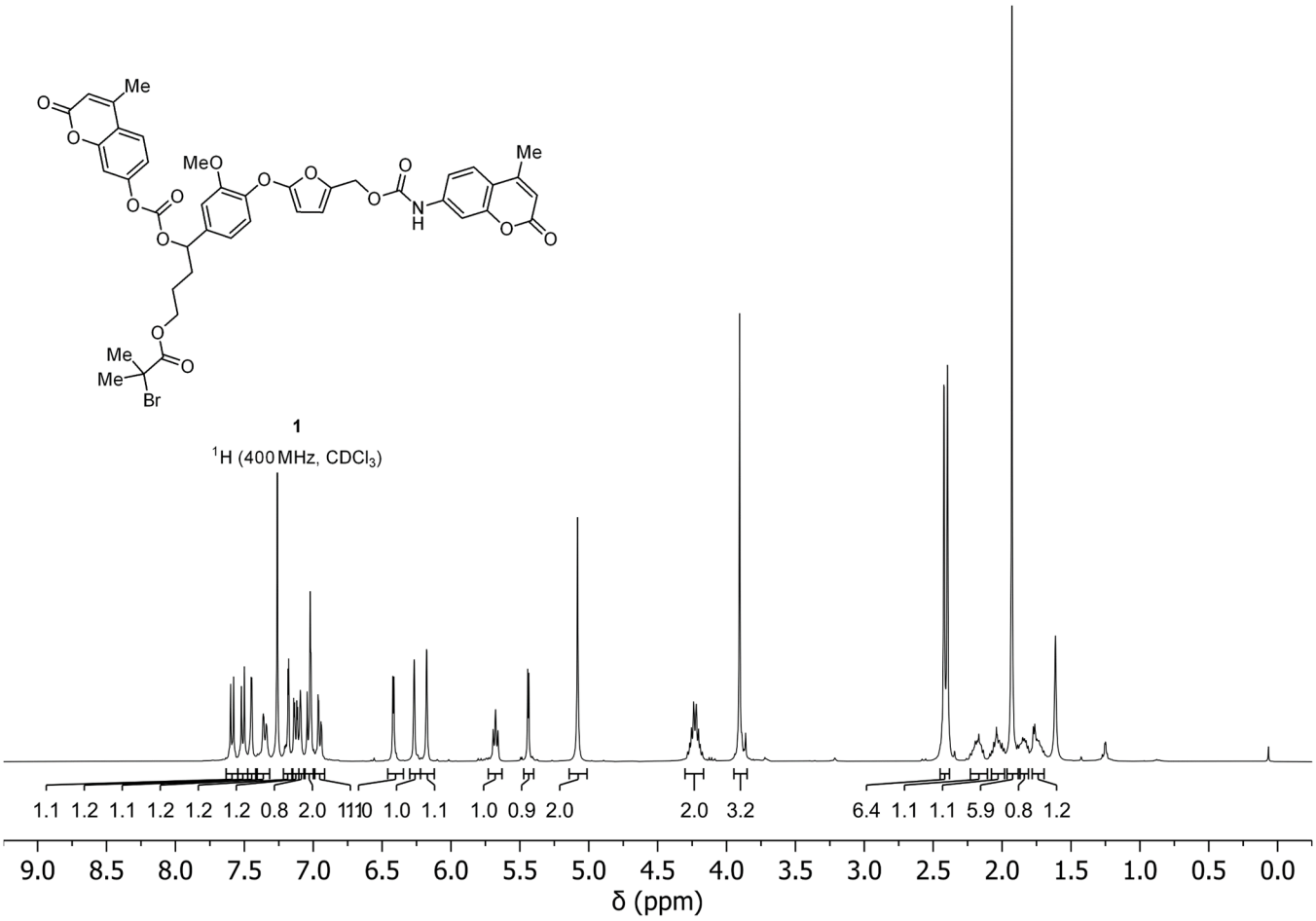

S6
^{13}C (125 MHz, CDCl$_3$)
154.2 152.7 152.6 151.4 151.4
142.8 142.7 142.4 141.7
135.6 135.5 135.4
155 150 145 140 135
35.2 30.7 24.9 24.8 18.6
174.3 173.8 171.7 161.3 154.2 152.7 152.6 151.4
142.8 142.7 142.4 141.7 125.4 122.8 117.9 115.4 114.0 114.0 112.9 110.3 106.1
83.9 83.9 73.3 65.7 62.8 56.1 56.1 50.4 49.1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
δ (ppm)

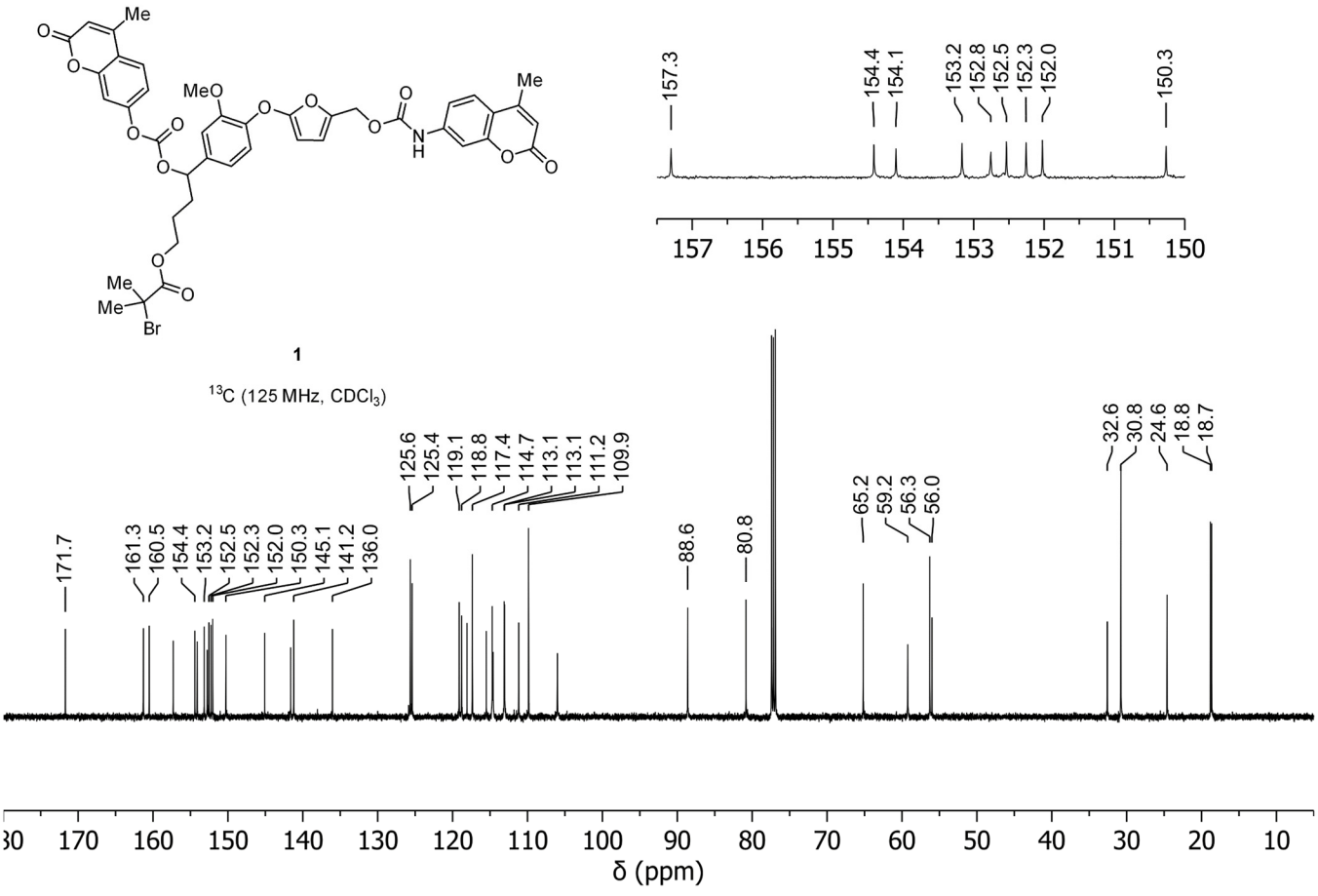

Me
N
O
H
O
ArO
OMe
NHAr
Ar=
Me
Me
Me
Br
S7
^{1}H (400 MHz, CDCl$_3$)
3.9 1.0 0.9 1.0 1.0 1.0
1.0 0.9 1.0 1.0
7.5 7.0 6.5 6.0
1.0 2.0 2.1 5.0 3.0 6.1 1.1 1.2 6.1 2.0
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
δ (ppm)

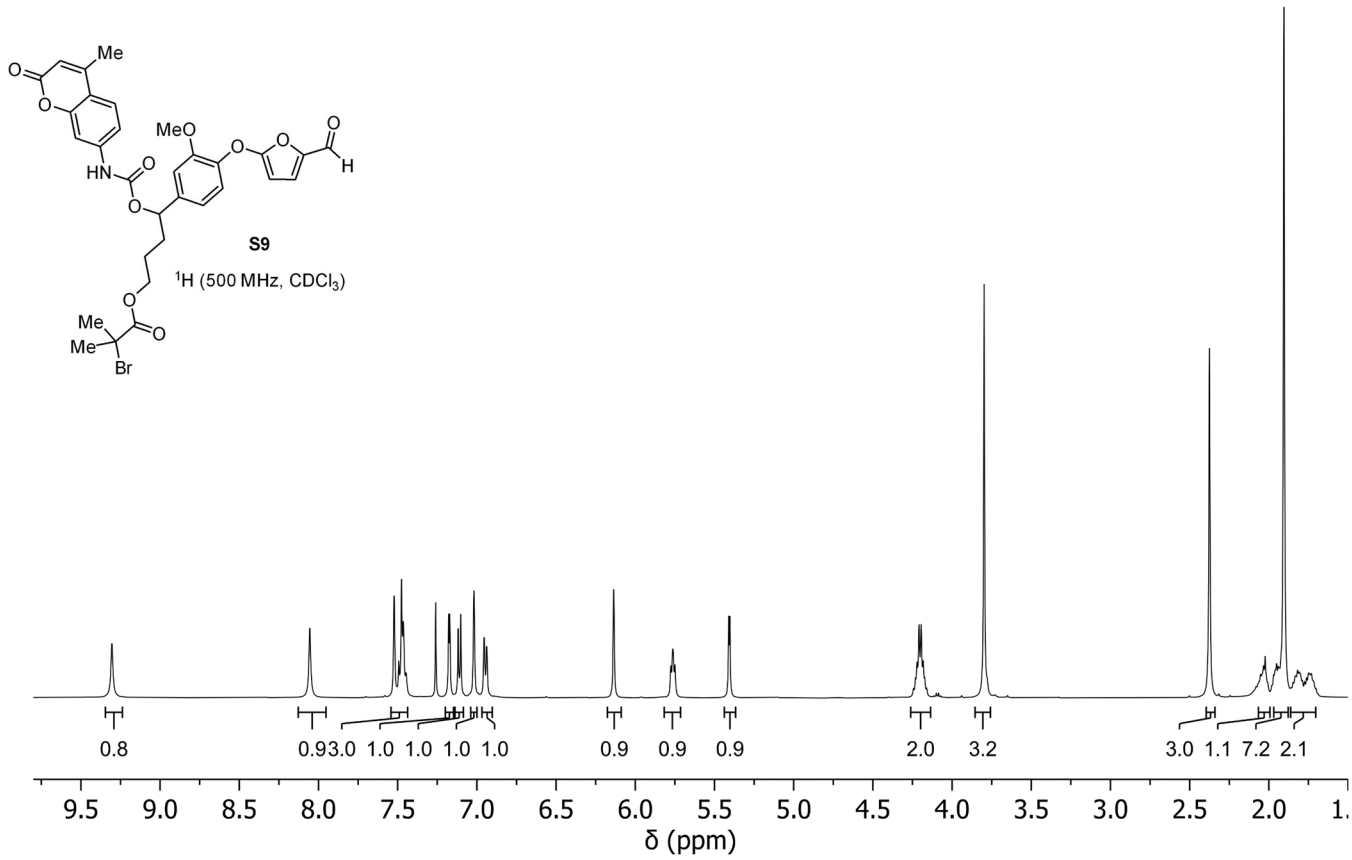

Me
N
O
H
O
ArO
OMe
NHAr
Ar=
Me
Me
Me
Br
S7
^{13}C (125 MHz, CDCl$_3$)
154.2 153.9 153.0 152.6 152.5 152.1 152.1 152.0 151.4 151.4
154.0 153.5 153.0 152.5 152.0 151.5 151.0
32.5 30.6 24.9 24.4 18.7 18.5
174.0 173.8 171.5 161.2 160.3 154.2 153.0 152.0 143.5 143.4 141.7 136.2 136.2 135.5 135.4
125.6 125.3 122.6 122.5 117.9 117.2 115.4 114.7 114.5 113.8 112.9 109.6 106.0
84.1 80.7 65.0 62.7 56.2 56.2 55.9 50.5 48.8
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
δ (ppm)

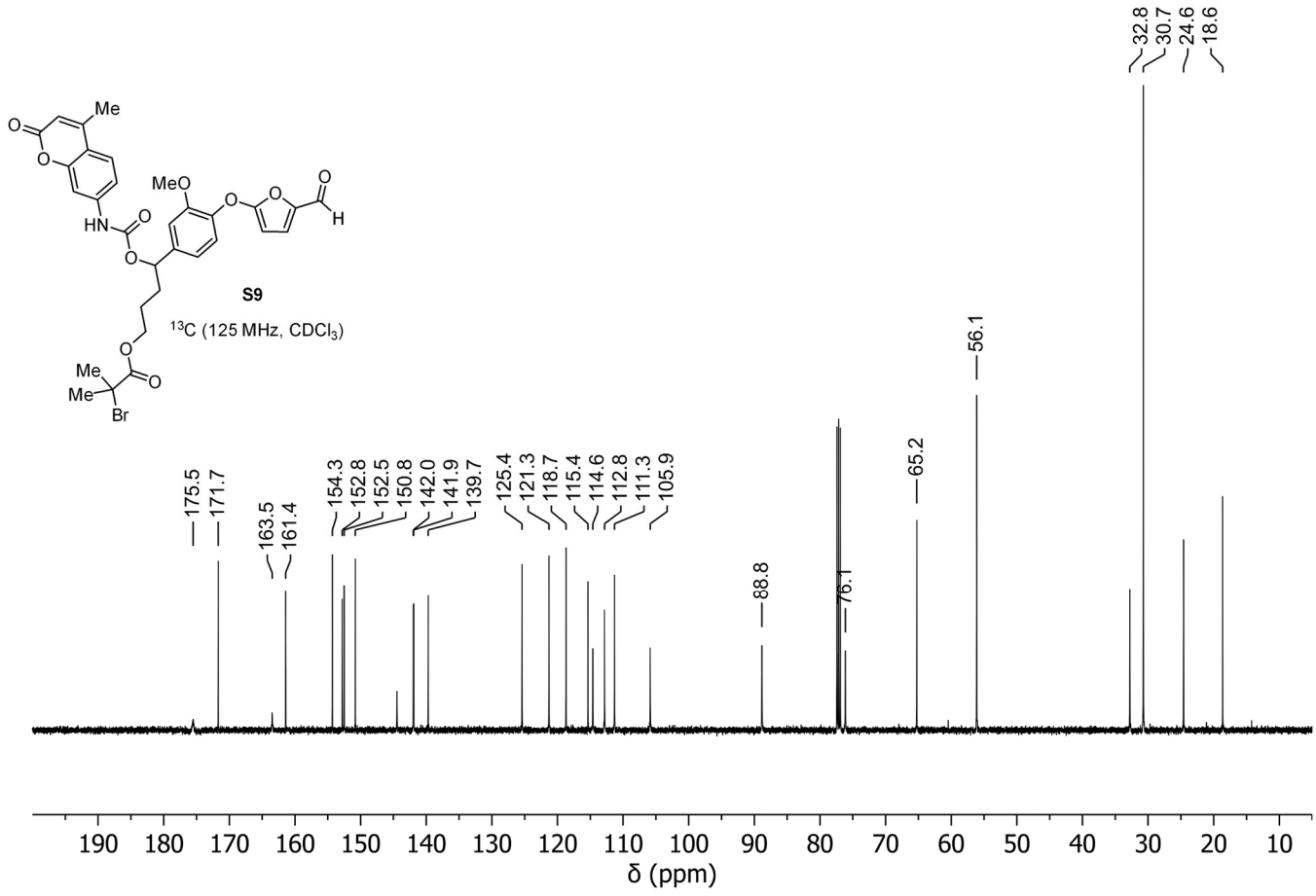

S8
^{1}H (500 MHz, $CDCl_3$)
0.8
1.0 3.0 1.0 1.1 1.0
0.9
1.0 0.9
2.0 3.1
3.2 0.9 1.0 7.4 1.0
10 9 8 7 6 5 4 3 2 1 0
δ (ppm)

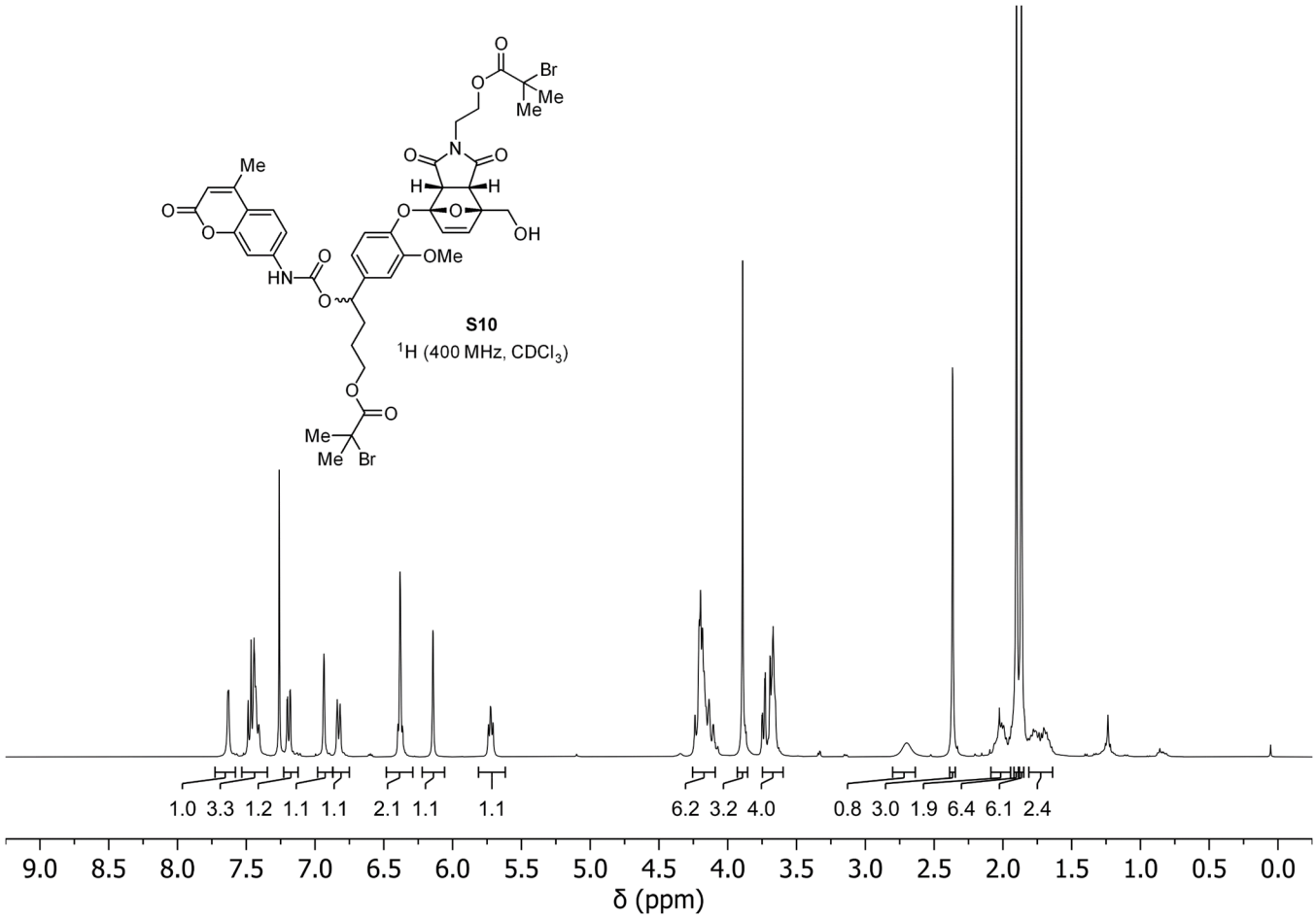

S8
^{13}C (125 MHz, $CDCl_3$)
175.6
171.6
163.1
160.3
154.1
153.1
152.1
151.9
151.0
144.6
142.6
138.0
125.9
125.6
121.4
119.1
118.0
117.3
114.6
111.4
109.7
89.0
80.5
65.0
56.2
56.0
32.6
30.7
24.5
18.7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
δ (ppm)

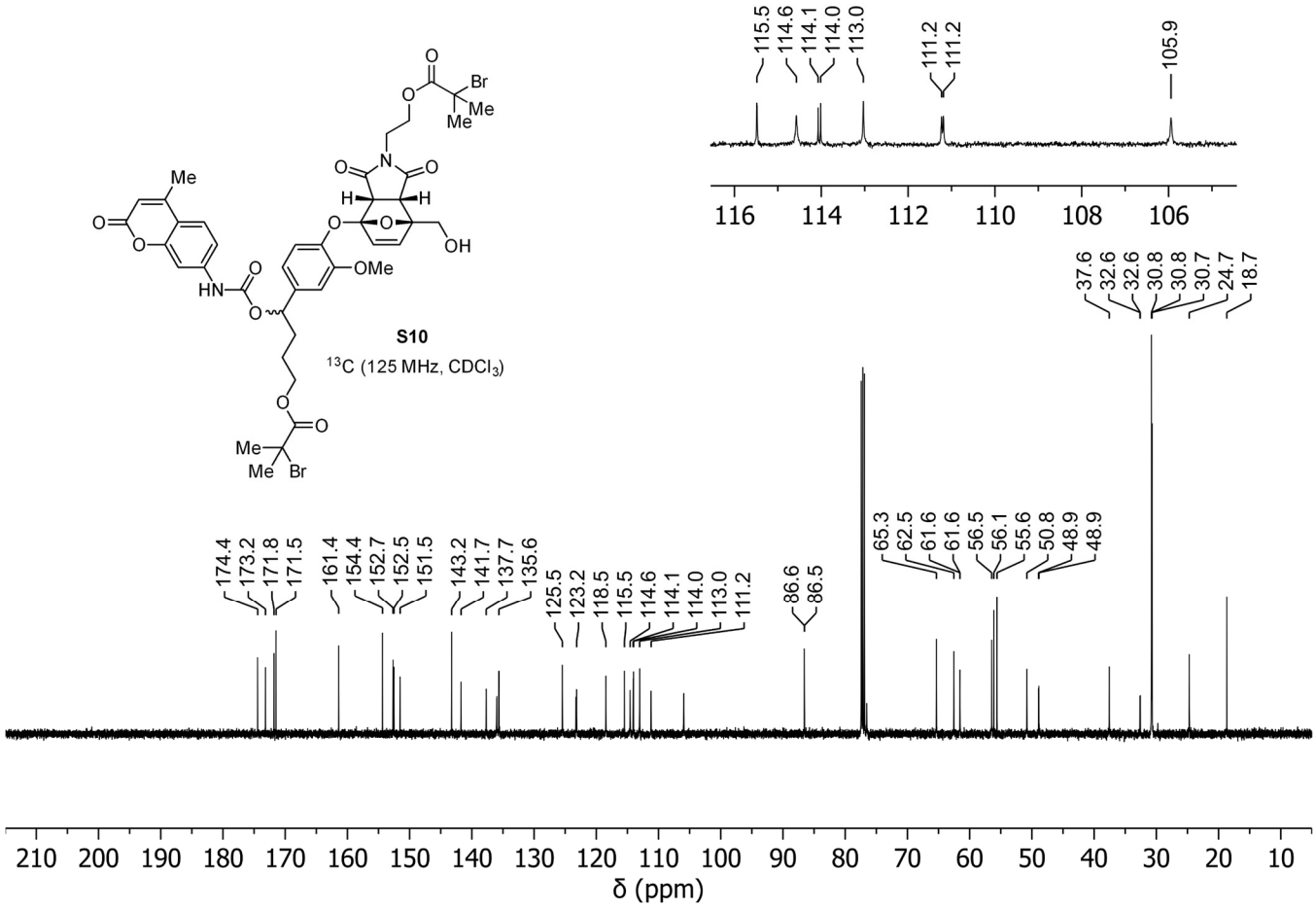

1
^{1}H (400 MHz, CDCl$_3$)
1.1 1.2 1.1 1.2 1.2 1.2 0.8 2.0 1.1 1.0 1.0 1.1 1.0 0.9 2.0 2.0 3.2 6.4 1.1 1.1 5.9 0.8 1.2
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

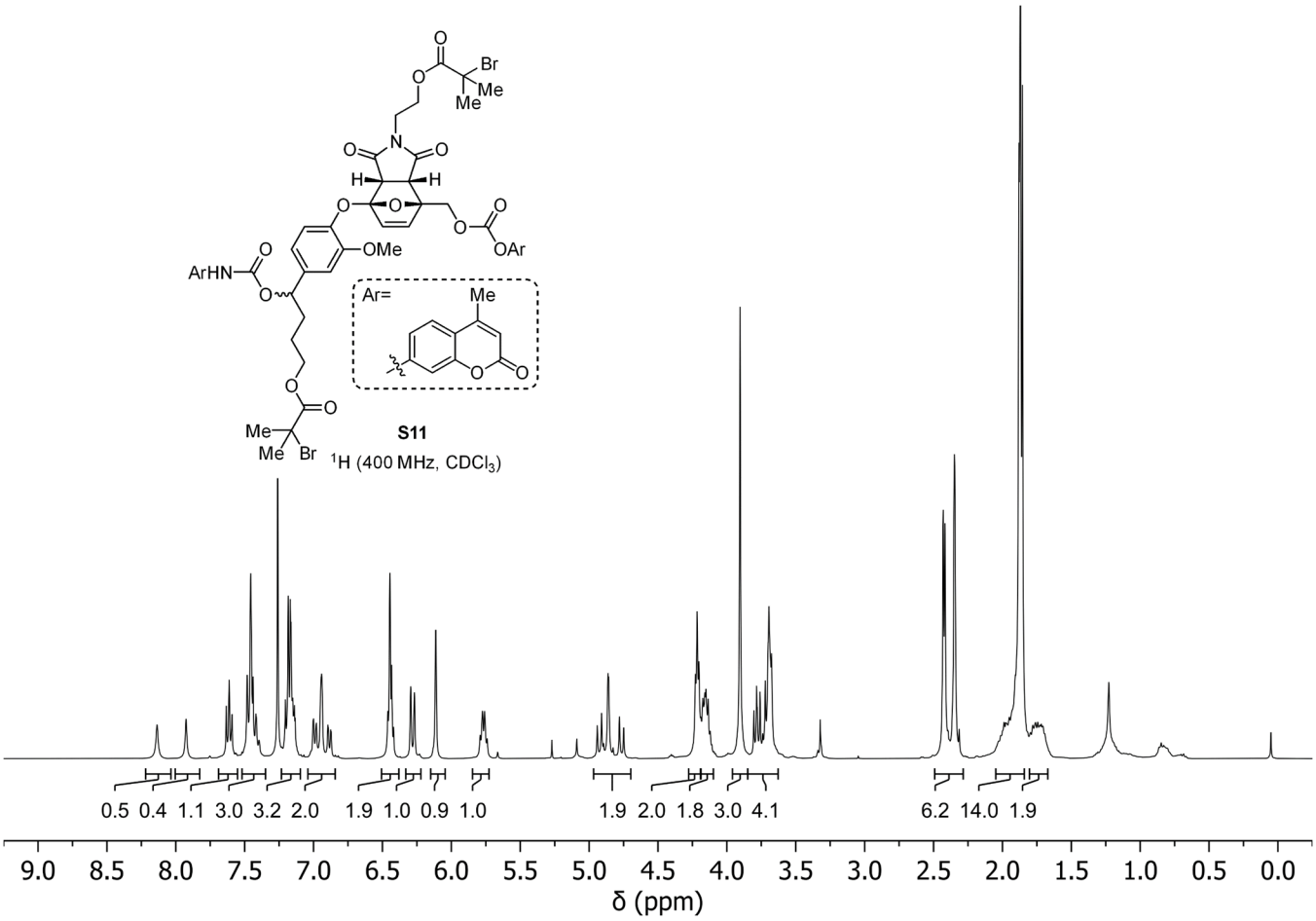

157.3
154.4
154.1
153.2
152.8
152.5
152.3
152.0
150.3
157 156 155 154 153 152 151 150
1
^{13}C (125 MHz, CDCl$_3$)
171.7
161.3
160.5
154.4
153.2
152.5
152.3
152.0
150.3
145.1
141.2
136.0
125.6
125.4
119.1
118.8
117.4
114.7
113.1
113.1
111.2
109.9
88.6
80.8
65.2
59.2
56.3
56.0
32.6
30.8
24.6
18.8
18.7
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
δ (ppm)

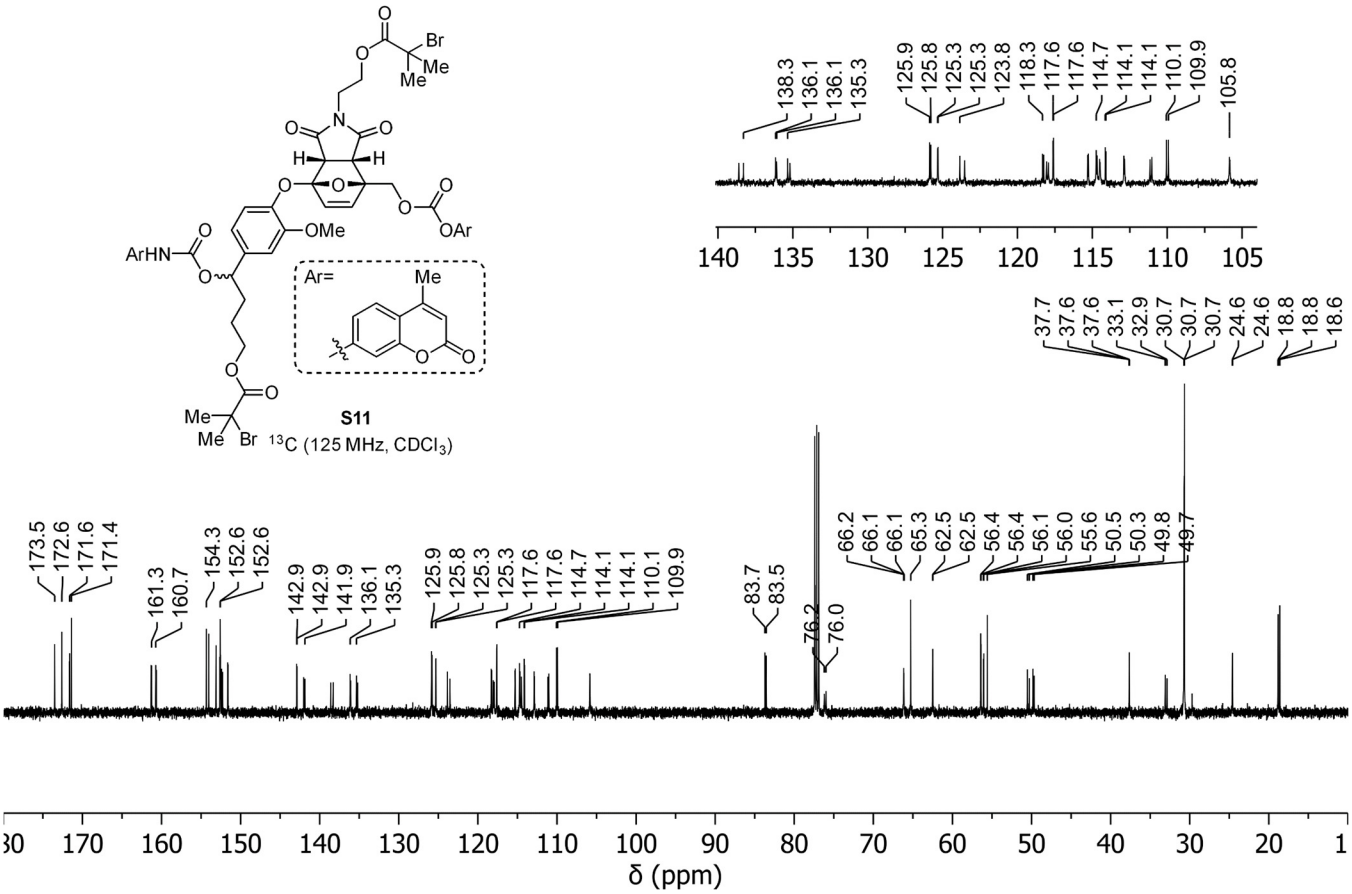

S9
^{1}H (500 MHz, $CDCl_3$)
0.8
0.93.0
1.0
1.0
1.0
1.0
0.9
0.9
0.9
2.0
3.2
3.0
1.1
7.2
2.1
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0
δ (ppm)


S9
^{13}C (125 MHz, $CDCl_3$)
175.5
171.7
163.5
161.4
154.3
152.8
152.5
150.8
142.0
141.9
139.7
125.4
121.3
118.7
115.4
114.6
112.8
111.3
105.9
88.8
76.1
65.2
56.1
32.8
30.7
24.6
18.6
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
δ (ppm)


S10
^{1}H (400 MHz, $CDCl_3$)
1.0 3.3 1.2 1.1 1.1 2.1 1.1 1.1 6.2 3.2 4.0 0.8 3.0 1.9 6.4 6.1 2.4
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)


S10
^{13}C (125 MHz, $CDCl_3$)
115.5 114.6 114.1 114.0 113.0 111.2 111.2 105.9
116 114 112 110 108 106
37.6 32.6 32.6 30.8 30.8 30.7 24.7 18.7
174.4 173.2 171.8 171.5 161.4 154.4 152.7 152.5 151.5 143.2 141.7 137.7 135.6 125.5 123.2 118.5 115.5 114.6 114.1 114.0 113.0 111.2 86.6 86.5 65.3 62.5 61.6 61.6 56.5 56.1 55.6 50.8 48.9 48.9
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
δ (ppm)


S11
^{1}H (400 MHz, CDCl$_3$)
Ar=
Me
OMe
OAr
ArHN
Br
Me
0.5 0.4 1.1 3.0 3.2 2.0 1.9 1.0 0.9 1.0 1.9 2.0 1.8 3.0 4.1 6.2 14.0 1.9
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)


S11
^{13}C (125 MHz, CDCl$_3$)
Ar=
Me
OMe
OAr
ArHN
Br
Me
138.3 136.1 136.1 135.3 125.9 125.8 125.3 125.3 123.8 118.3 117.6 117.6 114.7 114.1 114.1 110.1 109.9 105.8
140 135 130 125 120 115 110 105
37.7 37.6 37.6 33.1 32.9 30.7 30.7 30.7 24.6 24.6 18.8 18.8 18.6
173.5 172.6 171.6 171.4 161.3 160.7 154.3 152.6 152.6 142.9 142.9 141.9 136.1 135.3 125.9 125.8 125.3 125.3 117.6 117.6 114.7 114.1 114.1 110.1 109.9 83.7 83.5 76.2 76.0 66.2 66.1 66.1 65.3 62.5 62.5 56.4 56.4 56.1 56.0 55.6 50.5 50.3 49.8 49.7
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 1
δ (ppm)