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Electronic Supplementary Information

5-Aryloxy Substitution Enables Efficient Mechanically Triggered Release from a Synthetically Accessible Masked 2-Furylcarbinol Mechanophore

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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. Dry 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. Column chromatography was performed on a Biotage Isolera system using SiliCycle SiliaSep HP flash 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). 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 = broad.

High resolution mass spectra (HRMS) were analyzed by Fast Atom Bombardment (FAB) using a JEOL JMS-60H Double-focusing high resolution magnetic sector mass spectrometer operated in the positive ion mode. The instrument was calibrated with PEG clusters over the mass range of interest.

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.

Preparatory High-Performance Liquid Chromatography (HPLC) was performed with an Agilent Eclipse XDB-C18 column (990967-202) using a single-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).

LCMS measurements were performed with an Agilent 6140 Series Quadrupole LCMS Spectrometer System equipped with an Agilent Eclipse Plus C18 column using MeCN/water as the eluent.

II. Supplementary Figures

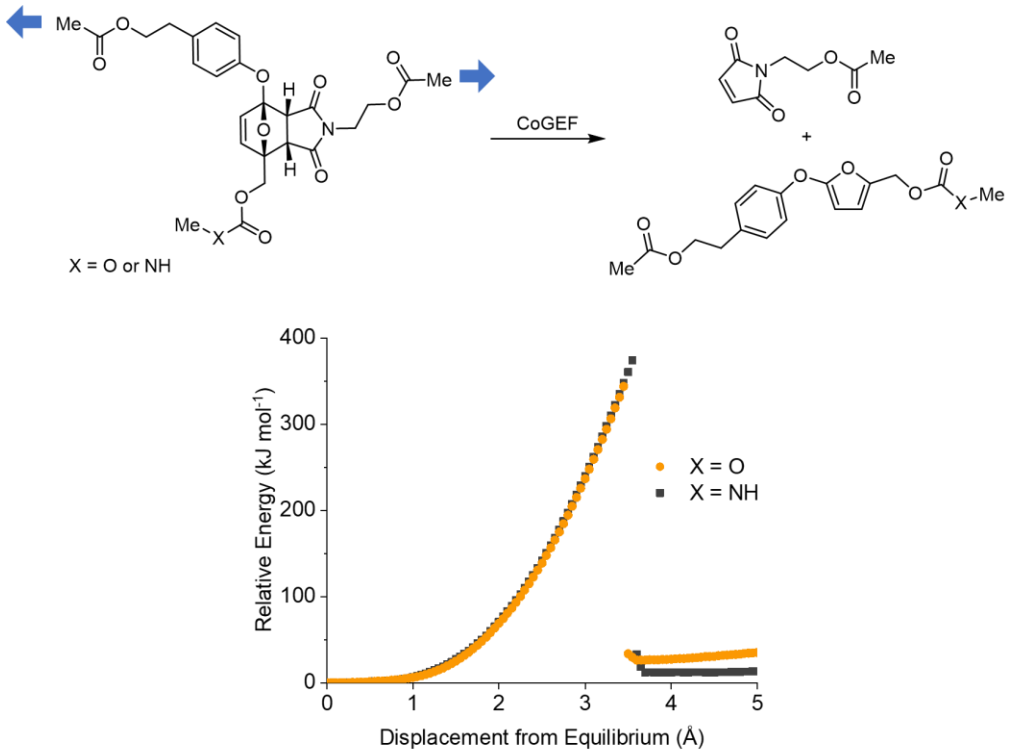


Figure S1. Density functional theory (DFT) calculations performed on truncated furan–maleimide Diels–Alder adducts using the constrained geometries simulate external force (CoGEF) method at the B3LYP/6-31G* level of theory. The F_{max} value calculated for the carbonate model (X = O) is 4.2 nN and that for the carbamate model (X = NH) is 4.4 nN. CoGEF calculations predict a retro-Diels–Alder reaction to generate the expected furan and maleimide products upon mechanical elongation.

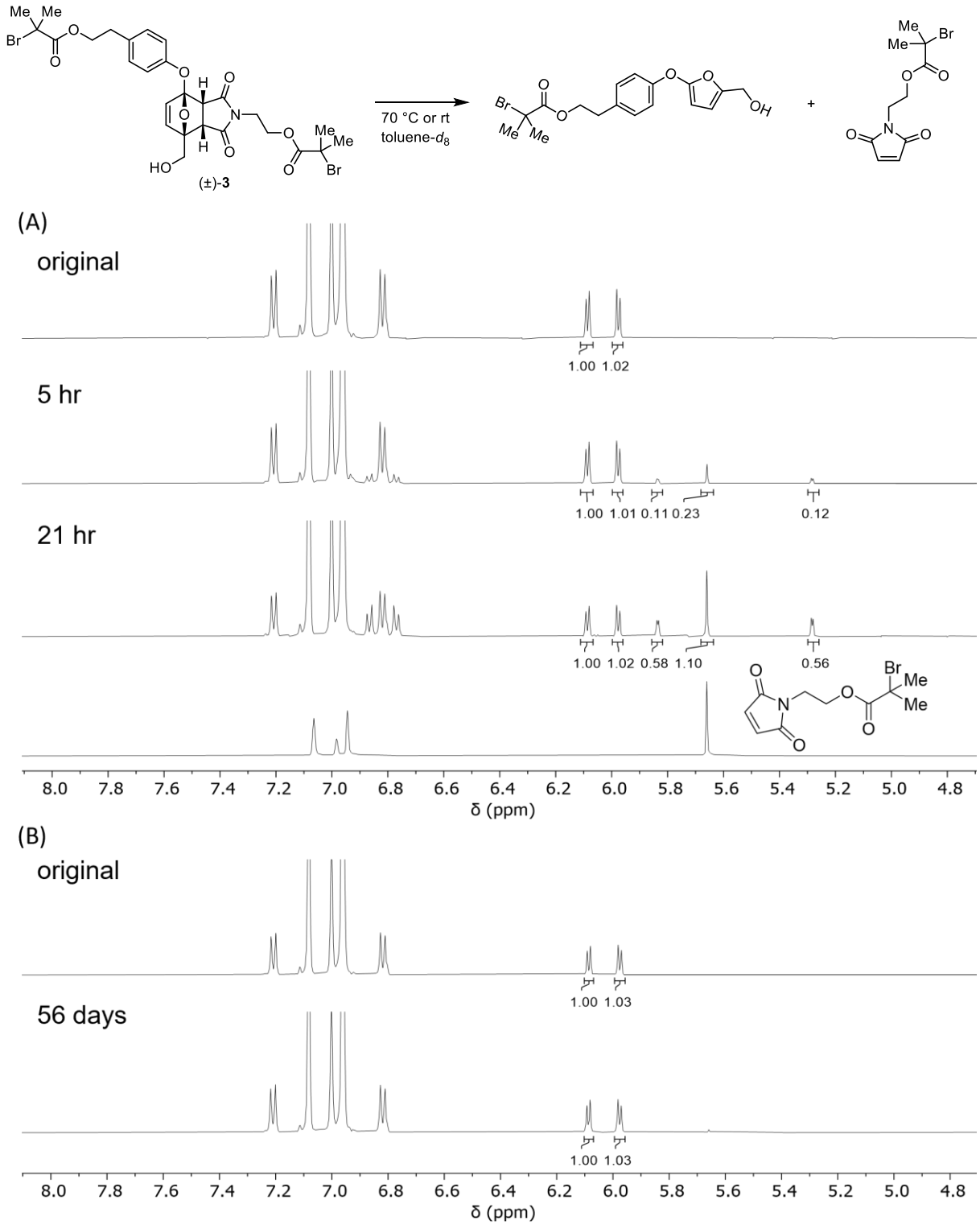


Figure S2. Thermal stability study of Diels–Alder adduct **3** in toluene-d_8 (7.7 mM). (A) Partial ^{1}H NMR spectra (500 MHz) of (±)-**3** (A) after heating at 70 °C for the indicated amount of time. Compound (±)-**3** undergoes a retro-Diels–Alder reaction upon heating at 70 °C with a conversion of approximately 10% after 5 h and 35% after 21 h. The ^{1}H NMR spectrum of the maleimide fragment in toluene-d_8 is shown for reference. (B) Partial ^{1}H NMR spectra of (±)-**3** after being kept at room temperature for the indicated amount of time, demonstrating negligible reaction.

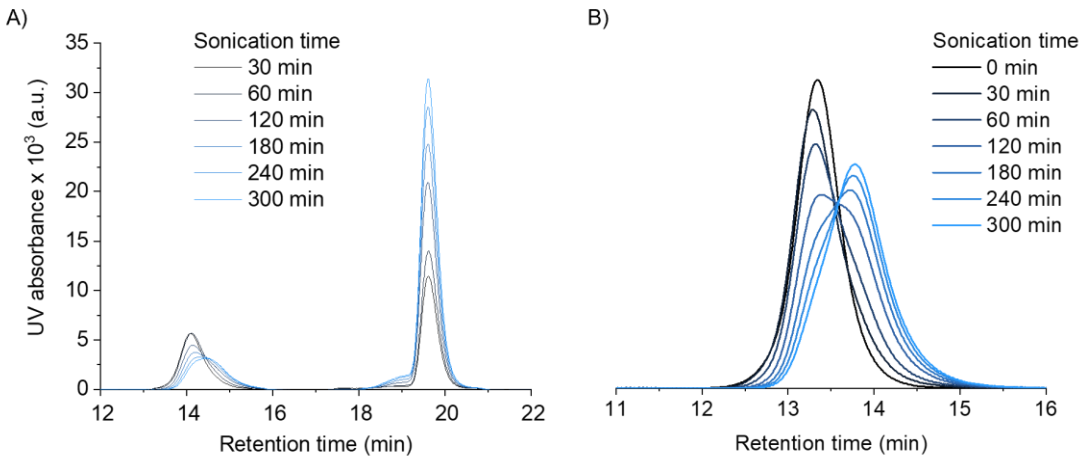


Figure S3. GPC traces as a function of ultrasonication time for **PMA(O)** monitored using a (A) UV-vis detector (λ = 322–338 nm) and (B) refractive index (RI) detector. Measurements were performed after incubation at room temperature for 30 mins post-sonication. The growth of the small molecule peak at an elution time of ~20 min in the UV-detected chromatograms is indicative of hydroxycoumarin generation. The M_n decreases steadily from 88 kg/mol to 49 kg/mol over 300 min of ultrasonication, with the GPC-RI chromatograms exhibiting characteristic features of midchain scission. Note that the GPC-RI chromatogram for the unactivated polymer (0 min) was acquired separately resulting in slight differences in retention time.

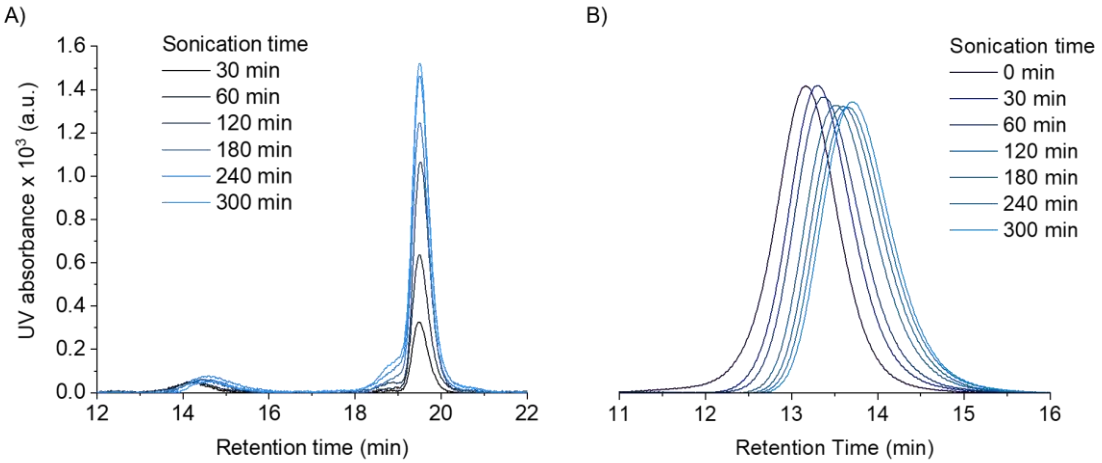


Figure S4. GPC traces as a function of ultrasonication time for **PMA(NH)** monitored using a (A) UV-vis detector (λ = 357–373 nm) and (B) refractive index (RI) detector. Measurements were performed after incubation at room temperature for 3 days post-sonication. The growth of the small molecule peak at an elution time of ~20 min in the UV-detected chromatograms is indicative of aminocoumarin generation. The M_n decreases steadily from 90 kg/mol to 50 kg/mol over 300 min of ultrasonication; however, unlike the behavior of **PMA(O)**, the GPC-RI peaks shift continuously to longer retention times without the characteristic features of midchain scission. This behavior is attributed, at least in part, to the broader molecular weight distribution of **PMA(NH)** ($Đ$ = 1.15) and greater competition between mechanophore activation and nonspecific backbone scission. Note that the GPC-RI chromatogram for the unactivated polymer (0 min) was acquired separately resulting in slight differences in retention time.

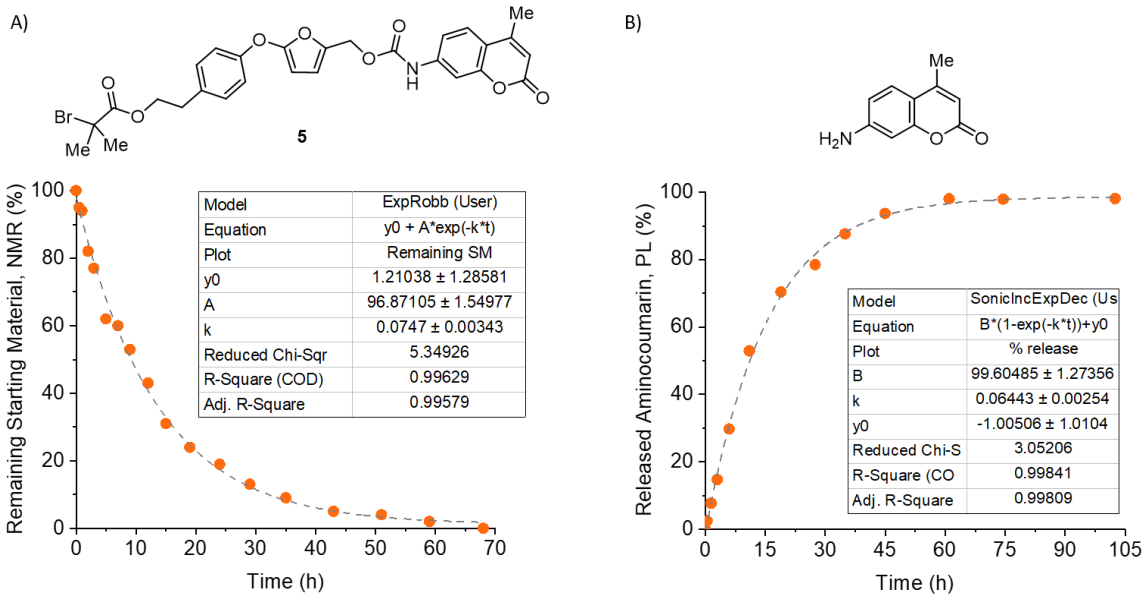


Figure S5. Results of small molecule model experiments measuring the room temperature decomposition of furfuryl carbamate **5** in acetonitrile/methanol (3:1 v/v). Time course experiments following (A) the conversion of model compound **5** by ^{1}H NMR spectroscopy (3:1 acetonitrile-d_3/methanol; $[\mathbf{5}]_0$ = 21 mM), and (B) the generation of aminocoumarin by photoluminescence spectroscopy (3:1 acetonitrile/methanol; λ_{ex} = 365 nm; λ_{em} = 424 nm; $[\mathbf{5}]_0$ = 7.0 µM). The concentration of aminocoumarin from PL spectroscopy was calculated based on a standard calibration curve (Fig. S8). Fitting the curves to a first-order rate expression (dashed grey lines) gives half-lives for consumption of **5** (NMR) and generation of aminocoumarin (PL) of $t_{1/2}$ = 9.3 and 10.8 h, respectively.

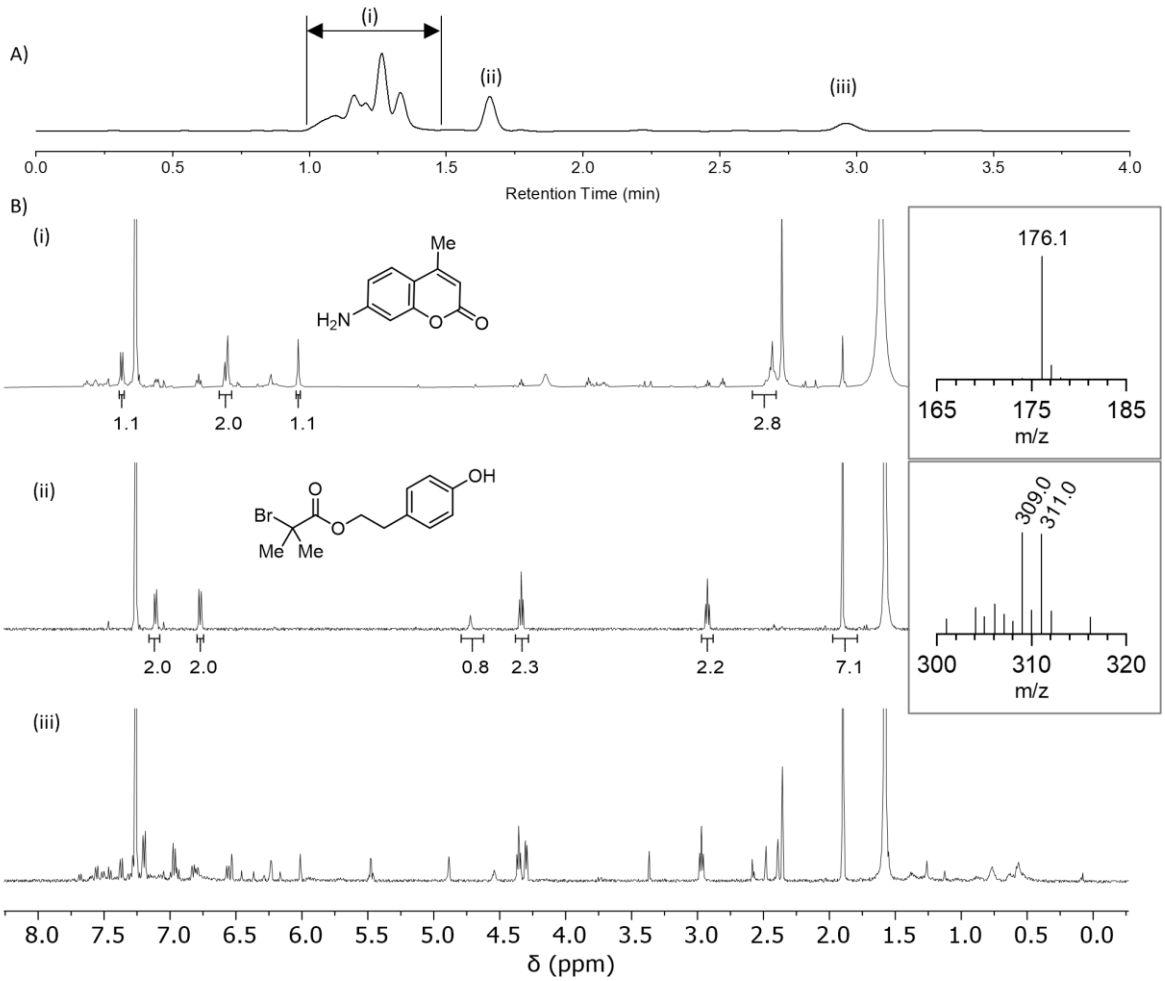


Figure S6. Product analysis of the decomposition of model compound **5** in 3:1 acetonitrile-d_3/methanol ([**5**]$_0$ = 7.0 μM). (A) The preparatory-HPLC trace of the mixture after 3 days of decomposition monitored at 285 nm. HPLC conditions: 80% acetonitrile in water, 8 mL/min. (B) ^{1}H NMR spectra (500 MHz, $CDCl_3$) of the fractions isolated after HPLC separation. (i) ^{1}H NMR spectrum corresponding to the retention times 1.0–1.5 min in the HPLC chromatogram showing aminocoumarin as a major product. The assignment is further supported by LCMS measurements. The mass of the analyte (m/z= 176.1 amu) matches the calculated m/z for 7-amino-4-methylcoumarin, $[C_{10}H_{10}NO_2]^+$ $(M+H)^+$ (176.1). (ii) ^{1}H NMR spectrum corresponding to the peak at 1.7 min in the HPLC chromatogram identified as a tyrosol alkyl ester derivative. The assignment is further supported by LCMS measurements. The mass of the analyte (m/z= 309.0 amu) matches the calculated m/z for 4-hydroxyphenethyl 2-bromo-2-methylpropanoate, $[C_{12}H_{15}BrO_3Na]^+$ $(M+Na)^+$ (309.0). (iii) ^{1}H NMR spectrum corresponding to the peak at 3.0 min in the HPLC chromatogram representing a mixture of products that was not identified.

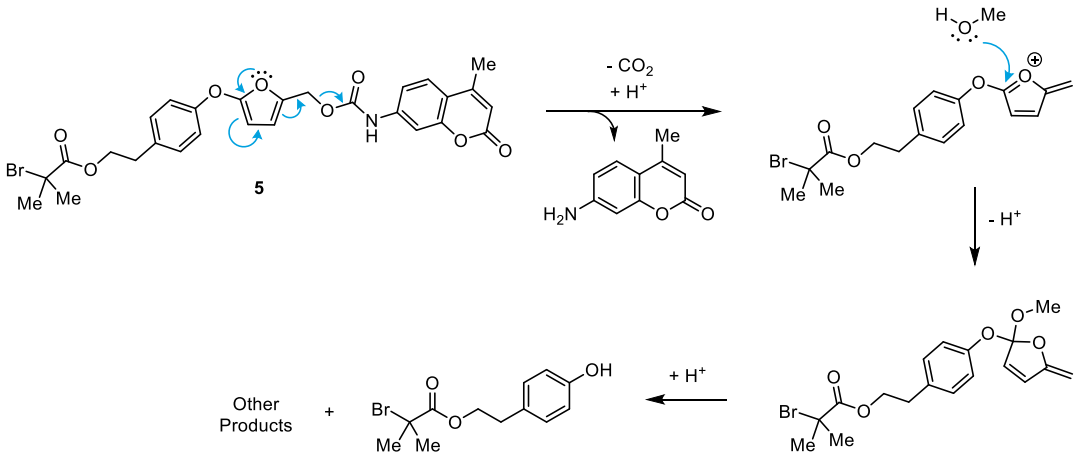


Figure S7. Proposed mechanism for the generation of major products aminocoumarin and the tyrosol alkyl ester via the room temperature decomposition of furfuryl carbamate **5** in 3:1 acetonitrile/methanol.

III. Characterization of Molecular Release Using PL Spectroscopy

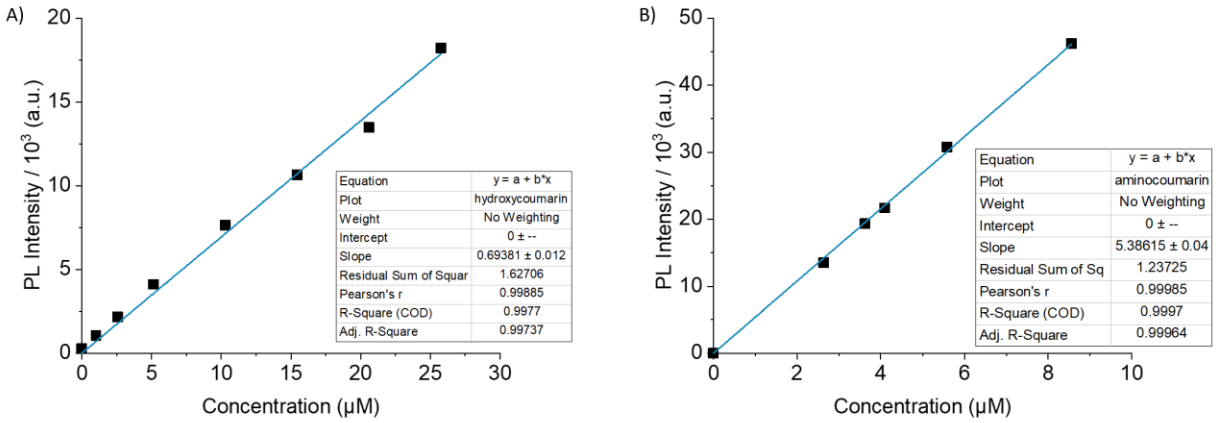


Figure S8. Calibration curves for experimental determination of the concentration of (A) 7-hydroxy-4-methylcoumarin (λ_{ex} = 330 nm, λ_{em} = 380 nm), and (B) 7-amino-4-methylcoumarin (λ_{ex} = 365 nm, λ_{em} = 424 nm) in acetonitrile/methanol (3:1 v/v).

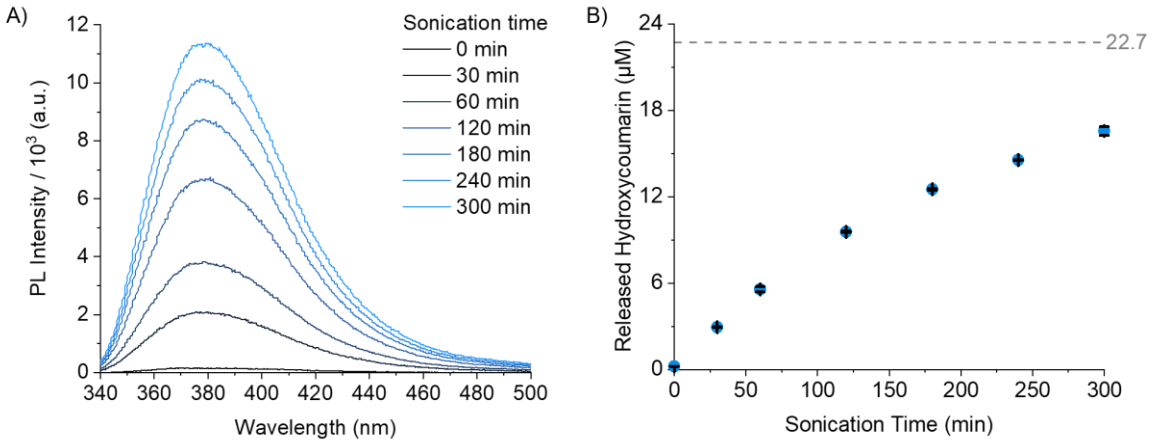


Figure S9. (A) Representative PL spectra of a 2.0 mg/mL solution of **PMA(O)** in acetonitrile/methanol (3:1 v/v) after being subjected to ultrasonication for the indicated amount of time. Aliquots were kept at room temperature for 30 min prior to analysis. λ_{ex} = 330 nm. (B) Concentrations of hydroxycoumarin released from **PMA(O)** as a function of ultrasonication time calculated from the fluorescence intensity at 378 nm using a standard calibration curve. The theoretical concentration of hydroxycoumarin based on 100% release from the mechanophore is 22.7 μM. Each data point is the average of two measurements with the error bars denoting the range of the two values.

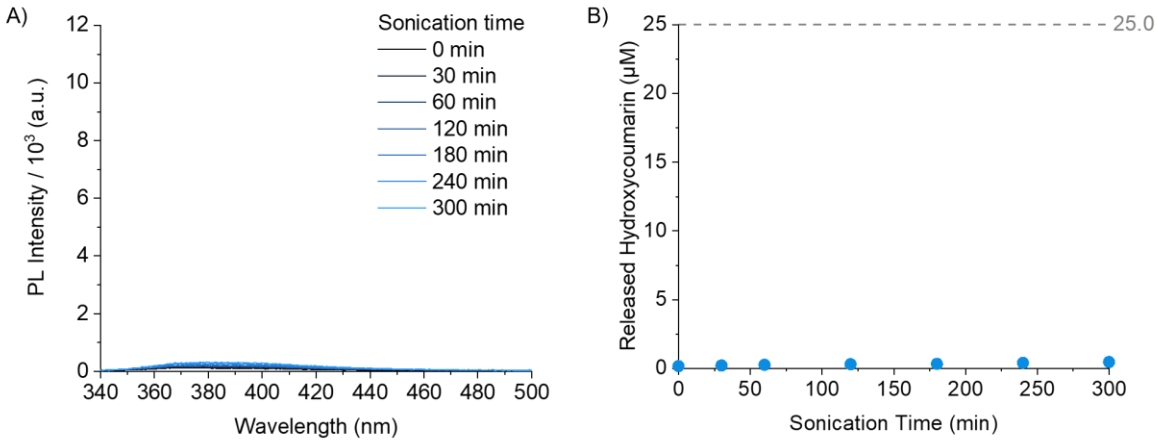


Figure S10. (A) PL spectra of a 2.0 mg/mL solution of chain-end functional control polymer **PMA(O)-control** in acetonitrile/methanol (3:1 v/v) after being subjected to ultrasonication for the indicated amount of time. Aliquots were kept at room temperature for 30 min prior to analysis. λ_{ex} = 330 nm. (B) Concentrations of hydroxycoumarin released from **PMA(O)-control** as a function of ultrasonication time calculated from the fluorescence intensity at 378 nm using a standard calibration curve. The theoretical concentration of hydroxycoumarin based on 100% release from the mechanophore is 25.0 μM.

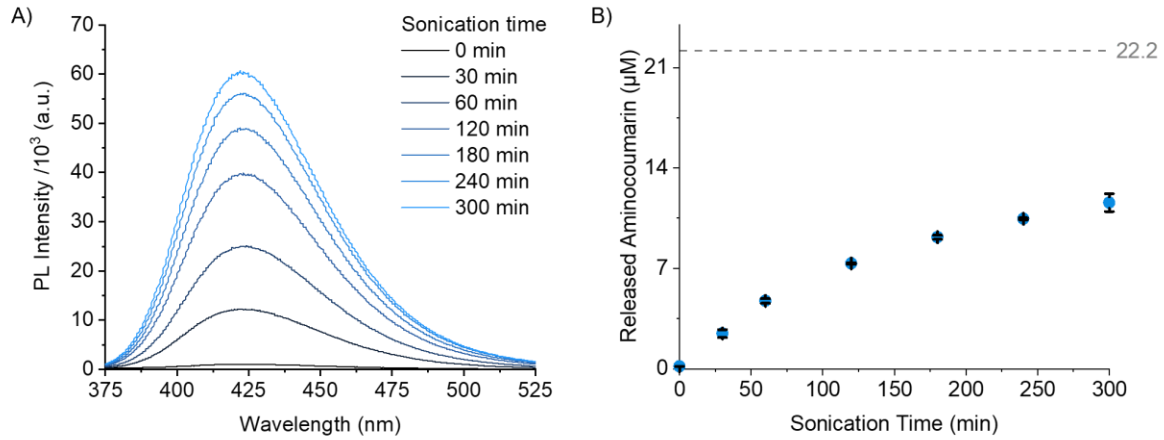


Figure S11. (A) Representative PL spectra of a 2.0 mg/mL solution of **PMA(NH)** in acetonitrile/methanol (3:1 v/v) after being subjected to ultrasonication for the indicated amount of time. Aliquots were kept at room temperature for 3 days prior to analysis. λ_{ex} = 365 nm. (B) Concentrations of aminocoumarin released from **PMA(NH)** as a function of ultrasonication time calculated from the fluorescence intensity at 424 nm using a standard calibration curve. The theoretical concentration of hydroxycoumarin based on 100% release from the mechanophore is 22.2 μM. Each data point is the average of two measurements with the error bars denoting the range of the two values.

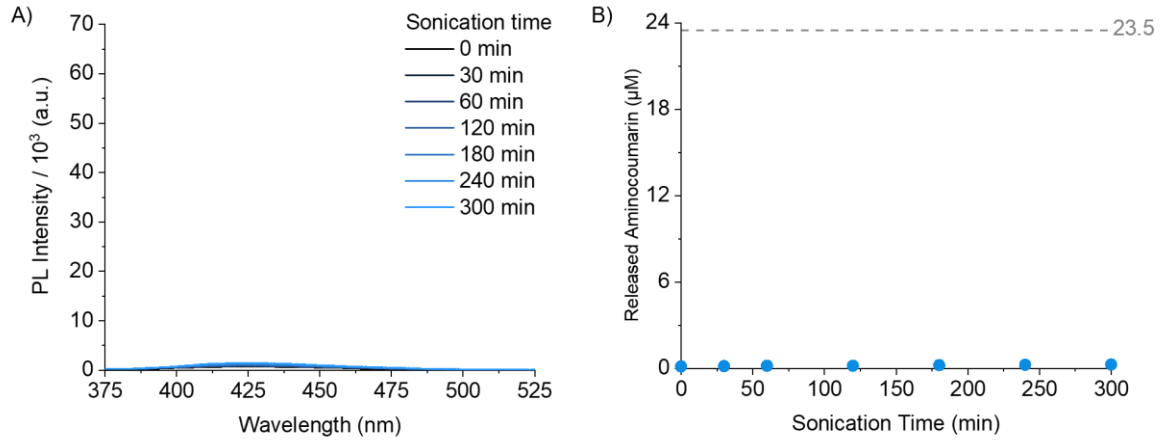


Figure S12. (A) PL spectra of a 2.0 mg/mL solution of chain-end functional control polymer **PMA(NH)-control** in acetonitrile/methanol (3:1 v/v) after being subjected to ultrasonication for the indicated amount of time. Aliquots were kept at room temperature for 3 days prior to analysis. λ_{ex} = 365 nm. (B) Concentrations of aminocoumarin released from **PMA(NH)-control** as a function of ultrasonication time calculated from the fluorescence intensity at 424 nm using a standard calibration curve. The theoretical concentration of hydroxycoumarin based on 100% release from the mechanophore is 23.5 μM.

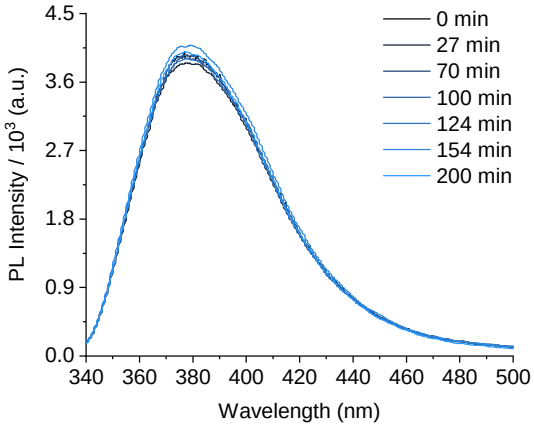


Figure S13. Characterization of hydroxycoumarin release from a 2.0 mg/ml solution of **PMA(O)** in acetonitrile/methanol (3:1 v/v) after ultrasound-induced mechanochemical activation for 60 min (sonication "on" time). The sonicated solution was warmed to room temperature and PL spectra were recorded at the indicated times after sonication ended. λ_{ex}= 330 nm. The data indicate that hydroxycoumarin release was completed prior to the first measurement.

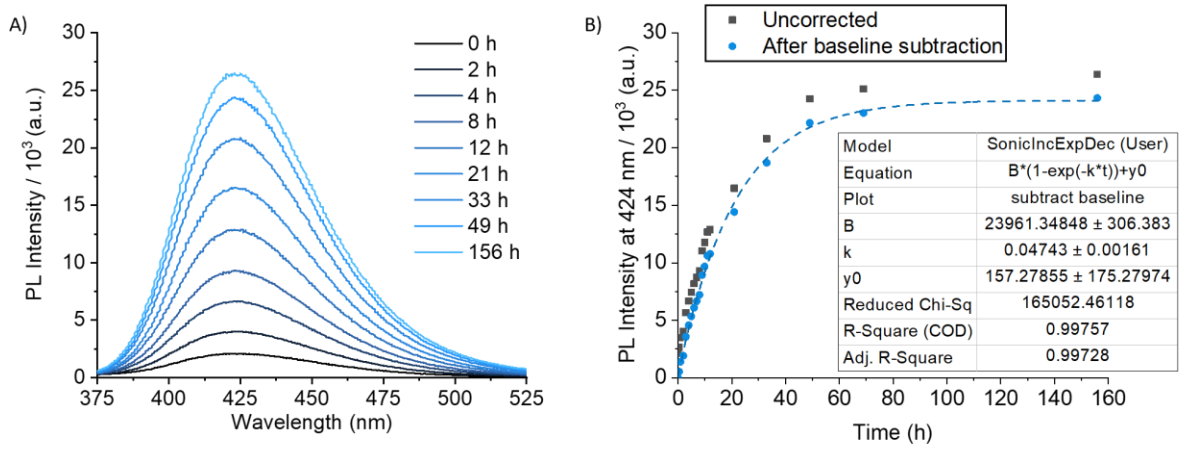
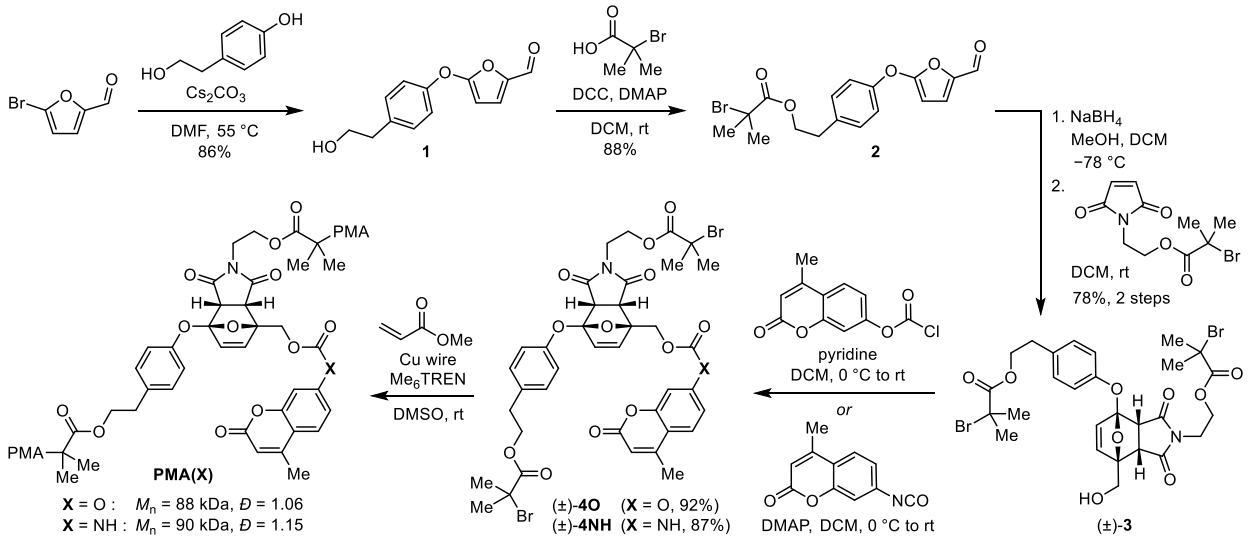


Figure S14. Characterization of aminocoumarin release from a 2.0 mg/ml solution of **PMA(NH)** in acetonitrile/methanol (3:1 v/v) after ultrasound-induced mechanochemical activation for 60 min (sonication "on" time). (A) Representative PL spectra of the sonicated solution at room temperature recorded at the indicated times after sonication ended. (B) PL intensity at 424 nm as a function of time post-sonication. The background fluorescence at the start of the experiment (resulting from the release of aminocoumarin cargo during ultrasonication) was subtracted from each subsequent measurement. λ_{ex}= 365 nm. Fitting the baseline corrected data to a first-order rate expression (dashed blue line) gives a half-life of $t_{1/2}$ = 14.6 h.

IV. Synthetic Details



5-(4-(2-hydroxyethyl)phenoxy)furan-2-carbaldehyde (1). A round bottom flask equipped with a stir bar was charged with 5-bromo-2-furaldehyde (1.0 g, 5.7 mmol), 4-(2-hydroxyethyl)phenol (1.0 g, 7.4 mmol), and Cs_2CO_3 (2.4 g, 7.4 mmol). The flask was purged with N_2 before DMF (11 mL) was added. The solution was then heated and kept at 55 °C in an oil bath for 4 h. The reaction was then cooled to room temperature before 10% NH_4Cl (50 mL) was added. The mixture was then extracted with Et_2O (3 x 50 mL) and the combined organic phase was washed with brine (150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was then purified by column chromatography (30–60% EtOAc/hexanes) to afford the title compound as a yellow oil, which solidified upon storage in the freezer (1.14 g, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.38 (s, 1H), 7.30 – 7.23 (m, 1H), 7.21 (d, *J* = 3.8 Hz, 1H), 7.15 – 7.06 (m, 1H), 5.55 (d, *J* = 3.8 Hz, 1H), 3.87 (t, *J* = 6.6 Hz, 2H), 2.88 (t, *J* = 6.6 Hz, 2H), 1.68 (s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 175.7, 163.1, 152.8, 144.8, 136.6, 130.6, 125.2, 119.1, 89.8, 63.4, 38.4 ppm. HRMS (FAB, *m/z*): calcd for $[C_{13}H_{13}O_4]^+$ $(M+H)^+$, 233.0808; found, 233.0814.

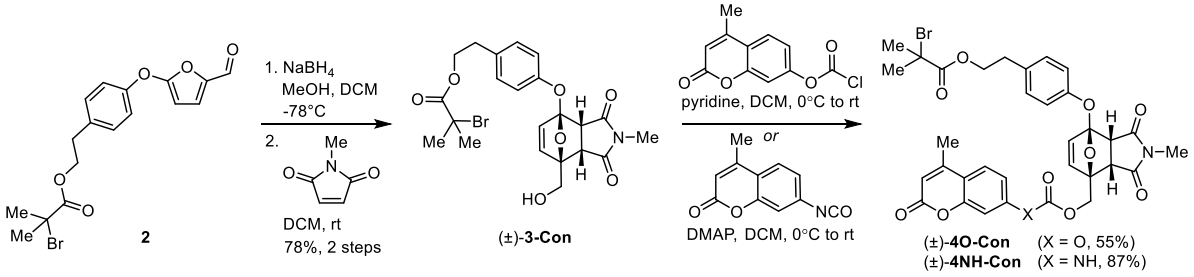
4-((5-formylfuran-2-yl)oxy)phenethyl 2-bromo-2-methylpropanoate (2). A round bottom flask equipped with a stir bar was charged with **1** (100 mg, 0.431 mmol), DCC (107 mg, 0.517 mmol), DMAP (13.1 mg, 0.108 mmol), and DCM (1 mL). The solution was then stirred to dissolve all reagents before α-bromoisobutyric acid was added (79.0 mg, 0.473 mmol). The solution was stirred at room temperature overnight and then the solid precipitate was filtered off and discarded. The filtrate was diluted with Et_2O (10 mL) and washed consecutively with 10% NH_4Cl (5 mL) and brine (5 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 (20–40% EtOAc/hexanes) to afford the title compound as a dark yellow oil, which solidified upon storage in the freezer (143 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.40 (s, 1H), 7.28 (app d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 3.8 Hz, 1H), 7.12 (app d, *J* = 8.3 Hz, 2H), 5.54 (d, *J* = 3.7 Hz, 1H), 4.38 (t, *J* = 6.8 Hz, 2H), 3.01 (t, *J* = 6.8 Hz, 2H), 1.89 (s,

6H) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ: 175.9, 171.7, 163.0, 153.2, 145.0, 135.5, 130.8, 125.5 119.3, 89.9, 66.3, 55.8, 34.3, 30.9 ppm. HRMS (FAB, *m/z*): calcd for $[C_{17}H_{18}BrO_5]^+$ $(M+H)^+$, 381.0332; found, 381.0335.

4-((2-(2-((2-bromo-2-methylpropanoyl)oxy)ethyl)-7-(hydroxymethyl)-1,3-dioxo-1,2,3,3a,7,7a-hexahydro-4H-4,7-epoxyisoindol-4-yl)oxy)phenethyl 2-bromo-2-methylpropanoate ((±)-3). A flame-dried round bottom flask equipped with a stir bar was charged with **2** (152 mg, 0.40 mmol), DCM (2 mL), and MeOH (2 mL). The solution was cooled to −78 °C in an acetone/dry ice bath before adding $NaBH_4$ (82.0 mg, 2.17 mmol) in three portions. The mixture was kept at −78 °C overnight before being quenched with 10% NH_4Cl (10 mL) and subsequently warmed to room temperature. The solution was then extracted with EtOAc (2 x 10 mL) and the organic phase was washed with brine (10 mL). The organic layer was dried over Na_2SO_4, and filtered. 2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl 2-bromo-2-methylpropanoate[3] (150 mg, 0.52 mmol) was then added to the filtrate, which was then concentrated under reduced pressure until ~2 mL of viscous solution remained. The solution was then reacted at room temperature for 12 h, and the crude mixture was purified by column chromatography (40–70% EtOAc/hexanes). A racemic mixture of the *endo* diastereomer of the title compound was isolated as a foamy white solid (210 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (s, 4H), 6.45 (d, *J* = 5.8 Hz, 1H), 6.41 (d, *J* = 5.8 Hz, 1H), 4.35 (m, 2H), 4.31 – 4.12 (m, 4H), 3.73 – 3.64 (m, 4H), 2.96 (t, *J* = 6.9 Hz, 2H), 2.05 (m, 1H), 1.90 (d, *J* = 1.2 Hz, 6H), 1.88 (s, 6H) ppm. $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ: 174.4, 173.4, 171.7, 171.5, 153.2, 135.7, 135.7, 134.0, 130.1, 120.9, 113.5, 86.7, 66.4, 62.6, 61.9, 55.9, 55.6, 50.6, 48.9, 37.7, 34.2, 30.9, 30.8 ppm. HRMS (FAB, *m/z*): calcd for $[C_{27}H_{32}Br_2NO_9]^+$ $(M+H)^+$, 672.0438; found, 672.0459.

4-((2-(2-((2-bromo-2-methylpropanoyl)oxy)ethyl)-7-(((((4-methyl-2-oxo-2H-chromen-7-yl)oxy)carbonyl)oxy)methyl)-1,3-dioxo-1,2,3,3a,7,7a-hexahydro-4H-4,7-epoxyisoindol-4-yl)oxy)phenethyl 2-bromo-2-methylpropanoate ((±)-4O). A round bottom flask equipped with a stir bar was charged with (±)-**3** (188 mg, 0.282 mmol) and DCM (15 mL). The solution was cooled to 0 °C in an ice bath before adding 4-methylcoumarin-7-chloroformate[1] (153 mg, 0.845 mmol) in DCM (10 mL) then anhydrous pyridine (68 µL, 0.85 mmol). The mixture was then warmed to room temperature, and stirred for 1 h. The mixture was then washed with 10% NH_4Cl (10 mL), extracted with EtOAc (10 mL) and washed with brine (10 mL). The organic layer was dried over Na_2SO_4, and filtered. The crude mixture was purified by column chromatography (40–70% EtOAc/hexanes) to afford the titled compound as a white foamy solid (228 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 8.7 Hz, 1H), 7.29 (d, *J* = 2.3 Hz, 1H), 7.23 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.19 (s, 4H), 6.51 (d, *J* = 5.8 Hz, 1H), 6.46 (d, *J* = 5.8 Hz, 1H), 6.30 (d, *J* = 1.4 Hz, 1H), 4.89 (ABq, $\Delta\nu_{AB}$ = 87.2 Hz, J_{AB} = 12.0 Hz, 2H), 4.43 – 4.31 (m, 2H), 4.25 (t, *J* = 5.1 Hz, 2H), 3.78 – 3.67 (m, 4H), 2.97 (t, *J* = 6.9 Hz, 2H), 2.45 (d, *J* = 1.2 Hz, 3H), 1.90 (s, 6H), 1.88 (s, 6H) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ: 173.6, 173.0, 171.7, 171.5, 160.5, 154.3, 153.2, 153.2, 152.8, 151.9, 136.1, 135.0, 134.2, 130.2, 125.8, 121.1, 118.4, 117.5, 115.0, 113.6, 110.2, 83.7, 66.4, 66.3, 62.6, 55.9, 55.6, 50.1, 49.7, 37.8, 34.3, 30.9, 30.8, 18.9 ppm. HRMS (FAB, *m/z*): calcd for $[C_{38}H_{38}Br_2NO_{13}]^+$ $(M+H)^+$, 874.0704; found, 874.0719.

4-((2-(2-((2-bromo-2-methylpropanoyl)oxy)ethyl)-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)phenethyl 2-bromo-2-methylpropanoate ((±)-4NH). A round bottom flask equipped with a stir bar was charged with (±)-**3** (100 mg, 0.149 mmol) and DCM (2 mL). The solution was cooled to 0 °C in an ice bath before adding 4-methylcoumarin-7-isocyanate[2] (38.9 mg, 0.845 mmol) and then DMAP (1.8 mg, 0.015 mmol). The mixture was warmed to room temperature and stirred for 1 h. The mixture was then washed with 10% NH_4Cl (10 mL), extracted with EtOAc (10 mL), and the organic phase was washed with brine (10 mL). The organic layer was dried over Na_2SO_4 and filtered. The crude mixture was purified by column chromatography (70–100% EtOAc/hexanes) to afford the title compound as a white foamy solid (113 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 8.7 Hz, 1H), 7.49 (d, *J* = 2.2 Hz, 1H), 7.43 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.30 (s, 1H), 7.16 (s, 4H), 6.47 (d, *J* = 5.7 Hz, 1H), 6.43 (d, *J* = 5.8 Hz, 1H), 6.22 – 6.19 (m, 1H), 4.82 (ABq, ΔνAB = 79.1 Hz, J_{AB} = 12.0 Hz, 2H), 4.34 (t, *J* = 6.9 Hz, 2H), 4.28 – 4.15 (m, 2H), 3.78 – 3.61 (m, 4H), 2.94 (t, *J* = 6.9 Hz, 2H), 2.41 (d, *J* = 1.2 Hz, 3H), 1.89 (d, *J* = 1.3 Hz, 6H), 1.87 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 173.5, 173.1, 171.7, 171.5, 161.1, 154.6, 153.1, 152.3, 152.3, 141.2, 135.8, 135.4, 134.2, 130.2, 125.6, 121.1, 115.9, 114.6, 113.6, 113.5, 106.3, 84.3, 66.4, 63.2, 62.6, 55.9, 55.7, 50.1, 49.6, 37.7, 34.2, 30.9, 30.8, 18.7 ppm. HRMS (FAB, *m/z*): calcd for $[C_{38}H_{39}Br_2N_2O_{12}]^+$ $(M+H)^+$, 873.0864; found, 873.0898.

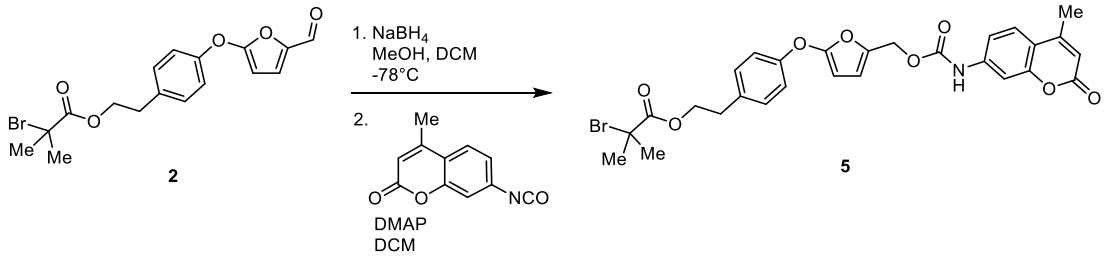


4-((7-(hydroxymethyl)-2-methyl-1,3-dioxo-1,2,3,3a,7,7a-hexahydro-4H-4,7-epoxyisoindol-4-yl)oxy)phenethyl 2-bromo-2-methylpropanoate ((±)-3-Con). The title compound was prepared following a similar procedure as that for compound (±)-**3**, with compound **2** (500 mg, 1.32 mmol), $NaBH_4$ (100 mg, 2.63 mmol), and N-methylmaleimide (175 mg, 1.58 mmol). The crude mixture was purified by column chromatography (40–70% EtOAc/hexanes). A racemic mixture of the *endo* diastereomer of the title compound was isolated as a foamy white solid (566 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (s, 4H), 6.39 (d, *J* = 5.8 Hz, 1H), 6.35 (d, *J* = 5.8 Hz, 1H), 4.39 – 4.31 (m, 2H), 4.28 (dd, *J* = 12.6, 5.4 Hz, 1H), 4.17 (dd, *J* = 12.6, 7.0 Hz, 1H), 3.72 – 3.62 (m, 2H), 2.95 (t, *J* = 6.9 Hz, 2H), 2.85 (s, 3H), 2.22 – 2.14 (m, 1H), 1.88 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 174.8, 173.8, 171.7, 153.3, 135.7, 135.6, 133.9, 130.1, 120.9, 113.5, 86.6, 66.4, 61.9, 55.9, 50.6, 49.0, 34.2, 30.9, 24.9 ppm. HRMS (FAB, *m/z*): calcd for $[C_{22}H_{25}BrNO_7]^+$ $(M+H)^+$, 494.0809; found, 494.0799.

4-((2-methyl-7-(((((4-methyl-2-oxo-2H-chromen-7-yl)oxy)carbonyl)oxy)methyl)-1,3-dioxo-1,2,3,3a,7,7a-hexahydro-4H-4,7-epoxyisoindol-4-yl)oxy)phenethyl 2-bromo-2-methylpropanoate ((±)-4O-Con). The title compound was prepared following a similar procedure as that for compound (±)-**4O**, with compound (±)-**3-Con** (44 mg, 0.089 mmol), 4-methylcoumarin-7-chloroformate[1] (30.0 mg, 0.125 mmol), anhydrous pyridine (13 µL,

0.13 mmol), and DCM (6 mL). The crude mixture was purified by column chromatography (40–70% EtOAc/hexanes) to afford the title compound as a foamy white solid (34 mg, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 8.7 Hz, 1H), 7.29 (d, *J* = 2.3 Hz, 1H), 7.22 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.19 (s, 4H), 6.45 (d, *J* = 5.8 Hz, 1H), 6.40 (d, *J* = 5.8 Hz, 1H), 6.29 (s, 1H), 4.89 (ABq, $\Delta\nu_{AB}$ = 99.5Hz, J_{AB} = 10.0 Hz, 2H), 4.39 – 4.31 (m, 2H), 3.73 (s, 2H), 2.96 (t, *J* = 6.9 Hz, 2H), 2.88 (s, 3H), 2.45 (s, 3H), 1.88 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 173.9, 173.4, 171.7, 160.5, 154.3, 153.2, 153.2, 152.8, 151.9, 136.0, 134.9, 134.1, 130.2, 125.7, 121.0, 118.4, 117.5, 114.9, 113.5, 110.2, 83.6, 66.4, 66.4, 55.9, 50.1, 49.7, 34.2, 30.9, 25.0, 18.9 ppm. HRMS (FAB, *m/z*): calcd for $[C_{33}H_{31}BrNO_{11}]^+$ $(M+H)^+$, 696.1075; found, 696.1060.

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)phenethyl 2-bromo-2-methylpropanoate ((±)-4NH-Con). The title compound was prepared following a similar procedure as that for compound (±)-**4NH**, with compound (±)-**3-Con** (100 mg, 0.2 mmol), 4-methylcoumarin-7-isocyanate[2] (52.9 mg, 0.263 mmol), DMAP (2.4 mg, 0.020 mmol), and DCM (3 mL). The crude mixture was purified by column chromatography (50–100% EtOAc/hexanes) to afford the title compound as a foamy white solid (121 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 8.7 Hz, 1H), 7.48 (d, *J* = 2.1 Hz, 1H), 7.43 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.29 (s, 1H), 7.19 – 7.13 (m, 4H), 6.41 (d, *J* = 5.8 Hz, 1H), 6.38 (d, *J* = 5.8 Hz, 1H), 6.22 – 6.19 (m, 1H), 4.83 (ABq, $\Delta\nu_{AB}$ = 66.9 Hz, J_{AB} = 12.0 Hz, 2H), 4.34 (t, *J* = 6.9 Hz, 2H), 3.73 (d, *J* = 7.9 Hz, 1H), 3.66 (d, *J* = 7.9 Hz, 1H), 2.94 (t, *J* = 6.9 Hz, 2H), 2.86 (s, 3H), 2.41 (d, *J* = 1.3 Hz, 3H), 1.87 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 174.0, 173.6, 171.7, 161.1, 154.6, 153.2, 152.3, 141.2, 135.8, 135.3, 134.1, 130.2, 125.6, 121.0, 116.0, 114.6, 113.5, 106.3, 84.2, 66.4, 63.3, 55.9, 50.2, 49.6, 34.2, 30.9, 25.0, 18.7 ppm. HRMS (FAB, *m/z*): calcd for $[C_{33}H_{32}BrN_2O_{10}]^+$ $(M+H)^+$, 695.1235; found, 695.1262.



4-((5-((((4-methyl-2-oxo-2H-chromen-7-yl)carbamoyl)oxy)methyl)furan-2-yl)oxy)phenethyl 2-bromo-2-methylpropanoate (5). A 20 mL flame-dried vial equipped with a stir bar was charged with **2** (104 mg, 0.272 mmol), MeOH (2 mL), and DCM (2 mL). The solution was cooled to −78 °C in an acetone/dry ice bath before adding $NaBH_4$ (82.0 mg, 2.17 mmol) in three portions. The mixture was kept at −78 °C overnight before being quenched with 10% NH_4Cl (10 mL) and warmed up to room temperature. The solution was then extracted with EtOAc (2 x 10 mL) and the organic phase was washed with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was then redissolved in DCM (2 mL) and cooled to 0 °C in an ice bath before adding 4-methylcoumarin-7-isocyanate[2] (72.8 mg, 0.353 mmol), followed by DMAP (1.0 mg, 0.031 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h before being quenched by adding a solution of glucose (35.0 mg, 0.194 mmol) in 3 mL DMF. The mixture was stirred at room temperature for 2 h to consume the excess isocyanate, then diluted with diethyl ether (20 mL)

and hexane (5 mL). A precipitate appeared immediately and the suspension was filtered to remove the excess glucose and other insoluble products. The filtrate was washed with aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, then concentrated. The crude material was again dispersed into a mixture of diethyl ether (5 mL) and hexane (10 mL), and then filtered 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 hexane (7 mL). The mixture was slowly concentrated to around half the original volume using a rotary evaporator causing an off-white precipitate to form. The off-white solid was collected carefully by removing the liquid using a pipet, and then the solid was washed with hexane and finally dried under high vacuum to yield metastable compound **5** a fluffy white solid (53 mg, 34% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.7 Hz, 1H), 7.47 – 7.44 (m, 1H), 7.35 (app d, *J* = 8.5 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.04 – 6.99 (m, 3H), 6.44 (d, *J* = 3.2 Hz, 1H), 6.19 (s, 1H), 5.49 (d, *J* = 3.3 Hz, 1H), 5.09 (s, 2H), 4.36 (t, *J* = 6.8 Hz, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.41 (s, 3H), 1.90 (s, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.7, 161.2, 157.5, 155.2, 154.6, 152.5, 152.3, 141.3, 133.7, 130.5, 125.5, 121.7, 117.6, 115.8, 114.5, 113.4, 113.2, 106.1, 89.5, 66.5, 59.5, 55.9, 34.2, 30.9, 18.7 ppm. HRMS (FAB, *m/z*): calcd for $[C_{28}H_{27}BrNO_8]^+$ $(M+H)^+$, 584.0915; found, 584.0916.

General Polymerization Procedure. Polymers were synthesized following the procedure reported previously.[1] A 10 mL Schlenk flask equipped with a stir bar was charged with the initiator (1 equiv), methyl acrylate (~1,500 equiv), Me_6TREN (2 equiv), and DMSO (equal volume to methyl acrylate). The flask was sealed, the solution was deoxygenated via 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 (ca. 1–2 h). The flask was then opened to air and the solution was diluted with DCM. The polymer was precipitated into cold methanol (2x) and the isolated polymer was thoroughly dried under vacuum and characterized by GPC-MALS. Molecular weight characterization data for all polymers studied are reported below in Table S1.

Table S1. Characterization of the polymers used in this study.

	M_n (kg/mol)	$Đ$
PMA(O)	88	1.06
PMA(NH)	90	1.15
PMA(O)-control	80	1.21
PMA(NH)-control	85	1.22

V. 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 anhydrous 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 20 min prior to sonication and for the duration of the sonication experiment. Pulsed ultrasound (1 s on/1 s off, 30% amplitude, 20 kHz, 8.2 W/cm^2) was then applied to the system. The solution temperature during sonication was measured to be 8–10 °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*.[4]

VI. Procedure for CoGEF calculations

CoGEF calculations were performed using Spartan ’18 Parallel Suite according to previously reported methods.[5,6] 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 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.

VII. References

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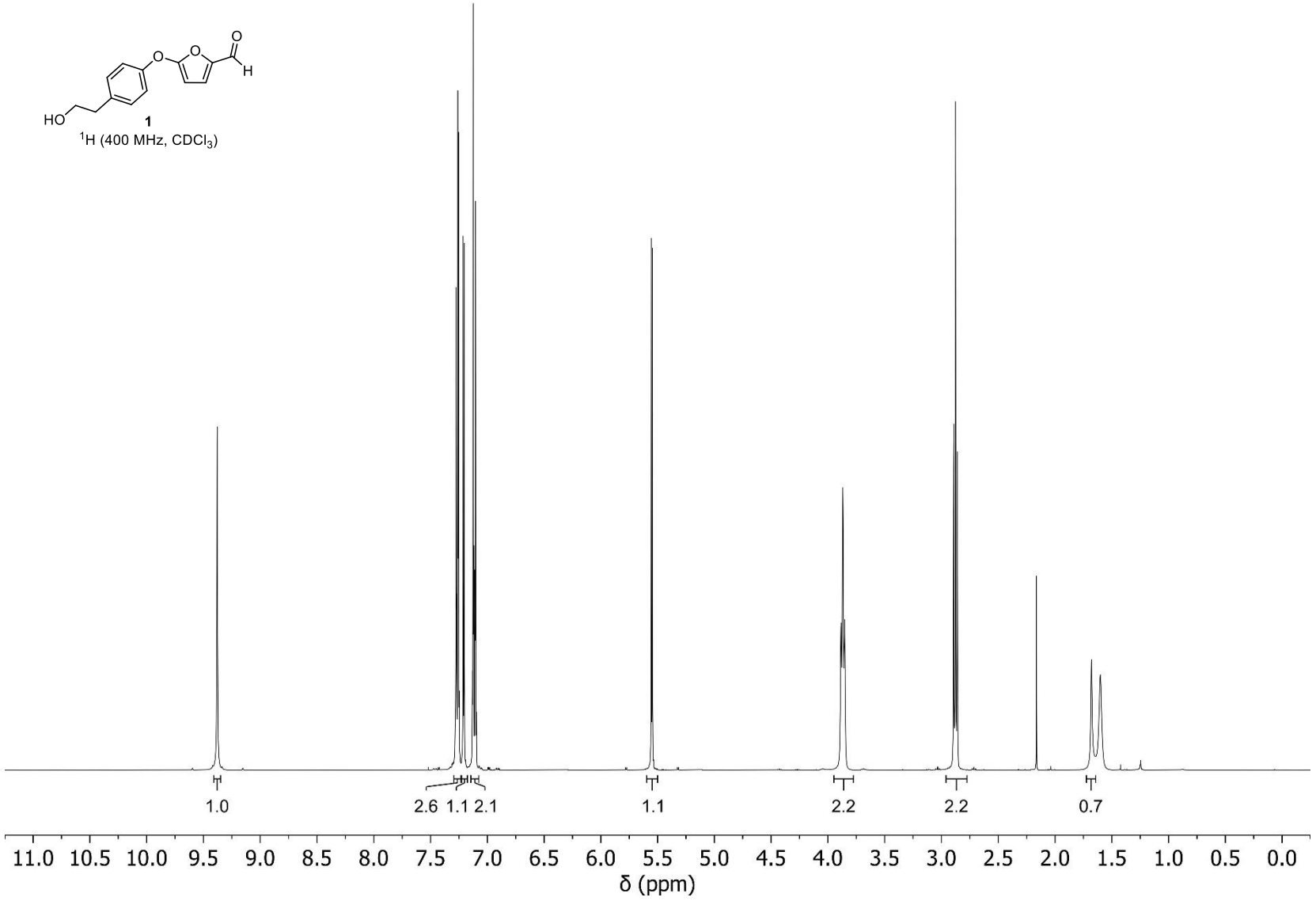
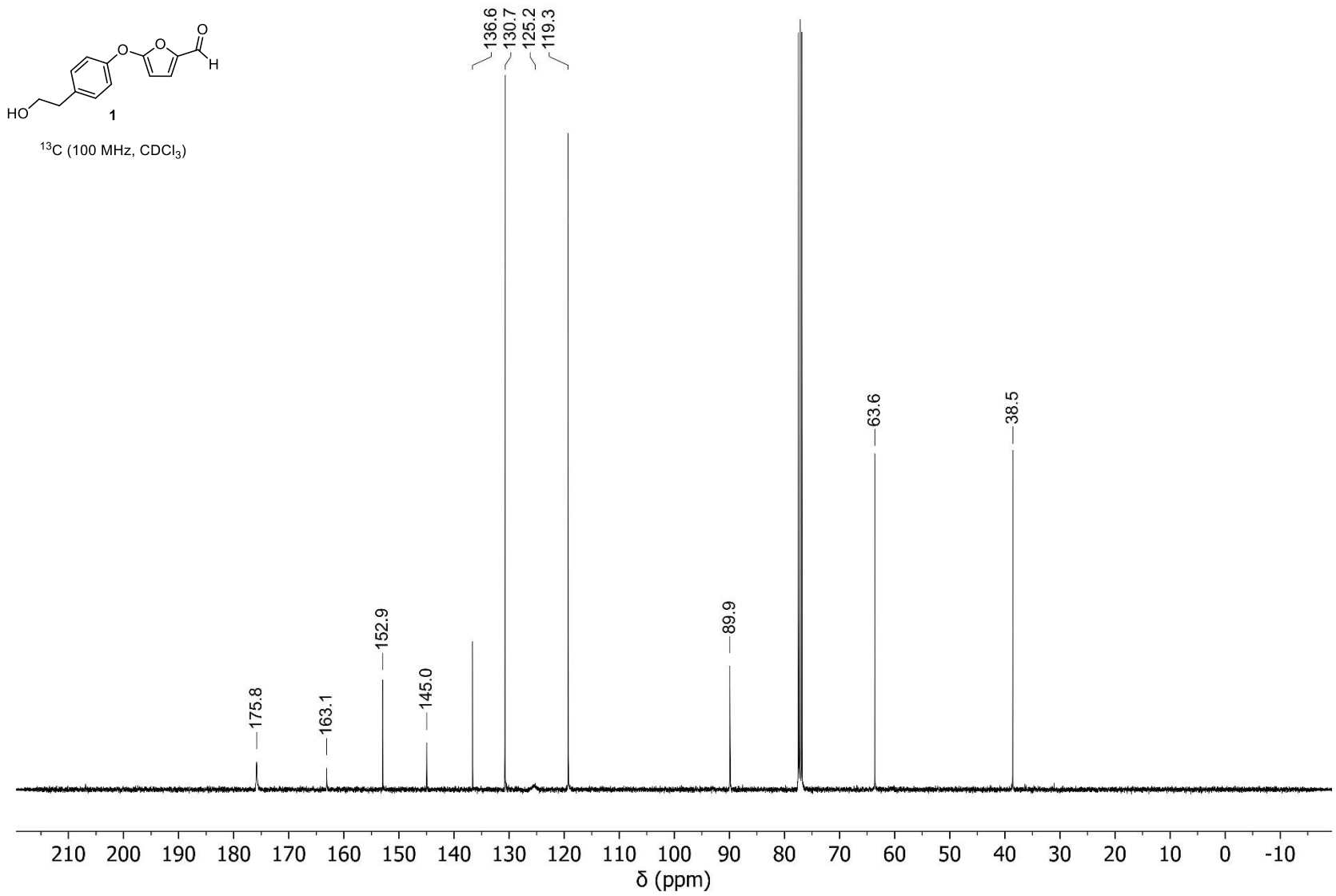
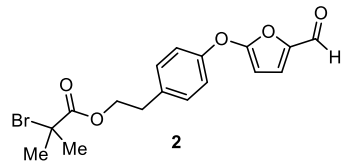
VIII. ^{1}H and ^{13}C NMR spectra

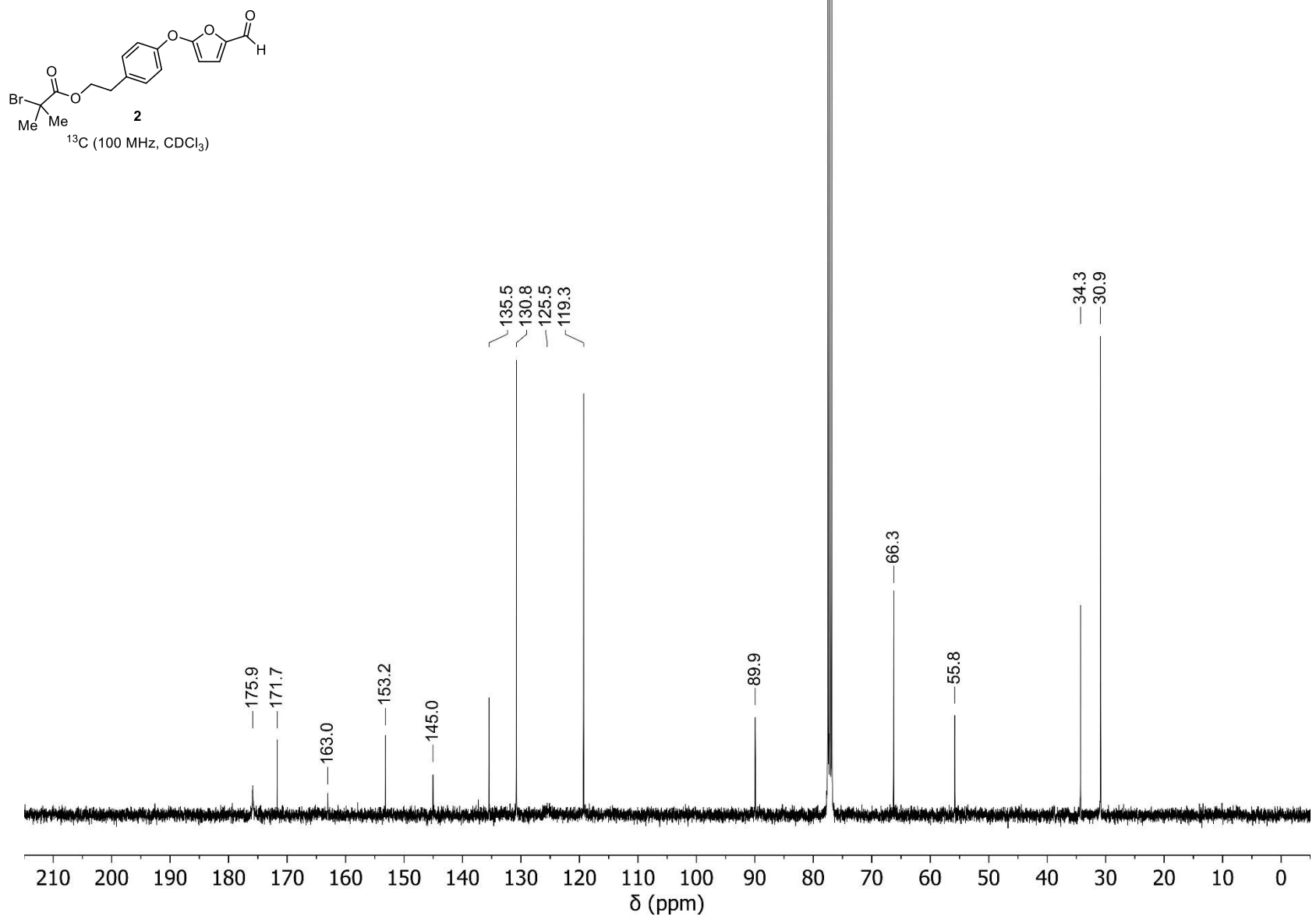


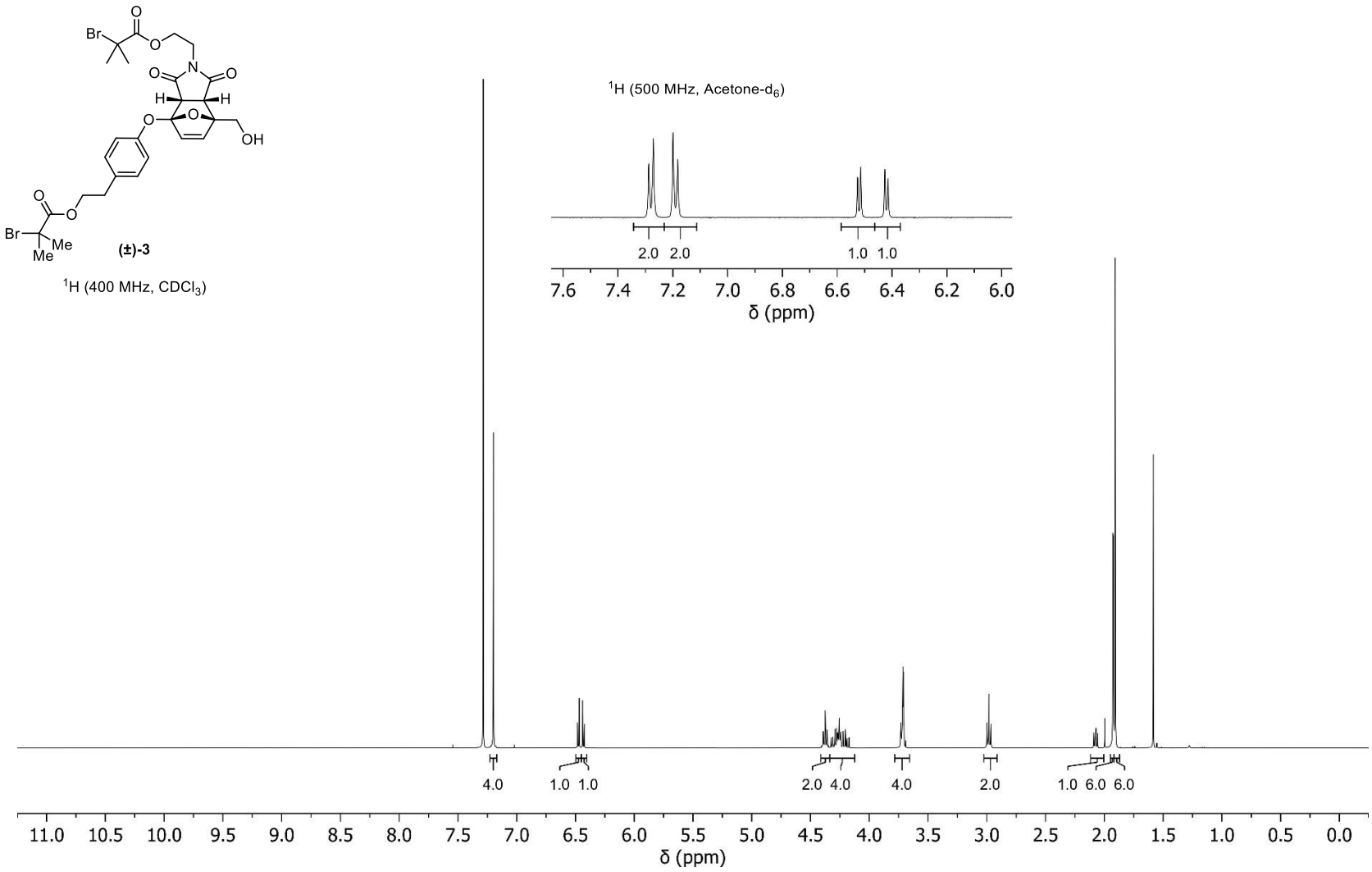

HO
O
O
O
H
1
^{13}C (100 MHz, CDCl$_3$)
136.6
130.7
125.2
119.3
175.8
163.1
152.9
145.0
89.9
63.6
38.5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

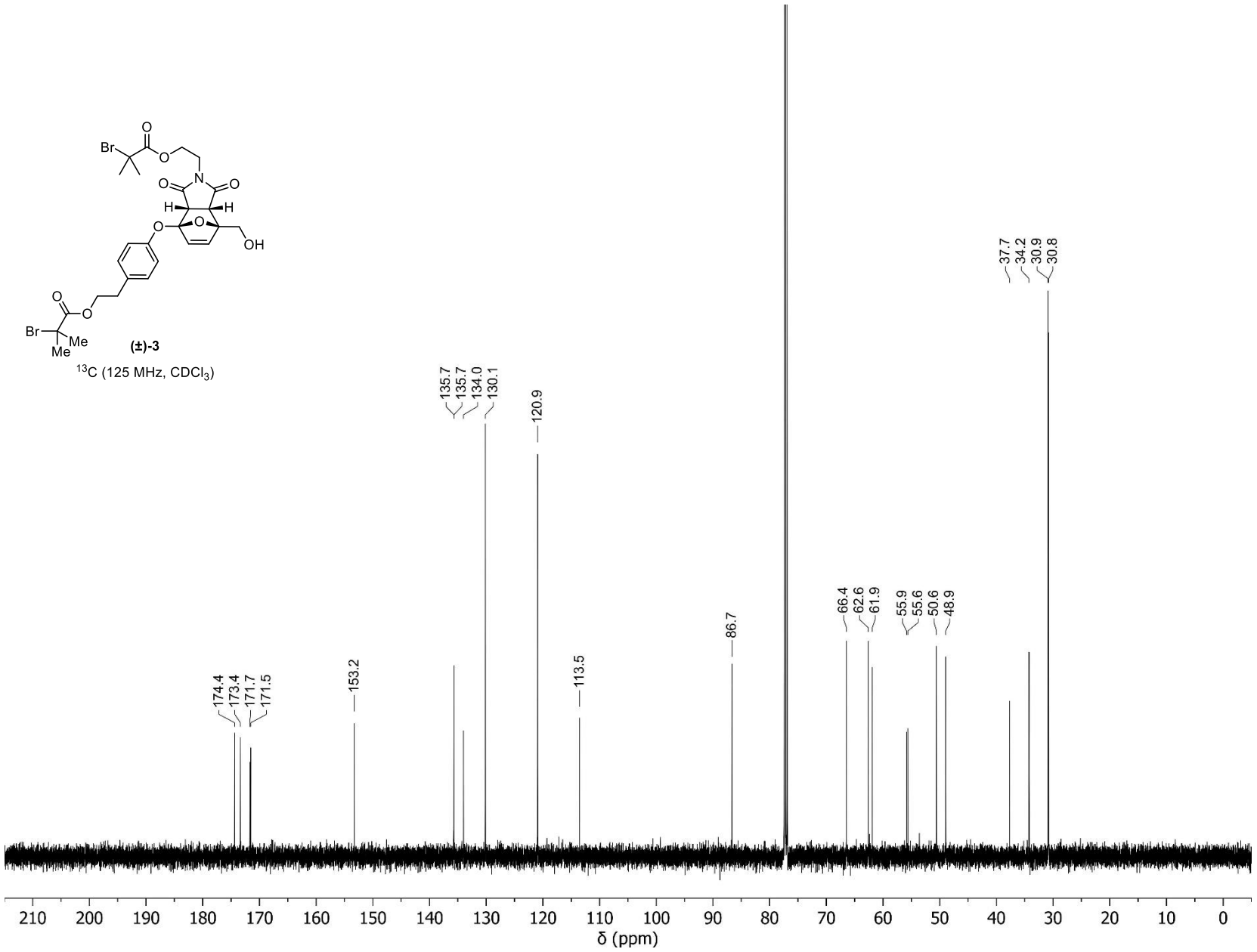


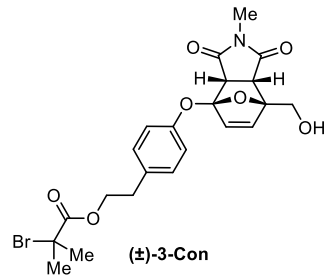
2

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


2
^{13}C (100 MHz, $CDCl_3$)
175.9
171.7
163.0
153.2
145.0
135.5
130.8
125.5
119.3
89.9
66.3
55.8
34.3
30.9
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
δ (ppm)

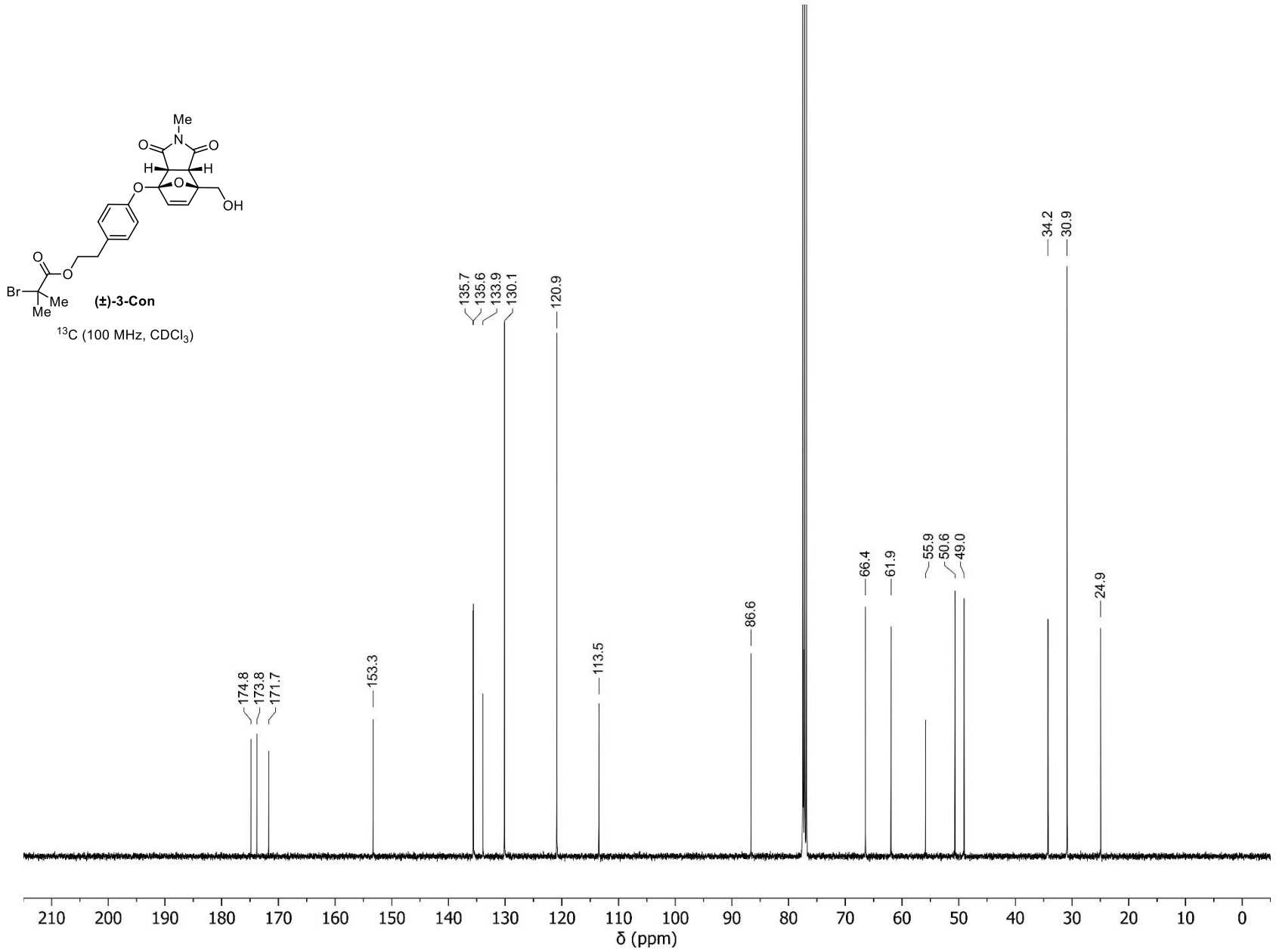

(±)-3
1H (400 MHz, CDCl3)
1H (500 MHz, Acetone-d6)
2.0 2.0
1.0 1.0
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0
δ (ppm)
4.0
1.0 1.0
2.0 4.0
4.0
2.0
1.0 6.0 6.0
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

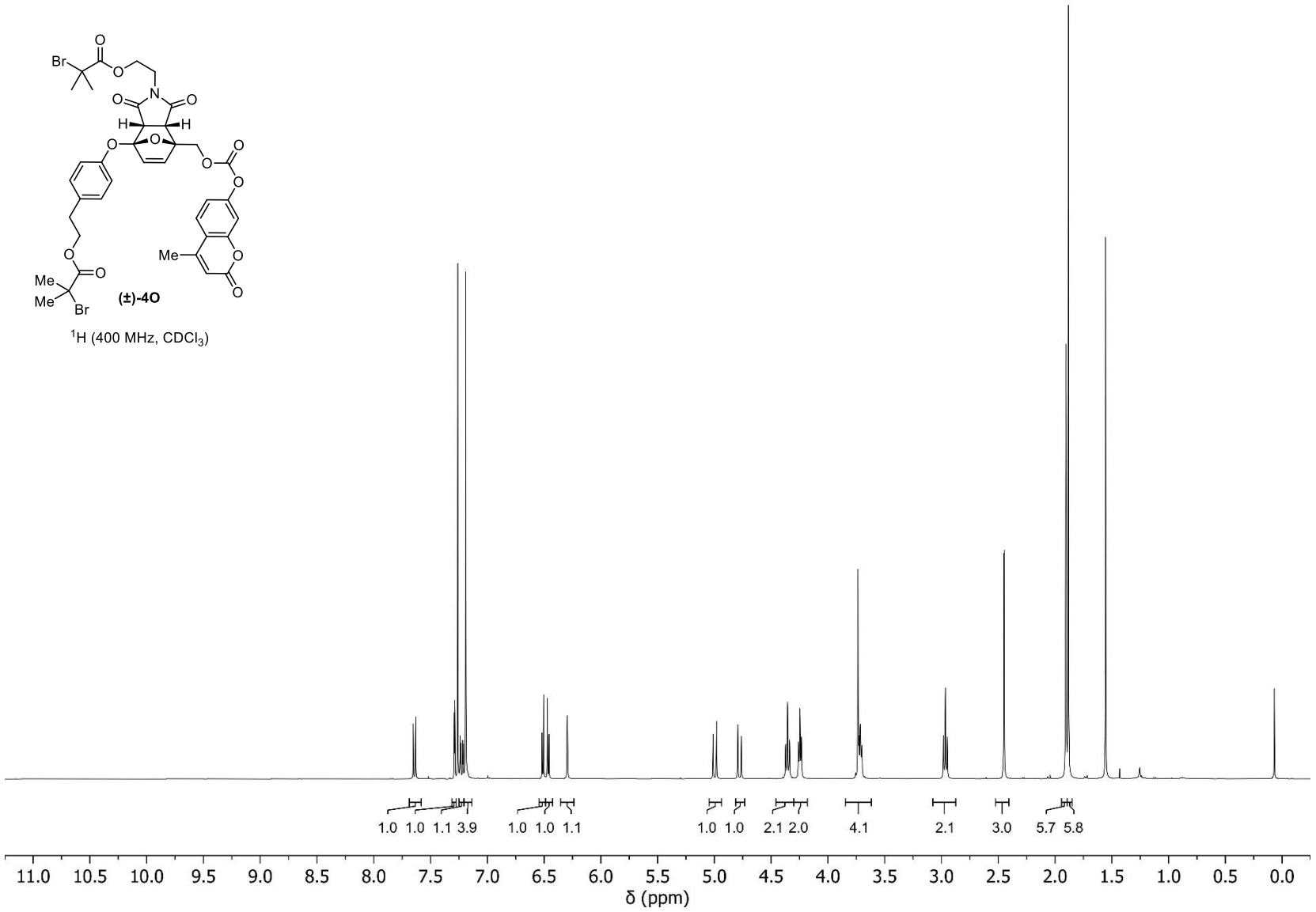

(±)-3
13C (125 MHz, CDCl3)
174.4
173.4
171.7
171.5
153.2
135.7
135.7
134.0
130.1
120.9
113.5
86.7
66.4
62.6
61.9
55.9
55.6
50.6
48.9
37.7
34.2
30.9
30.8
δ (ppm)

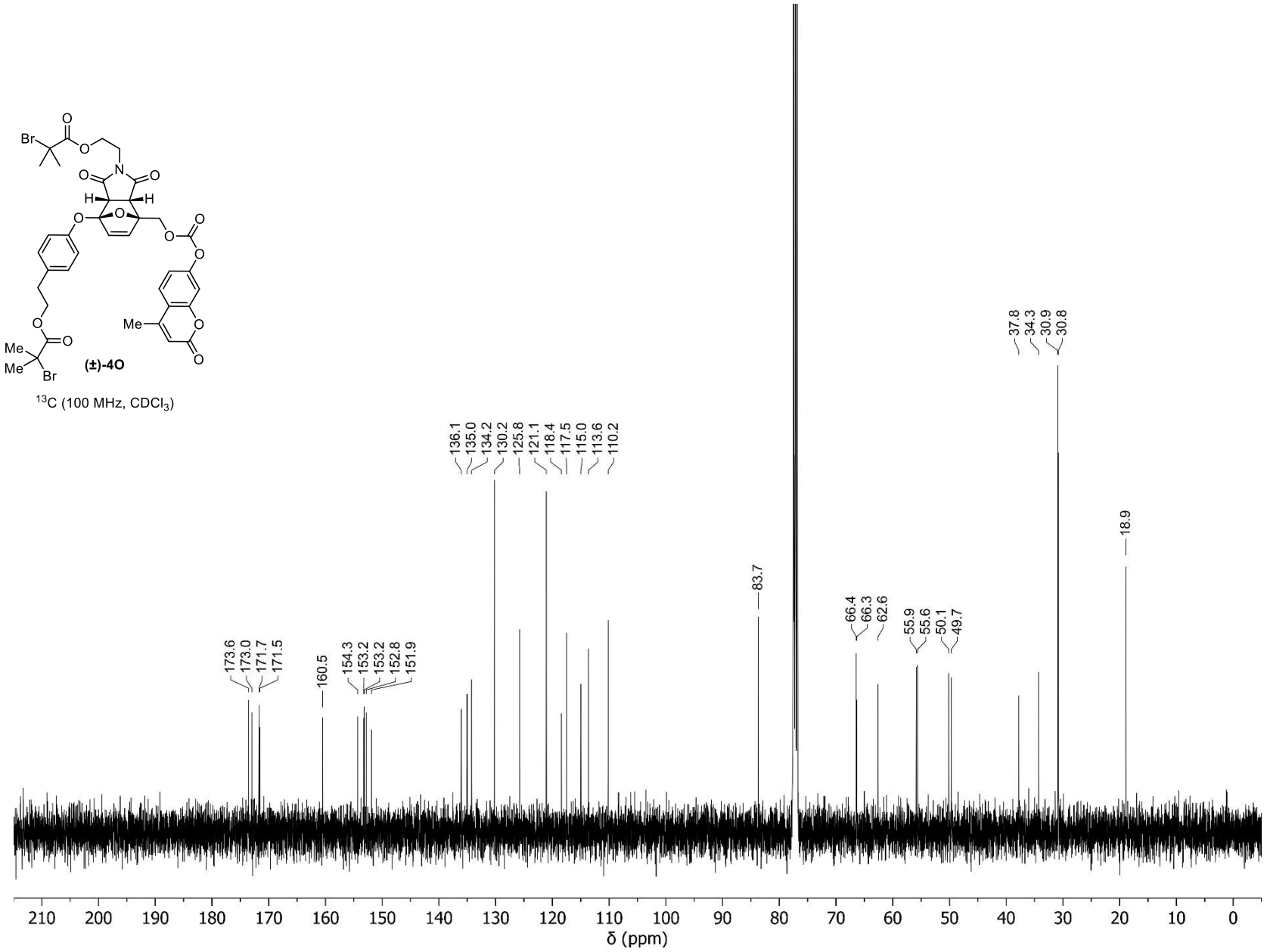


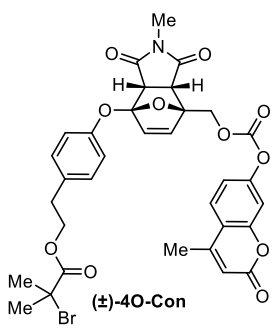
(±)-3-Con

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


Me
N
O
O
H
H
O
O
OH
O
O
Br
Me
Me
(±)-3-Con
^{13}C (100 MHz, $CDCl_3$)
174.8
173.8
171.7
153.3
135.7
135.6
133.9
130.1
120.9
113.5
86.6
66.4
61.9
55.9
50.6
49.0
34.2
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 0
δ (ppm)

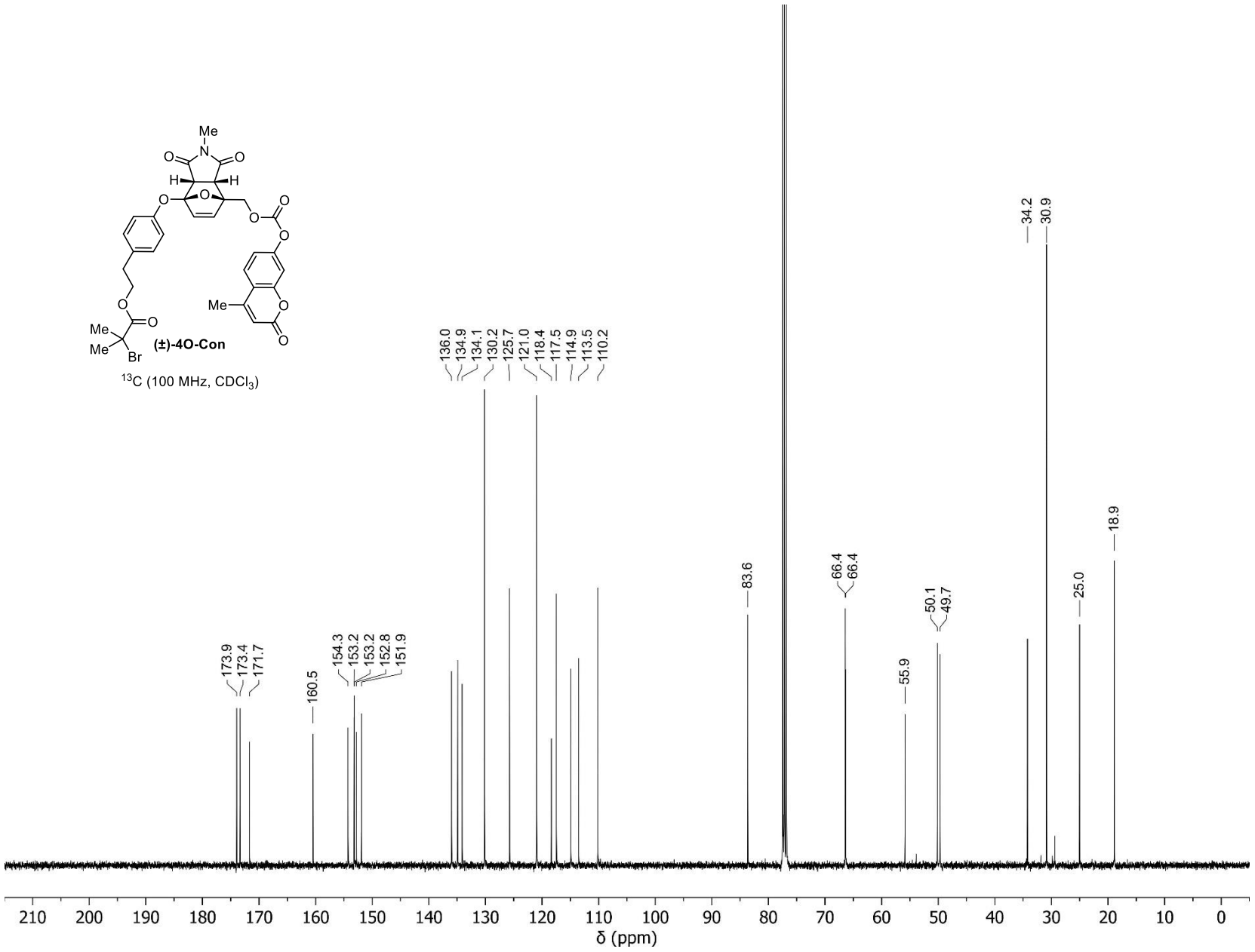

(±)-4O
^{1}H (400 MHz, CDCl$_3$)
1.0 1.0 1.1 3.9 1.0 1.0 1.1 1.0 1.0 2.1 2.0 4.1 2.1 3.0 5.7 5.8
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

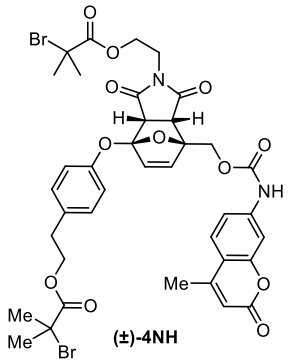

(±)-4O
^{13}C (100 MHz, CDCl$_3$)
173.6
173.0
171.7
171.5
160.5
154.3
153.2
153.2
152.8
151.9
136.1
135.0
134.2
130.2
125.8
121.1
118.4
117.5
115.0
113.6
110.2
83.7
66.4
66.3
62.6
55.9
55.6
50.1
49.7
37.8
34.3
30.9
30.8
18.9
δ (ppm)



(±)-4O-Con

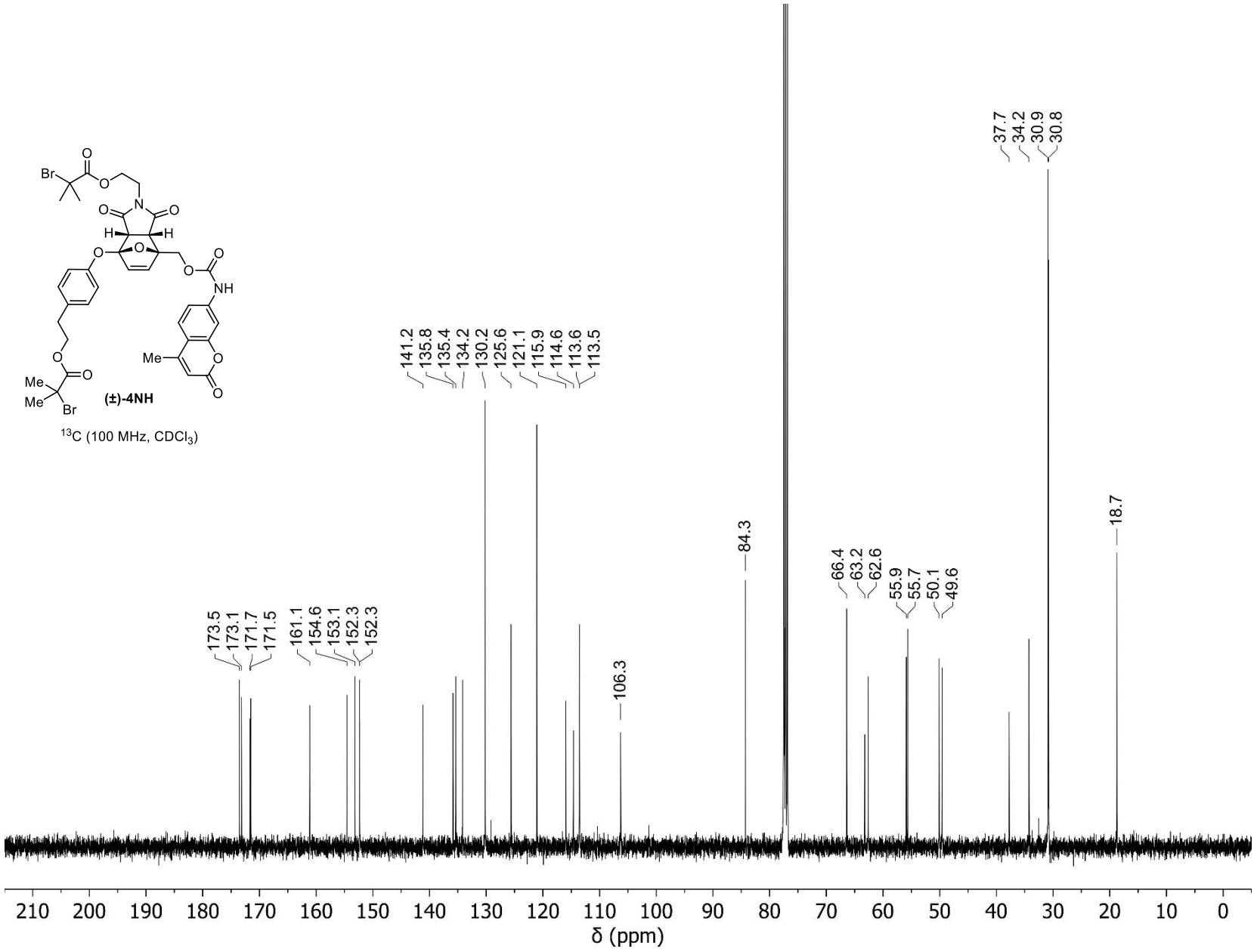
^{1}H (500 MHz, $CDCl_3$)

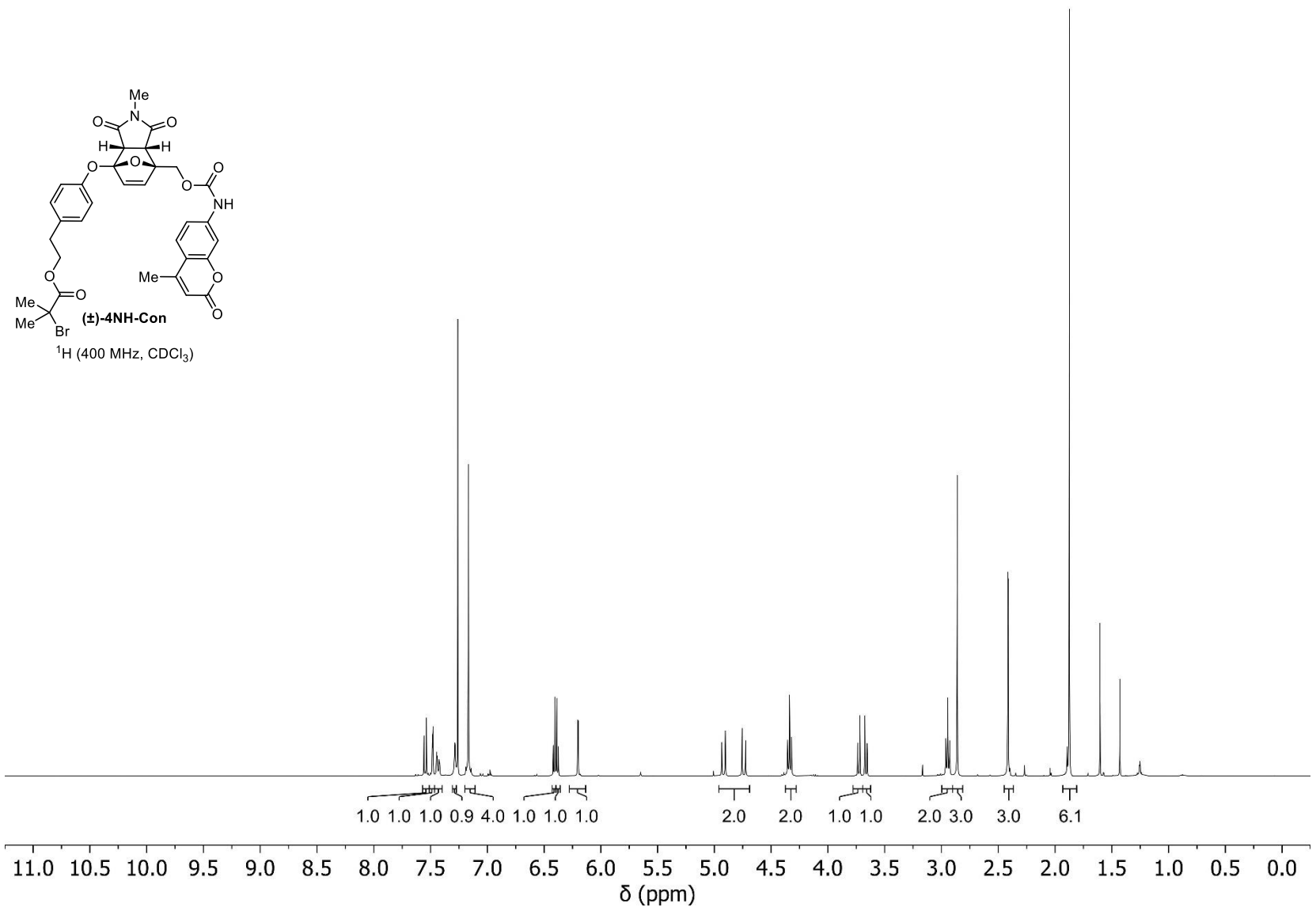

(±)-4O-Con
^{13}C (100 MHz, CDCl$_3$)
173.9
173.4
171.7
160.5
154.3
153.2
153.2
152.8
151.9
136.0
134.9
134.1
130.2
125.7
121.0
118.4
117.5
114.9
113.5
110.2
83.6
66.4
66.4
55.9
50.1
49.7
34.2
30.9
25.0
18.9
δ (ppm)

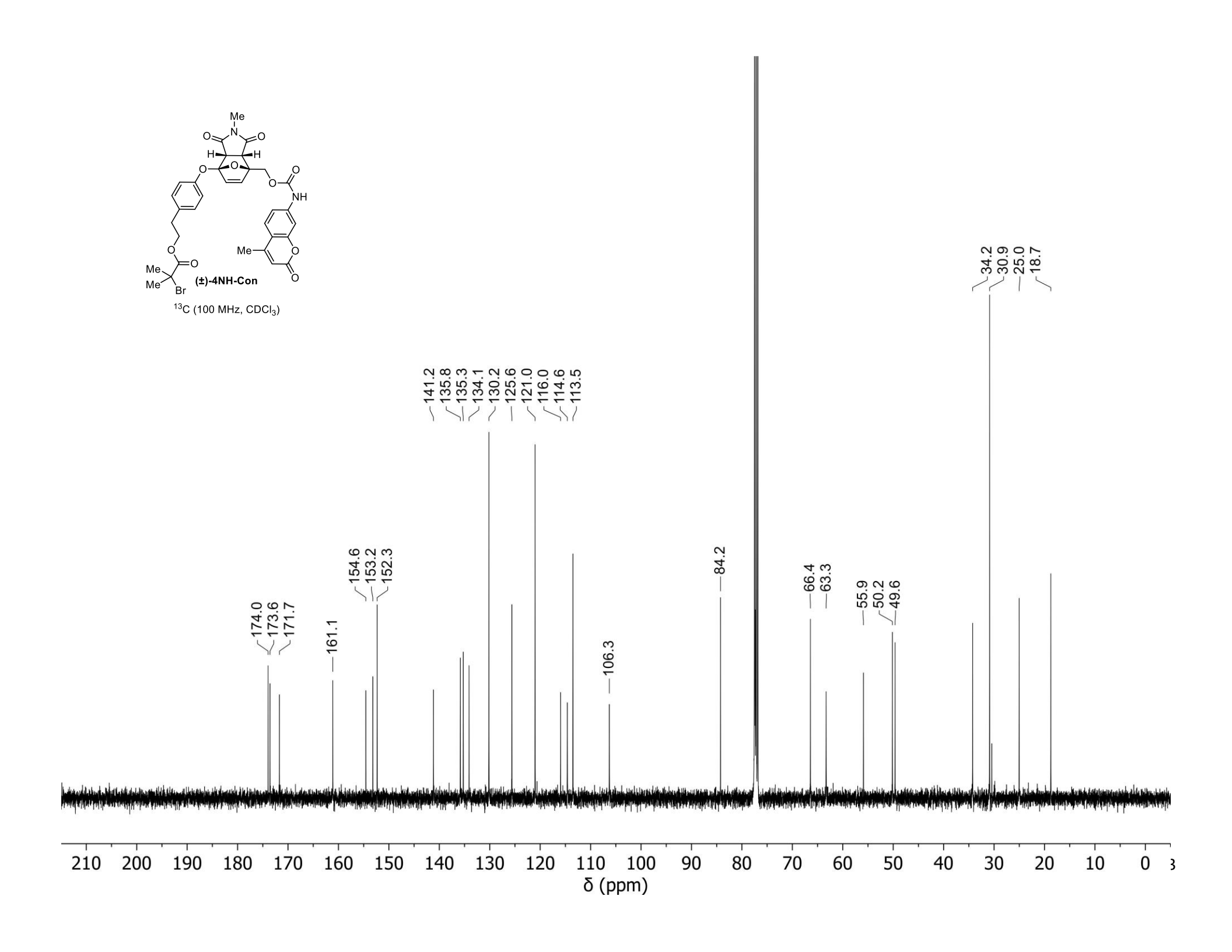


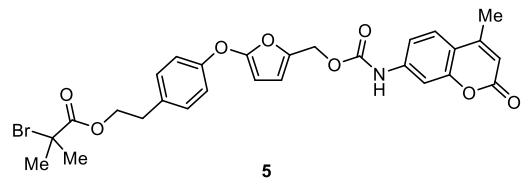
(±)-4NH

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


(±)-4NH
^{13}C (100 MHz, CDCl$_3$)
173.5
173.1
171.7
171.5
161.1
154.6
153.1
152.3
152.3
141.2
135.8
135.4
134.2
130.2
125.6
121.1
115.9
114.6
113.6
113.5
106.3
84.3
66.4
63.2
62.6
55.9
55.7
50.1
49.6
37.7
34.2
30.9
30.8
18.7
δ (ppm)

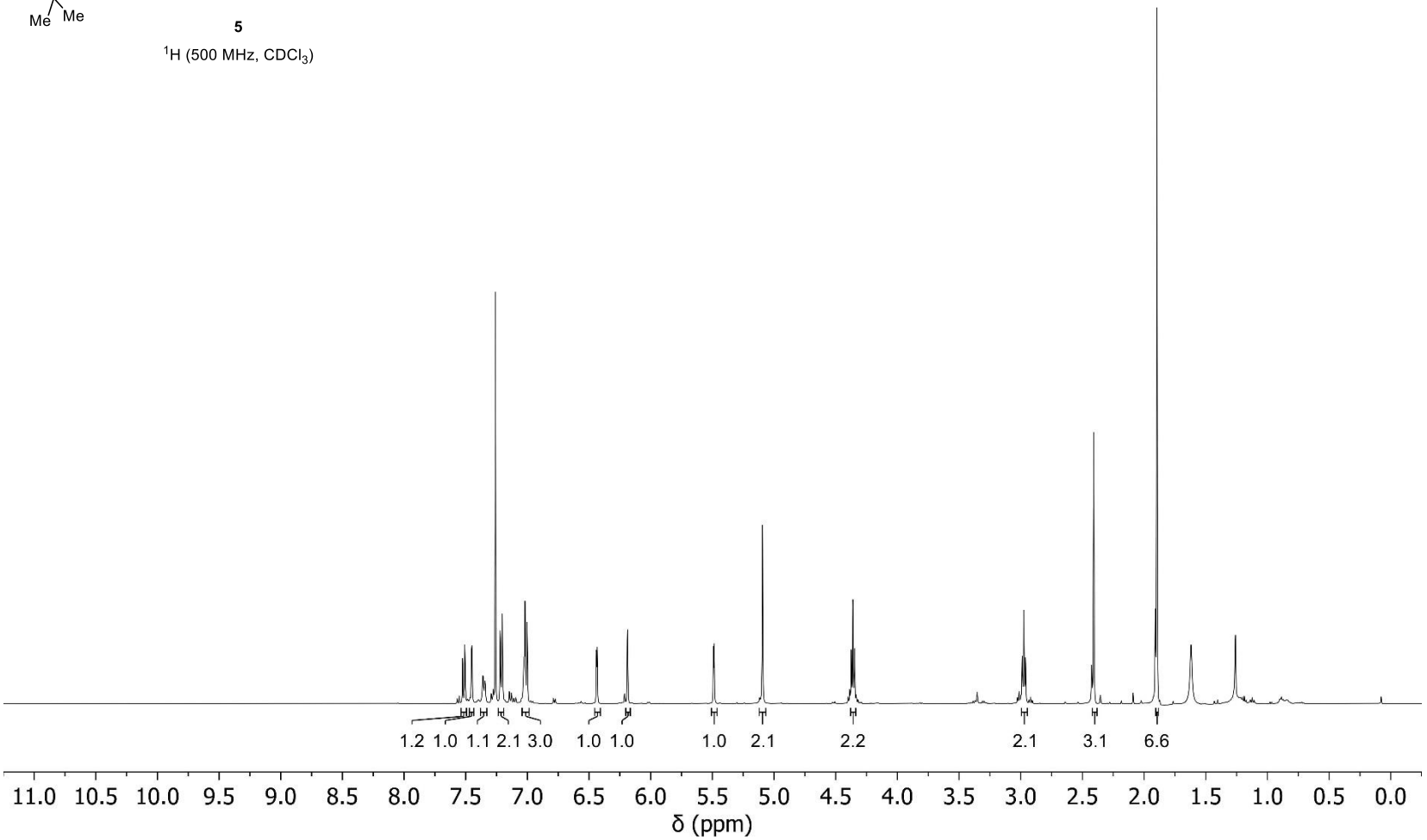

(±)-4NH-Con
^{1}H (400 MHz, $CDCl_3$)
1.0 1.0 1.0 0.9 4.0 1.0 1.0 1.0 2.0 2.0 1.0 1.0 2.0 3.0 3.0 6.1
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

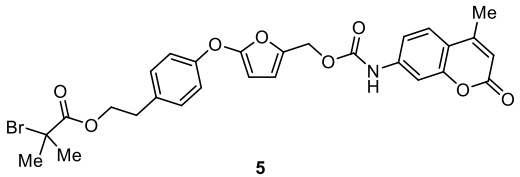

(±)-4NH-Con
^{13}C (100 MHz, CDCl$_3$)
174.0
173.6
171.7
161.1
154.6
153.2
152.3
141.2
135.8
135.3
134.1
130.2
125.6
121.0
116.0
114.6
113.5
106.3
84.2
66.4
63.3
55.9
50.2
49.6
34.2
30.9
25.0
18.7
δ (ppm)



5

^{1}H (500 MHz, $CDCl_3$)





5

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