Electronic Supplementary Material (ESI) for Polymer Chemistry.

Supplementary Information for

Catechol- and Ketone-Containing Multifunctional Bottlebrush Polymers for Oxime Ligation and Hydrogel Formation

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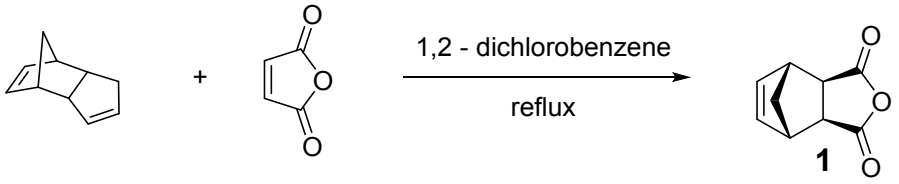
Contents

I. General Information

^{1}H NMR and ^{13}C NMR spectra were obtained on a 400 or 600 MHz "Bruker Ultrashield" spectrometer, using $CDCl_3$ or DCM-d_2 as the deuterated solvent. Chemical shifts are reported in parts per million (ppm), relative to residual $CHCl_3$ (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR) or DCM-d_2 (5.36 ppm for ^{1}H NMR and 54.00 for ^{13}C NMR). Coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded using electrospray ionization (ESI). All chemicals were used as received without further purification, unless specifically stated in the procedure, and all reactions were run under nitrogen atmosphere using standard Schlenk techniques. Glassware was oven-dried prior to use. All purifications were performed by flash column chromatography using silica gel with 40-63 micron particle size. Solvents (THF, DMF, CH_3CN, DCM, toluene) were purified using Waters SG SiO_2-based solvent purification system. Other solvents were used as received (HPLC grade).

II. Synthesis of monomers and polymers

(3aR,4R,7S,7aS)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione (**1**, racemic):[1]

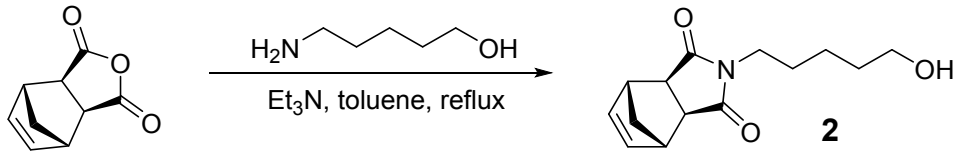


1 was prepared according to the literature method with minor modifications. The exact procedure is as follows: Maleic anhydride (94.12 g, 0.96 mol) and *o*-dichlorobenzene (100 mL), was added to the schlenk flask, fitted with a reflux condenser and the reaction was heated to reflux (200 °C bath temp.). Dicyclopentadiene (64.33 g, 0.48 mol), premelted by heating with heat gun in the separate round bottom flask, was then transferred dropwise via syringe in small portions (WARNING: using large portions and large syringe may result in dicyclopentadiene solidifying in the syringe, thus clogging the needle and complicating addition) dropwise. Reaction was then refluxed for 1.5 h and was then allowed to cool down to room temperature. 75 mL of cholorobenzene was then added to crystalize the product[a]. The product (~65 : 35 ratio of *exo* : *endo* mixture of isomers by ^{1}H NMR), was then filtered and recrystallized 3 times from cholorobenzene (cryst. conditions: minimum amount of solvent at 100 °C to rt. to 0 °C) to give 29.84 g pure *exo* product as a white solid (19 % yield). Multiple reactions on 0.12-0.48 mol scale provided yields in a range of 19 – 42 %.

White solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.33 (s, 2H), 3.46 (s, 2H), 3.00 (s, 2H), 1.67 (d, 1H, *J* = 10.3 Hz), 1.45 (d, 1H, *J* = 10.3 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.7, 138.1, 48.9, 47.0, 44.2. Full characterization data - reference 1.

[a] - Product did not crystalize on its own, even if left at rt. for overnight.

(3aR,4R,7S,7aS)-2-(5-hydroxypentyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**2**):[2]

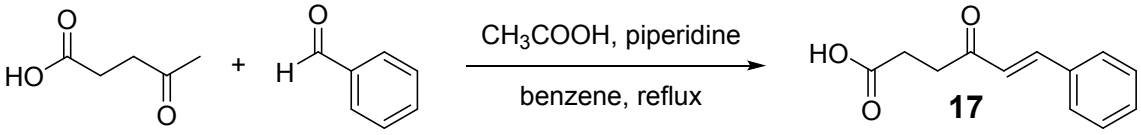


To a 500 mL round-bottom flask, were added: **1** (9.5 g, 58 mmol), toluene (200 mL), 5-amino-pentan-1-ol (6.3 g, 61 mmol) and triethylamine (0.80 mL, 5.8 mmol). Reaction was then fitted with a Dean-Stark trap and refluxed overnight, and was then concentrated using a rotary evaporator. The oil was then dissolved in ethyl acetate,

washed 2 times with: 1.0 M HCl, water, brine and then dried over magnesium sulfate. Removal of solvent under reduced pressure gave 13.73 g (95 % yield) of product, which was used without further purification.

Yellow oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.27 (t, 2H, *J* = 2.0 Hz), 3.61 (t, 2H, *J* = 6.5 Hz), 3.46 (t, 2H, *J* = 7.3 Hz), 3.25 (s, 2H), 2.66 (d, 2H, *J* = 1.3 Hz), 1.74 (broad s, 1H), 1.45-1.63 (m, 5H), 1.29-1.41 (m, 2H), 1.20 (d, 2H, *J* = 9.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.3, 138.0, 62.7, 48.0, 45.3, 42.9, 38.7, 32.2, 27.7, 23.2; **HRMS** (ESI^+): calcd. for $C_{14}H_{19}NO_3Na$: 272.12626; found: 272.12623.

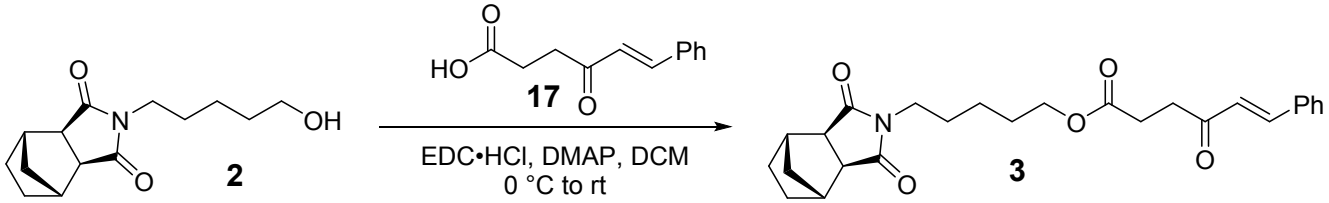
(E)-4-oxo-6-phenylhex-5-enoic acid (**17**):[3]



Prepared according to the reference 3, and additionally recrystallized from ethanol.

Yellow solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, 1H, *J* = 16.3 Hz), 7.50-7.58 (m, 2H), 7.34-7.45 (m 3H), 6.76 (d, 1H, *J* = 16.3 Hz), 3.02 (t, 2H, *J* = 6.6 Hz), 2.75 (t, 2H, *J* = 6.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.9, 178.6, 143.3, 134.5, 130.7, 129.1, 128.5, 125.8, 35.1, 28.1.

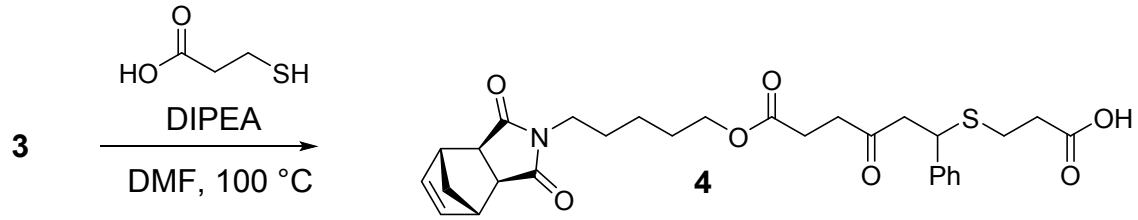
5-((3aR,4R,7S,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindol-2-yl)pentyl (E)-4-oxo-6-phenylhex-5-enoate (**3**):



To a 0 °C solution of **2** (500 mg, 2.45 mmol) in DCM (10 mL) was added **17** (610 mg, 2.45 mmol) in DCM (10 mL), followed by DMAP (30 mg, 0.25 mmol) and EDC•HCl (470 mg, 2.45 mmol). Reaction was then stirred under N_2 for 1 h at 0 °C after which it was warmed to rt overnight. Reaction was then washed with sat'd. NH_4Cl, sat'd. $NaHCO_3$, water, brine, and dried under $MgSO_4$. Solvent was then removed using rotary evaporator and crude mixture was chromatographed using gradient elution (20 % to 25 % ethyl acetate/hexanes) to give 630 mg (59 % yield) of pure title compound.

Yellow oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51-7.66 (m, 3H), 7.33-7.48 (m, 3H), 6.75 (d, 1H, *J* = 16.2 Hz), 6.26 (t, 2H, *J* = 2.0 Hz),), 4.06 (t, 2H, *J* = 6.6 Hz), 3.45 (t, 2H, *J* = 7.5 Hz), 3.26 (t, 2H, *J* = 1.8 Hz), 3.00 (t, 2H, *J* = 6.9 Hz), 2.63-2.72 (m, 4 H), 1.46-1.72 (m, 5H), 1.29-1.41 (m. 2H), 1.20 (d, 1H, *J* = 9.7 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.1, 178.1, 173.0, 143.0, 137.9, 134.5, 130.6, 129.0, 128.4, 126.0, 64.5, 47.9, 45.3, 42.8, 38.5, 35.4, 28.3, 28.2, 27.5, 23.5; **HRMS** (ESI^+): calcd. for $C_{26}H_{29}NO_5Na$: 459.19434; found: 458.19434.

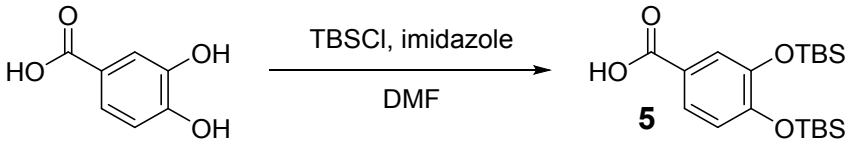
3-((6-((5-((3aR,4R,7S,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindol-2-yl)pentyl)oxy)-3,6-dioxo-1-phenylhexyl)thio)propanoic acid (**4**):



To **3** (820 mg, 1.88 mmol) in DMF (20 mL), 3-mercaptopropionic acid (0.18 mL, 2.07 mmol), and *N*,*N*-diisopolyethylamine (0.49 mL, 2.82 mmol) were added. Reaction was then heated at 100 °C for overnight and was then diluted with large volume of ethyl acetate (~200 mL), washed with 1.0 M HCl, brine and dried with $MgSO_4$. Reaction was then concentrated and purified using column chromatography (gradient elution of 40 % to 50 % to 60 % of ethyl acetate/hexanes) to give 400 mg of pure product (41 % yield). Typical yields for the reaction between multiple runs varied in the range of 25-41 %.

Yellow oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18-7.40 (m, 5H), 6.28 (t, 2H, *J* = 1.9 Hz), 4.38 (s, 1H, *J* = 7.3 Hz), 4.02 (t, 2H, *J* = 6.6 Hz), 3.47 (t, 2H, *J* = 7.4 Hz), 3.27 (t, 2H, *J* = 1.8 Hz), 2.92-3.06 (m, 2H), 2.43-2.80 (m, 10H), 1.47-1.65 (m, 5H), 1.28-1.40 (m, 2H), 1.21 (d, 1H, *J* = 9.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.5, 178.2, 175.9, 172.6, 141.4, 137.8, 128.6, 127.6, 127.4, 64.4, 49.0, 47.8, 45.1, 44.2, 42.7, 38.4, 37.8, 34.1, 28.0, 27.8, 27.3, 26.0, 23.3; **HRMS** (ESI^+): calcd. for $C_{29}H_{35}NO_7SNa$: 564.20319; found: 564.20319.

3,4-bis((tert-butyldimethylsilyl)oxy)benzoic acid (**5**):[4]

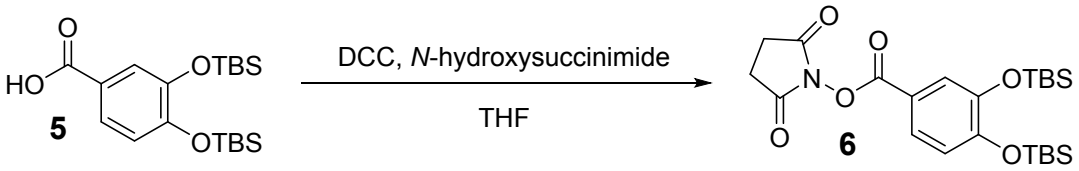


To a solution of 3,4-dihydroxybenzoic acid (3.08 g, 20 mmol) in DMF (50 mL), imidazole (6.12 g, 90 mmol) and *tert*-butyldimethylsilyl chloride (9.05 g, 60 mmol) were added. Reaction was then stirred for 18 h and was then poured into a mixture of Et_2O and 10 % citric acid[a]. The aqueous layer was then extracted 3 times with Et_2O and the organic layer was dried using $MgSO_4$. Organic solvent was then removed using rotary evaporator and resulting oil was then dissolved in 1:1:1 mixure of MeOH:THF:H_2O (30 mL total volume of the mixture), and K_2CO_3 (1.38 g, 8 mmol) was added, followed by stirring for 2 h 30 min. at rt. Reaction was then cooled down to 0 °C and diluted with saturated citric acid. Aqueous layer was then extracted 3 times with Et_2O and dried using $MgSO_4$. Organic fractions were concentrated and the crude product was purified using column chromatography (4 % ethyl acetate/hexanes), to give 6.15 g (80 % yield) of product as a white solid.

White solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54-7.63 (m, 2H), 6.87 (d, 2H, *J* = 8.3 Hz), 0.99 (2 x s, 12 H), 0.24 (s, 6H), 0.23 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.4, 152.6, 146.9, 124.5, 122.9, 122.4, 120.7, 26.1, 26.0, 18.7, 18.6, -3.9, -4.0; **HRMS** (ESI^+): calcd. for $C_{19}H_{34}O_4Si_2Na$: 405.18933; found: 405.19061.

[a] - 1.0 M HCl can be used as well.

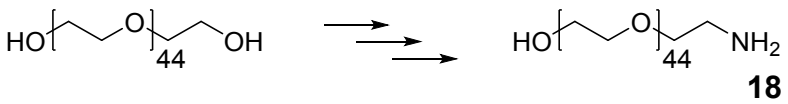
*2,5-dioxopyrrolidin-1-yl 3,4-bis((tert-butyldimethylsilyl)oxy)*benzoate (**6**):



To a solution of **5** (1.91 g, 5 mmol) in THF (50 mL), *N*-hydroxysuccinimide (1.15 g, 10 mmol), and DCC (2.06 g, 10 mmol) were added. Reaction was then stirred at room temperature overnight and filtered on SiO_2 (elution with pure ethyl acetate). Organic solvent was then removed via rotary evaporator and products were purified using column chromatography (gradient elution 20 % ethyl acetate/hexanes to 40 % ethyl acetate/hexanes) to give 2.07 g (86 % yield) of the title compound.

Colorless oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (dd, 1H, *J* = 8.4 Hz, 2.1 Hz), 7.56 (d, 1H, *J* = 2.2 Hz), 6.89 (d, 1H, *J* = 8.4 Hz), 2.88 (s, 4H), 0.98 (s, 18H), 0.24 (s, 6H), 0.21 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.4, 161.4, 153.7, 147.2, 125.0, 123.0, 120.9, 117.7, 25.8, 25.8, 25.7, 18.5, 18.4, -4.1, -4.2. **HRMS** (ESI^+): calcd. for $C_{19}H_{37}O_6Si_2NNa$: 502.20571; found: 502.20512.

poly(ethylene glycol) monoamine, M_n = ~2000 g / mol (**18**):[5]



Poly(ethylene glycol) monoamine (M_n = ~2000 g/mol) was prepared in 3 stages from commercial dihydroxypolyethylene glycol (M_n = ~2000, HO-PEG2K-OH), according to the analogy, previously reported for poly(ethylene glycol monoamine (M_n =~1450) in reference 5. The exact procedure is as follows:

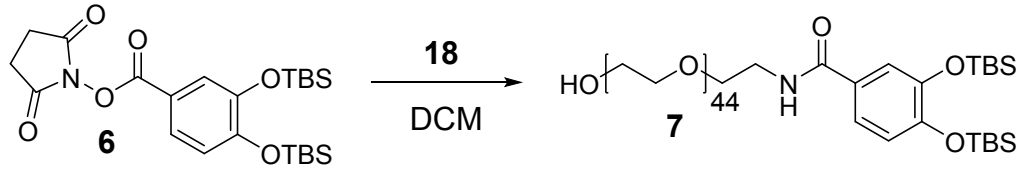
To a 250 mL round-bottom flask, fitted with Dean-Stark trap, HO-PEG2K-OH (6.0 g, 3.0 mmol) and 75 mL of dry toluene were added. Dean-stark trap was filled with dry toluene and solution was refluxed (bath temp 140 °C), until no more water was removed from HO-PEG2K-OH)[a]. Reaction was then cooled to rt., and flask was fitted with septa. Ag_2O (1.04 g, 4.5 mmol), KI (100 mg, 0.60 mmol) and TsCl (601 mg, 3.15 mmol) were then added and the reaction was stirred at rt. under N_2 overnight. Reaction was then filtered on celite (elution with DCM) and concentrated to give white solid, which was dissolved in minimal amount of DCM, and precipitated from ice-cold Et_2O to give 5.75 g (83 % yield) of monotosylated product. 5.38 g (2.33 mmol) of monotosylated product was then dissolved in 75 mL of DMF and NaN_3 (975 mg, 15.0 mmol) was added to the flask. Reaction was then heated at 90 °C overnight and then DMF was removed using rotary evaporator. The reaction mixture was then partitioned between DCM and brine (~3 : 1 ratio), and washed one more time with brine. Solvent was then removed using rotary evaporator, dissolved in minimal amount of DCM and precipitated from ice-cold Et_2O to give 4.45 g (93 % yield) of white solid (monoazide). 4.0 g (1.95 mmol) of the white solid was then dissolved in 80 mL of MeOH and 2.0 g (7.62 mmol) of triphenylphosphine was added. Reaction was refluxed overnight. Methanol was then removed using rotary evaporator and the product was dissolved in small amount of DCM and precipitated from ice-cold Et_2O. Process was repeated until all triphenylphosphene was removed to give 2.89 g (74 % yield, 57 % yield over 3 steps) of HO-PEG2K-NH_2, which was a co-mixture with HO-PEG2K-OH[b]. Multiple iterations of reactions on 6.0-21.0 g scale produced the yields were in the range between 48-70 %. The product was used as is, and any remaining HO-PEG2K-OH was removed after the next step during column chromatography.

White solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.41-3.84 (326 H), 2.84 (t, 2H, *J* = 5.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 73.2, 72.5, 70.5, 70.5, 70.4, 70.2, 61.6, 41.7.

[a] - Drying was monitored by monitoring the dean-stark trap. When the toluene layer was completely transparent no more cloudiness, and no more water from toluene was observed.

[b] – The HO-PEG2K-OH ammounts varied batch by batch and the exact ratio of products was estimated using ^{1}H NMR.

Monofunctionalization of poly(ethylene glycol) monoamine M_n = ~2000 (**7**):



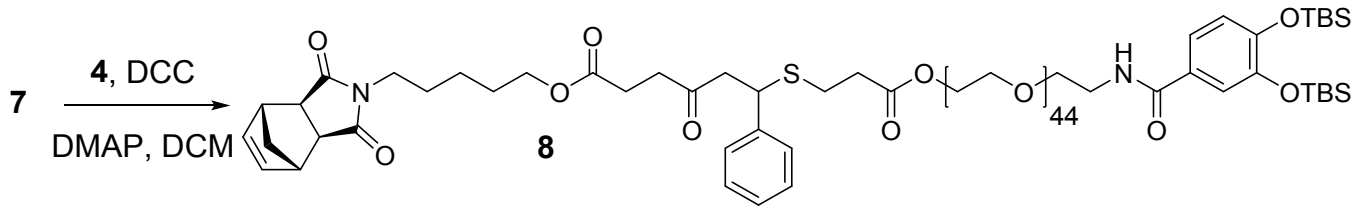
To a 250 mL roundbottom flask, **18** (6.91 g, 3.46 mmol, ~55 % -NH_2), **6** (2.00 g, 4.31 mmol) and DCM (70 mL) were added. Reaction was then stirred overnight at room temperature and solvent was removed using rotary evaporator. Crude product was then purified using column chromatography (gradient elution 3 % MeOH/$CHCl_3$ to 5 % MeOH/$CHCl_3$)[a] to give 2.26 g (28 % yield) of pure title compound.

In a separate experiment, >95 % pure HO-PEG2K-NH_2, obtained by dissolving HO-PEG2K-NH_2*HCl (M_n = ~2000 g/mol, supplier: JenKem Technologies) in DCM (~1 g / 10 mL) and washing twice with satd. $NaHCO_3$ (~3 mL), water (~3 mL) and brine (~3 mL), and drying under $MgSO_4$ with subsequent removal of solvent via rotary evaporation was used. In this instance, reaction on 500 mg scale with 1.75 equiv. of **6** in 5 mL of DCM, provided 319 mg (54 % yield) of pure product after column purification.

Colorless oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, 1H, *J* = 2.3 Hz), 7.19 (dd, 1H, *J* = 2.3 Hz, 8.3 Hz), 6.77 (d, 1H, *J* – 8.3 Hz), 6.72 (t, 1H, *J* = 5.2 Hz), 3.37-3.82 (m, 176H), 0.94 (s, 9H), 0.93 (s, 9H), 0.16 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.0, 150.1, 146.9, 128.0, 120.6, 120.5, 120.1, 70.6, 70.3, 70.3, 70.0, 61.7, 39.8, 26.0, 25.9, 18.5, 18.5, -4.0, -4.1.

[a] – The product and HO-PEG2K-OH impurity had very similar retention time during column chromatography and both of them stained standard $KMnO_4$ stain. Therefore, only UV-Active fractions, containing catechol moiety were collected in order not to contaminate the product with HO-PEG2K-OH.

DCC Coupling of **7** (**8**):

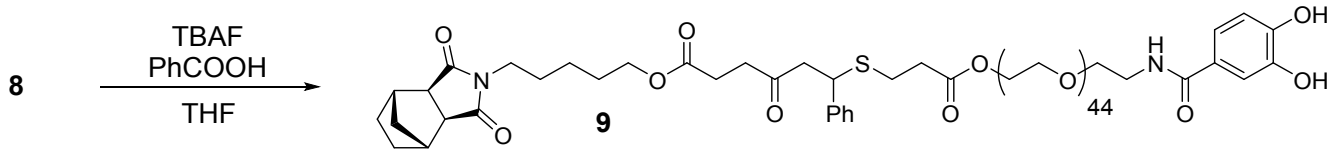


To DCM (5 mL), **7** (382 mg, 0.161 mmol), **4** (130 mg, 0.24 mmol), and DMAP (2 mg) were added. Reaction was then cooled at 0 ^{o}C and DCC (54 mg, 0.26 mmol) was then added and reaction was left to warm up and stir for

overnight at room temperature. Reaction was then concentrated using rotary evaporator and purified using column chromatography (3 % MeOH/$CHCl_3$ to 5 % MeOH/$CHCl_3$) to give 388 mg of pure product (82 % yield).

Colorless oil: **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 7.27=7.38 (m, 5H), 7.18-7.24 (m, 2H), 6.82 (d, 1H, *J* = 8.3 Hz), 6.65 (t, 1H, *J* = 5.6 Hz), 6.26 (s, 2H), 4.32 (t, 1H, *J* = 7.2 Hz), 4.15 (t, 2H, *J* = 4.8 Hz), 3.96 (d, 2H, *J* = 6.6 Hz), 3.42-3.76 (m, 202H), 3.40 (t, 2H, *J* = 7.4 Hz), 3.18 (s, 2H), 2.98 (dd, 2H, *J* = 1.5 Hz, 7.4 Hz), 2.59-2.71 (m, 3H), 2.51-2.59 (m, 3H), 2.36-2.49 (m, 4H), 1.47-1.61 (m, 4H), 1.46 (dt, 1H, *J* = 1.6 Hz, 9.8 Hz), 1.26-1.33 (m, 2H), 1.18 (d, 1H, *J* = 9.8 Hz), 0.97 (s, 9H), 0.95 (s, 9H), 0.20 (s, 6H), 0.19 (s, 6H); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ 205.3, 177.8, 172.3, 171.5, 166.4, 149.9, 146.8, 141.8, 137.8, 128.5, 128.2, 127.7, 127.3, 120.5, 120.4, 120.1, 70.5, 70.5, 70.5, 70.3, 69.9, 69.0, 64.3, 63.8, 48.9, 47.8, 45.2, 44.0, 42.7, 39.7, 38.3, 37.7, 34.3, 28.1, 27.7, 27.3, 26.1, 25.7, 25.7, 23.3, 18.4, 18.3, -4.3, -4.4; **GPC:** M_n = 2920 g/mol, PDI = 1.007.

Deprotection of **8** (**9**):

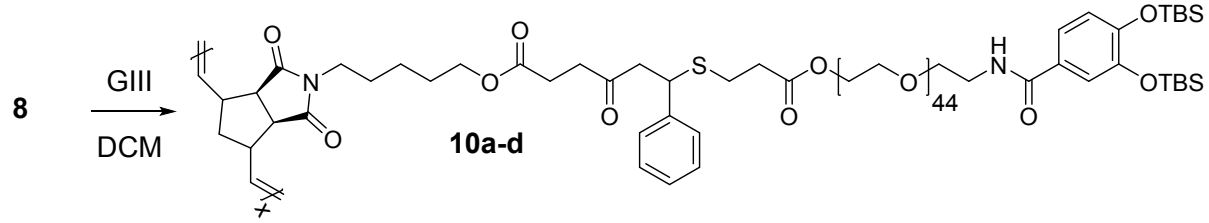


To a solution of **8** (330 mg, 0.11 mmol) in THF (11 mL), benzoic acid (54 mg, 0.44 mmol) and TBAF (0.44 mL of 1.0 M THF solution) were added. Reaction was then stirred for 30 min. and water (0.22 mL) was added. Reaction was then diluted with small amount of 10 % MeOH/$CHCl_3$ solution and filtered on short silica pad. Solvent was then removed via rotary evaporator and product was purified using column chromatography (3 % MeOH/$CHCl_3$ to 10 % MeOH/$CHCl_3$) to give 140 mg (46 % yield) of deprotected product[a].

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14-7.41 (8H + $CDCl_3$), 6.90 (d, 1H, *J* = 8.2 Hz), 6.28 (s, 2H), 4.35 (t, 1H, *J* = 7.3 Hz), 4.19 (t, 2H, *J* = 3.6 Hz), 4.0 (t, 2H, *J* = 6.6 Hz), 3.50-3.84 (m, 175H), 3.44 (t, 2H, *J* = 7.1 Hz), 3.26 (s, 2H + impurity), 2.98 (d, 2H, *J* = 7.2 Hz), 2.42-2.78 (m, 10H), 1.14-1.70 (m, 8 H + impurity).

[a] – The product had small amount of impurity, which corresponds to the chemical shift of tetrabutylammonium ion. While that somewhat complicated NMR analysis, the actual mass fraction impurity is low due to thehigh M_n of the macromonomer.

ROMP of **8** (**10a-d**):



To a scintillation vial, **8** (60 mg) in DCM (0.6 mL) and Grubbs' III[rd] generation catalyst[8], prepared from Grubbs' second generation catalyst, were added with 4 different ratios of catalyst:**8** (1:17, 1:50, 1:200, 1:500).[a] Reactions, containing 1 : 17 and 1 : 50 catalyst : monomer were complete in 2h., others were left to stir over weekend to ensure completion.[b] After the designated time, 2 drops of ethyl vinyl ether were added to quench the reaction, and the solvent was removed using rotary evaporator, which resulted in quantitiative recovery of

crude polymer.[c] Crude polymer was then dissolved in minimal amount of DCM and precipitated from cold ether to obtain purified products.

[a] - Molecular weight of 2888.1 g/mol, obtained assuming starting dihydroxy PEG of 2000 g/mol, and adding end-groups, was used to do the ratio calculations.

[b] - In a separate experiment, using different batch of macromonomer, reaction showed 100 % conversion by H NMR after 4 hours, therefore the actual reaction time is not 3 days, however keeping reaction for longer reaction time is not detrimental to the reaction since average molecular weights were reasonably consistent with theoretical values.

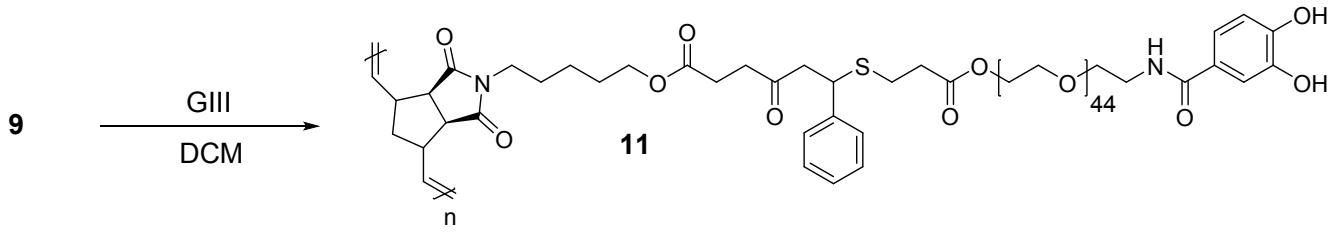
[b] – Polymer contained no macromonomer according to ^{1}H NMR, however it had some reddish coloration, resulting from catalyst.

Table S1: Synthetic results of the ROMP polymerization of **8** under various conditions.

Catalyst:8	Yield	Theo. M_n[a]	GPC M_n[a]	dn/dc[b]	PDI	DP (theo.)	DP (GPC)
8 only	-	2888	2920	0.0565	1.007	-	-
1:17 (**10a**)	58%	49101	63810	0.0319	1.098	17	22
1:50 (**10b**)	73%	144416	200700	0.0308	1.037	50	69
1:200 (**10c**)	68%	577662	795200	0.0344	1.144	200	272
1:500 (**10d**)	43%	1444155	1548000	0.0287	1.457	500	530

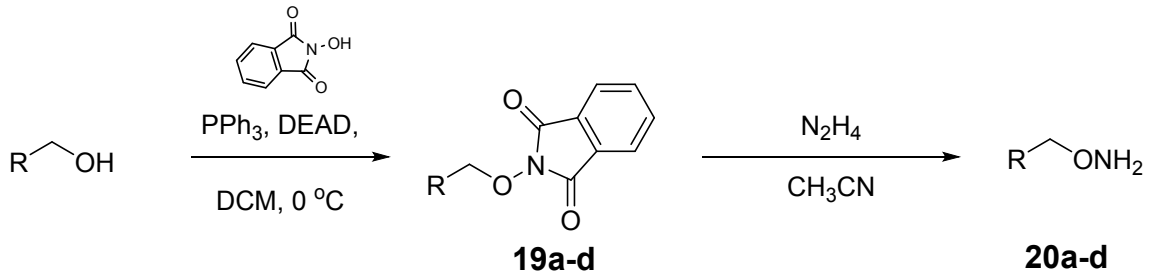
[a] - g/mol, [b] – mL/g in DMF + 0.02 M LiBr, calculated using standard Wyatt Astra 100 % mass recovery method.

ROMP of **9** (**11**):



Procedure, analogous to **10** was used. Catalyst:**9** ratio of 1:17 was used. The reaction was performed on 53 mg scale. After precipitation of product from ether it was additionally purified using dialysis against MeOH using MWCO:1kD Spectra/Por 6 membrane. 36 mg (67 % of product was isolated). We were not able to perform GPC analysis due to solubility issues of polymer in DMF eluant.

III. Synthesis of oxyamines 20a-d:



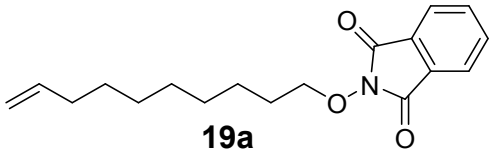
General procedure, stage 1:

To a solution of alcohol in DCM (0.25 M), 1.5 equiv. of triphenylphosphine and *N*-hydroxyphthalimide were added. Mixture was cooled to 0 °C and 1.5 equiv. of diethyl azodicarboxylate (DEAD) in DCM (2.36 M) was added dropwise. Reaction was then stirred for 1 h at 0 °C, and was then left over at room temperature for overnight. Reaction was then diluted with 40 % ethyl acetate/hexanes, flushed on short silica pad and concentrated to give crude products, which were purified using column chromatography.

General procedure, stage 2:

To a solution of **19a-d** in CH_3CN (0.1 M), hydrazine hydrate (2.0 - 3.0 equiv.) was added. Reaction was then stirred for 2 h at room temperature, and after that was diluted with ~10 - 20 mL of DCM and filtered on celite (elution with DCM). Reaction was then concentrated and used as is (**20b-d)**, otherwise purified by column chromatography (**20a**).

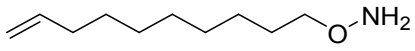
2-(dec-9-en-1-yloxy)isoindoline-1,3-dione (**19a**):



19a

Scale: 5 mmol
Isolated mass: 1.302 g (86 % yield).
White solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80-7.87 (m, 2H), 7.70-7.77 (m, 2H), 5.74-5.90 (m, 1H), 4.98 (dd, 1H, *J* = 1.0 Hz, 17.1 Hz), 4.92 (dd, 1H, *J* = 1.2 Hz, 10.2 Hz), 4.2 (t, 2H, *J* = 6.8 Hz), 2.05 (2H, q, *J* = 6.8 Hz), 1.78 (quint., 2H, *J* = 6.8 Hz), 1.48 (quint., 2H, *J* = 7.0 Hz), 1.23-1.42 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.7, 139.2, 134.4, 129.0, 123.5, 114.1, 78.6, 33.8, 29.3, 29.2, 29.0, 28.9, 28.1, 25.5; **HRMS** (ESI^+): calcd. for $C_{18}H_{23}O_3NNa$: 324.15756; found: 324.15774.

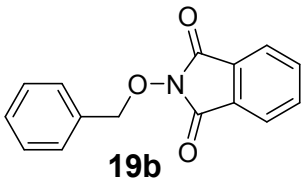
O-(dec-9-en-1-yl)hydroxylamine (**20a**):



20a

Scale: 1 mmol, 2.0 equiv. of N_2H_4, purification by column ($CHCl_3$ to 0.25 % MeOH / $CHCl_3$).
Isolated mass: 149 mg (87 % yield).
Yellow, non-viscous liquid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.74-5.88 (m, 1H), 4.98 (dd, 1H, *J* = 17.2 Hz, 1.9 Hz), 4.92 (dd, *J* = 10.2 Hz, 1.9 Hz), 3.65 (t, 2H, *J* = 6.7 Hz), 2.03 (q, 2H, *J* = 6.9 Hz), 1.57 (quint., 2H, *J* = 6.8 Hz), 1.22-1.44 (10H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.2, 114.1, 76.2, 33.8, 29.4, 29.4, 29.0, 28.9, 28.4, 26.0; **HRMS** (ESI^+): calcd. for $C_{10}H_{22}ON$: 172.17014; found: 172.17184.

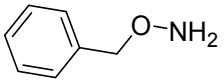
2-(benzyloxy)isoindoline-1,3-dione (**19b**):



19b

Scale: 2 mmol.
Isolated mass: 290 mg (54 % yield).
White solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78-7.84 (m, 2H), 7.70-7.77 (m, 2H), 7.52-7.57 (m, 2H), 7.34-7.42 (m, 3H), 5.21 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.5, 134.4, 133.7, 129.9, 129.3, 128.9, 128.5, 123.5, 79.9; **HRMS** (ESI^+): calcd. for $C_{15}H_{11}O_3NNa$: 276.06366; found: 276.06370.

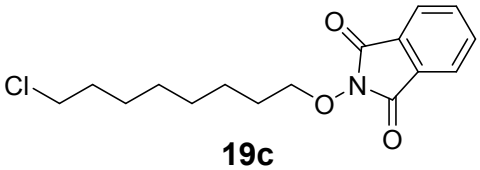
O-benzylhydroxylamine (**20b**):[6]



20b

Scale: 1 mmol, 3.0 equiv. N_2H_4.
Isolated mass: 69 mg (56 % yield).
Colorless oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28-7.41 (m, 5H), 5.50 (s, 2H), 4.70 (s, 2H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.6, 128.6, 128.5, 128.2, 78.2; **HRMS** (ESI^+): calcd. for $C_7H_{10}ON$: 124.07624; found: 124.07623.

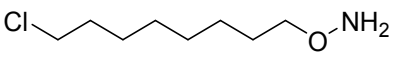
2-((8-chlorooctyl)oxy)isoindoline-1,3-dione (**19c**):



19c

Scale: 2 mmol
Isolated mass: 553 mg (89 % yield).
White solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80-7.89 (m, 2H), 7.69-7.78 (m, 2H), 4.20 (t, 2H, *J* = 6.7 Hz), 3.53 (t, 2H, *J* = 6.7 Hz), 1.71-1.86 (m, 4H), 1.28-1.56 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.8, 134.6, 129.2, 123.6, 78.7, 45.3, 32.8, 29.3, 28.9, 28.3, 26.9, 25.6; **HRMS** (ESI^+): calcd. for $C_{16}H_{20}O_3NClNa$: 332.10294; found: 332.10150.

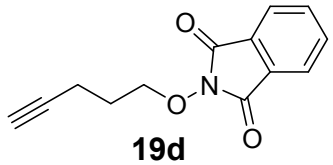
O-(8-chlorooctyl)hydroxylamine (**20c**):



20c

Scale: 1 mmol, 3.0 equiv. N_2H_4.
Isolated mass: 151 mg (84 % yield).
Colorless liquid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.34 (s, 2H), 3.65 (t, 2H, *J* = 6.6 Hz), 3.52 (t, 2H, *J* = 6.7 Hz), 1.78 (quint., 2H, *J* = 6.8 Hz), 1.56 (quint., 2H, *J* = 6.8 Hz), 1.42 (quint., 2H, *J* = 5.7 Hz), 1.23-1.37 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 76.3, 45.3, 32.8, 29.4, 29.0, 28.5, 27.0, 26.1; **HRMS** (ESI^+): calcd. for $C_8H_{19}ONCl$: 180.11552; found: 180.11740.

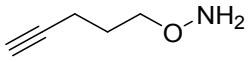
2-(pent-4-yn-1-yloxy)isoindoline-1,3-dione (**19d**):



19d

Scale: 2 mmol
Isolated mass: 400 mg (82 % yield).
White solid: **^{1}H NMR:** 7.82-7.91 (m, 2H), 7.73-7.81 (m, 2H), 4.35 (t, 2H, *J* = 6.2 Hz), 2.53 (td, *J* = 6.2 Hz, 2.5 Hz), 1.93-2.08 (m, 3H); **^{13}C NMR:** 158.2, 129.1, 123.6, 118.1, 77.7, 71.5, 63.7, 21.8, 9.6; **HRMS** (ESI^+): calcd. for $C_{13}H_1O_3NNa$: 252.06366; found: 252.06357.

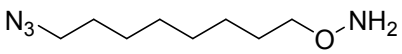
O-(pent-4-yn-1-yl)hydroxylamine (**20d**):[7]



20d

Scale: 1 mmol
Isolated mass: 51 mg (52 % yield).
Colorless liquid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.37 (broad s, 2H), 3.74 (t, 2H, *J* = 6.2 Hz), 2.26 (td. 2H, *J* = 2.6 Hz, 7.1 Hz), 1.95 (t, *J* = 2.6 Hz), 1.78 (quint., 2H, *J* = 6.9 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 84.0, 74.4, 68.6, 27.4, 15.3.

O-(8-azidooctyl)hydroxylamine (**20e**):



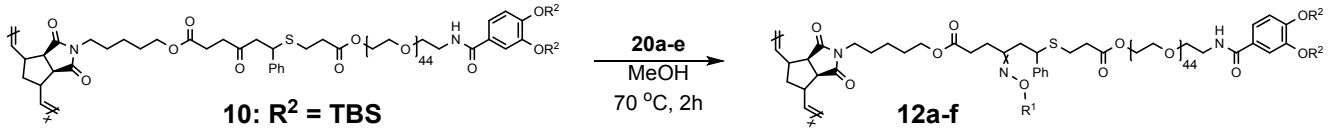
20e

To a solution of **19c** (465 mg, 1.78 mmol) in DMF (45 mL), was added sodium azide (585 mg, 9.0 mmol). Reaction was then stirred at 90 °C for 24 h, after which the reaction was concentrated using rotary evaporator, then partitioned between DCM and brine and washed additional time with brine. Reaction was then concentrated

and product was then dissolved in acetonitrile (18 mL), after which hydrazine hydrate (162 mg, 3.24 mmol) was added. Reaction was then stirred for 2h, filtered on celite, concentrated using rotary evaporator and purified using column chromatography (0.5 % MeOH/CHCl3) to give 321 mg (97 % yield) of pure product.

Colorless oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.35 (s, 2H), 3.65 (t, 2H, *J* = 6.6 Hz), 3.26 (t, 2H, *J* = 3.26 Hz), 1.50-1.63 (m, 4H, includes water peak), 1.28-1.42 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 76.1, 51.5, 29.3, 29.1, 28.8, 28.4, 26.6, 25.9.

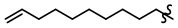
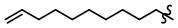
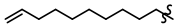
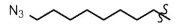
IV. Functionalization of polymers with oxyamines (S18a-f):



General procedure:

To starting polymers (**10a-d**, **11**) in MeOH (20 mg/mL), solutions of oxyamines **20a-e** in MeOH (~5.8 M in MeOH) were added. A small amount of acetic acid (1 drop per 20-30 mg of polymer) was then added. The vial was then sealed and heated in an oil bath at 70 °C for 2h, after which the solution was packed into dialysis tube and dialyzed against MeOH with frequent change of solvent. Solvent was then removed using rotary evaporator to give polymers **12a-f**. Small samples (1-2 mg), were removed for GPC analysis.

Table 2: Oxyamine functionalization of bottlebrush polymers **10a-d** and **11**.

Entry	S. M.	m_{SM}[b]	m_{OX}[c]	R^1	R^2	m_P[d]	D.F.[e]	Dialysis Membrane Porosity[f]
12a[a]	**10a**	20 mg	10 mg		TBS	16 mg	46 %	MWCO 1kD
12a'[g]	**10a**	25 mg	12.5 mg		TBS	19 mg	100 %	MWCO 1kD
12b	**10b**	26 mg	9.3 mg		TBS	14 mg	18 %	MWCO 1kD
12c	**10c**	30 mg	16 mg		TBS	22 mg	61 %	MWCO 25 kD
12d	**10d**	21 mg	6 mg		TBS	15 mg	63 %	MWCO 25 kD
12e[a]	**11**	26 mg	15 mg		H	18 mg	43 %	MWCO 1kD
12f[h]	**10b**	75 mg	30 mg		TBS	75 mg	100 %	MWCO 1kD

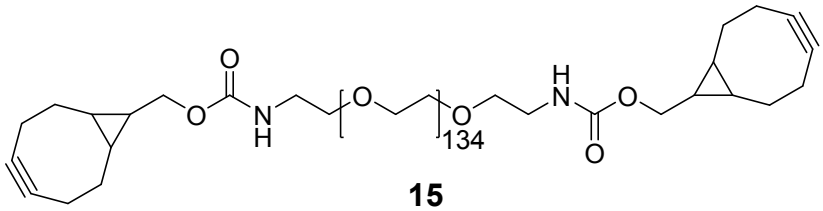
[a] – reaction time = 1h; [b] – mass of starting polymer; [c] – mass of oxyamine, added as a solution in methanol; [d] – mass of isolated product after dialysis; [e] – rough estimate of degree of functionalization, obtained from ^{1}H NMR integration. [f] – Porosity of membrane, used for dialysis. [g] – reaction time = 16h. [h] – reaction time = 8h.

V. GPC Experiments, general guidelines:

~1.5 - 5.0 mg of polymer was dissolved in DMF, containing 0.02 M LiBr. 50 μL of sample was then injected and GPC trace was recorded using Wyatt GPC system, equipped with 8 light scattering and one RI detector. Chromatogram was recorded for 40 min. The high molecular weight polymeric region of 0-28 min. was analyzed, and the signals that contain peaks both in LS and RI signals were attributed to polymer signals. First, the dn/dc value was calculated using standard Wyatt 100 % mass recovery method, and the dn/dc value from each individual measurement was used to calculate molecular weight.

VI. Crosslinking studies:

Synthesis of **15:**



15

A solution of PEG6000 (3.0 g, 0.50 mmol) in DCM (20 mL), was cooled to 0 °C in an ice bath. Tosyl chloride (1.91 g, 10 mmol) was then added, followed by dropwise addition of 2.1 mL of triethylamine. Reaction was then stirred for 1 h at 0 °C under N_2 and then was left overnight to warm to rt. Reaction was then diluted with DCM and solution was then washed 2 times with satd. sodium bicarbonate, one time with water and brine and then was dried under $MgSO_4$. Organic solvent was then removed and the oil obtained was dissolved in minimum ammount of DCM and then precipitated into ~300 ml of ice-cold diethyl ether. White solid was then collected using vacuum filtration to give 2.69 g (85 % yield) of PEG6000 ditosylate. To a solution of PEG6000 ditosylate (2.104 g, 0.33 mmol) in DMF (25 mL), sodium azide (434 mg, 6.67 mmol) was then added. Reaction was then heated at 90 °C overnight and then DMF was removed using rotary evaporator. Resulting slurry was then partitioned between brine and DCM, and washed an additional time with brine. Organic fraction was then dried using $MgSO_4$, concentrated using rotary evaporator, dissolved in minimum ammount of DCM and precipitated in ice-cold Et_2O to give 1.54 g (77 % yield) of PEG6000 diazide. To a solution of PEG6000 diazide (726 mg, 0.12 mmol) in MeOH (20 mL), PPh_3 (472 mg, 1.8 mmol) was added. Reaction was then refluxed overnight, then cooled down to room temperature, concentrated using rotary evaporator, dissolved in minimal ammount of DCM and precipitated in ice-cold Et_2O to give 435 mg (60 % yield) of PEG6000 diamine. To a 200 mg (0.033 mmol) solution of PEG6000 diamine, in DCM (5 mL), (1R,8S,9s)-Bicyclo[6.1.0]non-4-yn-9-ylmethyl *N*-succinimidyl carbonate (33.3 mg, 0.115 mmol) and triethylamine (34.9 mg, 0.345 mmol) in 1 mL of DCM were added. Reaction was then stirred for 6 h and precipitated from ice-cold Et_2O. Dialysis (2 days) over MWCO1000 kD membrane then afforded 65 mg (31 %) of pure **15**.

White solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.24-5.41 (broad s, 2H), 4.14 (t, 4H, *J* = 9.1 Hz), 3.41-3.88 (m, 588 H), 3.28-3.45 (broad s, 4H) 2.07-2.49 (m, 12H), 1.13-1.48 (m, 4H), 0.82-1.01 (m, 4H).

Deprotection of **12f** (**16**):

To a solution of **12f** (70 mg) in THF (3 mL), precooled to 0 °C, benzoic acid (28 mg, 0.23 mmol) and a 1.0 M solution of TBAF in THF (0.23 mL, 0.23 mmol) were added. Reaction was then stirred for 30 min. at 0 °C, followed by 1 h at rt. Reaction was then dialyzed against methanol for overnight using MWCO 1kD membrane with frequent change of solvents. Concentration of the product using rotary evaporator then yielded 36 mg of **16**.

Crosslinking Test

36 mg of polymer **16** was dissolved in 144 μL of 1:1 EtOH:H_2O in a small GC vial. To this solution, another solution of 200 mg/mL **15** (220 μL) was added. Vial was then placed in an water-bath, preheated to 37 ^oC and stirred for 15 minutes Within first few minutes, a stirbar movement decreased significantly and after incubation for 15 minutes, the vial contained completely soft-rubber like gel, which did not move when the vial was flipped over.

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

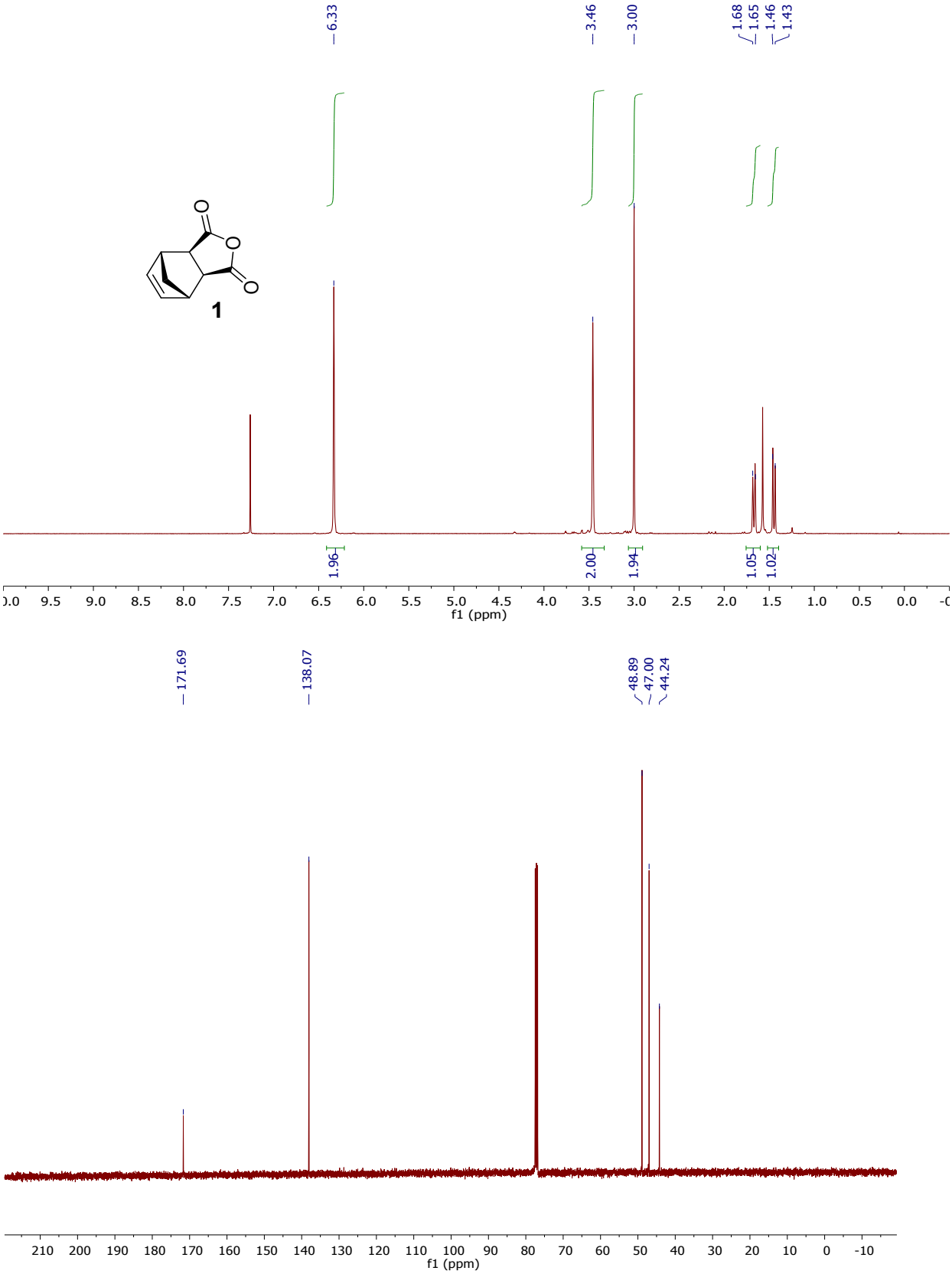


Fig. S1: ^{1}H and ^{13}C spectra of compound **1**

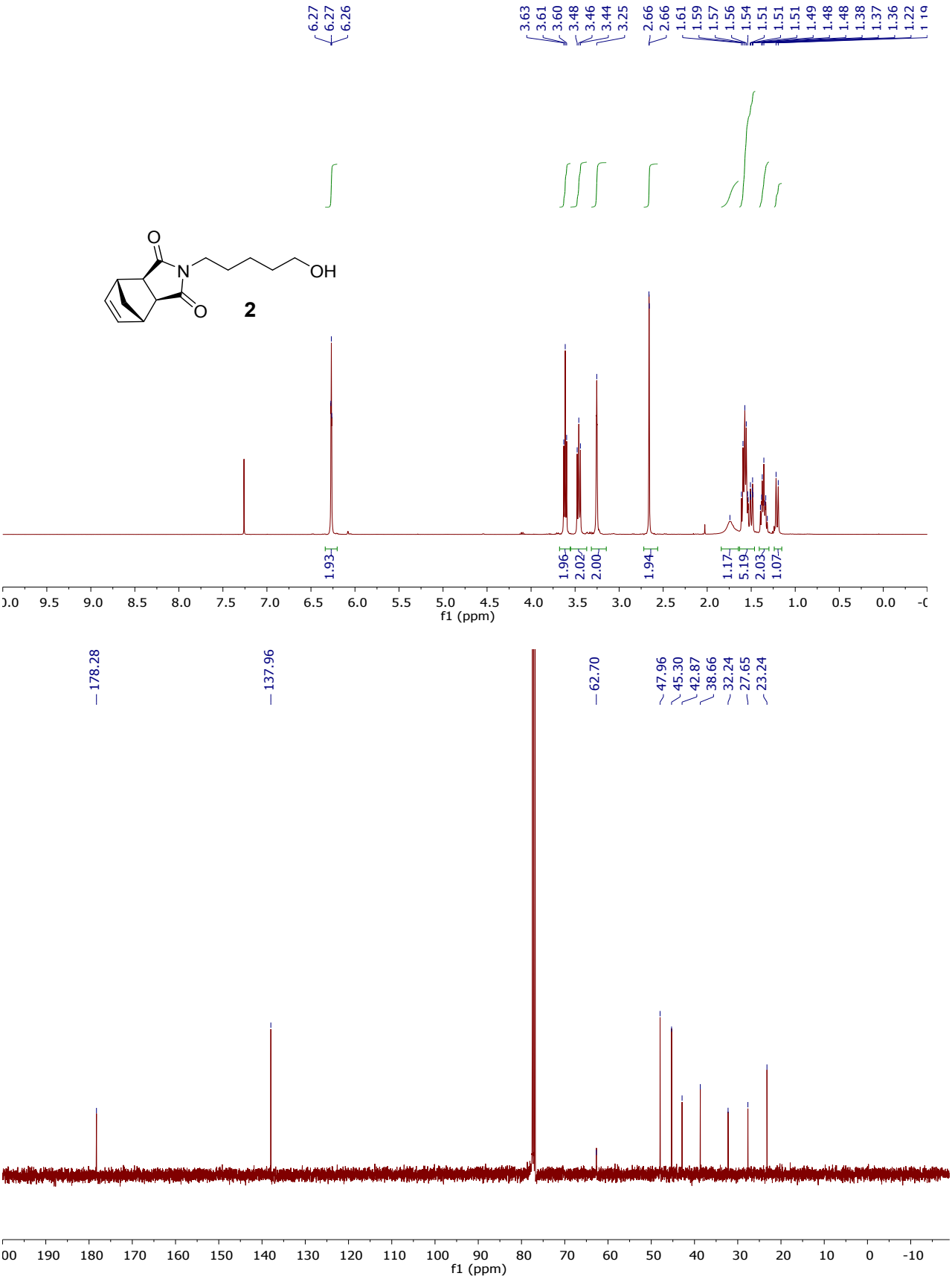


Fig. S2: ^{1}H and ^{13}C spectra of compound **2**

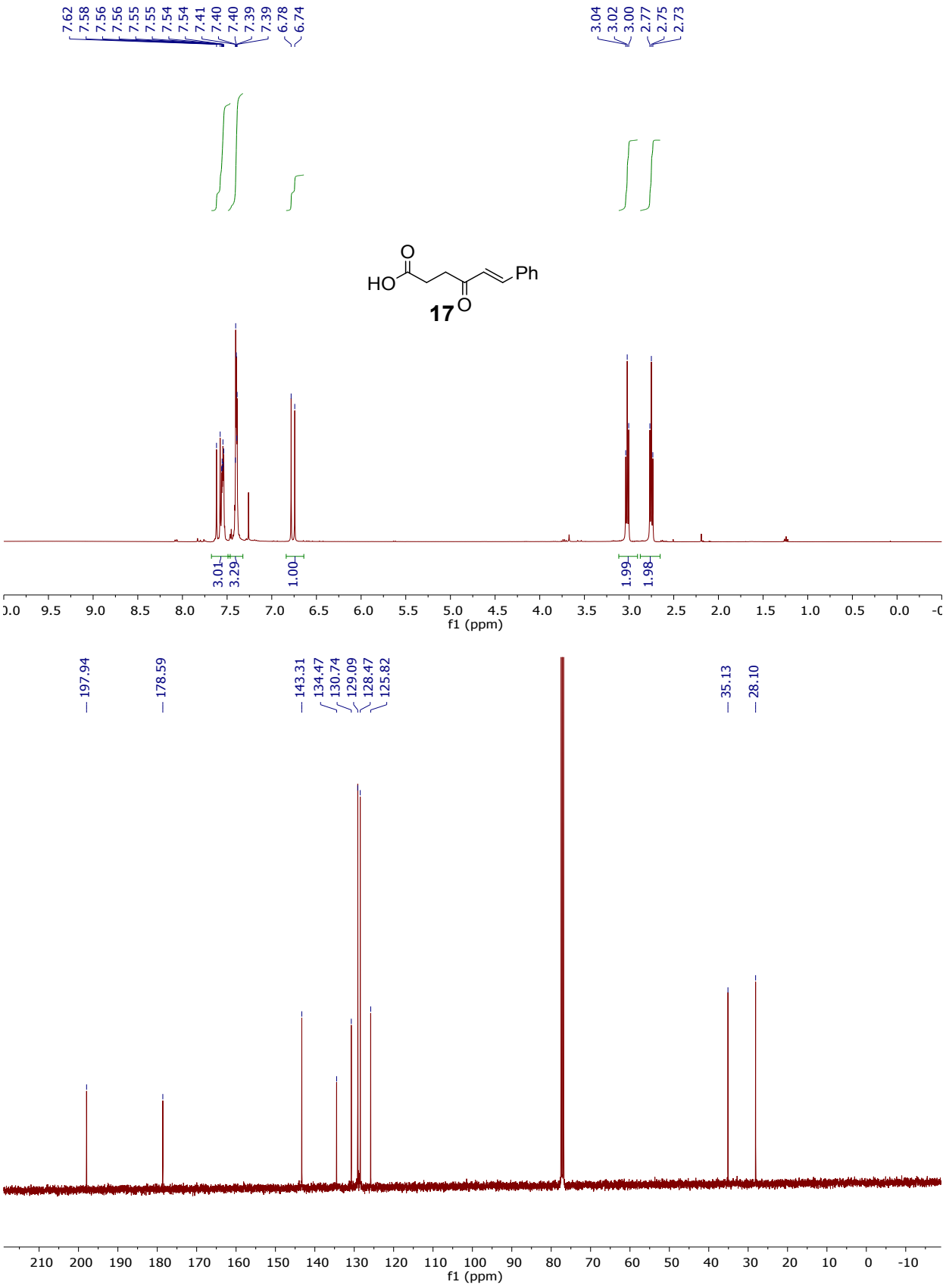


Fig. S3: ^{1}H and ^{13}C spectra of compound **17**

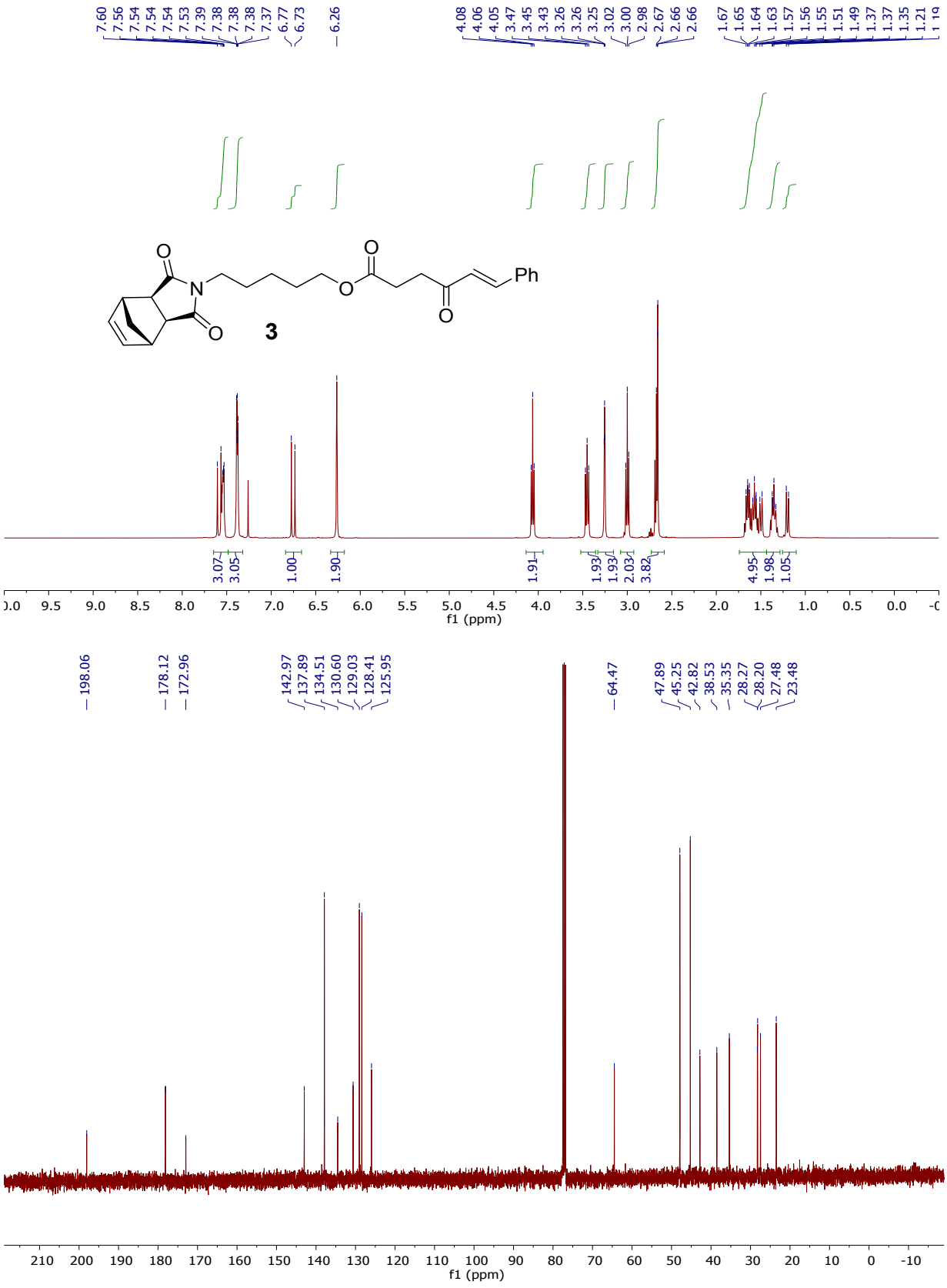


Fig. S4: ^{1}H and ^{13}C spectra of compound **3**

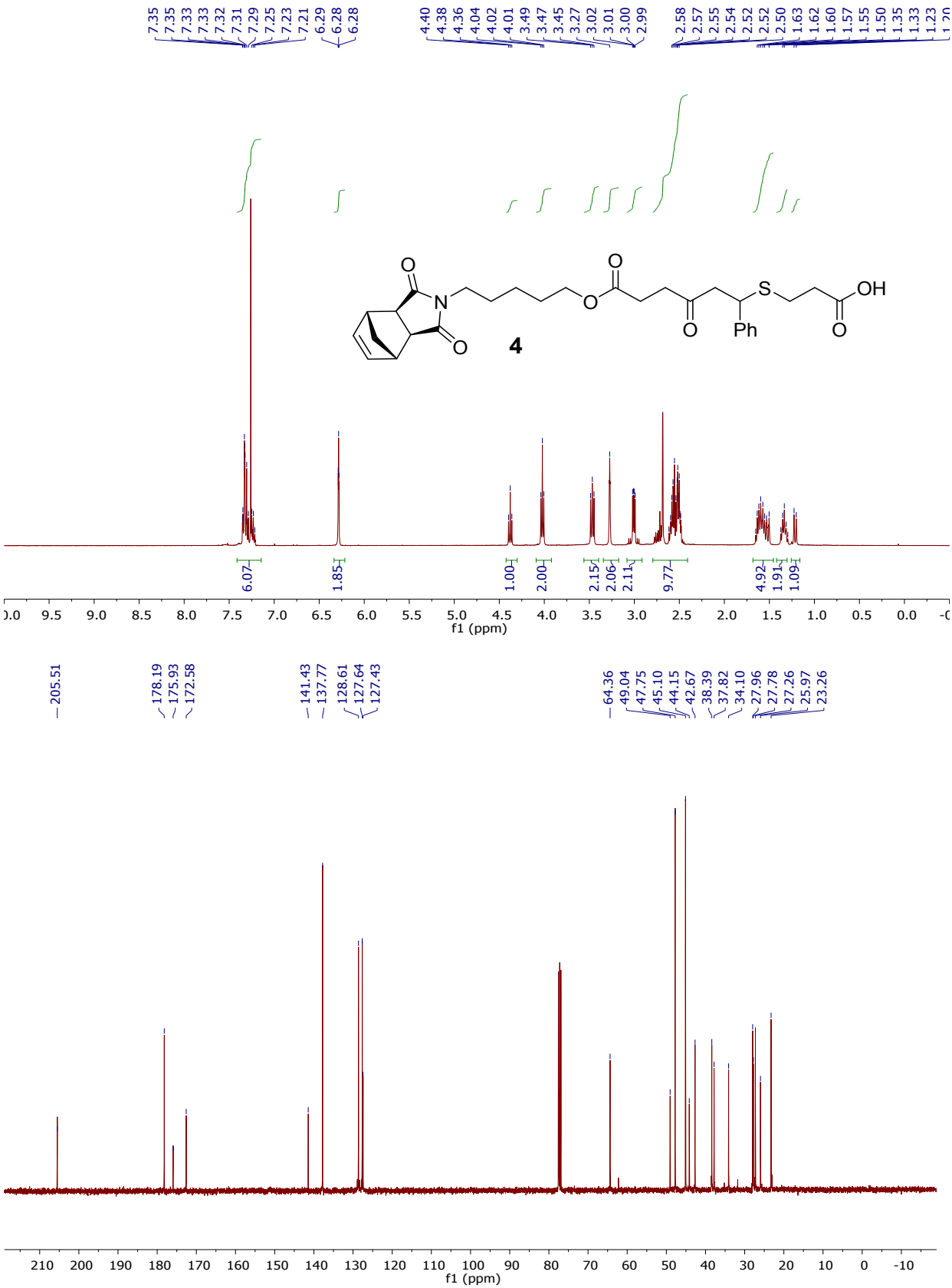


Fig. S5: ^{1}H and ^{13}C spectra of compound **4**

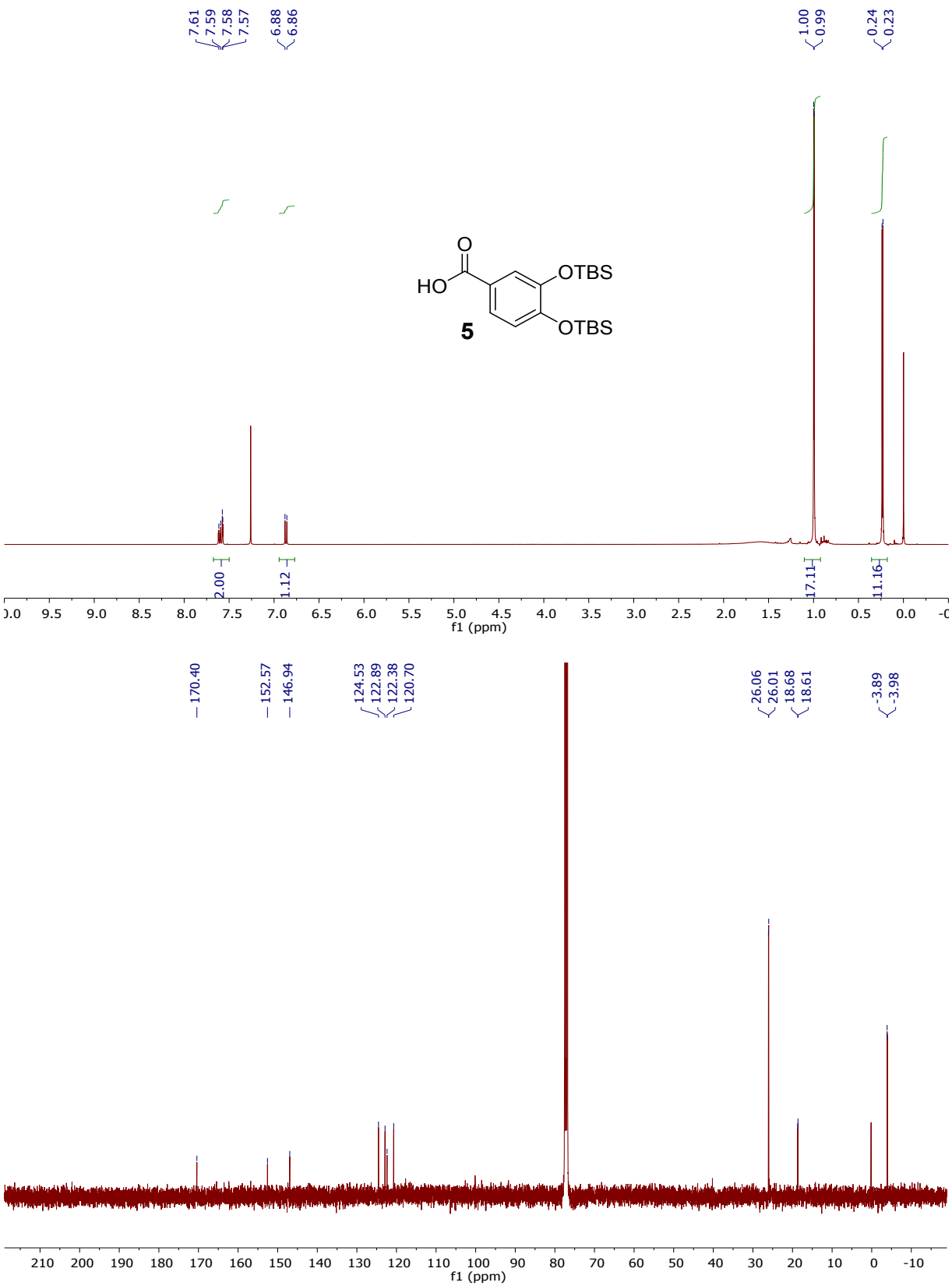


Fig. S6: ^{1}H and ^{13}C spectra of compound **5**

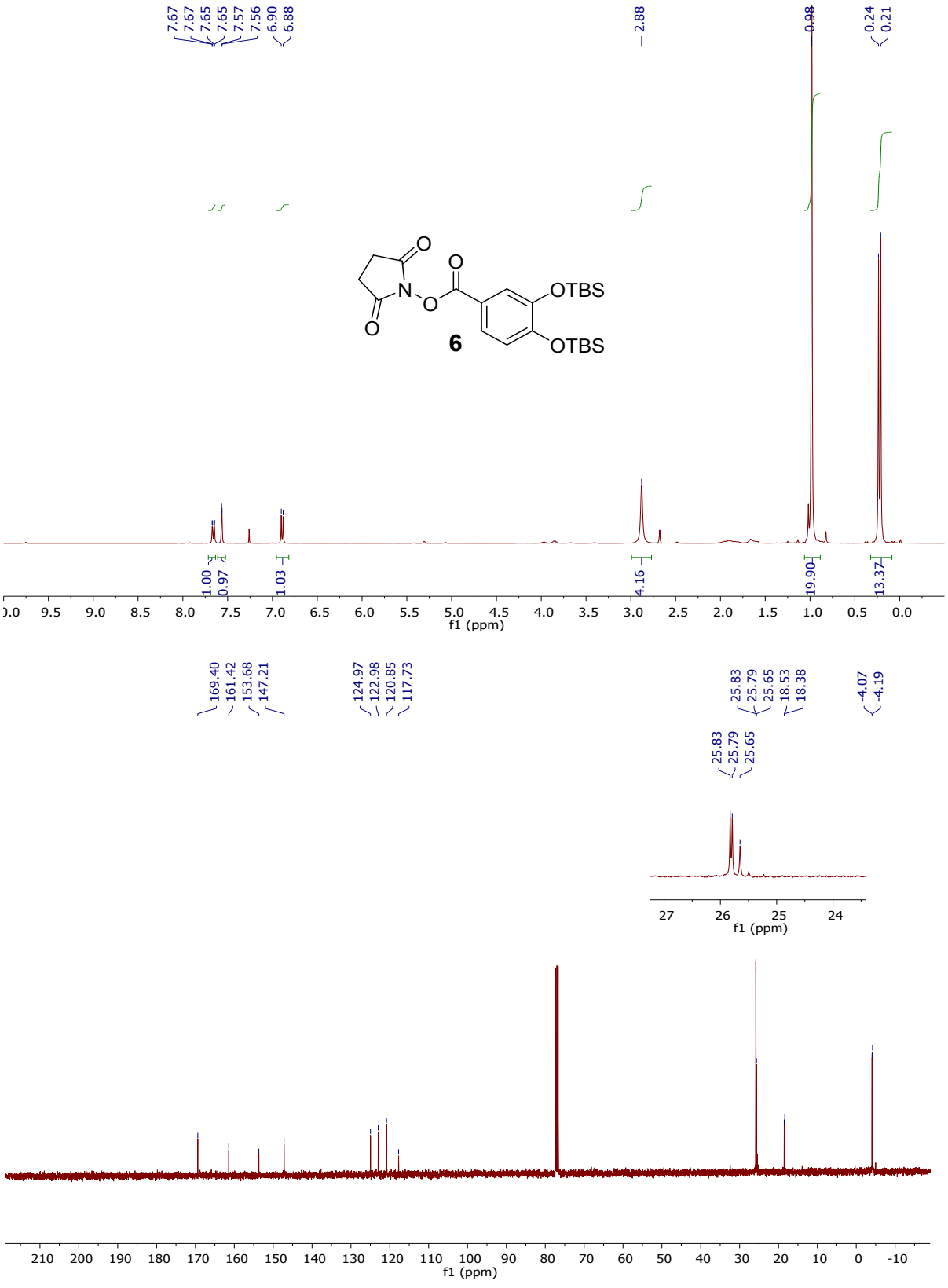


Fig. S7: ^{1}H and ^{13}C spectra of compound **6**

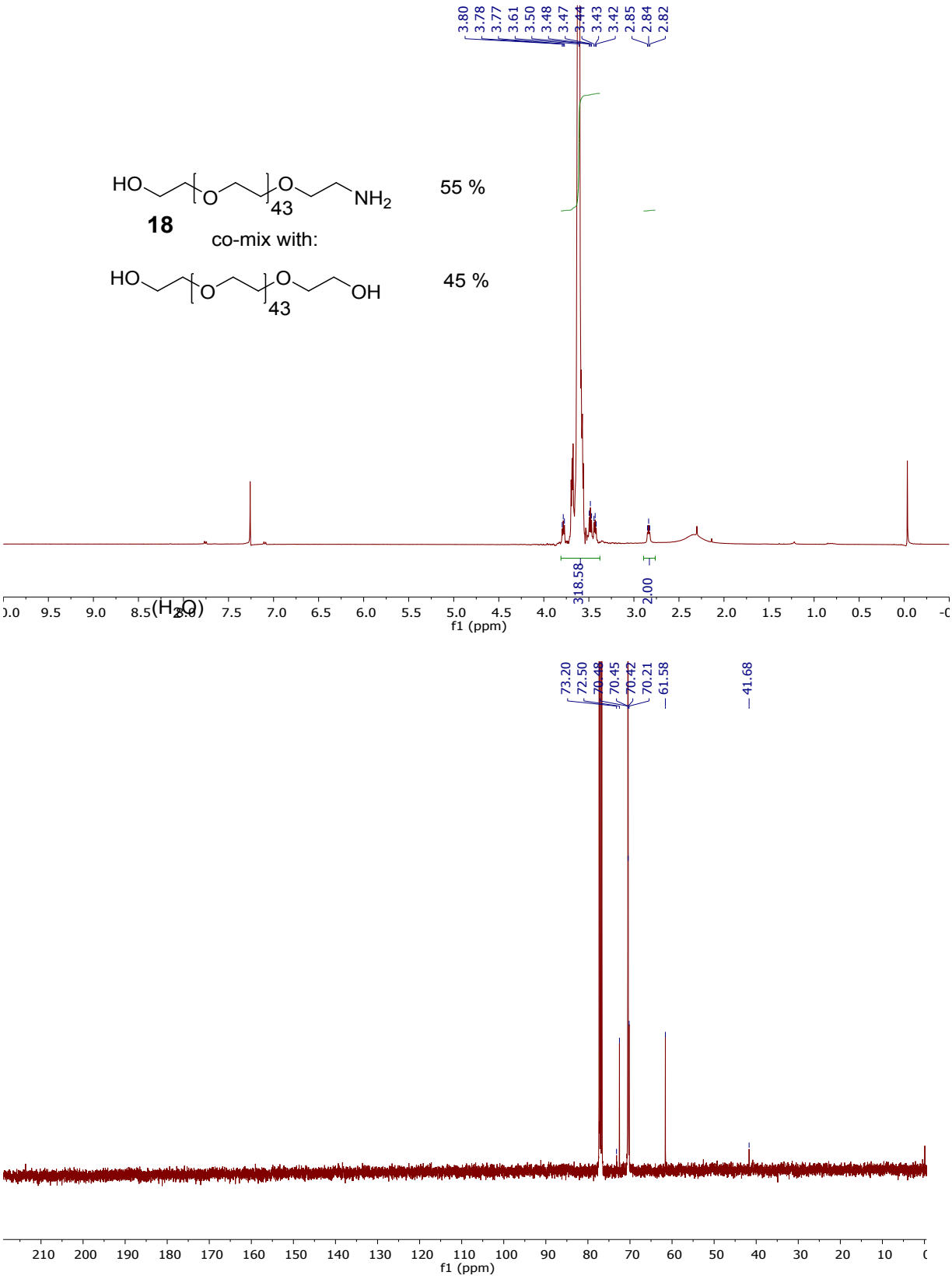


Fig. S8: ^{1}H and ^{13}C spectra of compound **18**

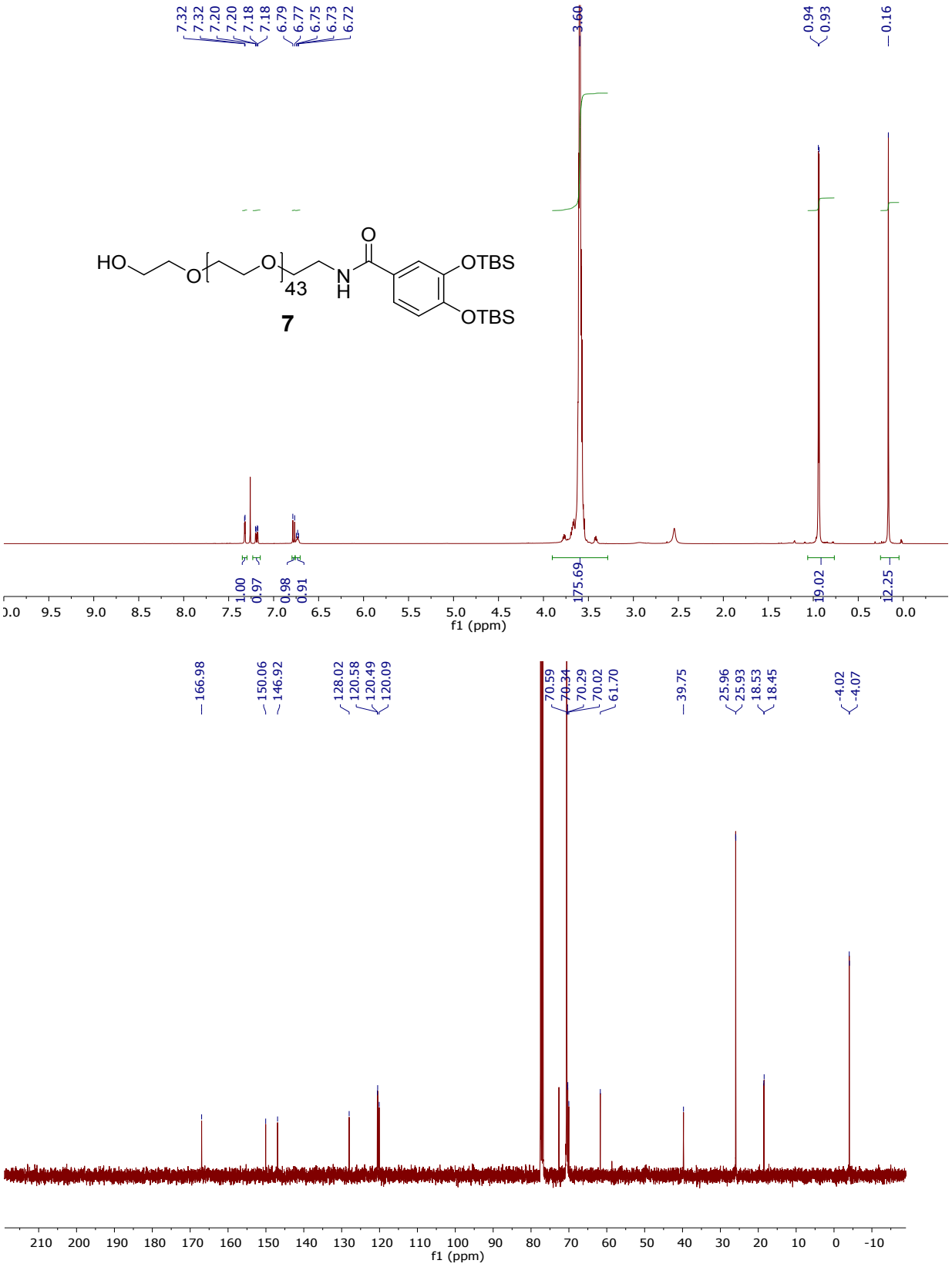


Fig. S9: ^{1}H and ^{13}C spectra of compound **7**

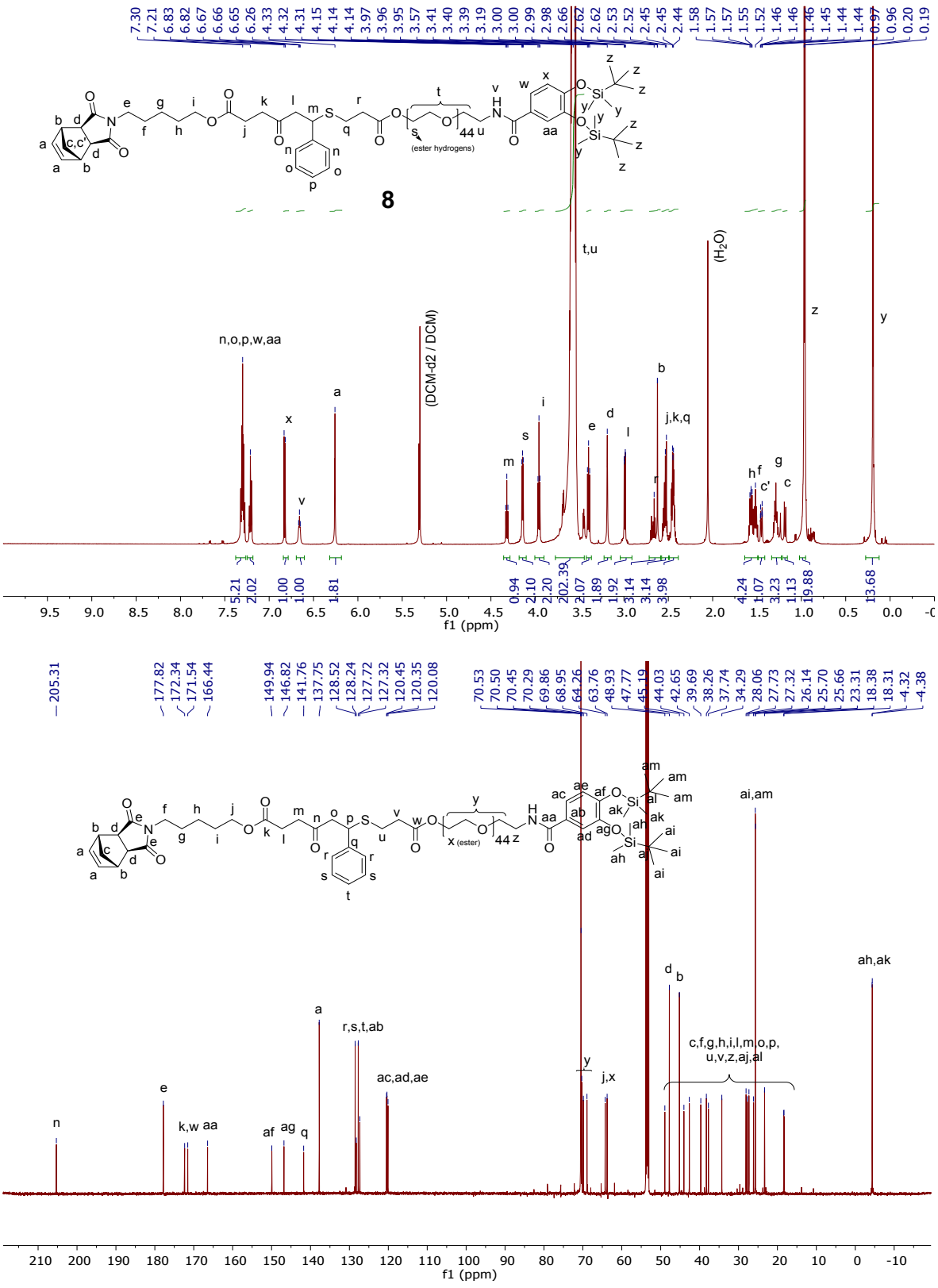


Fig. S10: ^{1}H and ^{13}C spectra and peak assignments for compound **8**

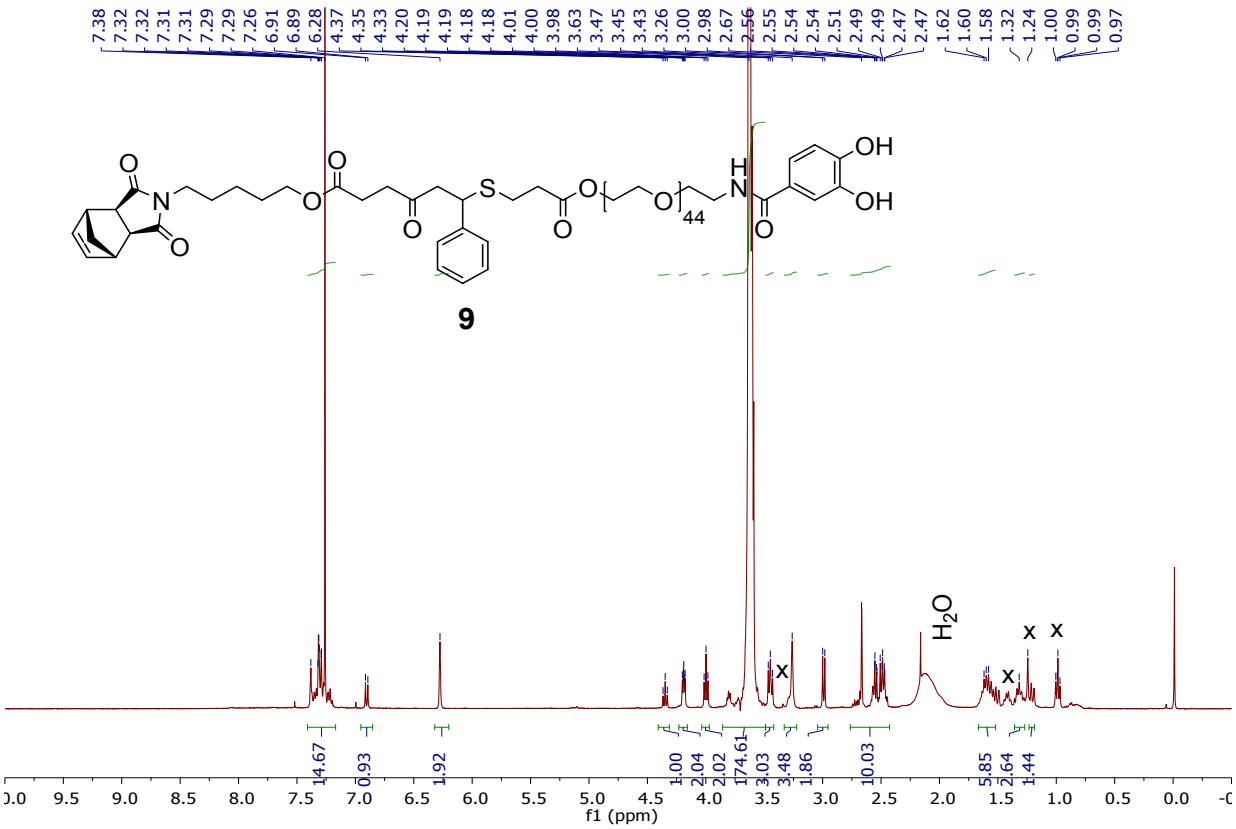


Fig. S11: ^{1}H NMR spectrum of product **9**, with tetrabutylammonium impurities marked by an "x"

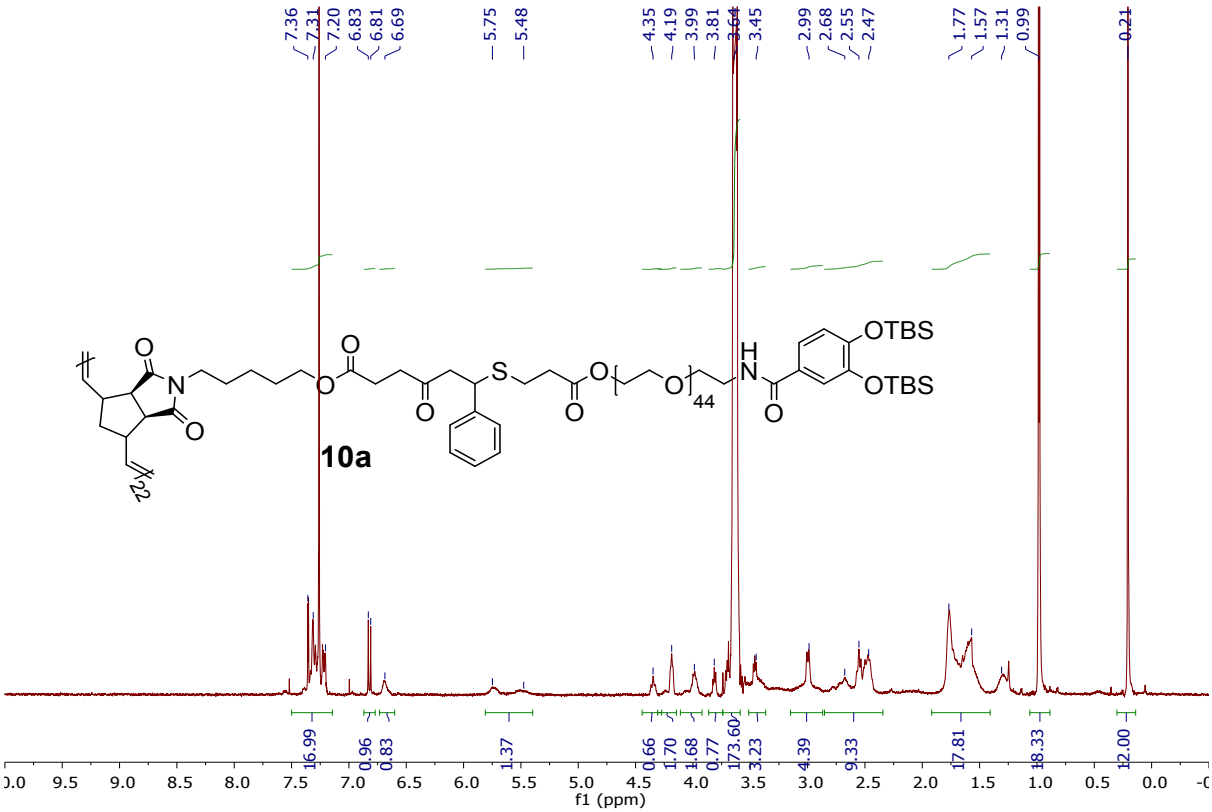


Fig. S12: ^{1}H NMR spectrum for compound **10a**

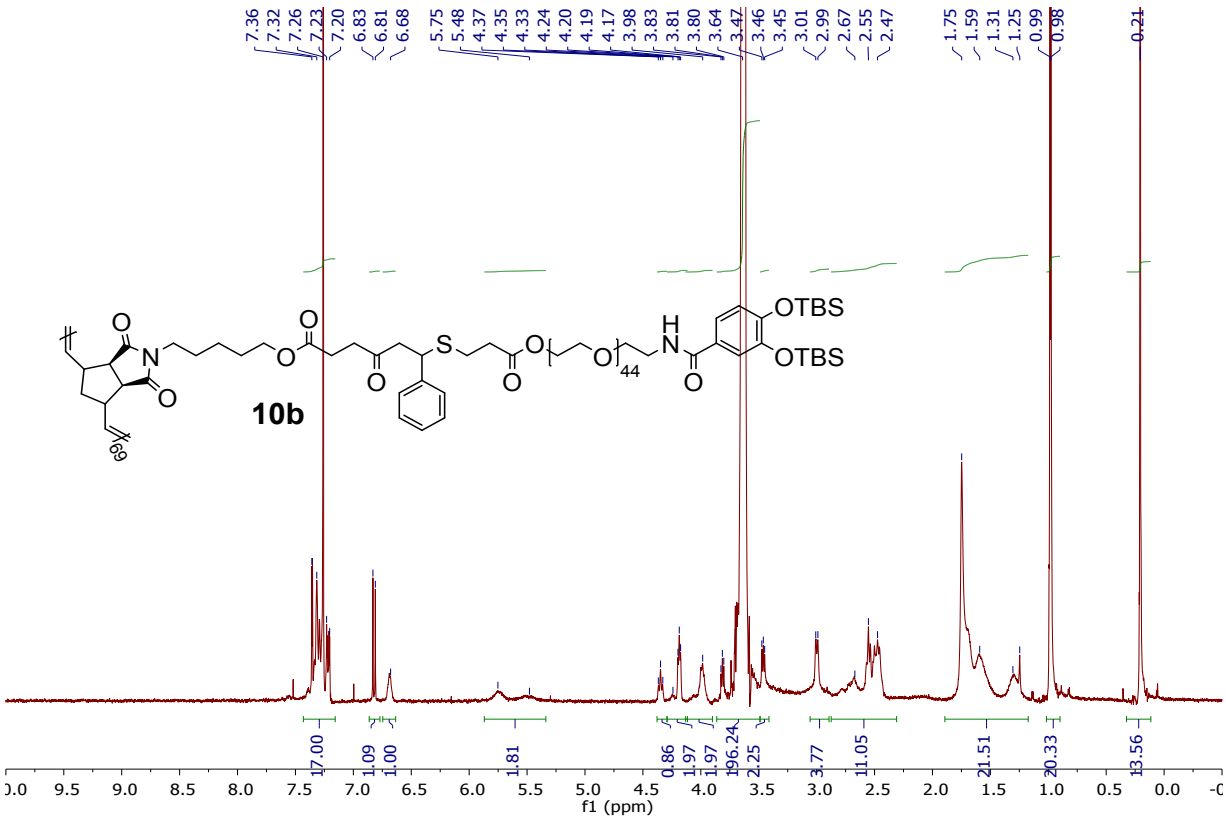


Fig. S13: ^{1}H NMR spectrum of compound **10b**

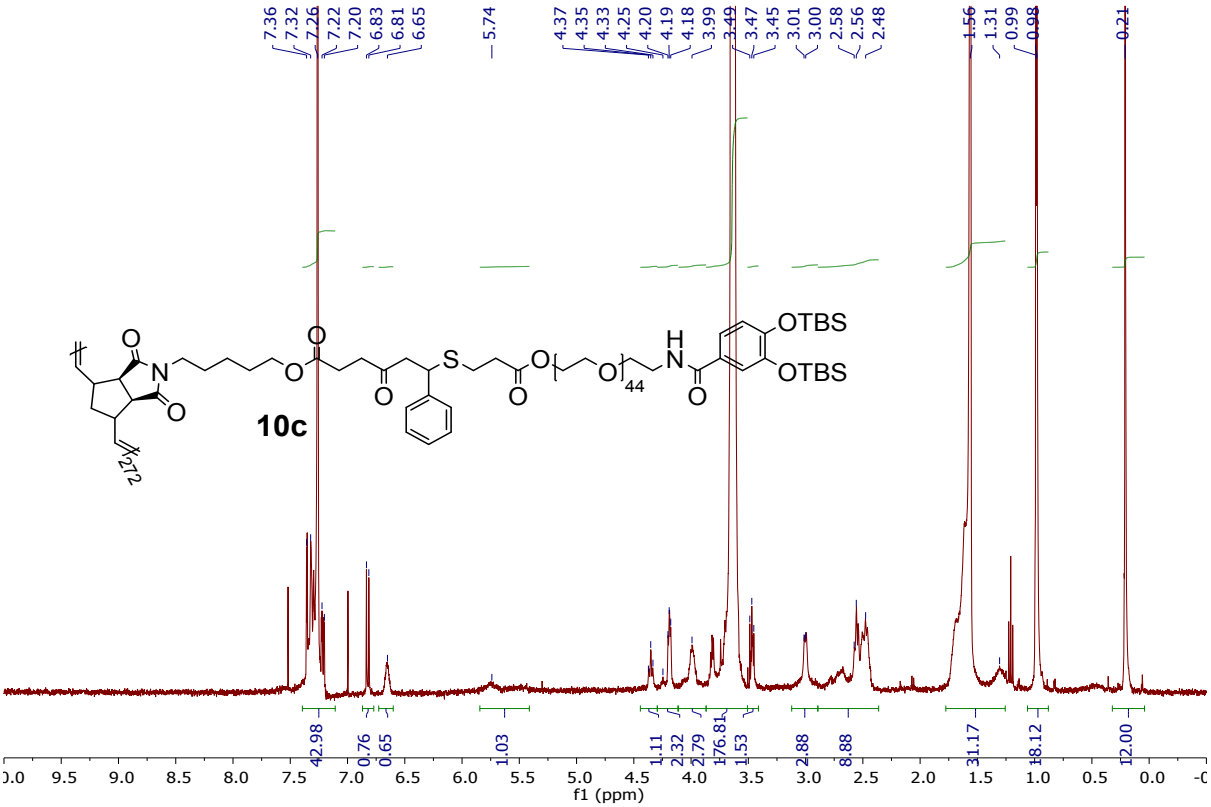


Fig. S14: ^{1}H NMR spectrum of compound **10c**

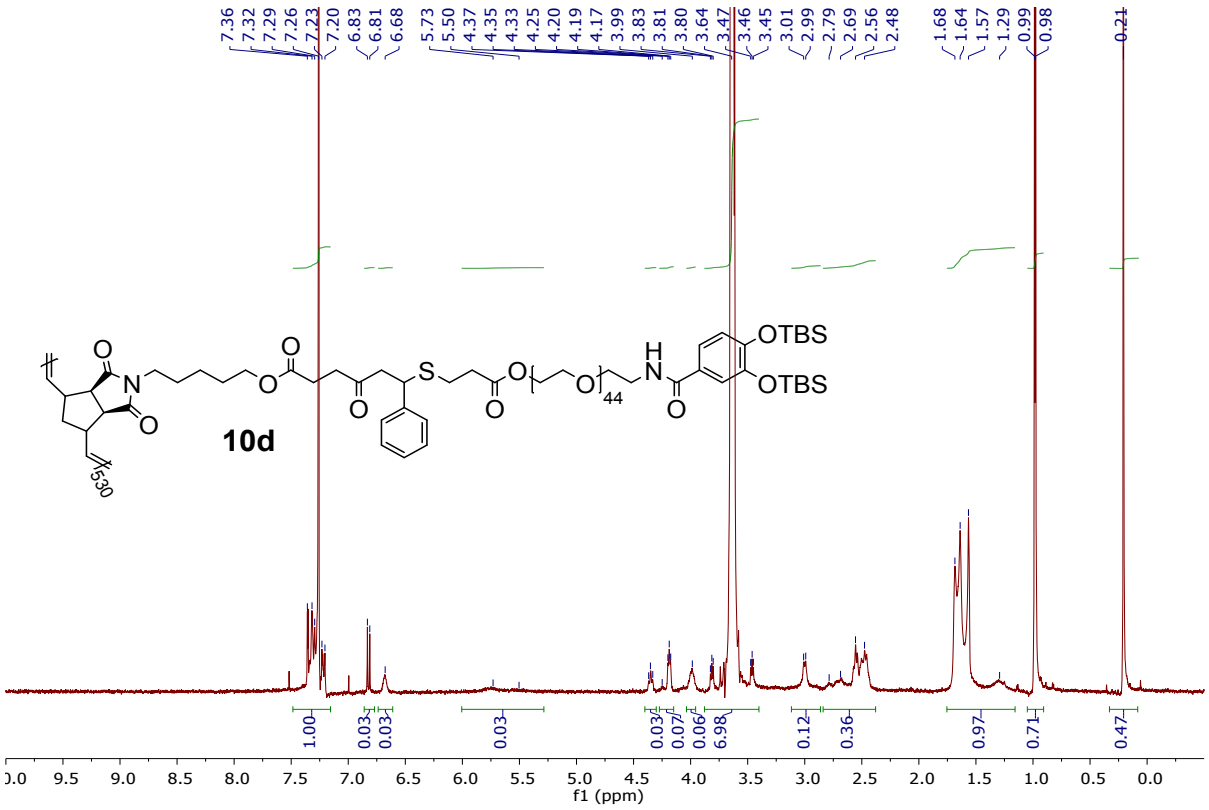


Fig. S15: ^{1}H NMR spectrum of compound **10d**

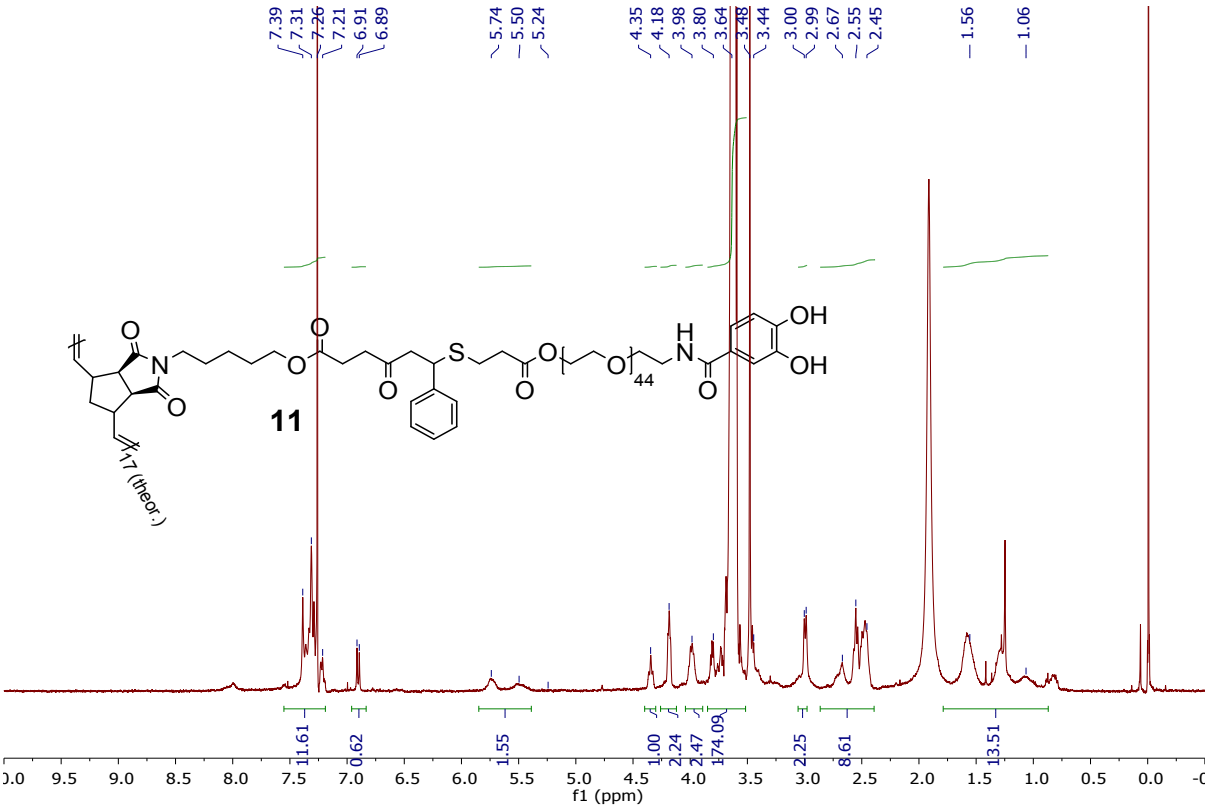


Fig. S16: ^{1}H NMR spectrum of compound **11**

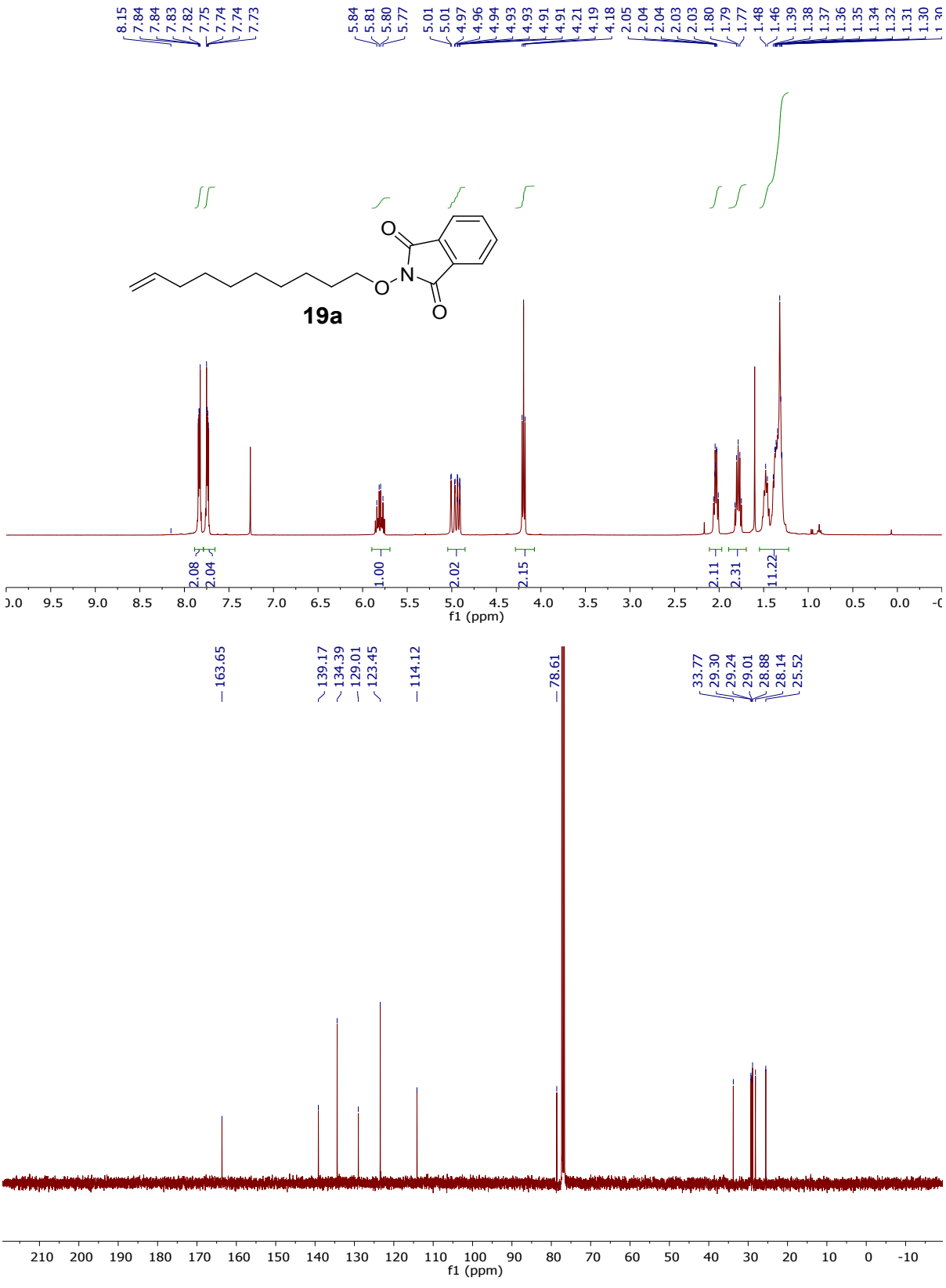


Fig. S17: ^{1}H and ^{13}C spectra of compound **19a**

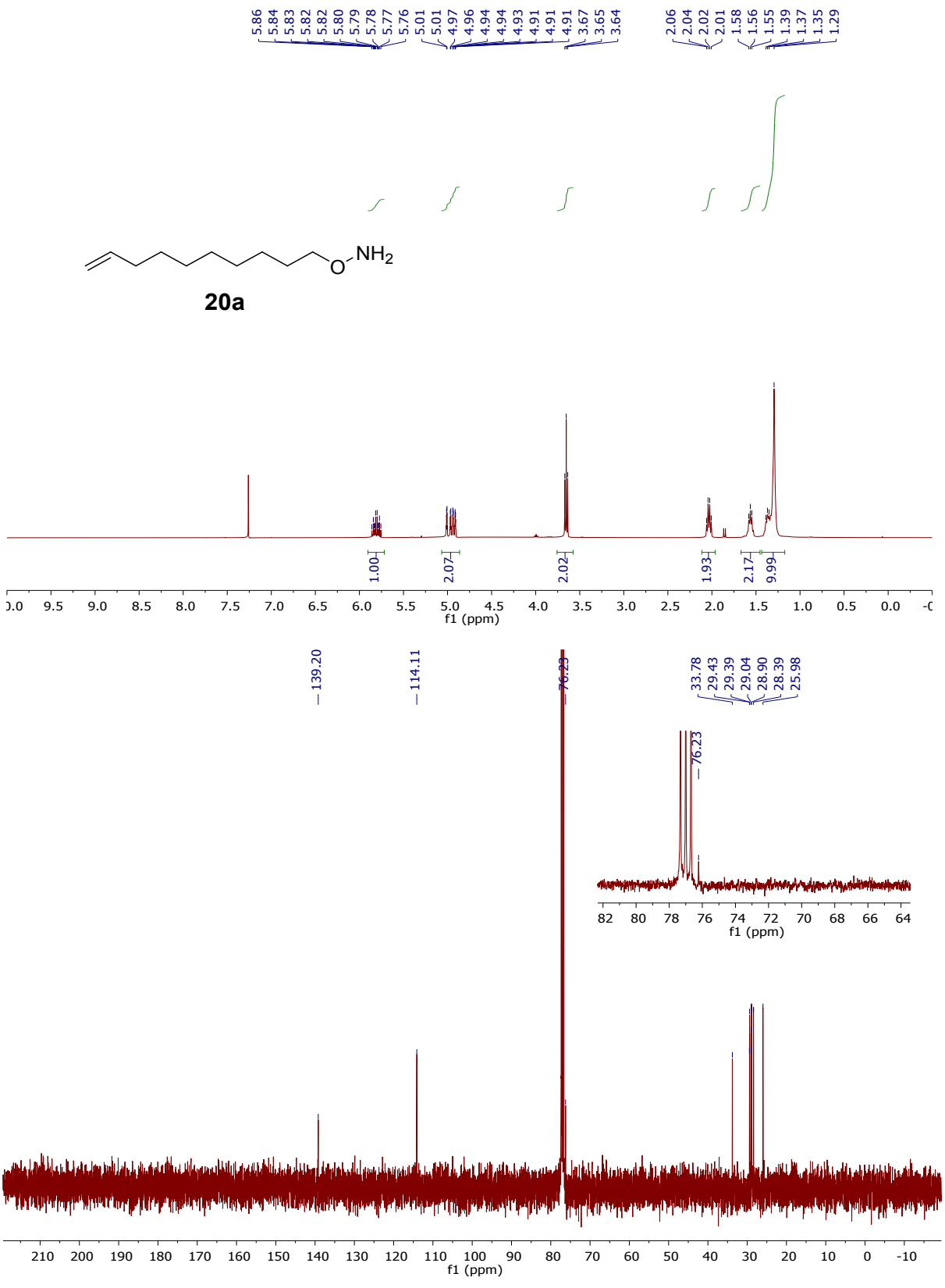


Fig. S18: ^{1}H and ^{13}C spectra of compound **20a**

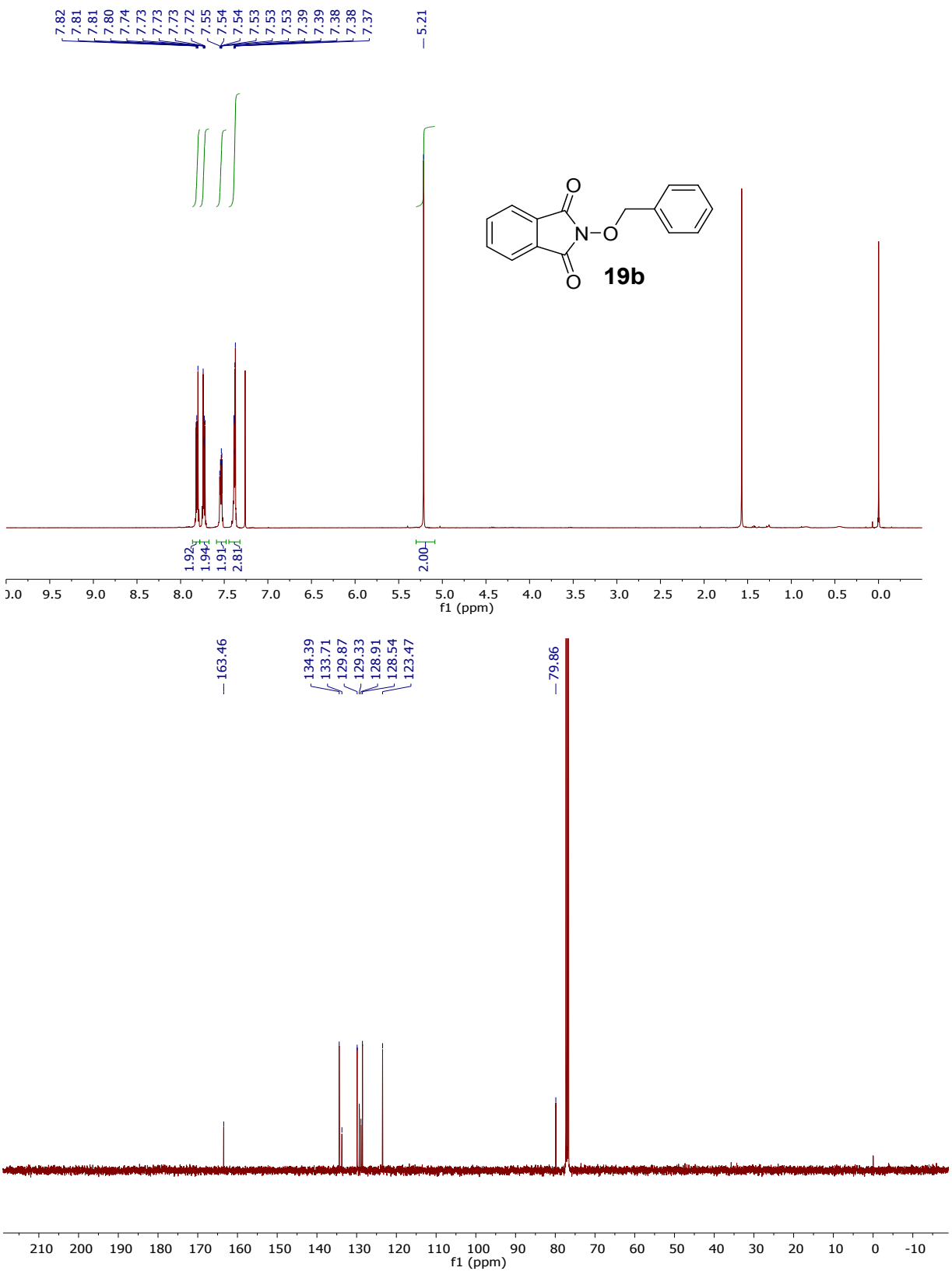


Fig. S19: ^{1}H and ^{13}C spectra of compound **19b**

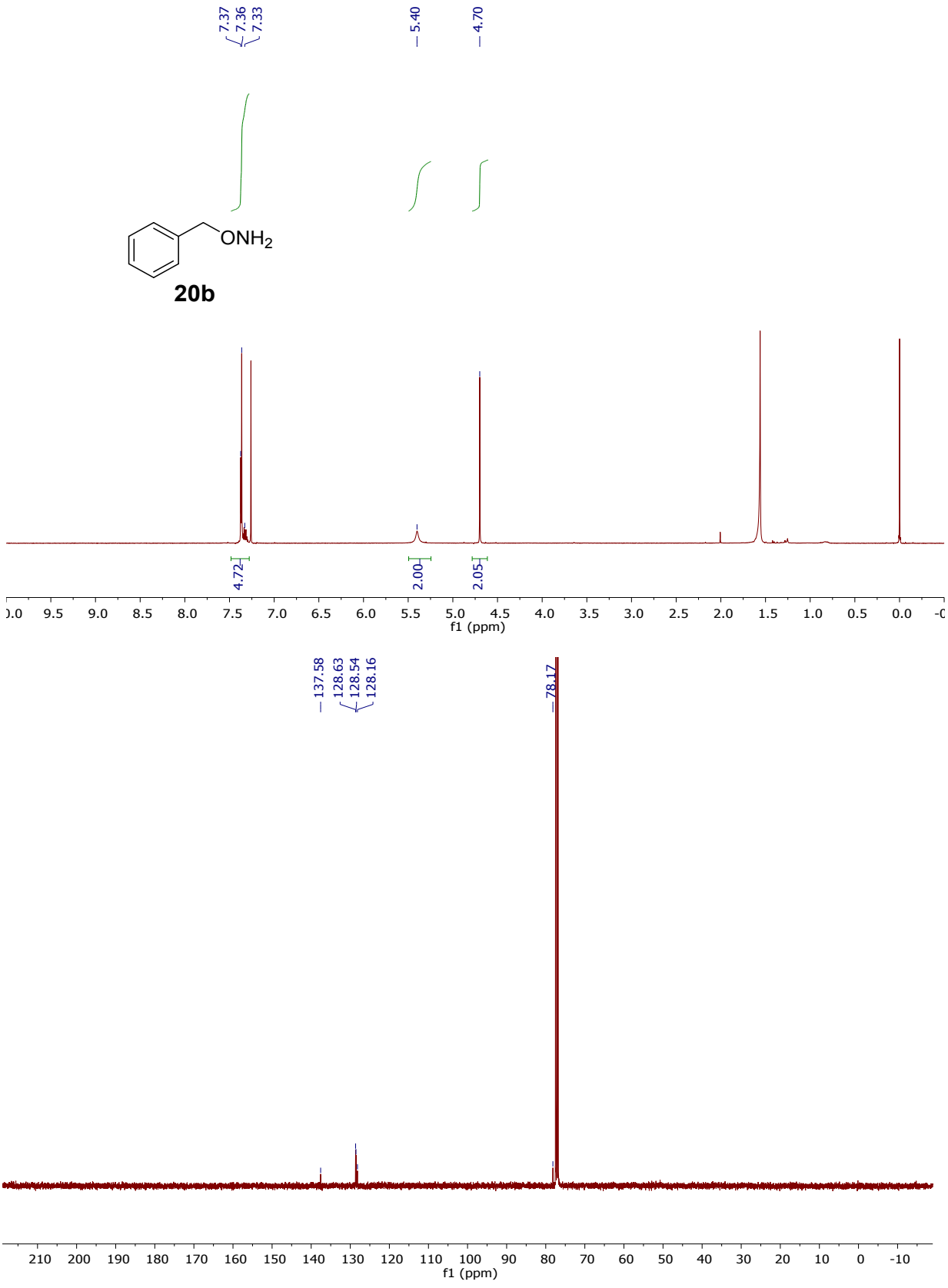


Fig. S20: ^{1}H and ^{13}C spectra of compound **20b**

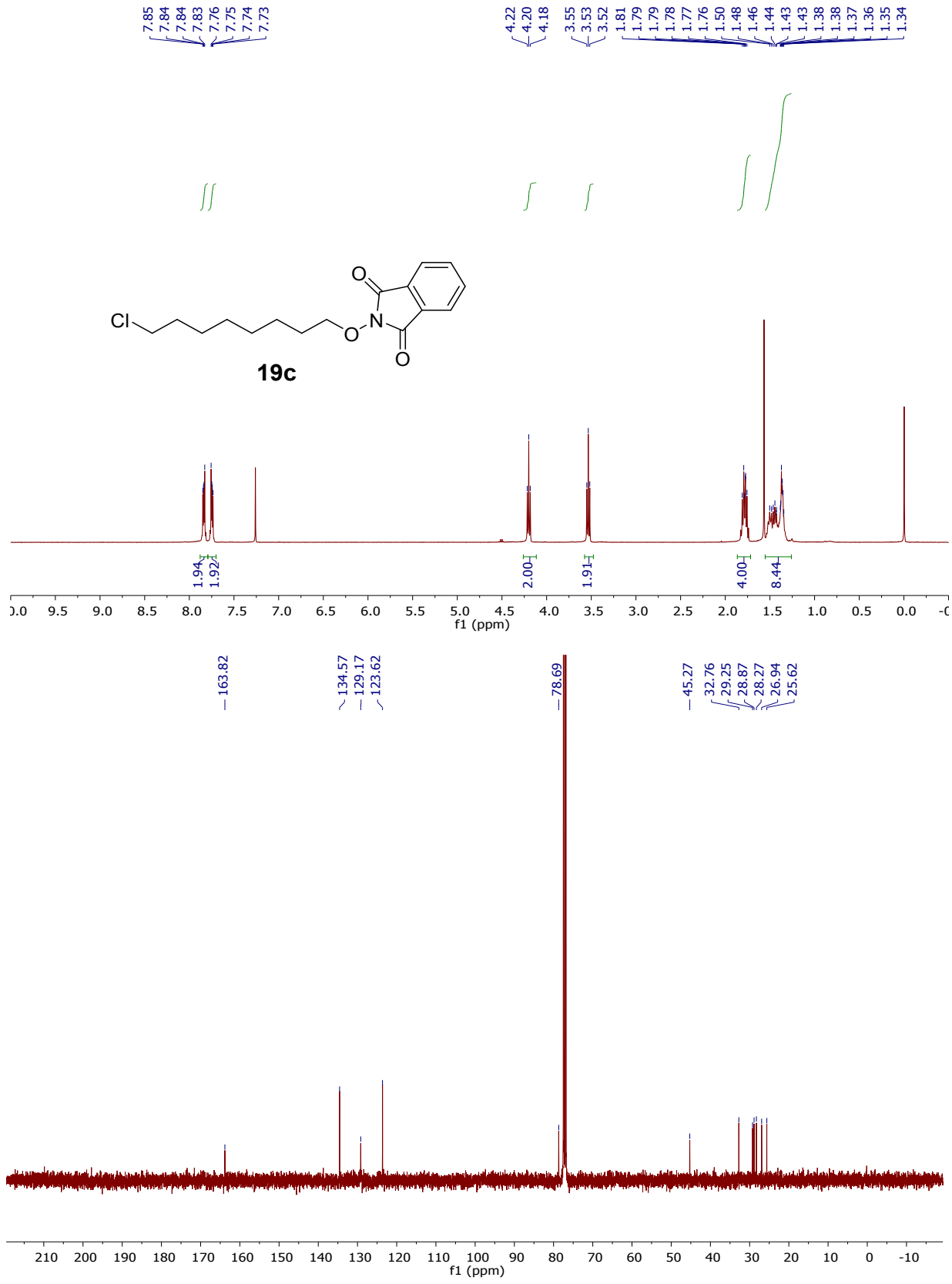


Fig. S21: ^{1}H and ^{13}C spectra of compound **19c**

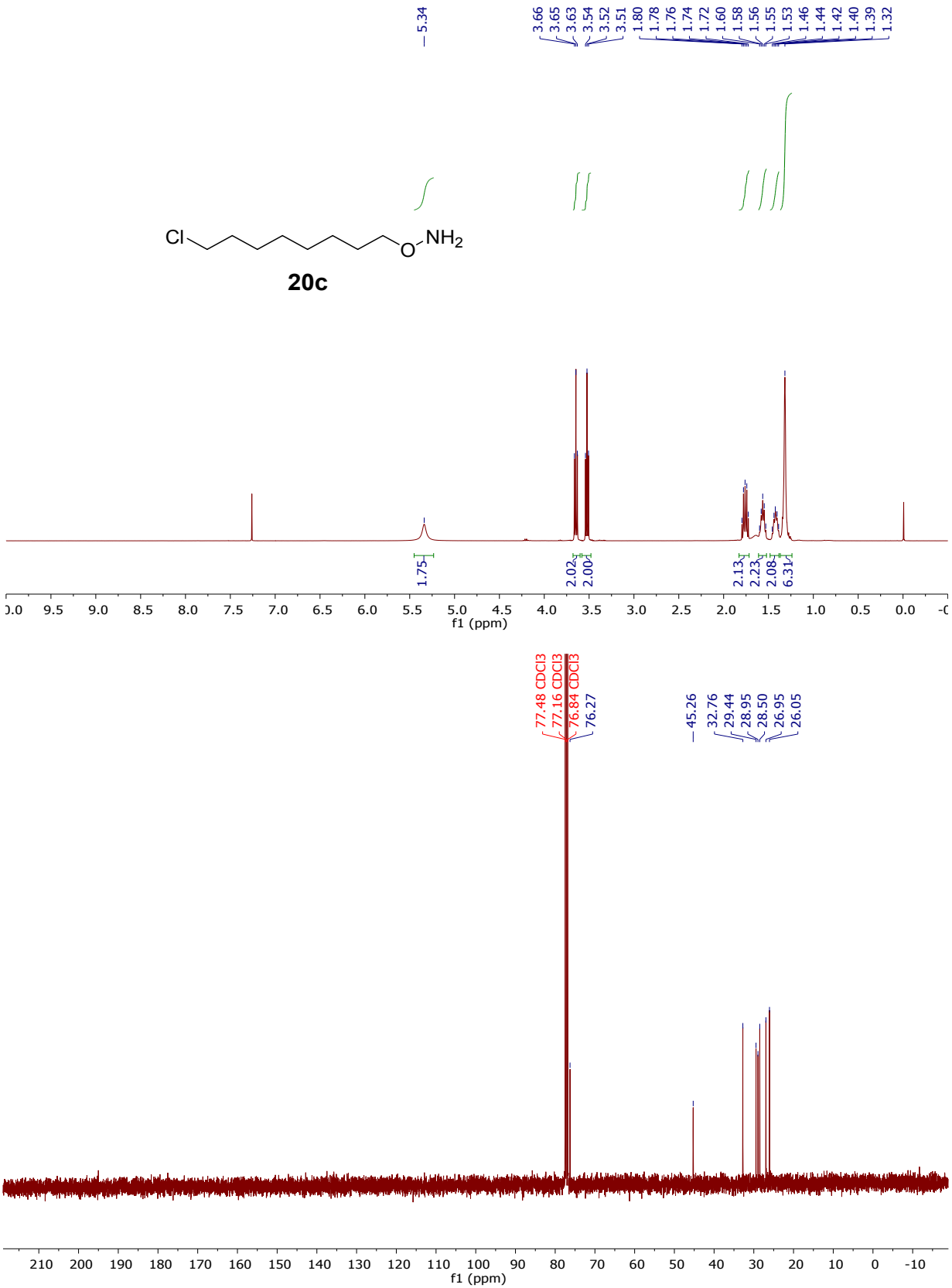


Fig. S22: ^{1}H and ^{13}C spectra of compound **20c**

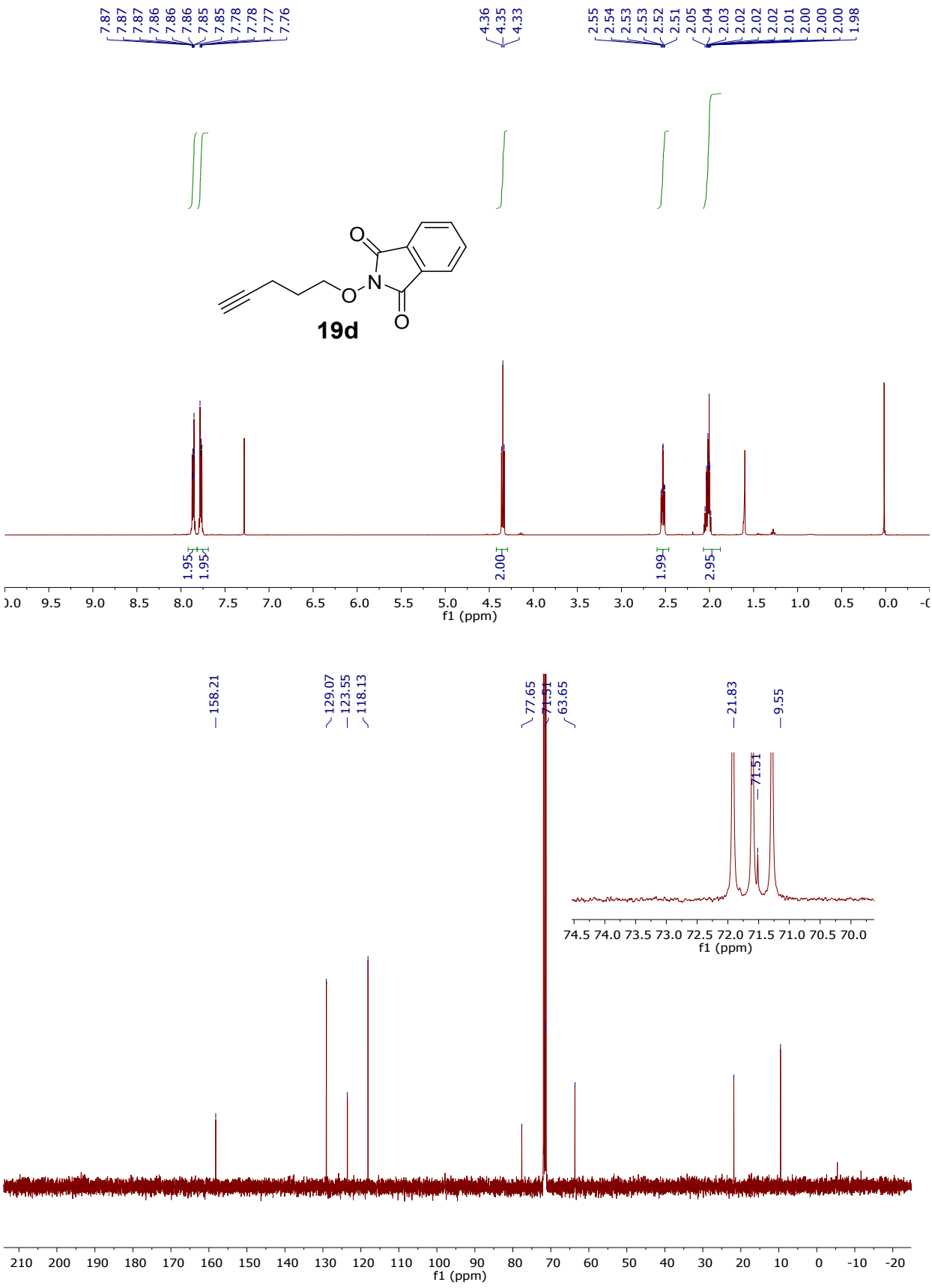


Fig. S23: ^{1}H and ^{13}C spectra of compound **19d**

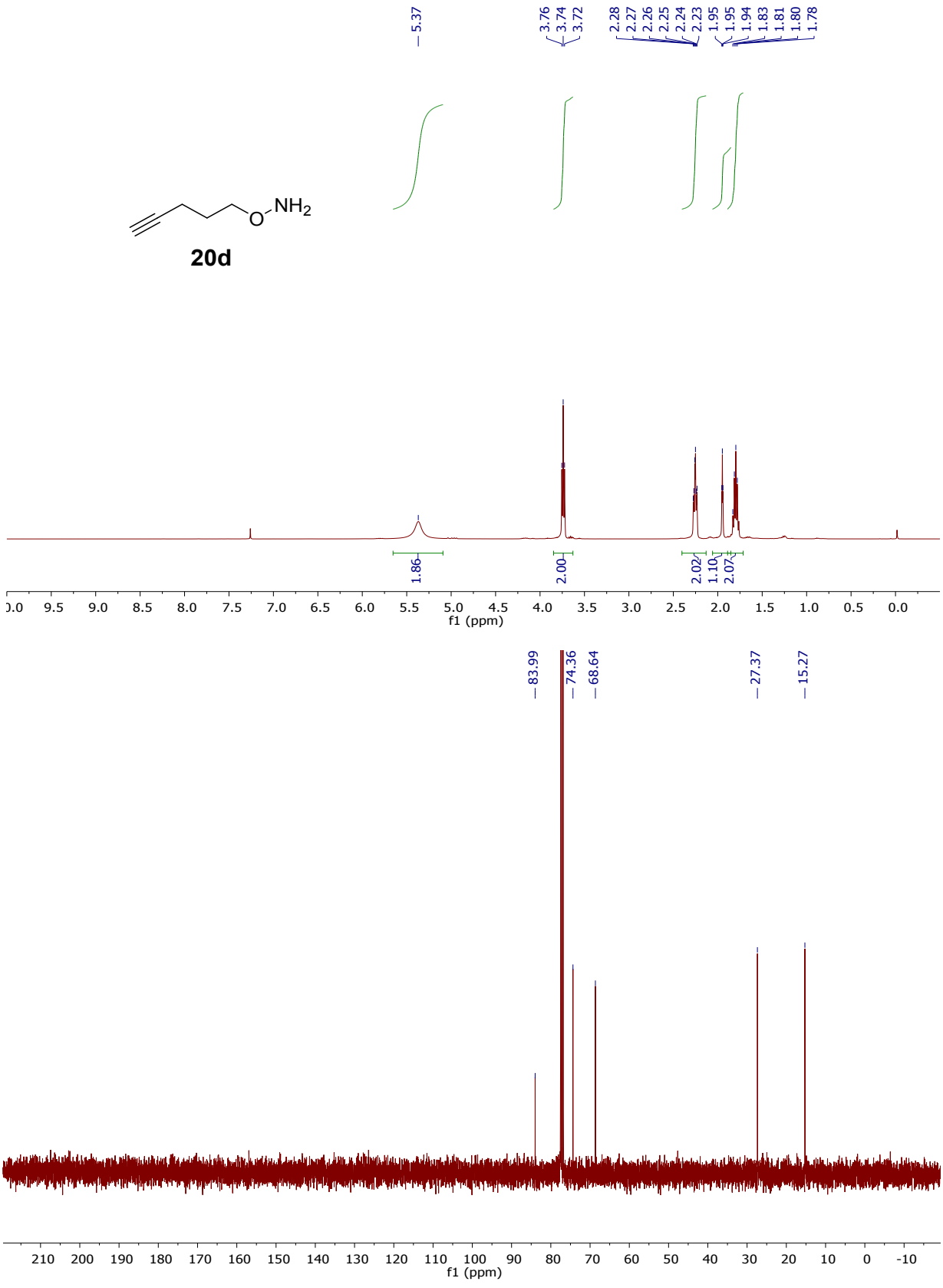


Fig. S24: ^{1}H and ^{13}C spectra of compound **20d**

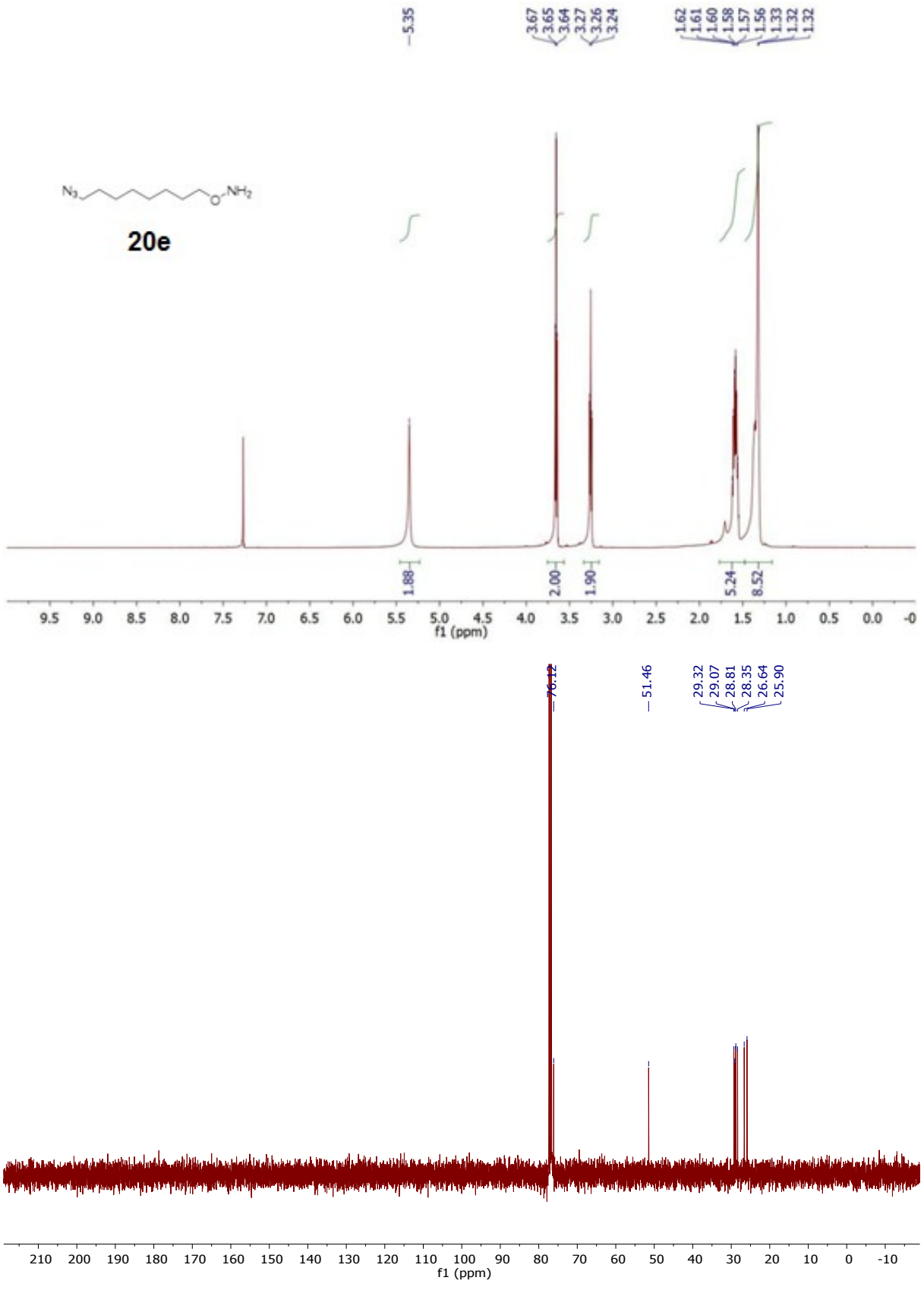


Fig. S25: ^{1}H and ^{13}C spectra of compound **20e**

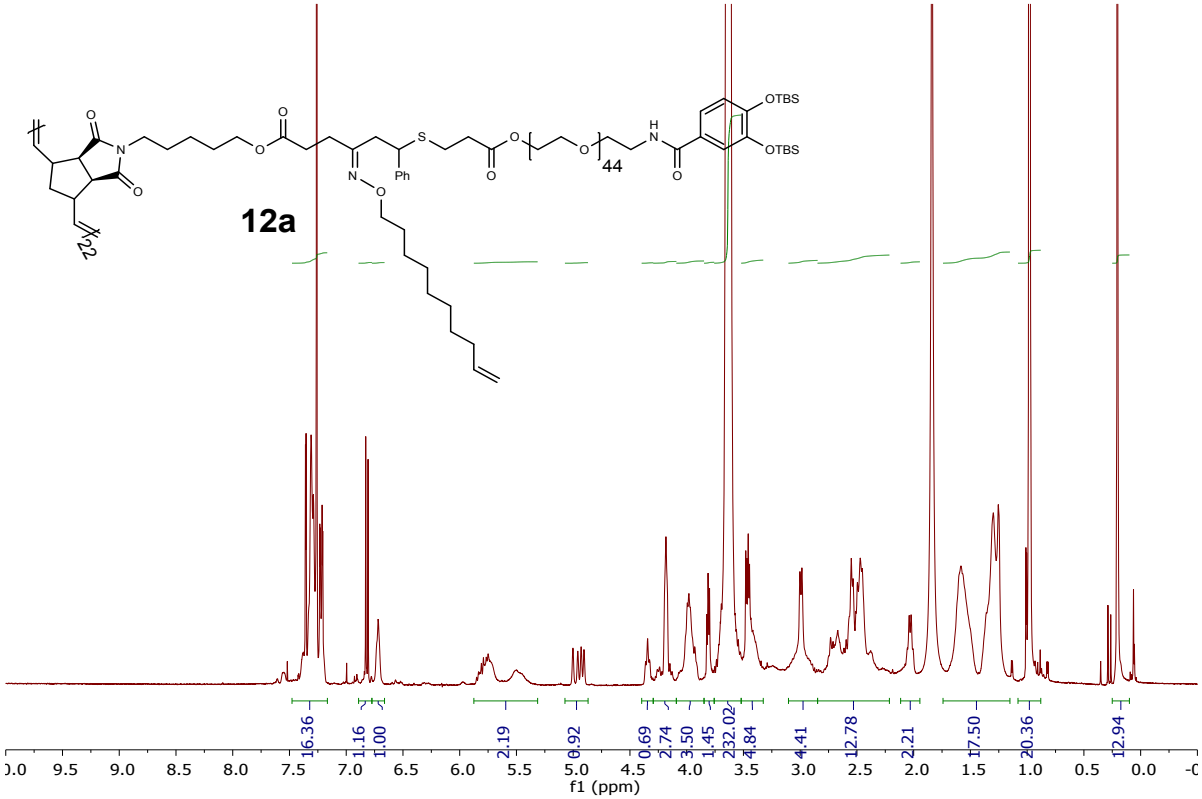


Fig. S26: ^{1}H NMR spectrum of compound **12a**

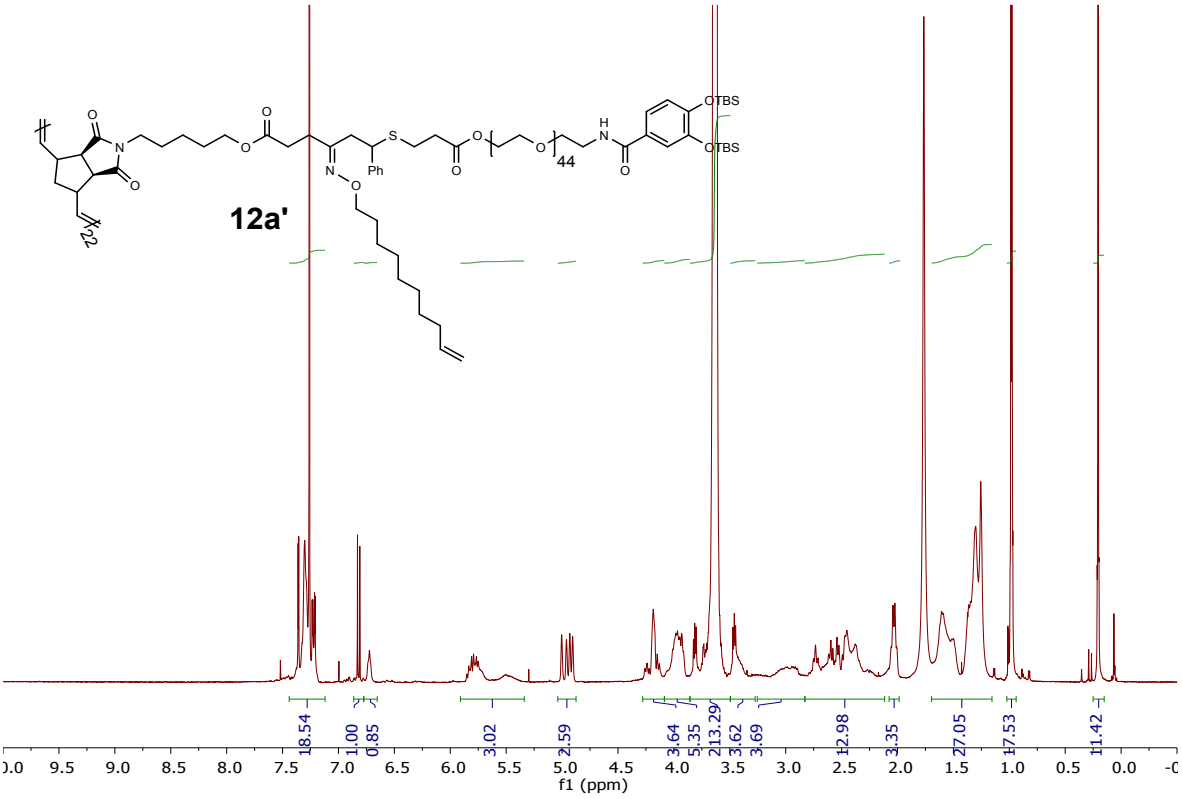


Fig. S27: ^{1}H NMR spectrum of compound **12a'**

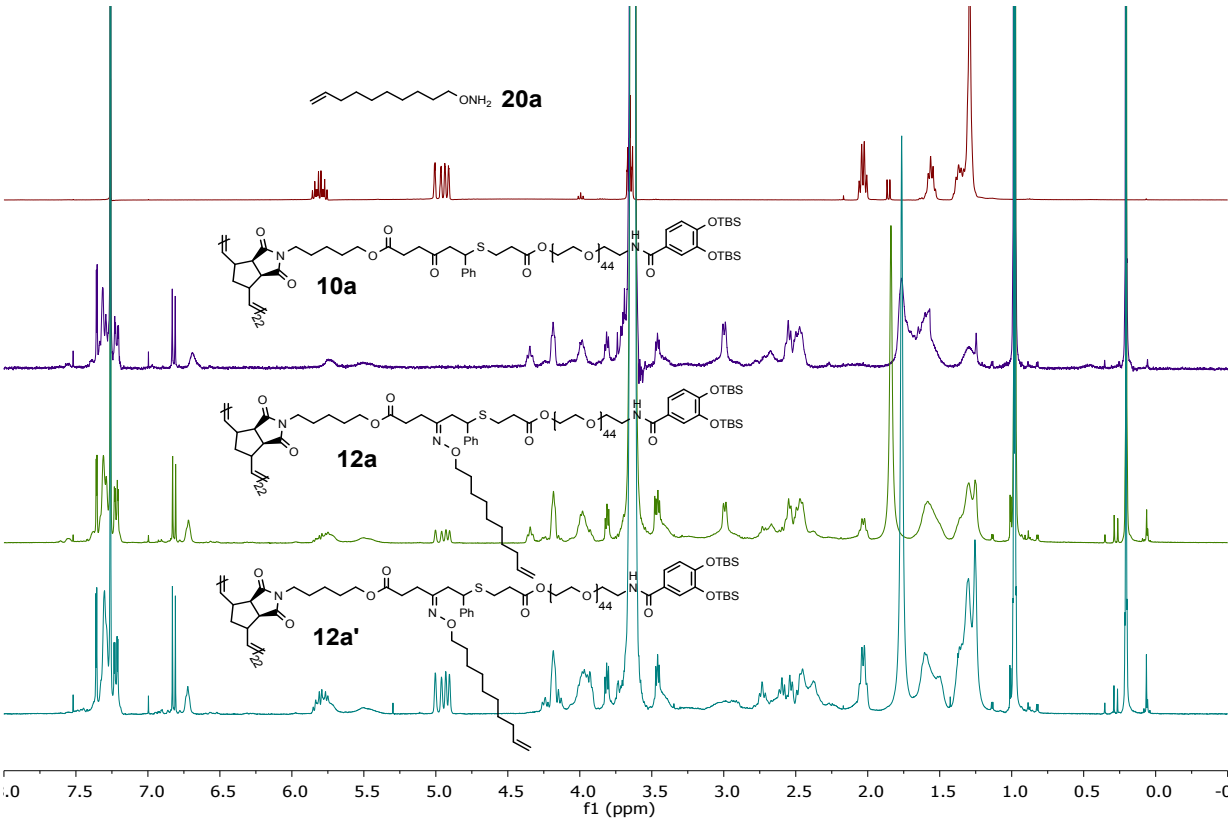


Fig. S28: Overlay of the ^{1}H NMR spectrum of compounds **20a**, **10a**, **12a**, and **12a'**

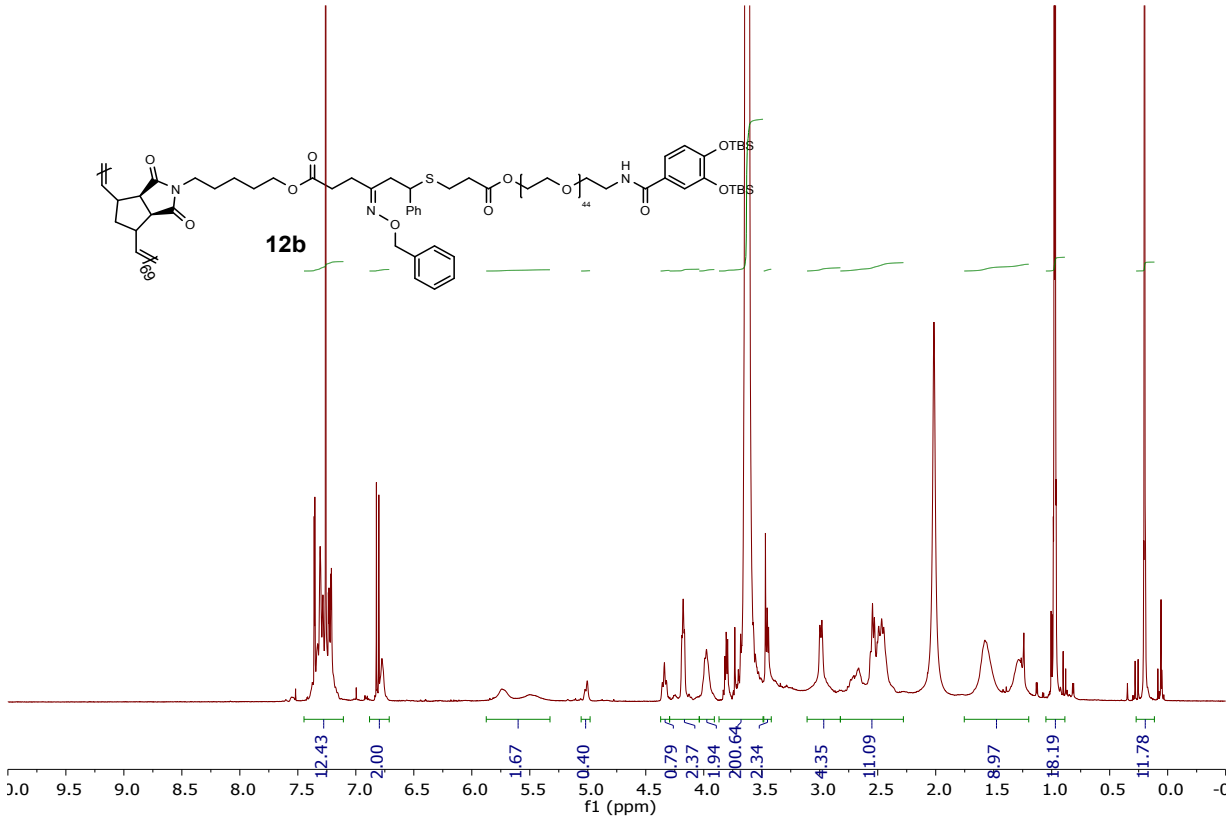


Fig. S29: ^{1}H NMR spectrum of compound **12b**

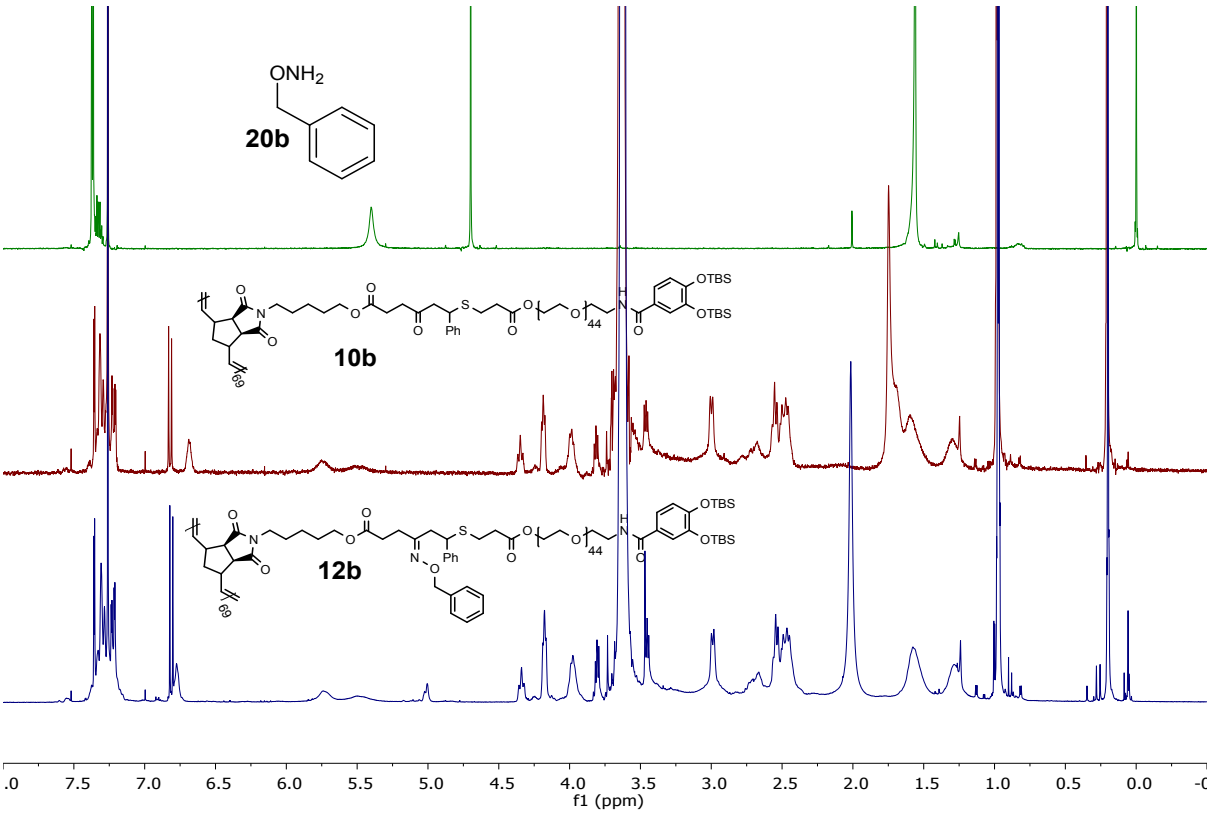


Fig. S30: Overlay of the ^{1}H NMR spectrum of compounds **20b**, **10b**, and **12b**

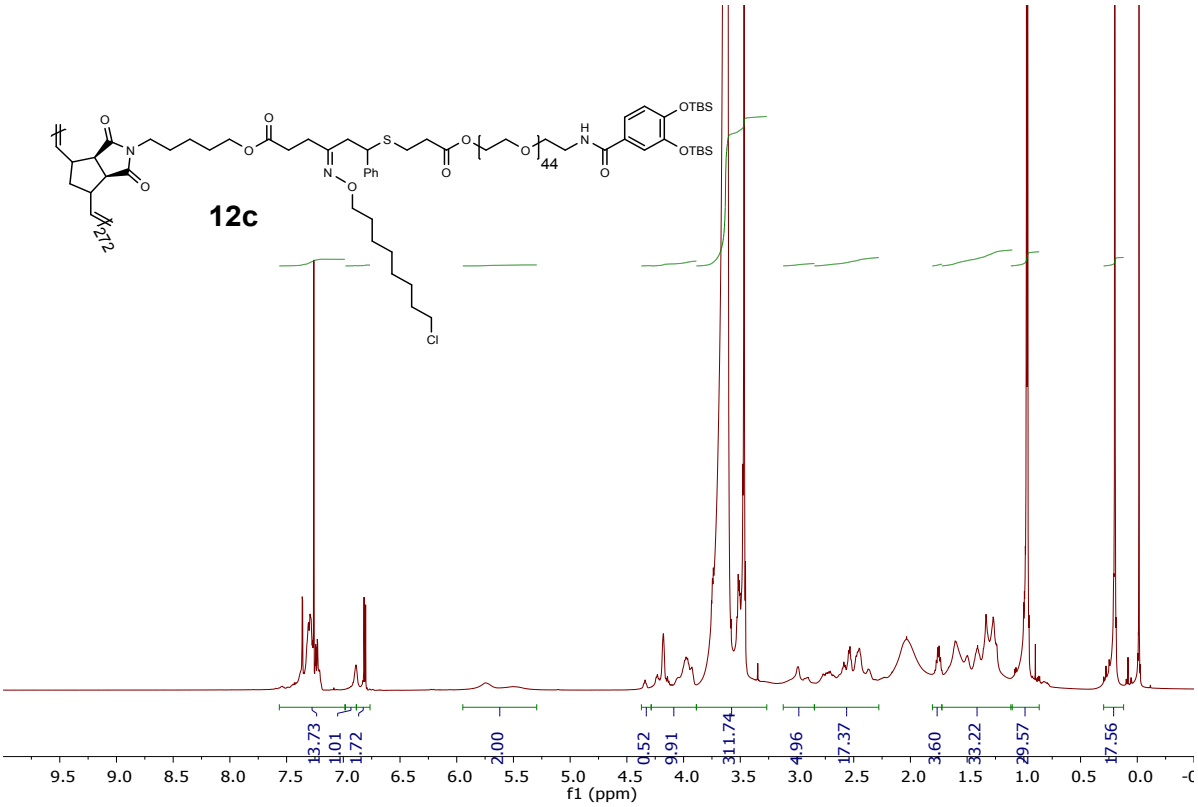


Fig. S31: ^{1}H NMR spectrum of compound **12c**

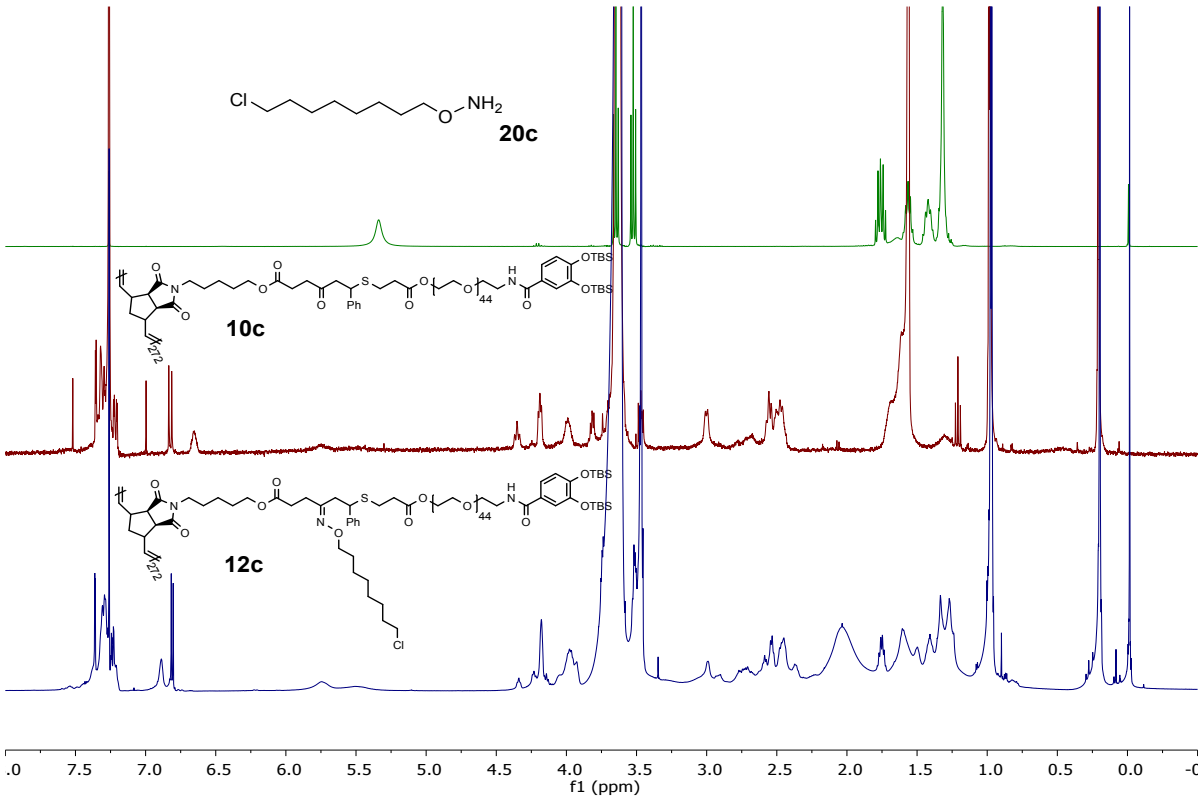


Fig. S32: Overlay of the ^{1}H NMR spectrum of compounds **20c**, **10c**, and **12c**

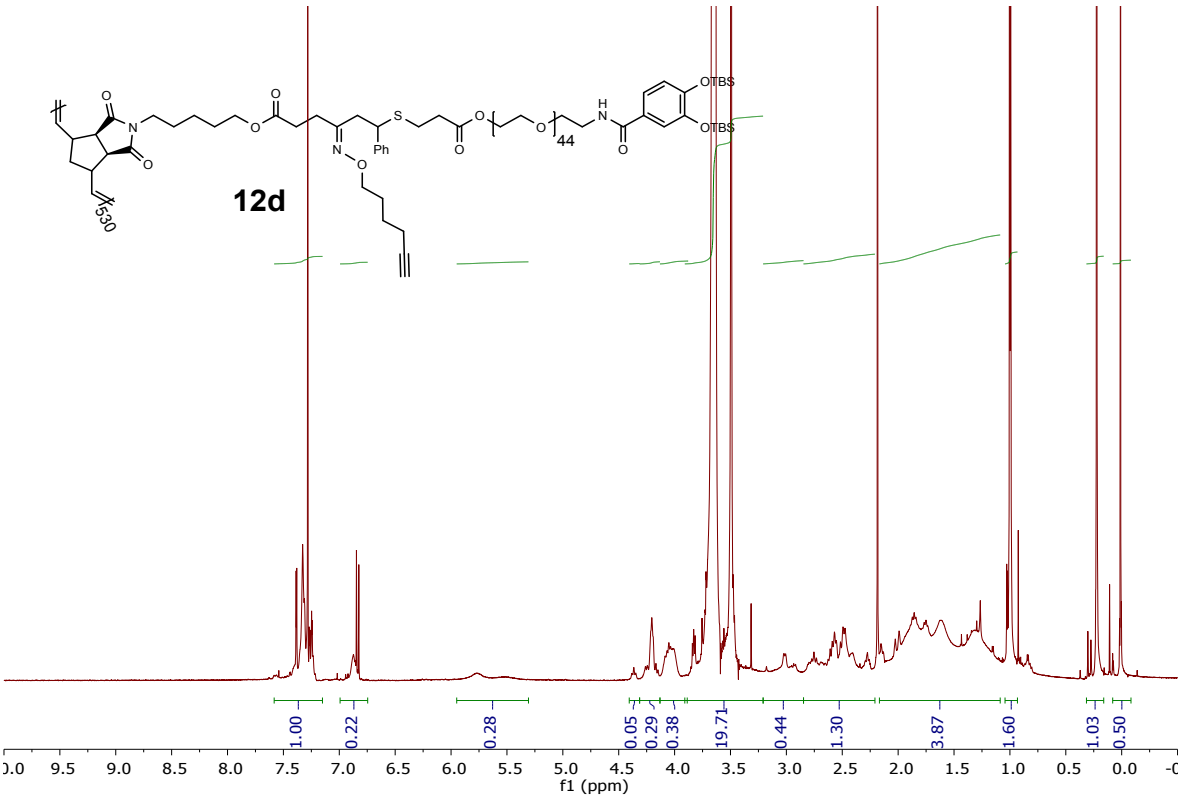


Fig. S33: ^{1}H NMR spectrum of compound **12d**

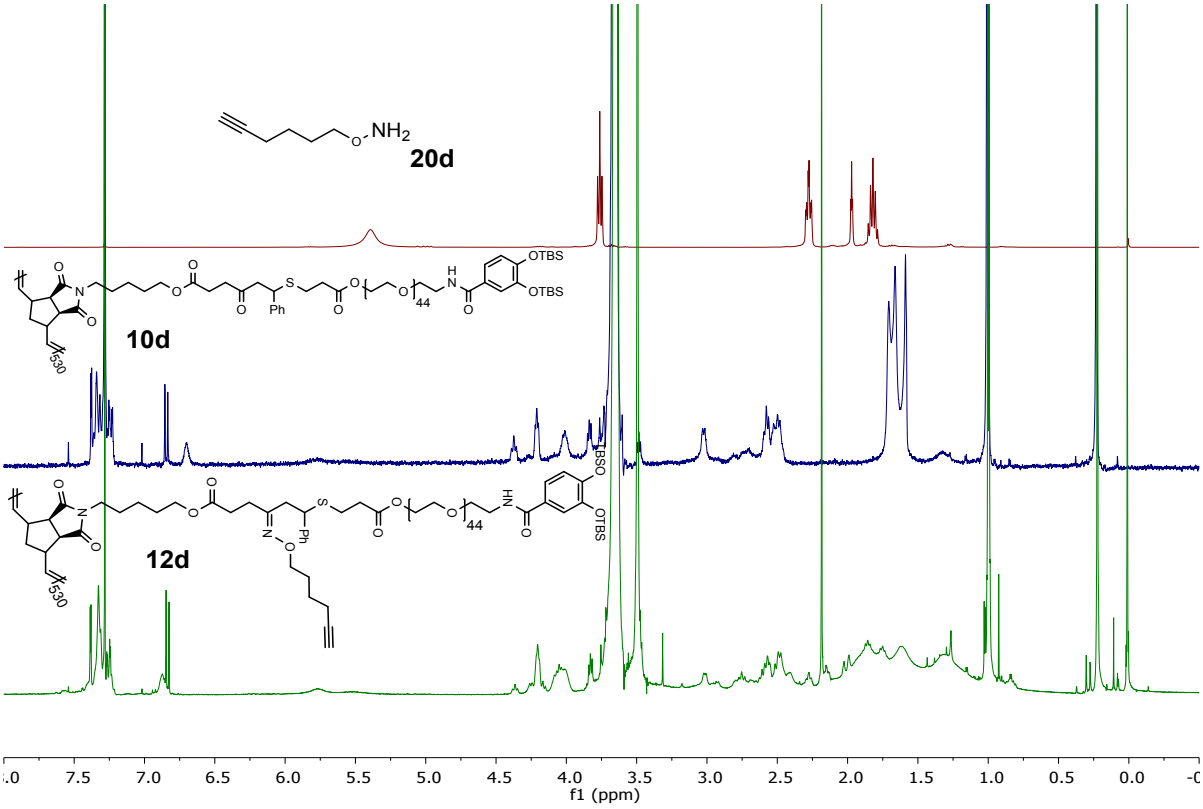


Fig. S34: Overlay of the ^{1}H NMR spectrum of compounds **20d**, **10d**, and **12d**

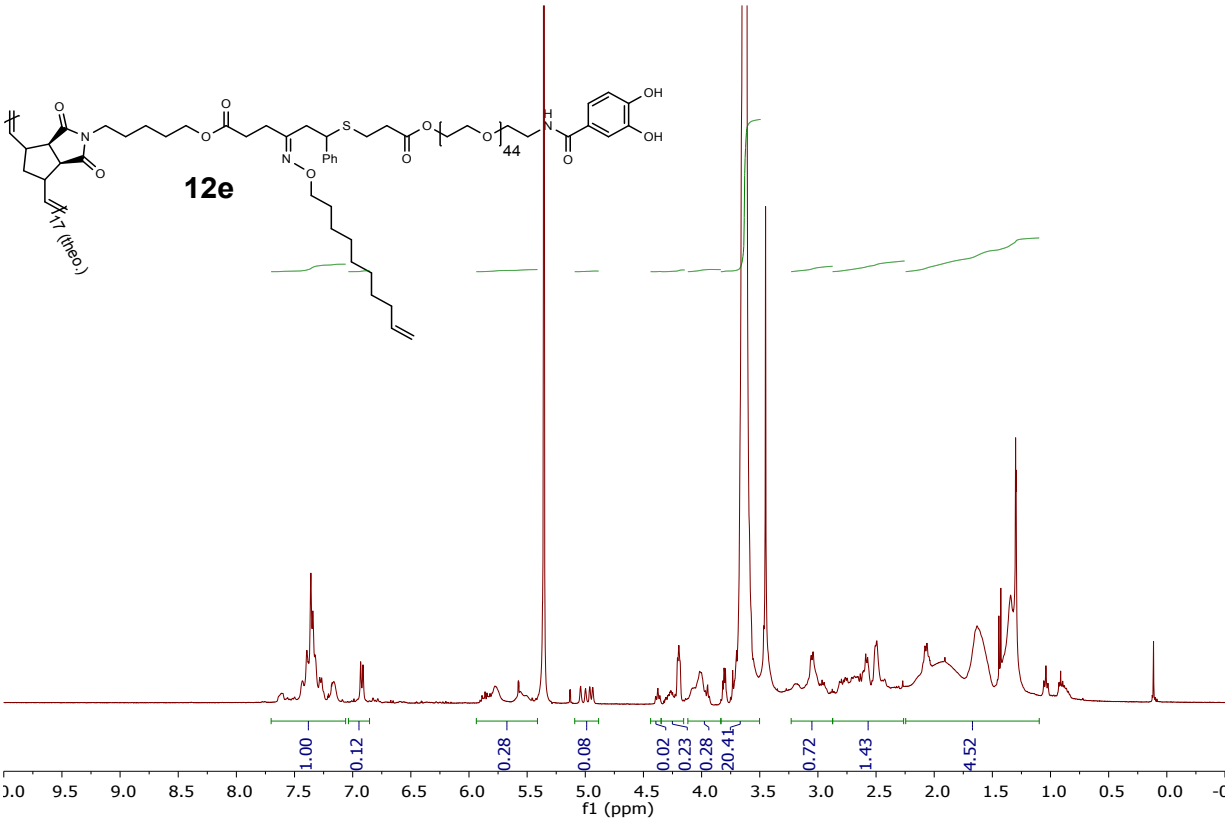


Fig. S35: ^{1}H NMR spectrum of compound **12e**

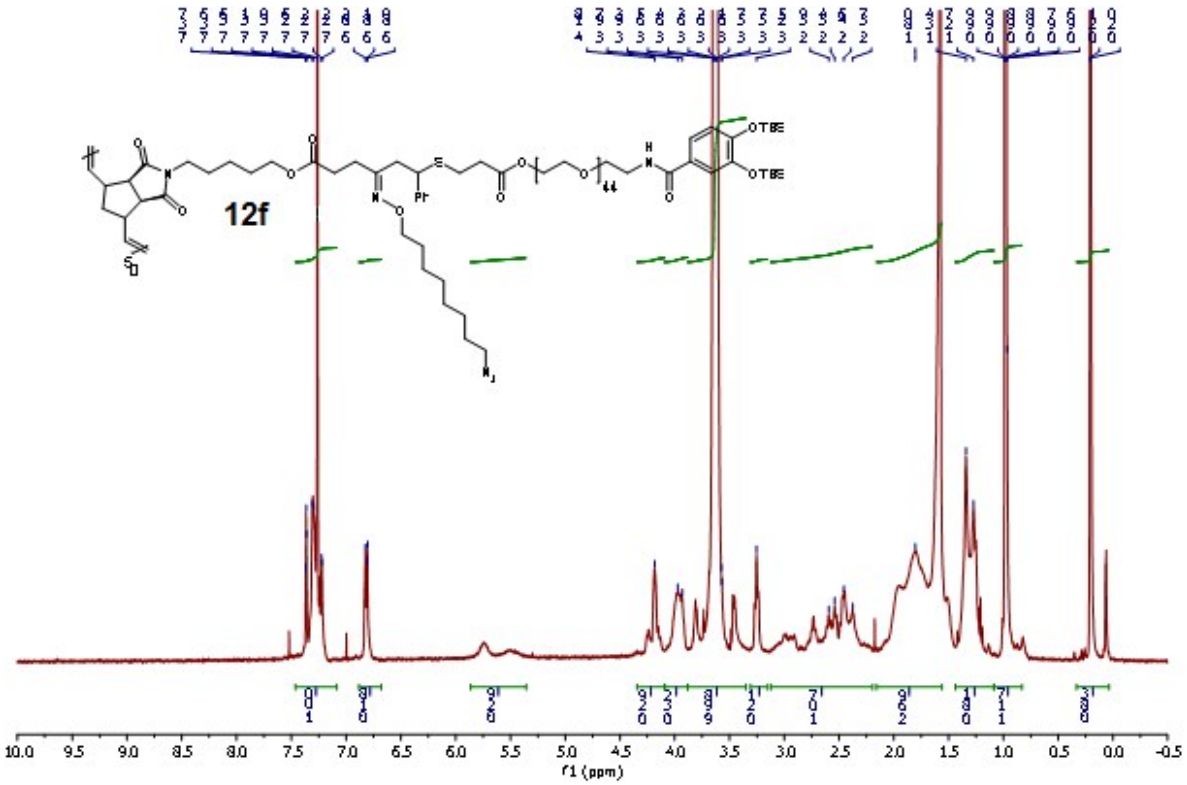


Fig. S36: ^{1}H NMR spectrum of compound **12f**

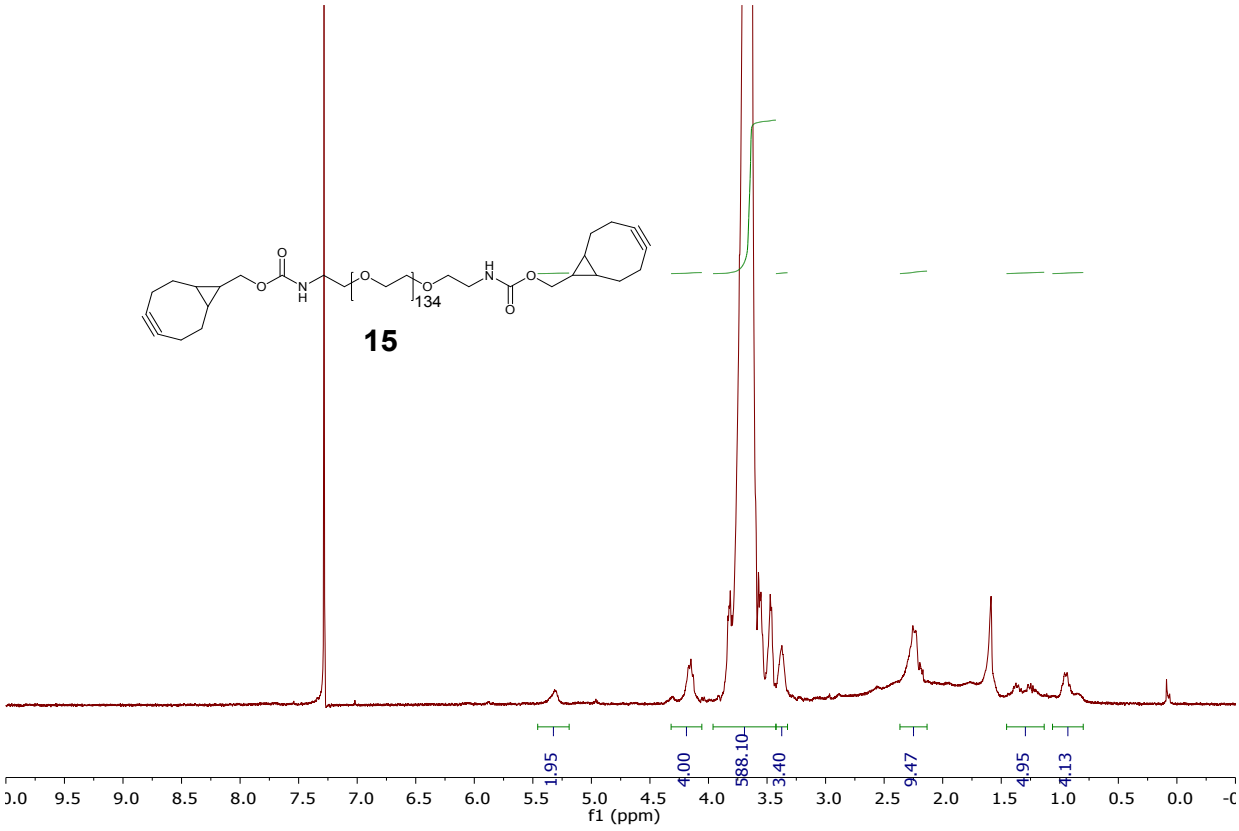


Fig. S37: ^{1}H NMR spectrum of compound **15**

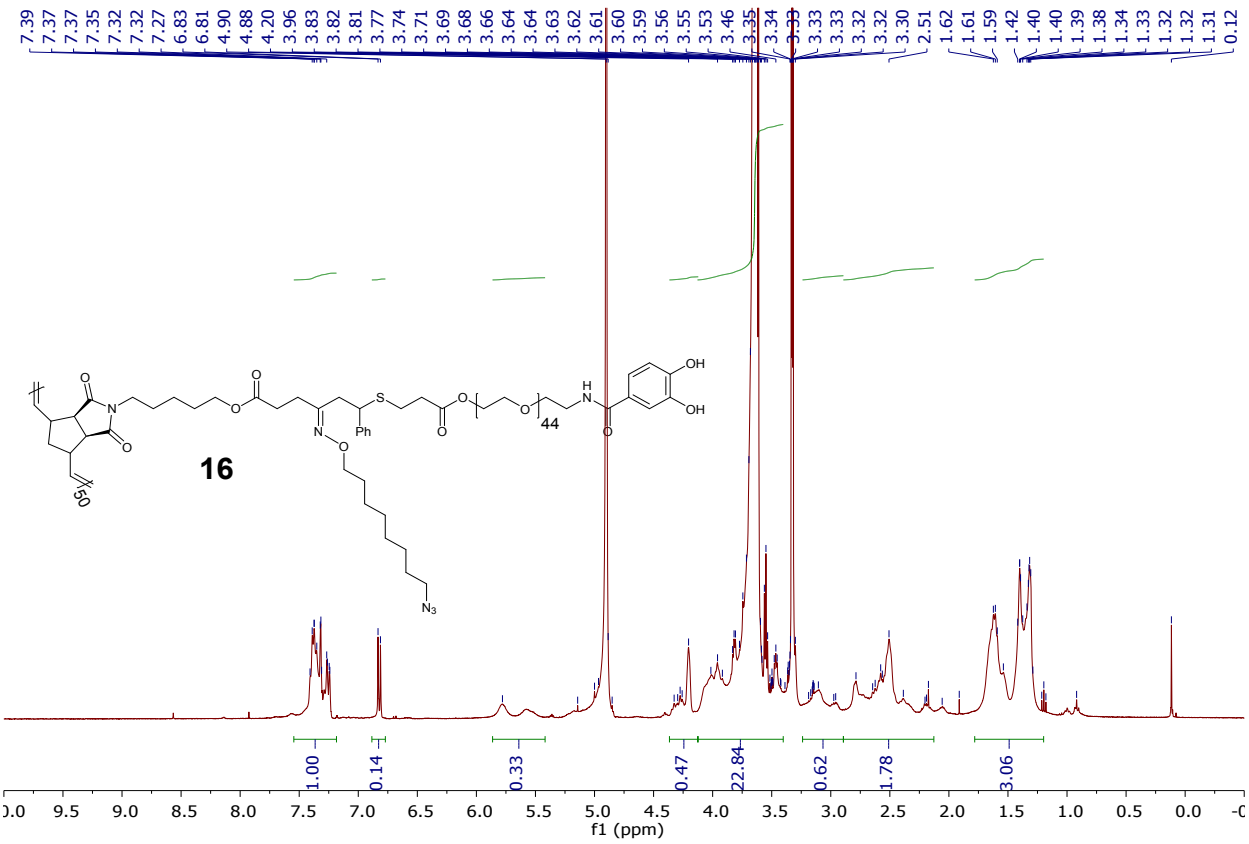


Fig. S38: ^{1}H NMR spectrum of compound **16**

VII: GPC Traces:

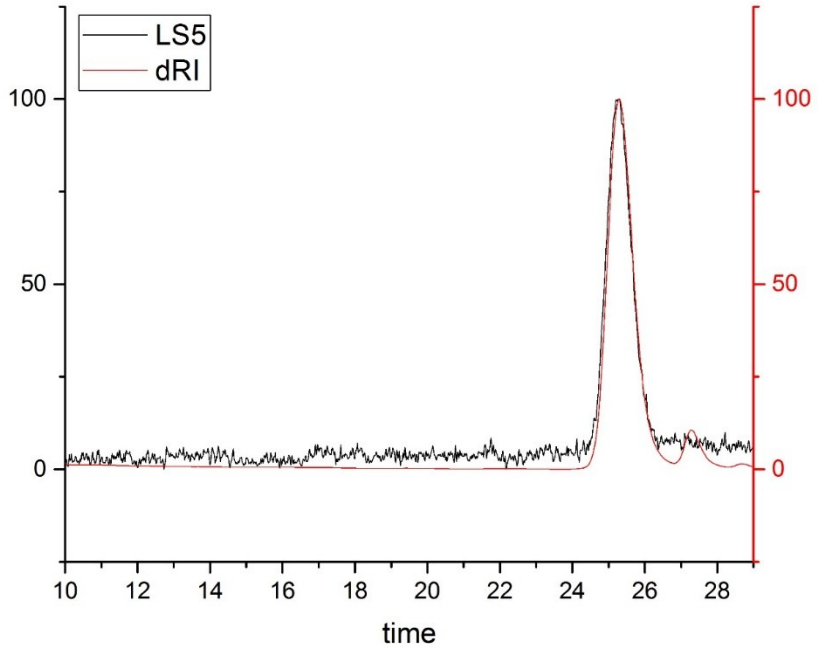


Fig. S39: LS and dRI signals for the GPC traces of macromonomer **8**

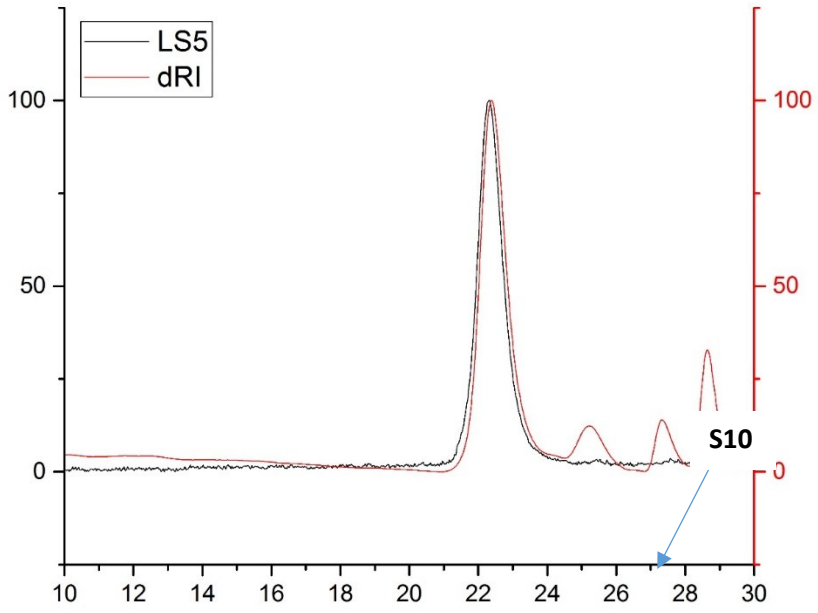


Fig. S40: LS and dRI signals for the GPC traces of **10a**

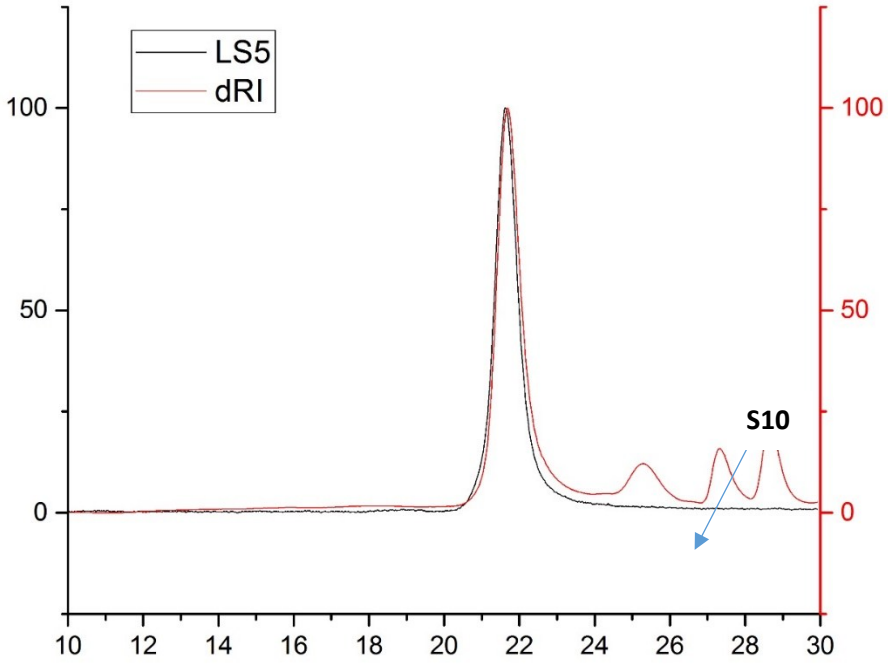


Fig. S41: LS and dRI signals for the GPC traces of **10b**

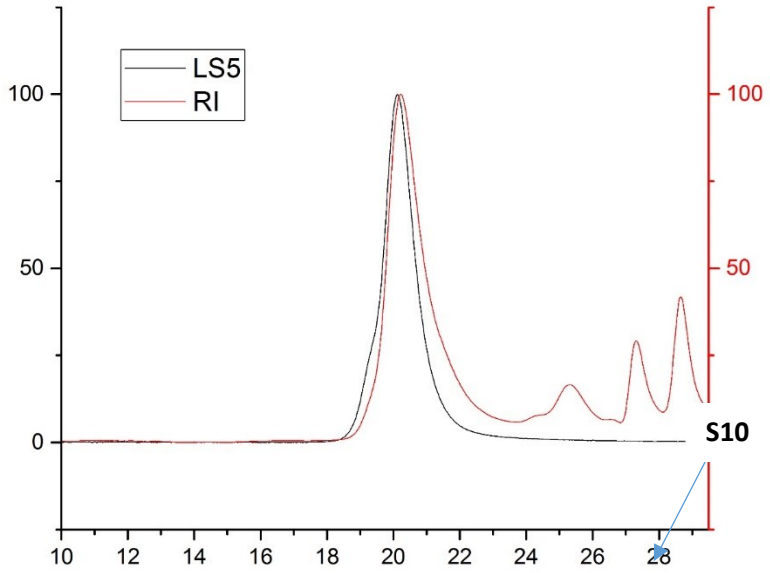


Fig. S42: LS and dRI signals for the GPC traces of **10c**

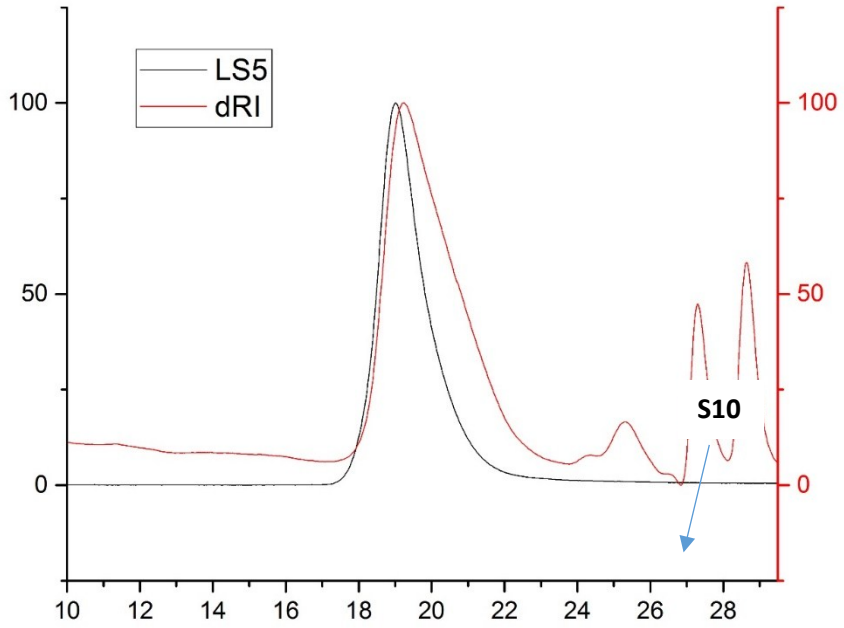


Fig. S43: LS and dRI signals for the GPC traces of **10d**

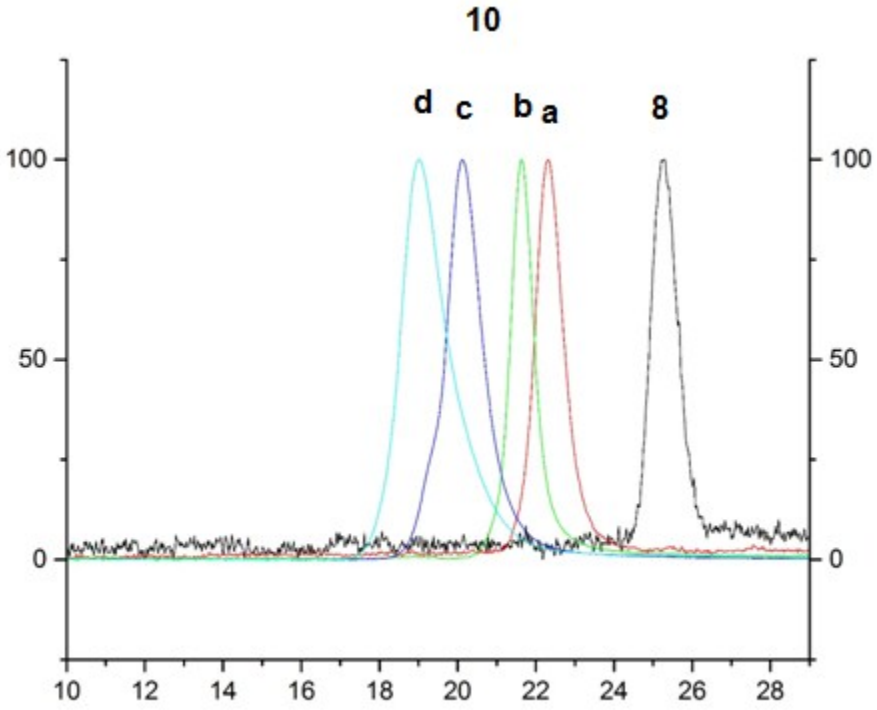


Fig. S44: Overlay of LS GPC signals for **8**, and **10a-d**

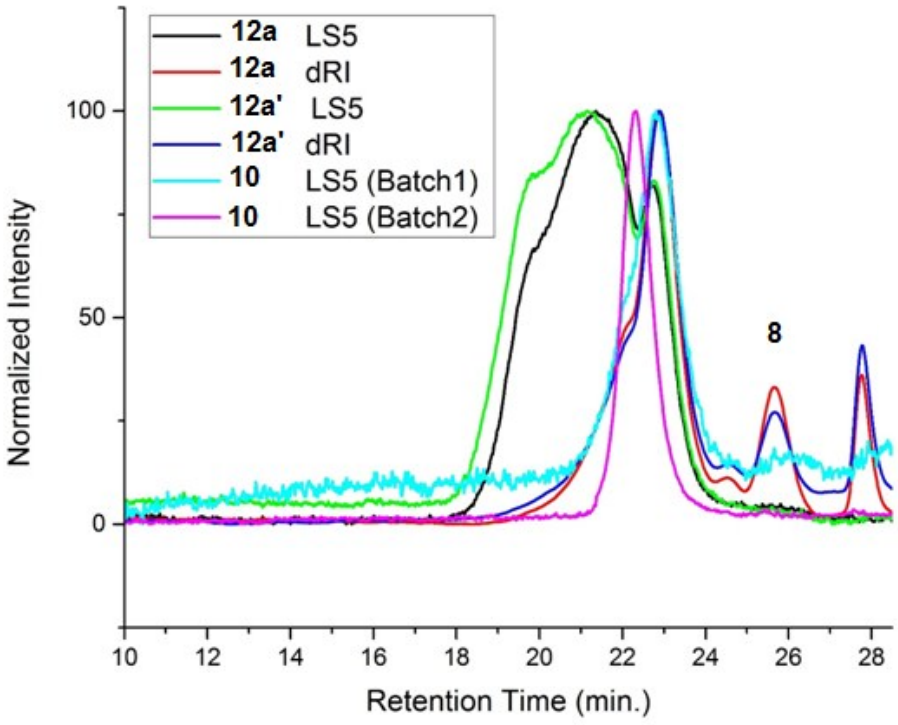


Fig. S45: Overlay of GPC traces for **10**, **12a**, and **12a'**

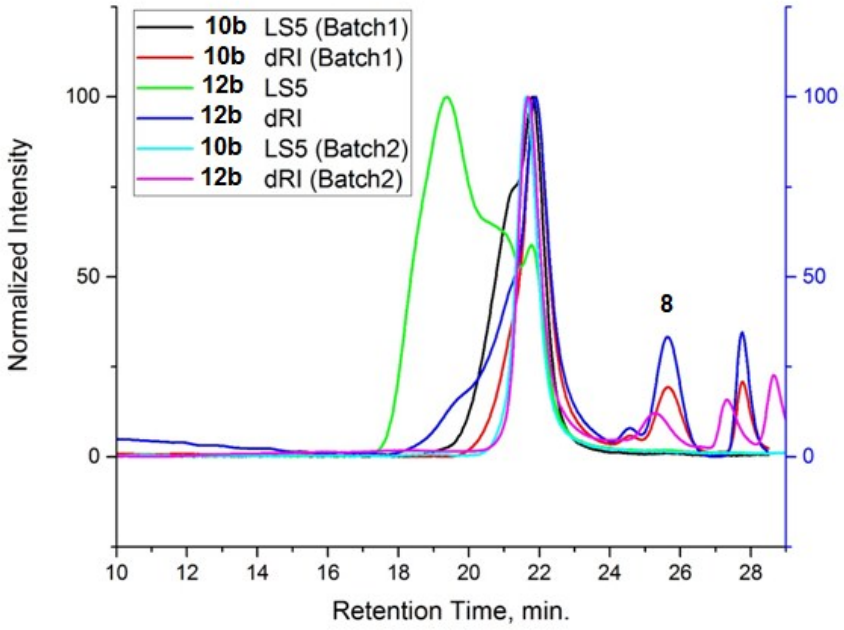


Fig. S46: Overlay of GPC traces for **10b** and **12b**

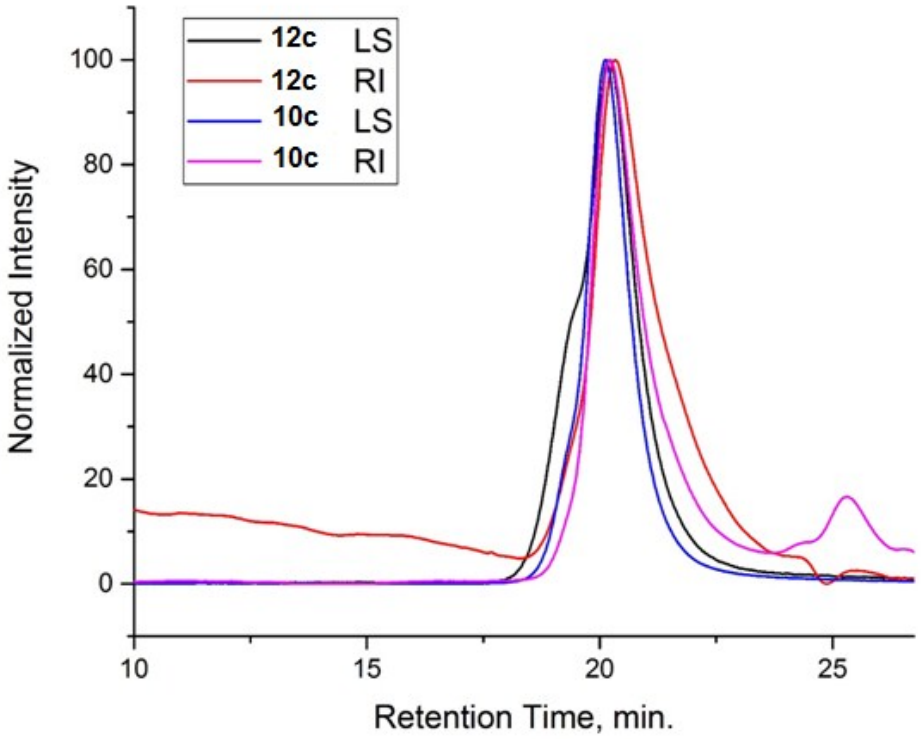


Fig. S47: Overlay of GPC traces for **10c** and **12c**

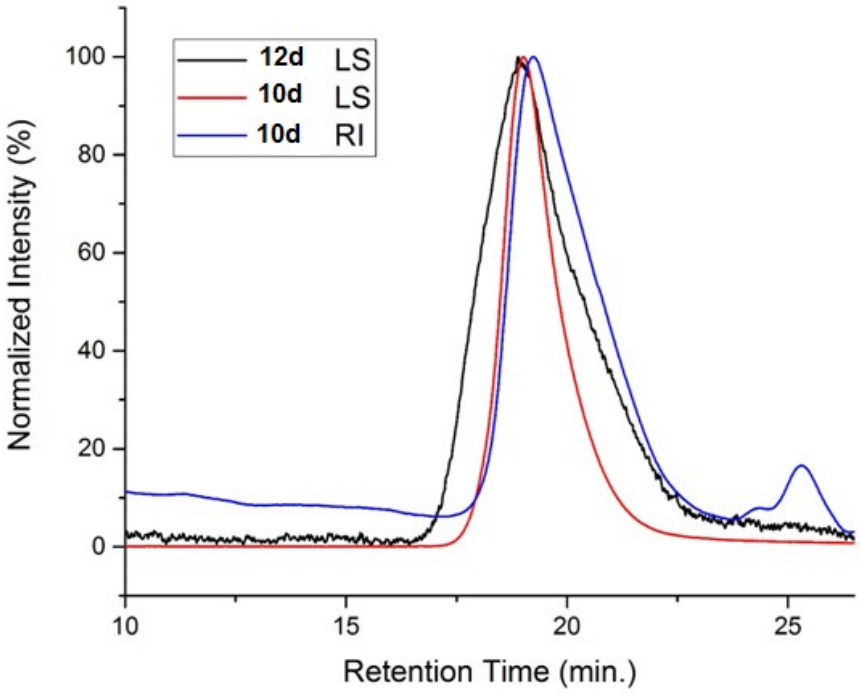


Fig. S48: Overlay of GPC traces for **10d** and **12d**

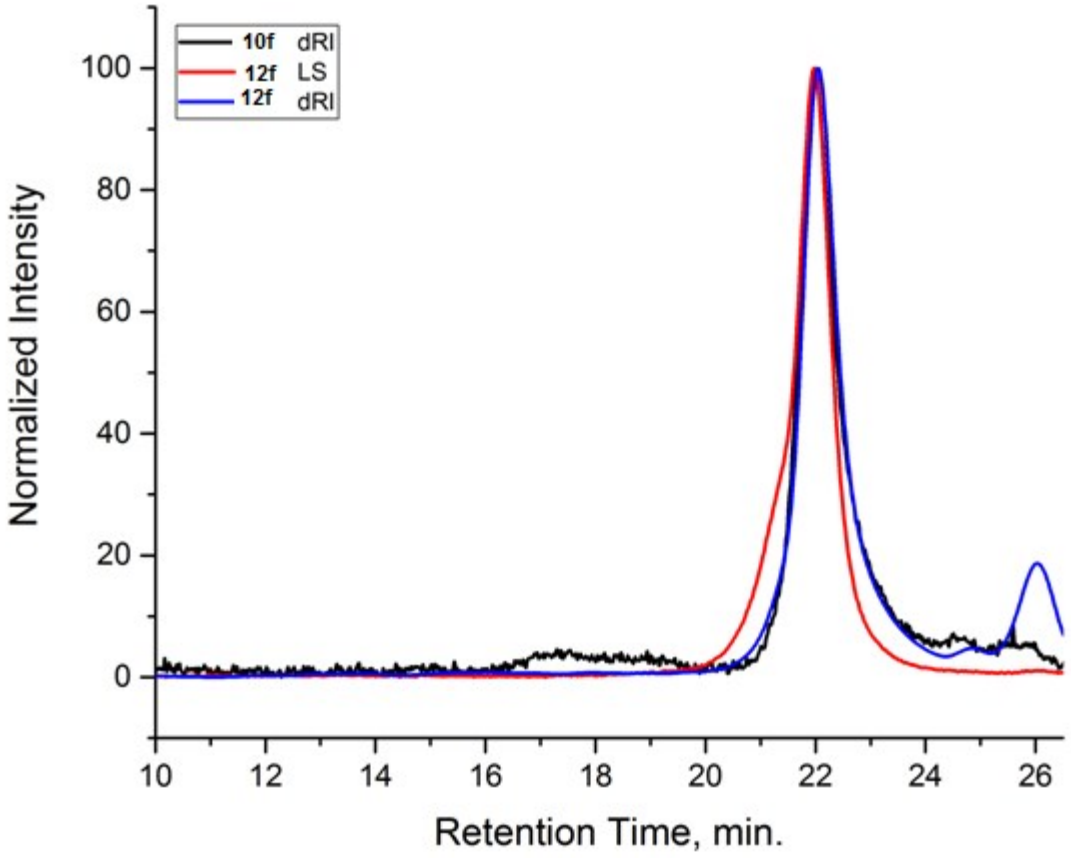


Fig. S49: Overlay of GPC traces of **10f** and **12f**

VIII. References

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