Breaking the *tert*-Butyllithium Contact Ion Pair:

A Gateway to Alternate Selectivity in Lithiation Reactions

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Supplementary Information

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1. Materials and Methods

Reactions were performed using glassware that had been flame-dried under vacuum or oven-dried (150 °C) overnight. All reactions were conducted under an inert atmosphere using argon connected to a drying tube equipped with phosphorous pentoxide, calcium sulfate, and potassium hydroxide.

1.1 Materials

Solvents used for extraction were ACS reagent grade. Reaction solvents tetrahydrofuran (Sigma, anhydrous, inhibitor free), diethyl ether (Sigma, ACS reagent), hexanes (Sigma, anhydrous), pentane (Sigma, ACS grade), cyclohexane (Sigma, ACS grade), toluene (Sigma, ACS grade) were distilled over sodium.

Commercial reagents were purified by distillation, sublimation, or recrystallization prior to use unless otherwise noted. All deuterated solvents for NMR experiments were purchased from Cambridge Isotope Labs.

Compound suppliers:

Commercial reagents were purified by distillation or recrystallization prior to use unless otherwise noted. *t*-butyl lithium (1.7 M in pentane), *s*-butyl lithium (1.6 M in cyclohexane), *n*-butyl lithium (2.5 M in hexanes), anhydrous dioxane, triethylamine, acetic acid, and 1-bromooctane were all purchased from Millipore Sigma. 1,6-dibromohexane, 1,2,3,4-tetramethylbenzene, bromocyclohexane, piperidine, and bis(tri-tert-butylphosphine)palladium were purchased from Aldrich. 1,3-dibromopropane, acetonitrile, DMF, DCM, glyoxal, sodium hydride, potassium hydride, and sodium bicarbonate were purchased from Sigma Aldrich. 4-chromanone, meta-Chloroperoxybenzoic acid (MCPBA), 1-benzyl-4-piperidone, thiosemicarbazide, hexamethylphoshphoramide, 4-bromo-tetrahydropyran, 2-bromomethyl-1,3-dioxolane, 3-methyl-1H-indole, 2-(thiophen-2-yl)ethan-1-ol, sodium *tert*-butoxide , and 6-fluoro-4-chromanone were all purchased from Oakwood Chemical. 6-methyl-4-chromanone, 6-bromo-4-chromanone, and 6-chloro-4-chromanone were purchased from Ambeed. 4-pentyn-1-ol, tert-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate, 6-(trifluoromethyl)nicotinic acid, 4-bromopiperidine-hydrobromide, 1-Boc-piperazine, 2-hydroxy-4-methylquinoline, (2-

bromoethoxy)-tert-butyldimethylsilane, bromocyclopentane, bromocycloheptane, 3-bromooxetane, were all purchased from Combi-Blocks. Zinc powder and RuPhosPdG4 were purchased from Strem Chemical and used without further purification. Methyl magnesium chloride (3.0 M in THF) was purchased from Acros Organics. Oxalyl chloride, methyl iodide, and phosphoryl chloride were purchased from Alfa Aesar. Ethanol was purchased from Fischer. Hydrochloric acid (12.1 M) was purchased from VWR. Pyrrolidine and 1,2,4,5-tetramethylbenzene were purchased from Bean Town Chemical. Sodium acetate (99 %, ^{13}C) was purchased from Cambridge Isotope Labs. All deuterated solvents for NMR experiments were purchased from Cambridge Isotope Labs. THF-d_8 was distilled over NaK directly prior to use. HMPA-d_{18} was distilled over CaH_2 directly prior to use. Tris(4-methoxyphenyl)boroxine was dehydrated and recrystallized from toluene following literature procedure.[1]

1.2. NMR Spectroscopy

^{1}H, ^{13}C, ^{6}Li, ^{7}Li, ^{11}B, ^{31}P and ^{19}F NMR spectra for substrate characterization were recorded on Bruker Avance Neo 400 MHz NMR spectrometer (^{1}H, 400 MHz; ^{13}C, 101 MHz; ^{19}F, 376 MHz) or Varian VnmrS 500 MHz NMR spectrometer (^{1}H, 500 MHz; ^{19}F 470 MHz; ^{6}Li 74 MHz; ^{7}Li 194 MHz; ^{13}C 126 MHz; ^{11}B 160 MHz; ^{31}P 202 MHz). Spectra are referenced to residual chloroform (7.26 ppm, ^{1}H; 77.16 ppm, ^{13}C), residual THF (1.72 ppm, ^{1}H; 67.21 ppm, ^{13}C) and external trifluorotoluene (–63.72 ppm, ^{19}F), LiCl (0.0 ppm, ^{6}Li and ^{7}Li) or $BF_3{\cdot}Et_2O$ (0.0 ppm, ^{11}B). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz (Hz).

1.3. Infrared Spectroscopy (IR)

Infrared spectra were recorded on IRAffinity-1S spectrometer equipped with a diamond laminate ATR. Infrared spectra were acquired from neat samples. If required, substances were dissolved in CH_2Cl_2 prior to direct application on the ATR unit.

1.4. Mass Spectrometry (MS)

High-resolution mass spectra were recorded on a Thermo Scientific Q Exactive Focus High-resolution Orbitrap instrument configured for routine small molecule analysis. Analysis was

carried out in either electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) positive ion modes.

1.5. Gas Chromatography (GC)

Gas Chromatography (GC) spectra were recorded on an Agilent 8860 GC System using a flame ionization detector (FID) or mass spectrometer (MS). The standard method for reductive lithiation reaction monitoring holds a temperature of 50 °C for 3 min and ramps up (10 °C/min) to a final temperature of 275 °C which is held for 5 min.

1.6. Rapid Injection NMR (RI-NMR)

Rapid Injection NMR experiments were carried out using an injection apparatus consisting of a glass capillary affixed to a gas tight syringe. Controlled injections were carried out using air pressure and delivered a volume into the NMR sample of 96.4 µL on average.

2. Experimental Procedures and Characterization

2.1. Procedures for Experiments Found in Figures 5, 6 & Table 1

General Procedure A for Experiments Found in Figure 5

An oven dried, 1 dram vial equipped with septum cap and stir bar was placed under argon. The vial was charged with phosphoramide (0.48 mmol, 6.0 equiv) and freshly distilled (NaK) THF (0.50 mL, 7.7 mmol, 77 equiv). The vial was then chilled to an external temperature of –78 °C with a dry-ice acetone bath. The solution was allowed to sit for 5 min for temperature equilibration, followed by the dropwise addition of R-Li (0.080 mmol, 1.0 equiv), during which time it typically developed a color. After 5 min, the neat benzoyl chloride (10 µL, 0.088 mmol, 1.1 equiv) was added and after 5 min the reaction mixture was removed from the bath and allowed to warm to rt. After 1 h, methanol (50 µL, 1.24 mmol, 15.4 equiv) and a solution of 1,2,4,5-tetramethylbenzene (100 µL, 0.10 mmol, 1.0 M in hexane) were added sequentially and the volatile components of the reaction were removed *in vacuo*. The crude products were analyzed by ^{1}H NMR to determine the product ratios. Integration of the internal alkene C-H (5.88 ppm) vs the methyl of the standard (2.19 ppm) were used for all entries to determine yield.

Entry 1:

Carried out by the general procedure A using HMPA (84 µL, 0.48 mmol, 6.0 equiv) and *n*-BuLi (32.0 µL, 0.080 mmol, 1.0 equiv, 2.50 M). After NMR analysis the yield was determined to be 5 %.

Entry 2:

Carried out by the general procedure A using TPPA (110 µL, 0.48 mmol, 6.0 equiv) and *n*-BuLi (32.0 µL, 0.080 mmol, 1.0 equiv, 2.50 M). After NMR analysis the yield was determined to be 31 %.

Entry 3:

Carried out by the general procedure A using HMPA (84 µL, 0.48 mmol, 6.0 equiv) and *s*-BuLi (94.5 µL, 0.080 mmol, 1.0 equiv, 0.85 M). After NMR analysis the yield was determined to be 6 %.

Entry 4:

Carried out by the general procedure A using TPPA (110 µL, 0.48 mmol, 6.0 equiv) and *s*-BuLi (94.5 µL, 0.080 mmol, 1.0 equiv, 0.85 M). After NMR analysis the yield was determined to be 36 %.

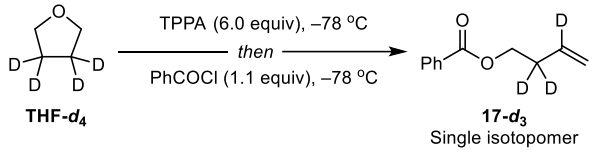
Entry 5:

Carried out by the general procedure A using HMPA (84 µL, 0.48 mmol, 6.0 equiv) and *t*-BuLi (41.0 µL, 0.080 mmol, 1.0 equiv, 1.97 M). After NMR analysis the yield was determined to be 27 %.

Entry 6:

Carried out by the general procedure A using TPPA (110 µL, 0.48 mmol, 6.0 equiv) and *t*-BuLi (41.0 µL, 0.080 mmol, 1.0 equiv, 1.97 M). After NMR analysis the yield was determined to be 55 %.

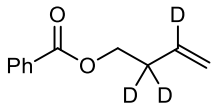
Lithiation of THF-d_4



An oven dried, 1 dram vial equipped with septum cap and stir bar was placed under argon. The vial was charged with phosphoramide (0.48 mmol, 6.0 equiv) and freshly distilled (NaK) THF-d_4 (0.50 mL, 7.7 mmol, 77 equiv). The vial was then chilled to an external temperature of –78 °C with a dry-ice acetone bath. The solution was allowed to sit for 5 min for temperature equilibration, followed by the dropwise addition of *t*-BuLi (0.080 mmol, 1.0 equiv), during which time it developed a color. After 5 min, the neat benzoyl chloride (10 µL, 0.088 mmol, 1.1 equiv) was added and after 5 min the reaction mixture was removed from the bath and allowed to warm to rt. After 1 h, methanol (50 µL, 1.24 mmol, 15.4 equiv) and a solution of 1,2,4,5-tetramethylbenzene (100 µL, 0.10 mmol, 1.0 M in hexane) were added sequentially and the volatile components of the reaction were removed *in vacuo*. The crude products were analyzed by GC-FID and GC-MS to determine the product ratios. The product was further

purified by preparatory TLC on silica gel (5% EtOAc in hexanes) to afford the desired product at sufficient purity for ESI-MS. This analysis resulted in data most consistent with the product containing 3-deuterium atoms. Mass spectrometry results are detailed in Table S1 below.

Table S1:

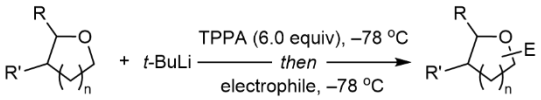


17-d_3

Calculated Isotopic Masses for **17**-d_3	Relative Abundances	Experimentally Derived Masses	Relative Abundances
180.1098	100.00 %	180.1096	100 %
181.1132	11.90 %	181.1129	11.93 %
182.1165	0.64 %	182.1167	0.46 %

Procedures for Experiments Found in Table 1

Table 1. Altered site selectivity is general using phosphoramide ligands.



entry	starting material	electrophile	product	yield (%)[a]
1	THF	24	17	(57%)
2	25	24	26	(8%)
3	27	24	28	(95%)
4	29	30	31	(94%) d.r. 59:41
5	29	Octyl—Br 32	33	(85%)

traditional site selectivity this work

a) NMR yields by integration relative to a 1,2,4,5-tetramethylbenzene internal standard.

Entry 1:

An oven dried, 1 dram vial equipped with septum cap and stir bar was placed under argon. The vial was then charged with TPPA (110 µL, 0.48 mmol, 6.0 equiv) and freshly distilled (NaK) THF (0.50 mL, 7.7 mmol, 77 equiv). The vial was then chilled to an external temperature of –78 °C with a dry-ice acetone bath. The solution was allowed to sit for 5 min for temperature equilibration, followed by the dropwise addition of *t*-BuLi (52 µL, 0.080 mmol, 1.0 equiv), during which time it typically developed a color. After 5 min, the neat benzoyl chloride (10.0 µL, 0.088 mmol, 1.1 equiv) was added and after 5 min the reaction mixture was removed from the bath and allowed to warm to rt. After 1 h, methanol (50 µL, 1.24 mmol, 15.4 equiv) and a solution of 1,2,4,5-tetramethylbenzene (100 µL, 0.10 mmol, 1.0 M in hexane) were added

sequentially and the volatile components of the reaction were removed *in vacuo*. The crude products were analyzed by ^{1}H NMR to determine the product ratios. Integral values of the internal alkene C-H (5.88 ppm) vs the methyl of the standard (2.19 ppm) were used to determine yield. After NMR analysis the yield was determined to be 57 %.

Entry 2:

An oven dried, 1 dram vial equipped with septum cap and stir bar was placed under argon. The vial was then charged with TPPA (110 µL, 0.48 mmol, 6.0 equiv) and freshly distilled (Na) oxepane (0.50 mL, 4.5 mmol, 56 equiv). The vial was then chilled to an external temperature of –78 °C with a dry-ice acetone bath. The solution was allowed to sit for 5 min for temperature equilibration, followed by the dropwise addition of *t*-BuLi (52 µL, 0.080 mmol, 1.0 equiv), during which time it typically developed a color. After 5 min, the neat benzoyl chloride (10.0 µL, 0.088 mmol, 1.1 equiv) was added and after 5 min the reaction mixture was removed from the bath and allowed to warm to rt. After 1 h, methanol (50 µL, 1.24 mmol, 15.4 equiv) and a solution of 1,2,4,5-tetramethylbenzene (80 µL, 0.080 mmol, 1.0 M in hexane) were added sequentially and the volatile components of the reaction were removed *in vacuo*. Integral values of the internal alkene C-H (5.76 ppm) vs the methyl of the standard (2.19 ppm) were used to determine yield. After NMR analysis the yield was determined to be 8 %.

Entry 3:

An oven dried, 1 dram vial equipped with septum cap and stir bar was placed under argon. The vial was then charged with TPPA (110 µL, 0.48 mmol, 6.0 equiv) freshly distilled (NaK) THF (0.50 mL) and 2,3-dihydrobenzofuran (90.3 µL, 0.80 mmol, 10.0 equiv). The vial was then chilled to an external temperature of –78 °C with a dry-ice acetone bath. The solution was allowed to sit for 5 min for temperature equilibration, followed by the dropwise addition of *t*-BuLi (52 µL, 0.080 mmol, 1.0 equiv), during which time it typically developed a color. After 5 min, the neat benzoyl chloride (10.0 µL, 0.088 mmol, 1.1 equiv) was added and after 5 min the reaction mixture was removed from the bath and allowed to warm to rt. After 1 h, methanol (50 µL, 1.24 mmol, 15.4 equiv) and a solution of 1,2,4,5-tetramethylbenzene (80 µL, 0.080 mmol, 1.0 M in hexane) were added sequentially and the volatile components of the reaction were removed *in vacuo*. The crude products were analyzed by ^{1}H NMR to determine the product ratios. Integral values of a terminal alkene C-H (5.28 ppm) vs the methyl of the standard (2.19 ppm) were used to determine yield. After NMR analysis the yield was determined to be 95 %.

Entry 4:

An oven dried, 1 dram vial equipped with septum cap and stir bar was placed under argon. The vial was then charged with TPPA (110 µL, 0.48 mmol, 6.0 equiv) freshly distilled (NaK) THF (0.50 mL) and chromane (101 µL, 0.80 mmol, 10 equiv). The vial was then chilled to an external temperature of –78 °C with a dry-ice acetone bath. The solution was allowed to sit for 5 min for temperature equilibration, followed by the dropwise addition of *t*-BuLi (52 µL, 0.080 mmol, 1.0 equiv), during which time it typically developed a color. After 5 min, the neat benzaldehyde (9.0 µL, 0.088 mmol, 1.1 equiv) was added and after 5 min the reaction mixture was removed from the bath and allowed to warm to rt. After 1 h, methanol (50 µL, 1.24 mmol, 15.4 equiv) and a solution of 1,2,4,5-tetramethylbenzene (80 µL, 0.080 mmol, 1.0 M in hexane) were added sequentially and the volatile components of the reaction were removed *in vacuo*. The crude products were analyzed by ^{1}H NMR to determine the product ratios. Integral values of the benzylic C-H (5.21 ppm minor diast., 4.80 ppm major diast.) vs the methyl of the standard (2.19 ppm) were used to determine yield. After NMR analysis the combined yield of the diastereomers was determined to be 94 %, d.r. 59:41.

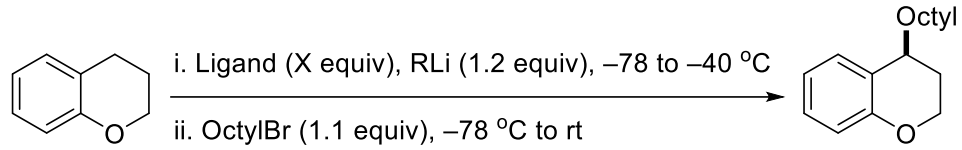
Entry 5:

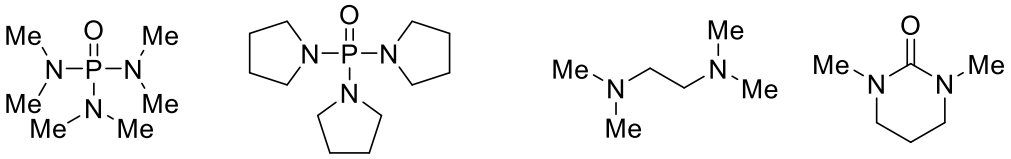
An oven dried, 1 dram vial equipped with septum cap and stir bar was placed under argon. The vial was then charged with TPPA (110 µL, 0.48 mmol, 6.0 equiv) freshly distilled (NaK) THF (0.50 mL) and chromane (15.1 µL, 0.12 mmol, 1.5 equiv). The vial was then chilled to an external temperature of –78 °C with a dry-ice acetone bath. The solution was allowed to sit for 5 min for temperature equilibration, followed by the dropwise addition of *t*-BuLi (52 µL, 0.080 mmol, 1.0 equiv), during which time it typically developed a color. After 5 min, the neat 1-bromooctane (15.2 µL, 0.088 mmol, 1.1 equiv) was added and after 5 min the reaction mixture was removed from the bath and allowed to warm to rt. After 1 h, methanol (50 µL, 1.24 mmol, 15.4 equiv) and a solution of 1,2,4,5-tetramethylbenzene (80 µL, 0.080 mmol, 1.0 M in hexane) were added sequentially and the volatile components of the reaction were removed *in vacuo*. The crude products were analyzed by ^{1}H NMR to determine the product ratios. Integral values of the benzylic C-H (2.78 ppm) vs the methyl of the standard (2.19 ppm) were used to determine yield, 85 %.

2.2. General Procedures for Trapping Experiments

Procedure for screening reactions in Table S2: An oven dried, 1 dram vial equipped with septum cap and stir bar was placed under argon. The vial was then charged with chromane (0.1 mmol, 1.0 equiv), ligand (X equiv) and freshly distilled (NaK) THF (0.5 mL). The vial was then chilled to an external temperature of –78 °C with a dry-ice acetone bath. The solution was allowed to sit for 5 min for temperature equilibration, followed by the dropwise addition of *R*Li (0.12 mmol, 1.2 equiv,), during which time it typically developed a color. The reaction vessel was quickly transferred to a –40 °C dry-ice acetonitrile bath and stirred for 1 h followed by re-cooling to –78 °C. The neat 1-bromooctane (19 µL, 0.11 mmol, 1.1 equiv) was added and after 5 min the reaction mixture was removed from the bath and allowed to warm to rt. After 1 h the solution was poured into a 1:1 mixture of brine and water (1 mL) and extracted with hexanes (3 x 1 mL). A solution of 1,2,4,5-tetramethylbenzene (100 µL, 0.10 mmol, 1.0 M) in hexane was added to the combined organic extracts. The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude products were analyzed by GC/FID to determine the product ratios and yield.

Table S2: Screening data for the Lithium Nucleophilic Capture (LiNC) of chromane with 1-bromooctane





L1 **L2** **L3** **L4**

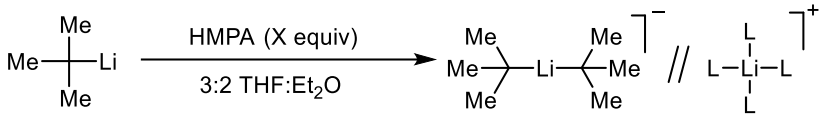
Entry	Rli	Ligand	X equiv	Yield (%)
1	*t*-BuLi	L1	1.0	68
2	*t*-BuLi	L2	1.0	79
4	*t*-BuLi	L3	1.0	2
5	*t*-BuLi	L4	1.0	5
6	*t*-BuLi	L1	0.5	55
7	*t*-BuLi	L1	1.0	68
8	*t*-BuLi	L1	1.5	79
9	*t*-BuLi	L1	2.0	87
10	*t*-BuLi	L1	3.0	88
11	*t*-BuLi	L1	6.0	78
12	*t*-BuLi	L1	2.0	87
13	*s*-BuLi	L1	2.0	0
14	*n*-BuLi	L1	2.0	4

General Procedure A: A flame dried, 5 mL round bottom flask was placed under argon and charged with chromane (0.50 mmol, 1.0 equiv), HMPA (174 μL, 1.0 mmol, 2.0 equiv) and freshly distilled (NaK) THF (2.5 mL). The flask was then chilled to an external temperature of –78 °C with a dry-ice acetone bath. The solution was allowed to sit for 5 min for temperature equilibration, followed by the dropwise addition of *t*-BuLi (365 μL, 0.60 mmol, 1.2 equiv, 1.65 M), during which time it developed a bright orange/red color. The reaction vessel was quickly transferred to a –40 °C dry-ice acetonitrile bath and stirred for 30 min followed by re-cooling to –78 °C. The neat alkyl halide (0.55 mmol, 1.1 equiv) was added and after 5 min the reaction mixture was removed from the bath and allowed to warm to rt. After 1 h the solution was poured into a 1:1 mixture of brine and water (5 mL) and extracted with hexanes (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude products were purified by flash-column chromatography on silica gel to afford the desired product.

General Procedure B: A flame dried, 5 mL round bottom flask was placed under argon and charged with chromane (0.50 mmol, 1.0 equiv), HMPA (520 μL, 1.0 mmol, 6.0 equiv) and freshly distilled (NaK) THF (2.5 mL). The flask was then chilled to an external temperature of –78 °C with a dry-ice acetone bath. The solution was allowed to sit for 5 min for temperature equilibration, followed by the dropwise addition of *t*-BuLi (365 μL, 0.60 mmol, 1.2 equiv, 1.65 M), during which time it developed a bright orange/red color. The reaction was stirred for 10 min at –78 °C. The neat alkyl halide (0.55 mmol, 1.1 equiv) was added and after 5 min the reaction mixture was removed from the bath and allowed to warm to rt. After 1 h the solution was poured into a 1:1 mixture of brine and water (5 mL) and extracted with hexanes (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude products were purified by flash-column chromatography on silica gel to afford the desired product.

General Procedure C: A flame dried, 5 mL round bottom flask was placed under argon and charged with chromane (0.50 mmol, 1.0 equiv), TPPA (230 μL, 1.0 mmol, 2.0 equiv) and freshly distilled (NaK) THF (2.5 mL). The flask was then chilled to an external temperature of –78 °C with a dry-ice acetone bath. The solution was allowed to sit for 5 min for temperature equilibration, followed by the dropwise addition of *t*-BuLi (300 μL, 0.60 mmol, 1.2 equiv, 1.97 M), during which time it developed a bright orange/red color. The reaction vessel was quickly transferred to a –40 °C dry-ice acetonitrile bath and stirred for 30 min followed by re-cooling to –78 °C. The neat alkyl halide (0.55 mmol, 1.1 equiv) was added and after 5 min the reaction mixture was removed from the bath and allowed to warm to rt. After 1 h the solution was poured into a 1:1 mixture of brine and water (5 mL) and extracted with hexanes (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude products were purified by flash-column chromatography on silica gel to afford the desired product.

2.3. Procedures for Preparation of NMR Samples



NMR titration of natural abundance *tert*-butyllithium: An oven-dried 5 mm NMR tube was placed under argon using a septum capped NMR tube adapter. To this tube was added *tert*-butyllithium (30 µL, 50 µmol, 1.67 M in pentane). The tube was placed under vacuum for 5 min to remove the pentane solvent. After refilling with argon, the tube was capped with an NMR tube septum and cooled to –115 °C. Freshly distilled (Na) Et_2O (200 µL) was added and the solid *tert*-butyllithium was dissolved by mixing on a vortexer in 2-3 s bursts, not shaken. Freshly distilled (NaK) THF-d_8 (300 µL) was then added and mixed in a vortexer in 1-2 s bursts. HMPA (8.7 µL, 50 µmol) was dissolved in THF-d_8 (60 µL) and Et_2O (40 µL). This solution was then added to the *tert*-butyllithium solution and mixed in a vortexer in 1-2 s bursts. The tube was maintained in the –115 °C bath until it was placed into the NMR spectrometer (Less than 10 min) that was precooled to –125 °C. The samples were analyzed at this temperature for ^{7}Li, ^{13}C and ^{1}H NMR. Samples often had to be prepared multiple times due to the time needed to retune the spectrometer between each type of spectra. The samples with higher equivalents of HMPA were prepared analogously. When the amount of HMPA exceeded 30 µL the solutions began to freeze during the addition and required additional time in the vortexer to make a homogenous sample (usually 10 bursts on the vortexer instead of 5). The lines were too broad to derive any value and are depicted below.

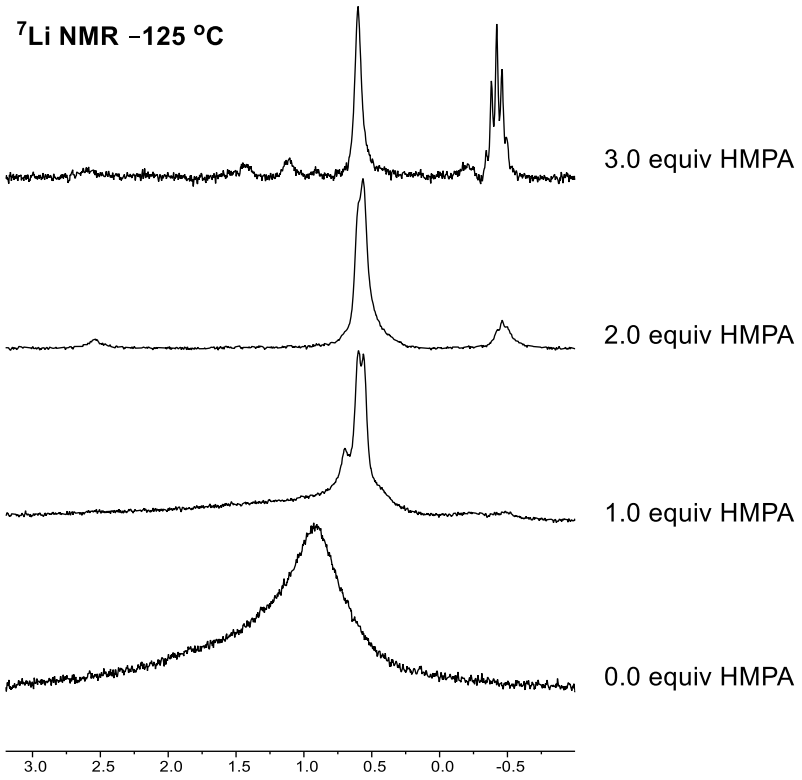
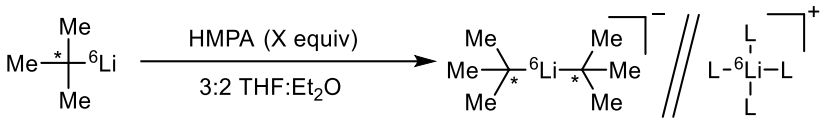


Figure S1. ^{7}Li NMR spectrum of *t*-BuLi with 0.0 to 3.0 equiv HMPA at –125 °C, referenced to external LiCl (0.5 M in MeOH, 0.0 ppm).



NMR titration of ^{13}C and ^{6}Li enriched *tert*-butyllithium 60: An oven-dried 5 mm NMR tube was placed under argon using a septum capped NMR tube adapter. To this tube was added ^{13}C and ^{6}Li enriched *tert*-butyllithium (83 µL, 60 µmol, 0.72 M in pentane). The tube was placed under vacuum for 5 min to remove the pentane solvent. After refilling with argon, the tube was capped with an NMR tube septum and cooled to –115 °C. Freshly distilled (Na) Et_2O (200 µL) was added and the solid *tert*-butyllithium was dissolved by mixing on a vortexer in 2-3 s bursts, not shaken. Freshly distilled (NaK) THF-d_8 (300 µL) was then added and mixed in a vortexer in 1-2 s bursts. HMPA (10.4 µL, 60 µmol) was dissolved in THF-d_8 (60 µL) and Et_2O (40 µL). This solution was then added to the *tert*-butyllithium solution and mixed in a vortexer in 1-2 s bursts. The tube was maintained in the –115 °C bath until it was placed into the NMR spectrometer (Less than 10 min) that was precooled to –125 °C. The samples were analyzed at this temperature for ^{6}Li, ^{13}C and ^{1}H NMR. Samples often had to be prepared multiple times due to the time needed to retune the spectrometer between each type of spectra. The samples with higher equivalents of HMPA were prepared analogously. When the amount of HMPA exceeded 30 µL the solutions began to freeze during the addition and required additional time in the vortexer to make a homogenous sample (usually 10 bursts on the vortexer instead of 5). Additional samples were cooled further to –130 °C for ^{31}P NMR collection; however, the Li-P coupling constants could not be resolved in the ^{31}P NMR spectra.

Table S3:

Compound	^{6}Li (ppm)	^{13}C (ppm)
CIP-58a	1.03	17.2
CIP-58b	0.76	17.5
TIP-58^{-}	2.78	18.6
Li(HMPA)$_4^{+}$	-0.38	-

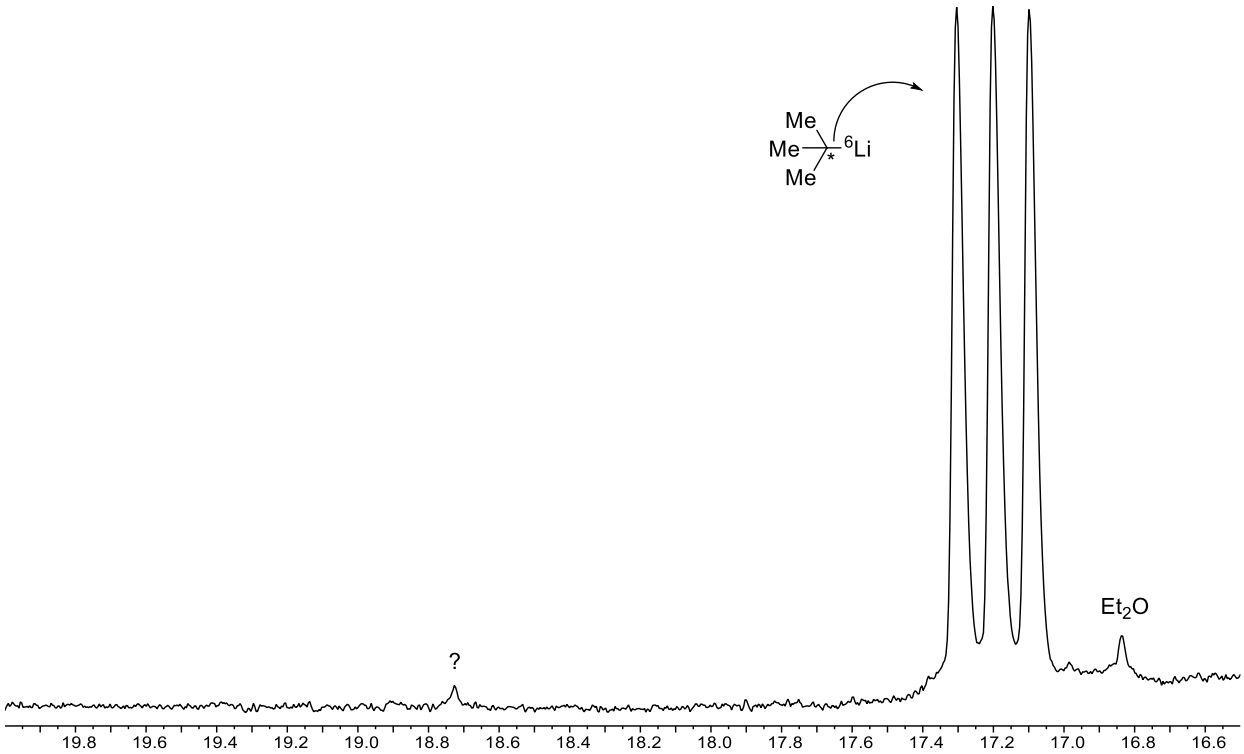


Figure S2. ^{13}C NMR spectrum of **60** with 0.0 equiv HMPA at –115 °C, referenced to THF-d_8 (67.21 ppm).

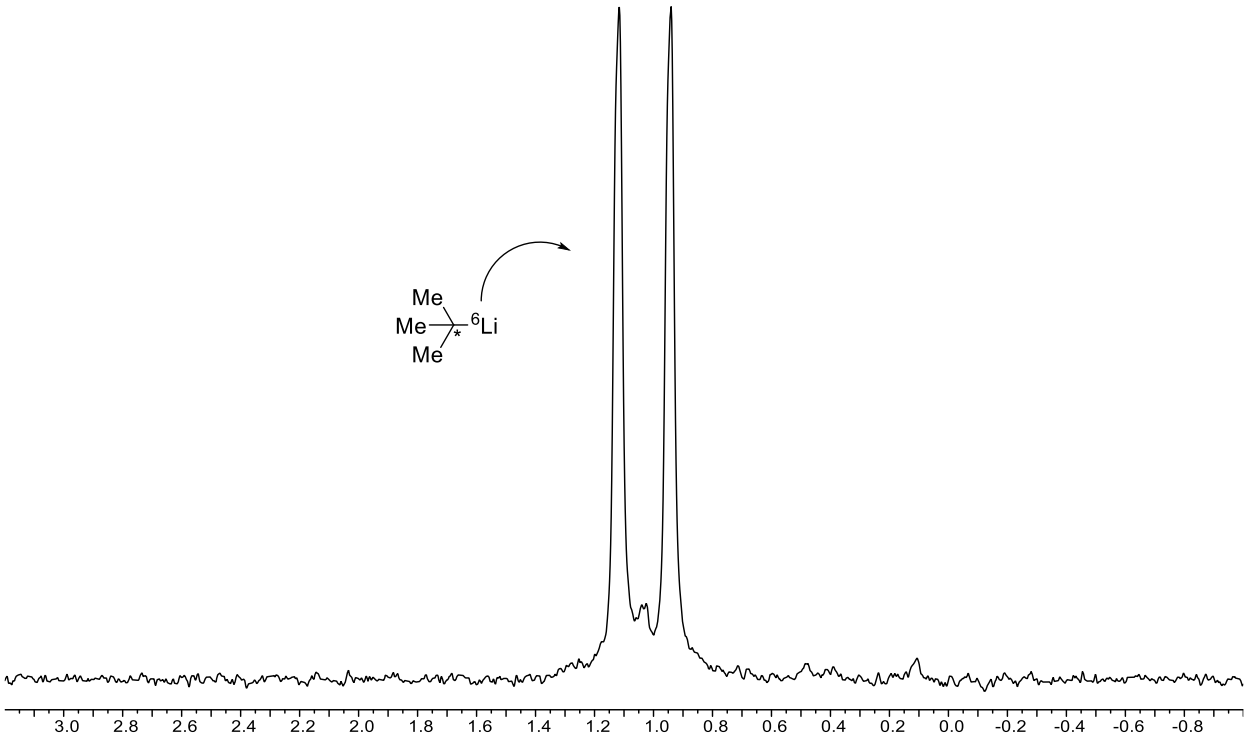


Figure S3. ^{6}Li spectrum of **60** at –115 °C, referenced to external LiCl (0.5 M in THF, 0.0 ppm).

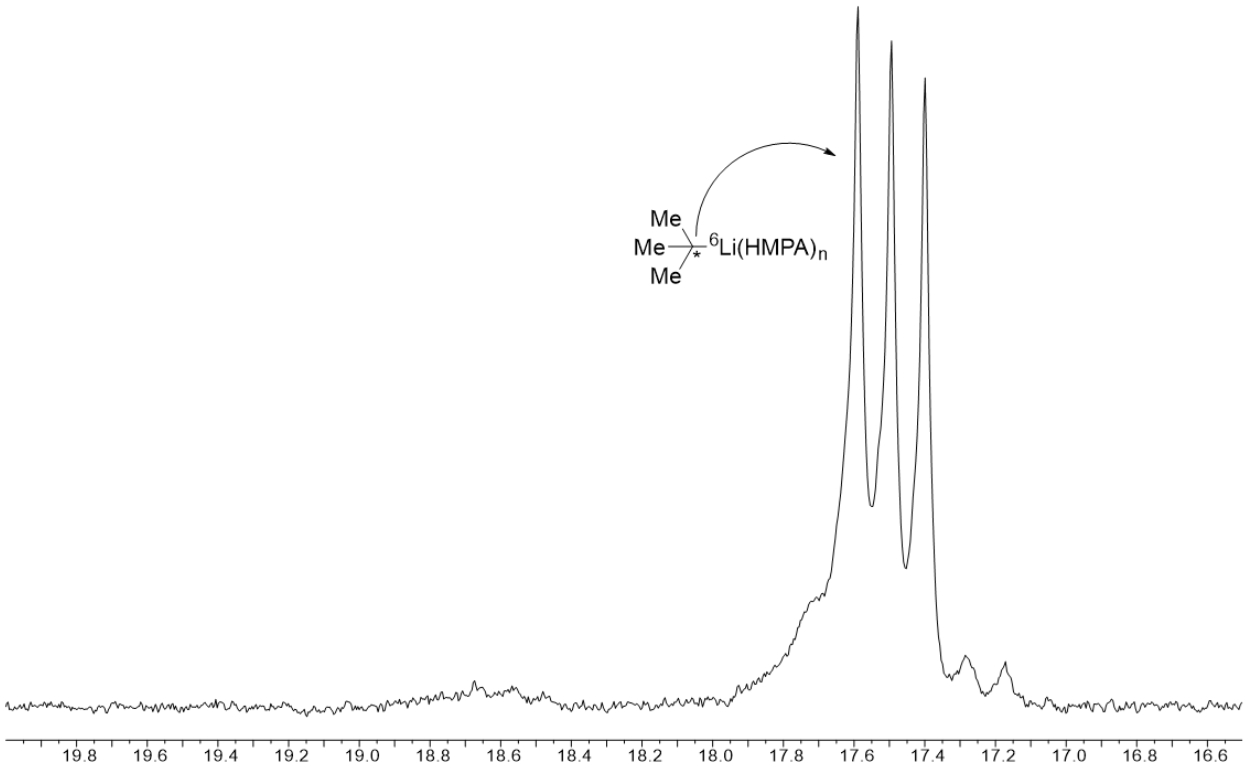


Figure S4. ^{13}C NMR spectrum of **60** with 1.0 equiv HMPA at –125 °C, referenced to THF-d_8 (67.21 ppm).

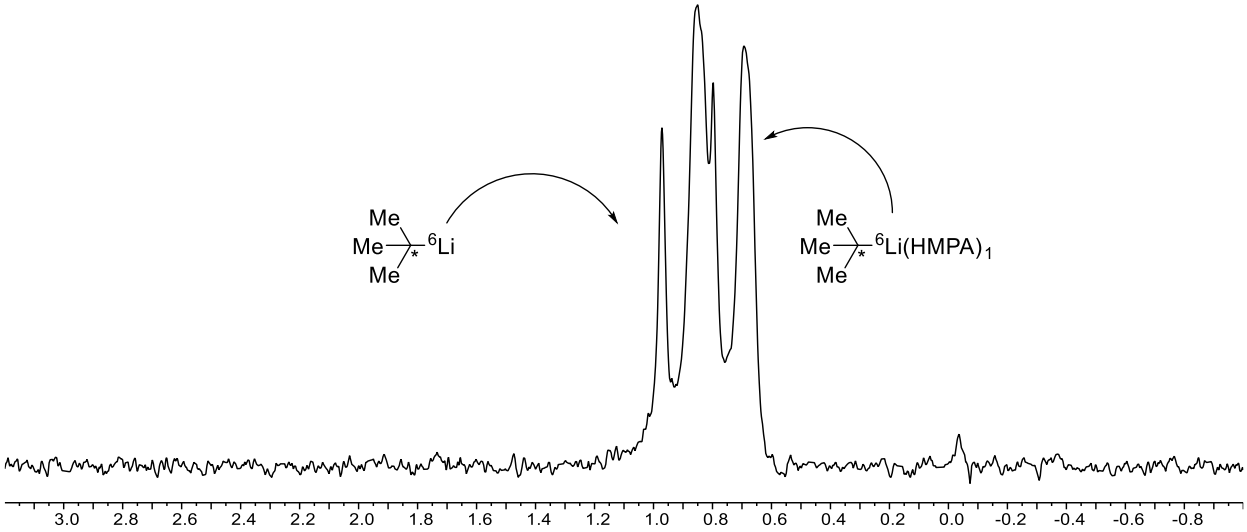


Figure S5. ^{6}Li spectrum of **60** with 1.0 equiv HMPA at –125 °C, referenced to external LiCl (0.5 M in THF, 0.0 ppm).

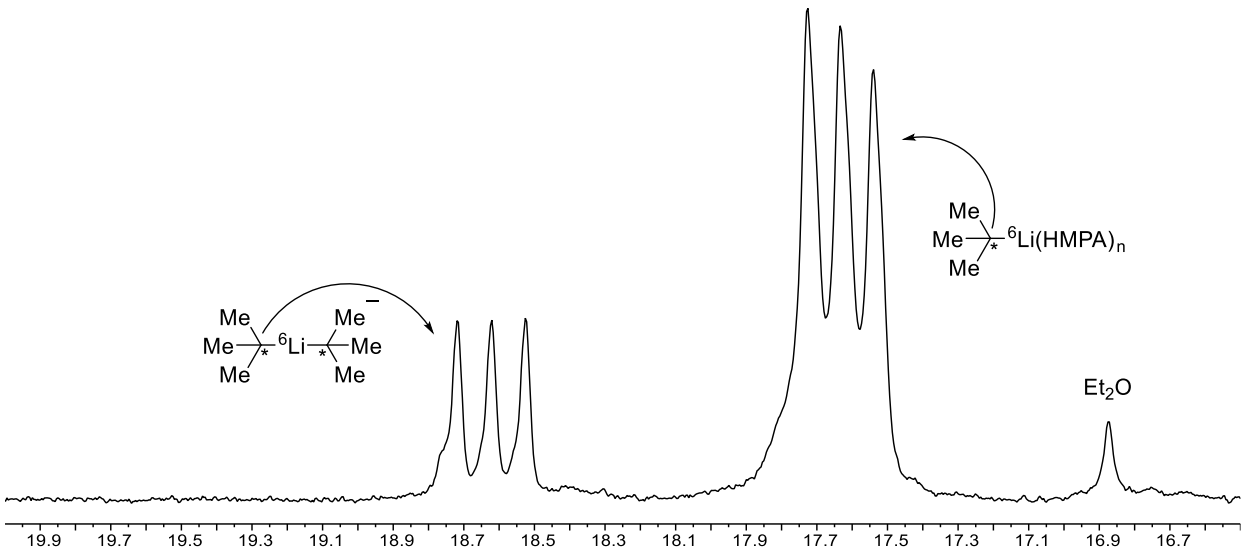


Figure S6. ^{13}C NMR spectrum of **60** with 2.0 equiv HMPA at –125 °C, referenced to THF-d_8 (67.21 ppm).

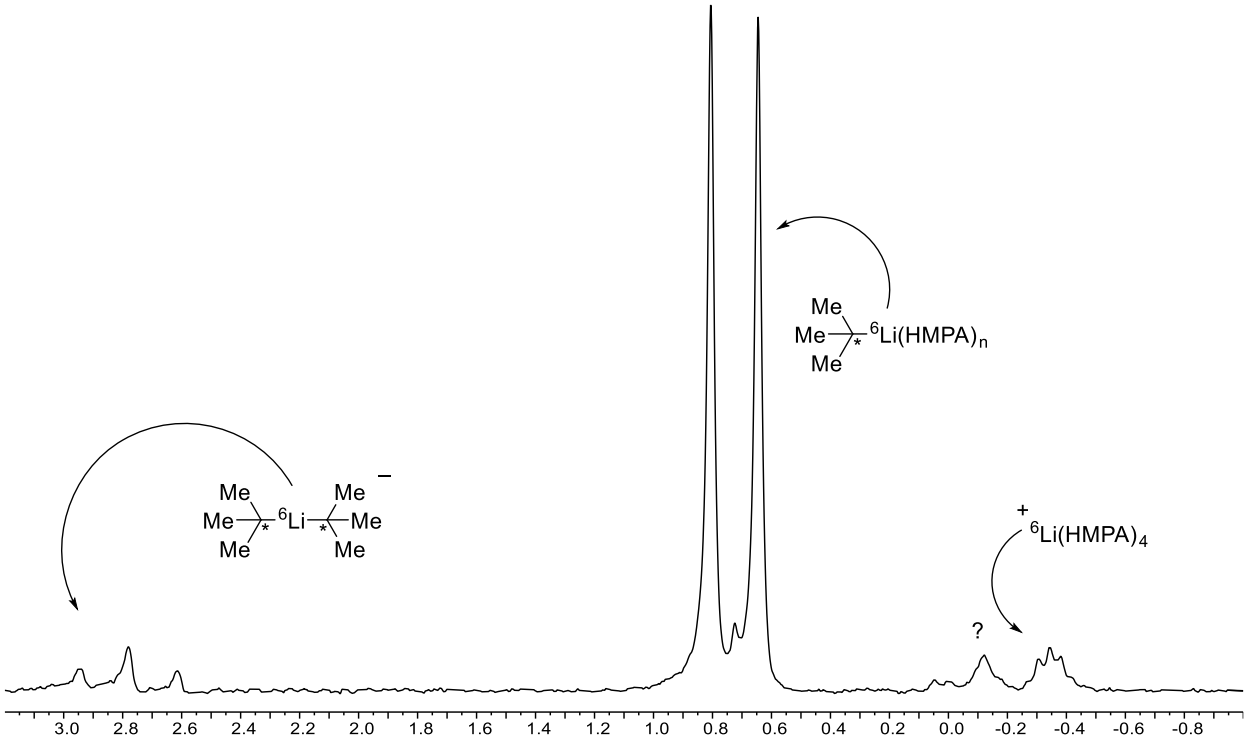


Figure S7. ^{6}Li spectrum of **60** with 2.0 equiv HMPA at –125 °C, referenced to external LiCl (0.5 M in THF, 0.0 ppm).

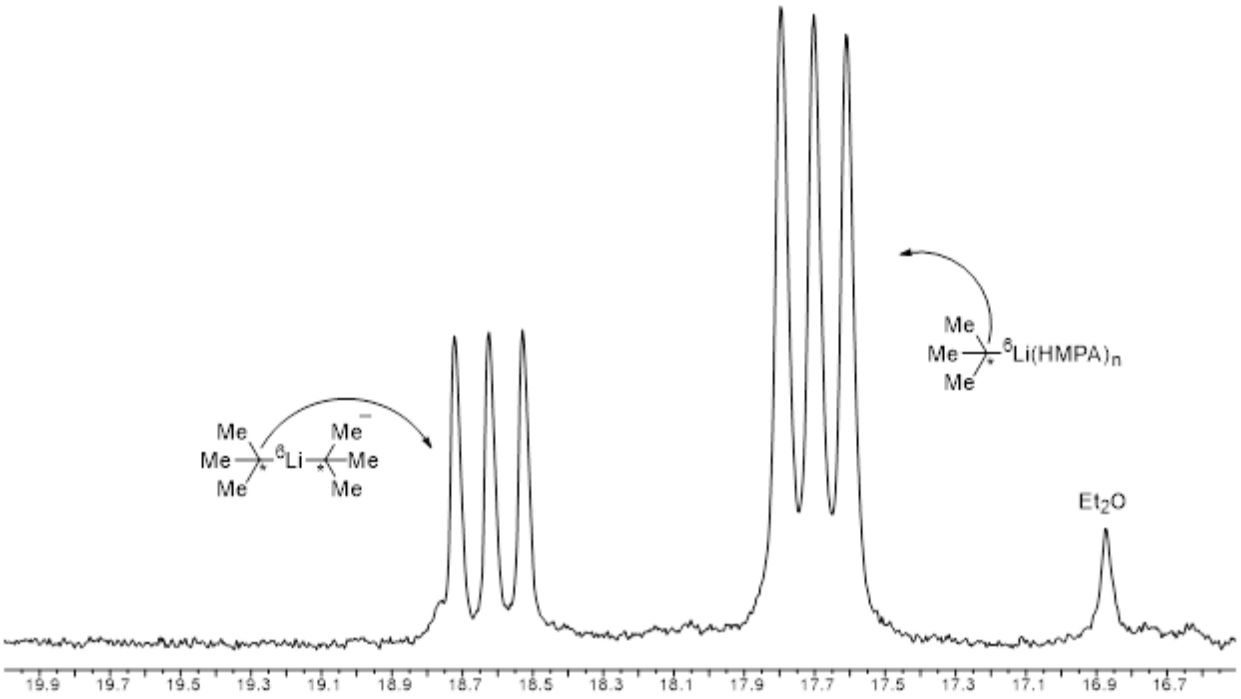


Figure S8. ^{13}C NMR spectrum of **60** with 3.0 equiv HMPA at –125 °C, referenced to THF-d_8 (67.21 ppm).

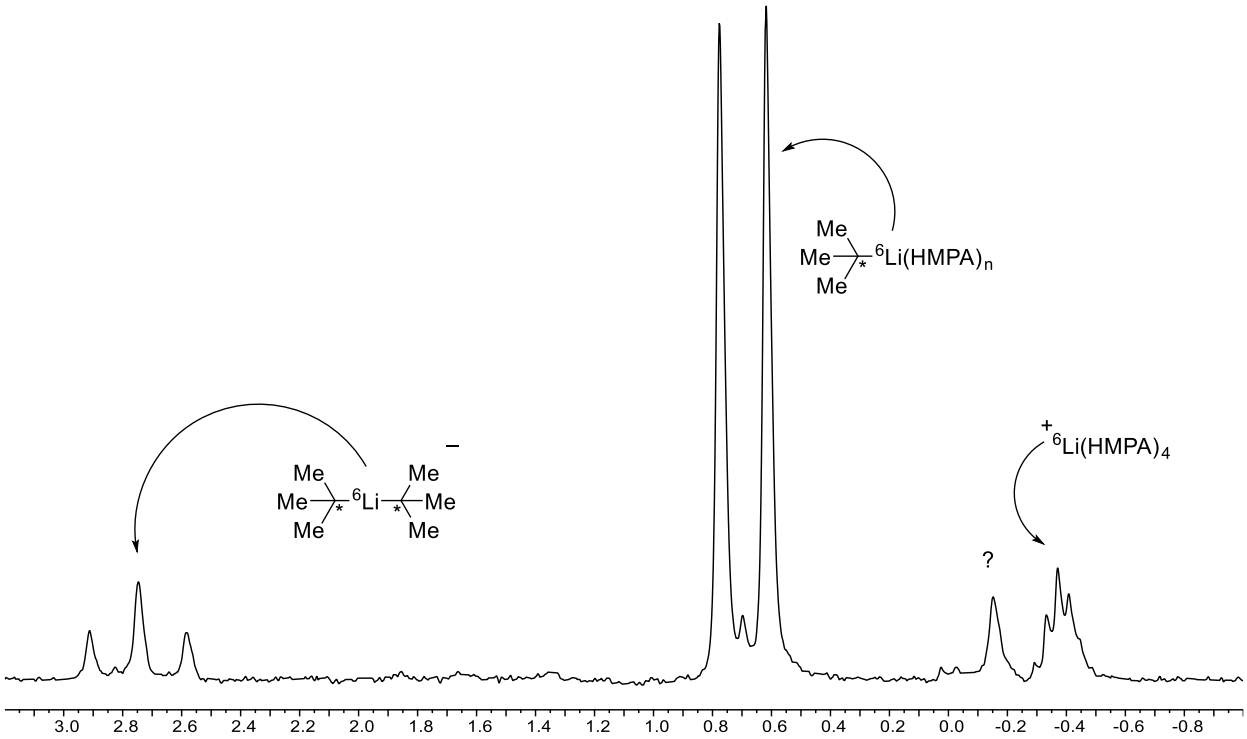


Figure S9. ^{6}Li spectrum of **60** with 3.0 equiv HMPA at –125 °C, referenced to external LiCl (0.5 M in THF, 0.0 ppm).

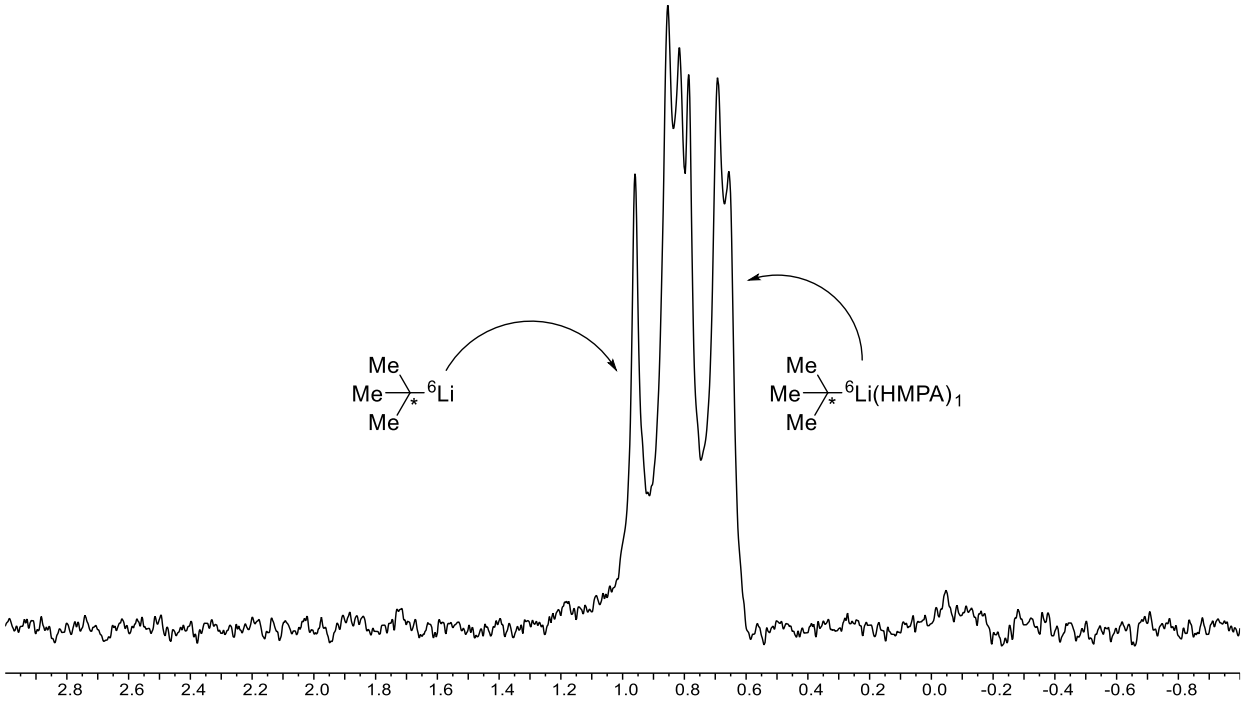
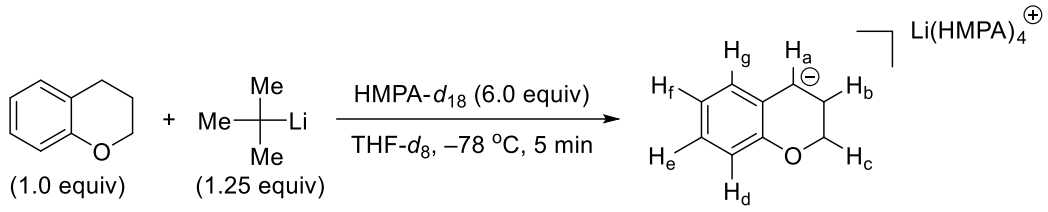


Figure S10. ^{6}Li spectrum of **60** with 1.0 equiv HMPA at –130 °C, referenced to external LiCl (0.5 M in THF, 0.0 ppm).



(1.0 equiv) (1.25 equiv)

57

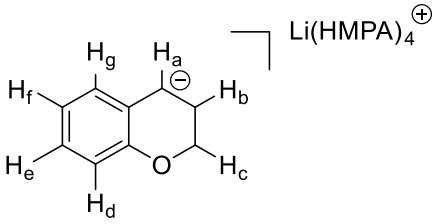
Preparation of 4-lithiochromane 57 for collection of analytical data: An oven-dried 5 mm NMR tube was placed under argon using a septum capped NMR tube adapter. To this tube was added *tert*-butyllithium (30 µL, 50 µmol, 1.25 equiv, 1.66 M in pentane). The tube was placed under vacuum for 5 min to remove the pentane solvent. After refilling with argon the tube was capped with an NMR tube septum and cooled to –78 °C. Freshly distilled (NaK) THF-d_8 (400 µL) was then added and the solid *tert*-butyllithium was dissolved by mixing on a vortexer in 1-2 s bursts. Freshly distilled (CaH_2) HMPA-d_{18} (42 µL, 240 µmol, 6.0 equiv) and chromane (4.9 µL, 40 µmol, 1.0 equiv) were dissolved in THF-d_8 (200 µL). This solution was then added to the *tert*-butyllithium solution and mixed in a vortexer in 1-2 s bursts. The tube was maintained in the –78 °C bath until it was placed into the NMR spectrometer that was precooled to –80 °C. All the spectroscopic data required to assign the spectrum was collected in a 12-hour period from initial sample preparation and on a single sample. Analysis of the ^{1}H NMR spectrum after collection of each dataset determined that the sample had experienced minimal decomposition.

^{1}H NMR (500 MHz, THF-d_8): δ 5.61 (t, J = 7.4 Hz, 1H), 5.42 (d, J = 6.7 Hz, 1H), 5.15 (d, J = 7.8 Hz, 1H), 4.28 (t, J = 6.9 Hz, 1H), 3.71 (s, 2H), 2.65 (s, 1H), 2.50 (s, 2H).

^{13}C NMR (126 MHz, THF-d_8): δ 142.7, 139.1, 123.2, 111.1, 107.1, 89.6, 65.5, 54.4, 30.3.

^{7}Li NMR (194 MHz, THF-d_8): δ –1.03.

^{31}P NMR (202 MHz, THF-d_8): δ 26.71, 26.09.



57

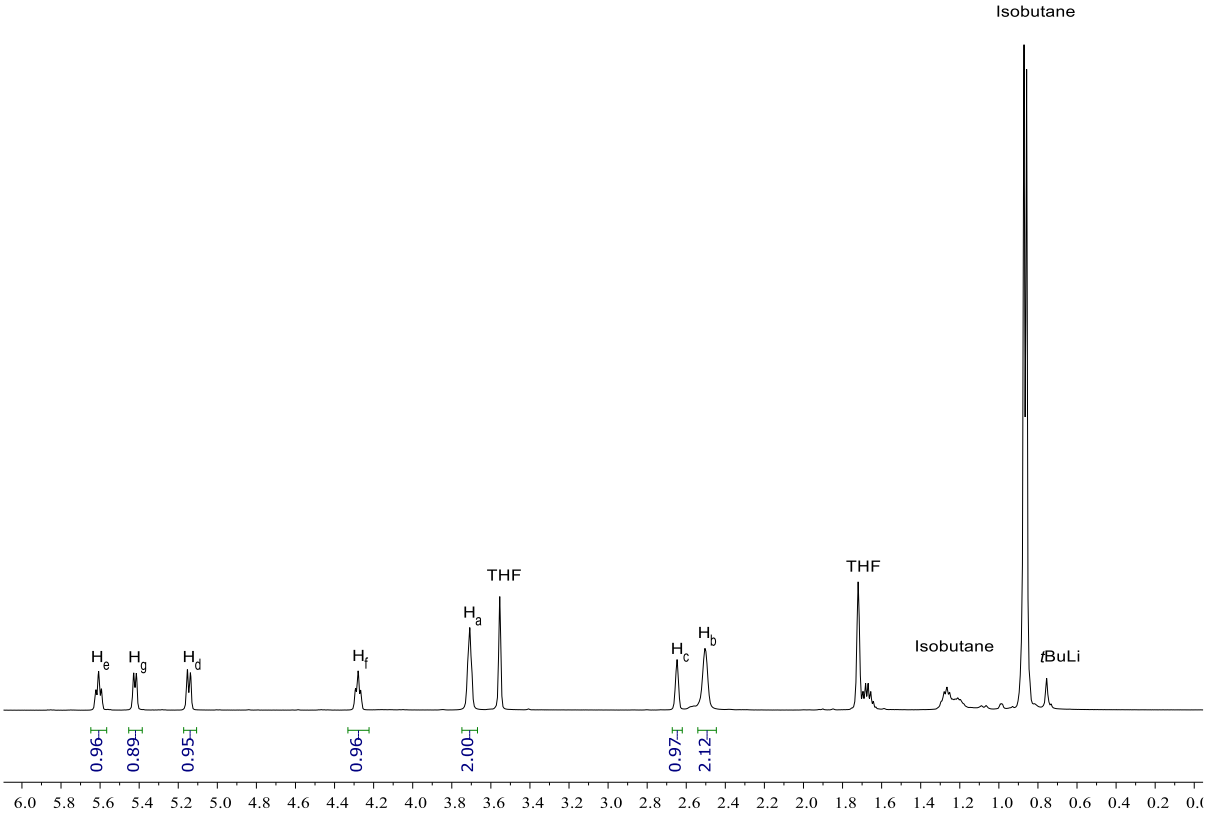


Figure S11. ^{1}H NMR spectrum of **57** at –80 °C, referenced to THF-d_8 (1.72 ppm).

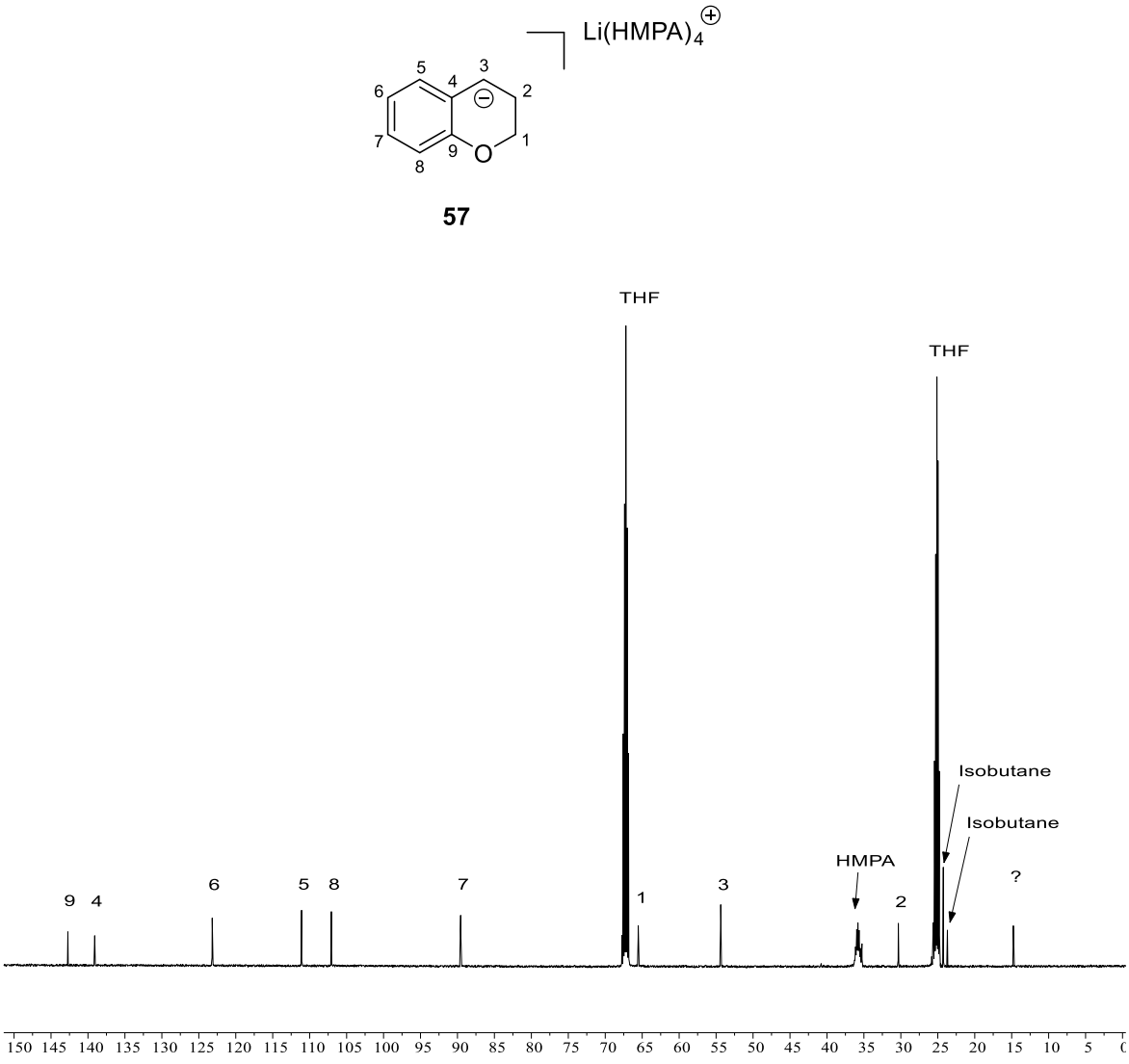


Figure S12. ^{13}C NMR spectrum of **57** at –80 °C, referenced to THF-d_8 (67.21 ppm).

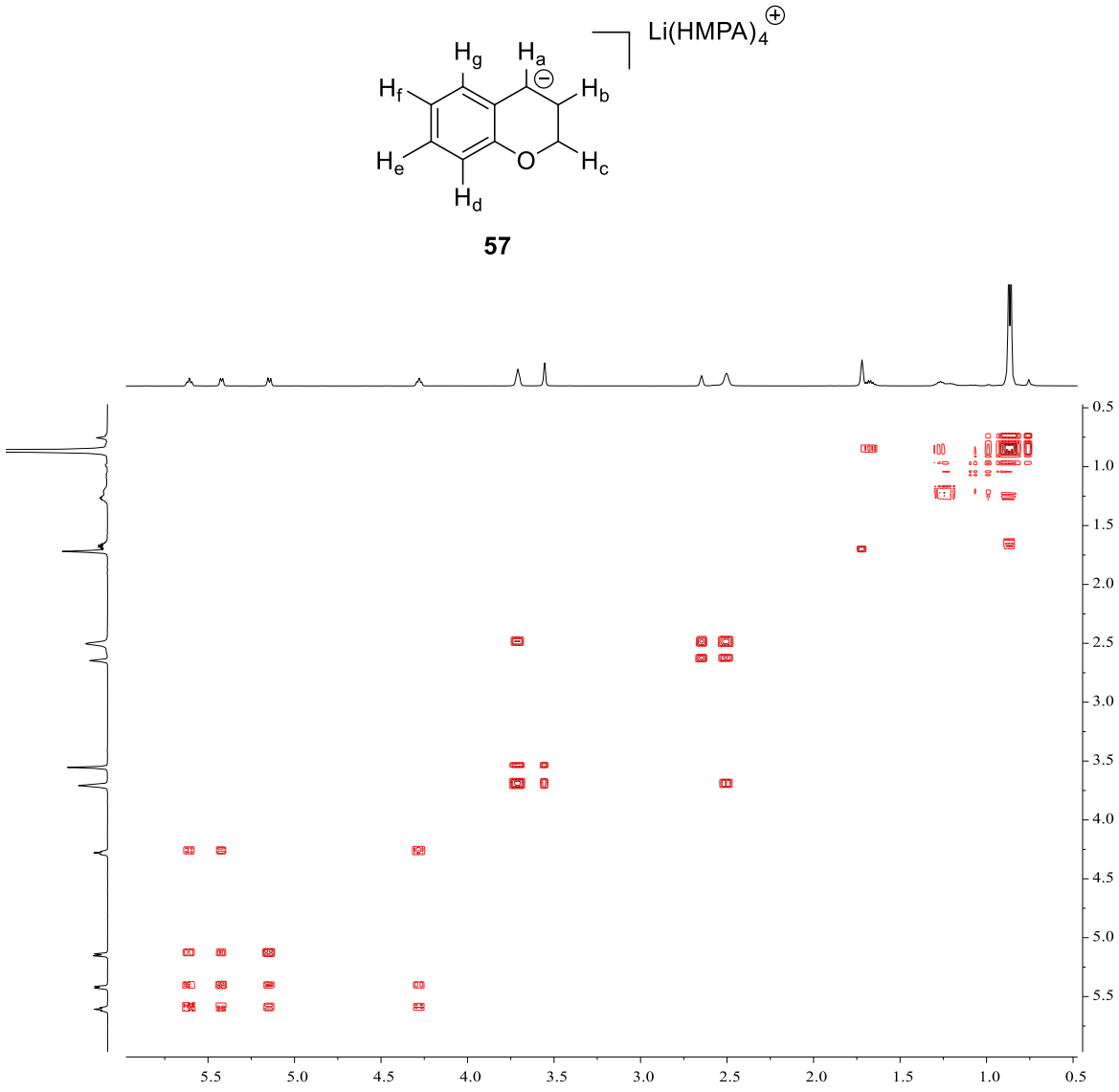


Figure S13. COSY spectrum of **57** at –80 °C, referenced to THF-d_8 (1.72 ppm).

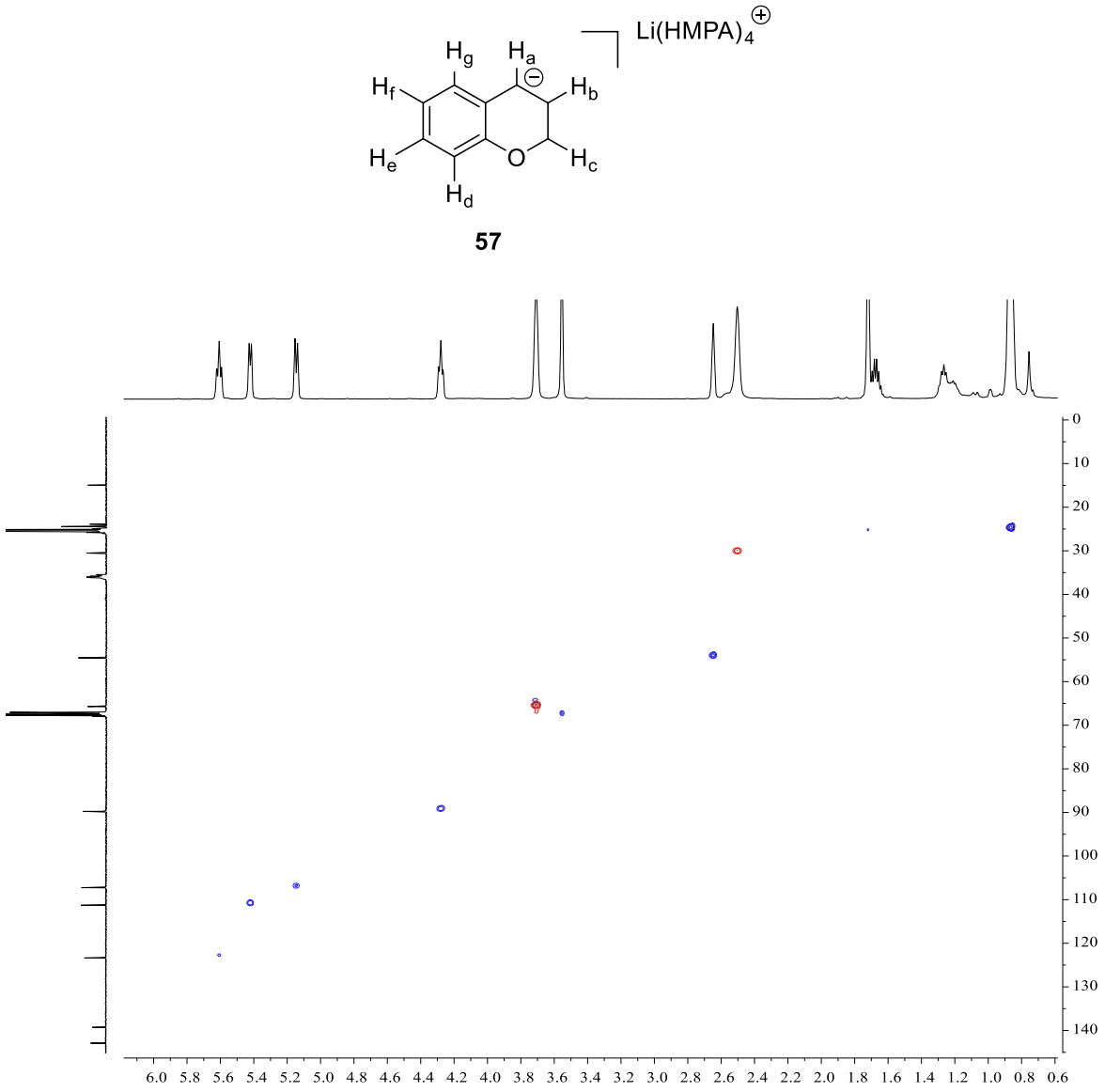


Figure S14. HSQC spectrum of **57** at –80 °C, referenced to THF-d_8 (1.72 and 67.21 ppm).

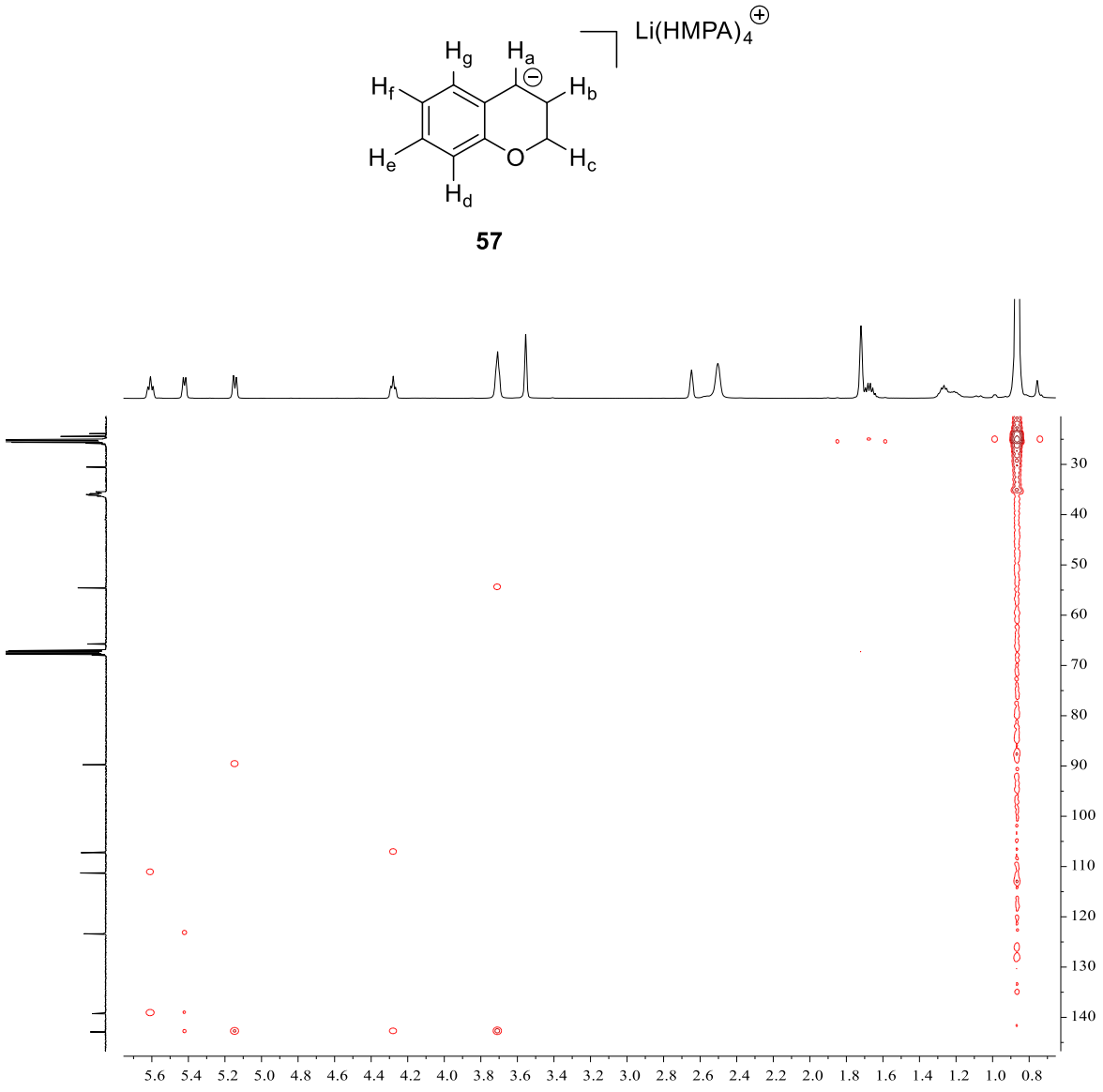


Figure S15. HMBC spectrum of **57** at –80 °C, referenced to THF-d_8 (1.72 and 67.21 ppm).

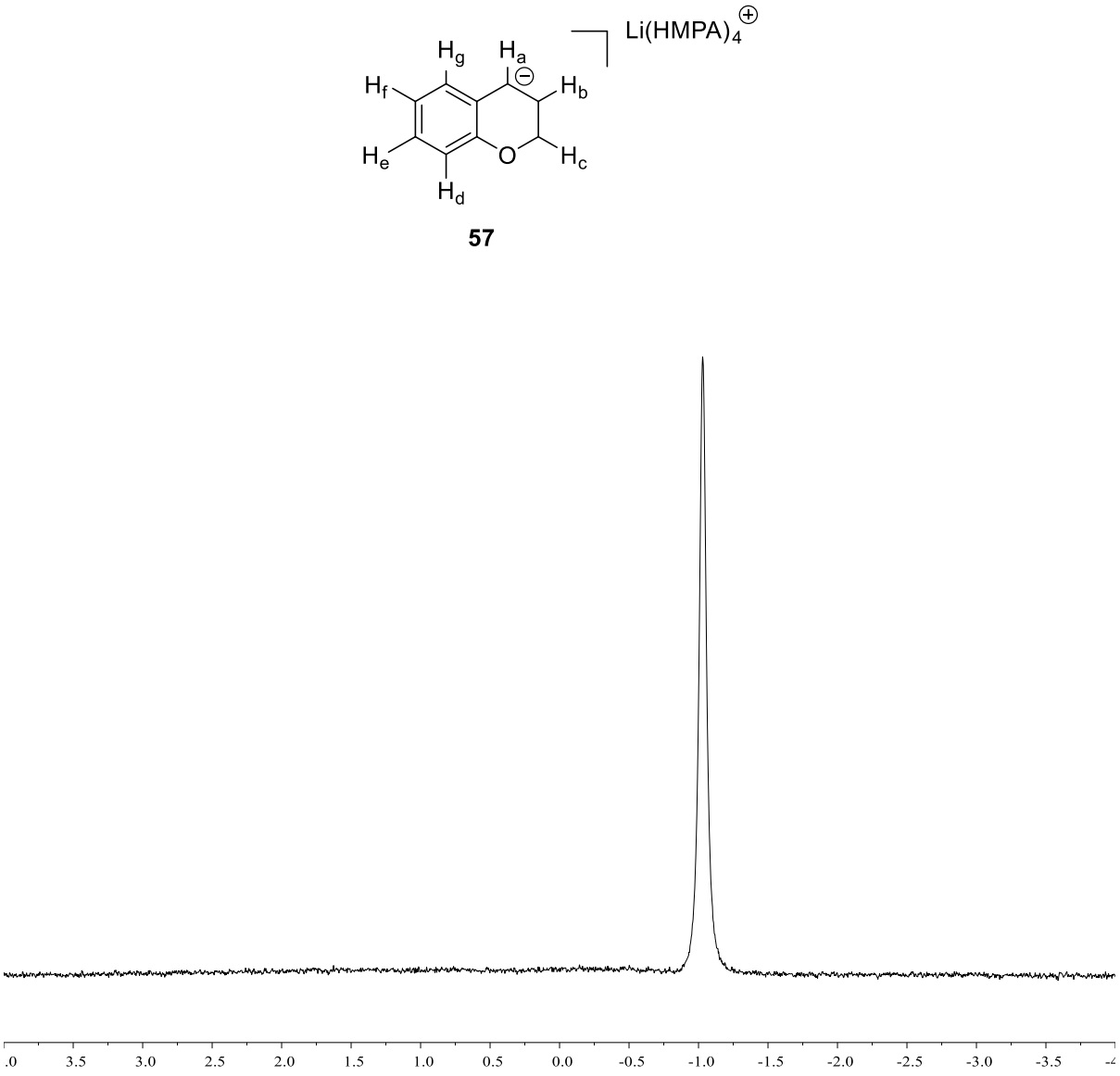
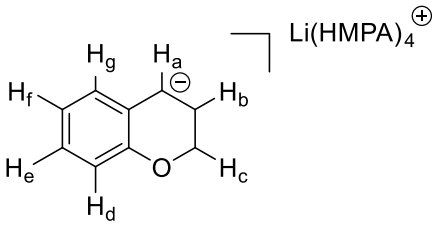


Figure S16. ^{7}Li spectrum of **57** at –80 °C, referenced to external LiCl (0.5M in THF, 0.0 ppm).



57

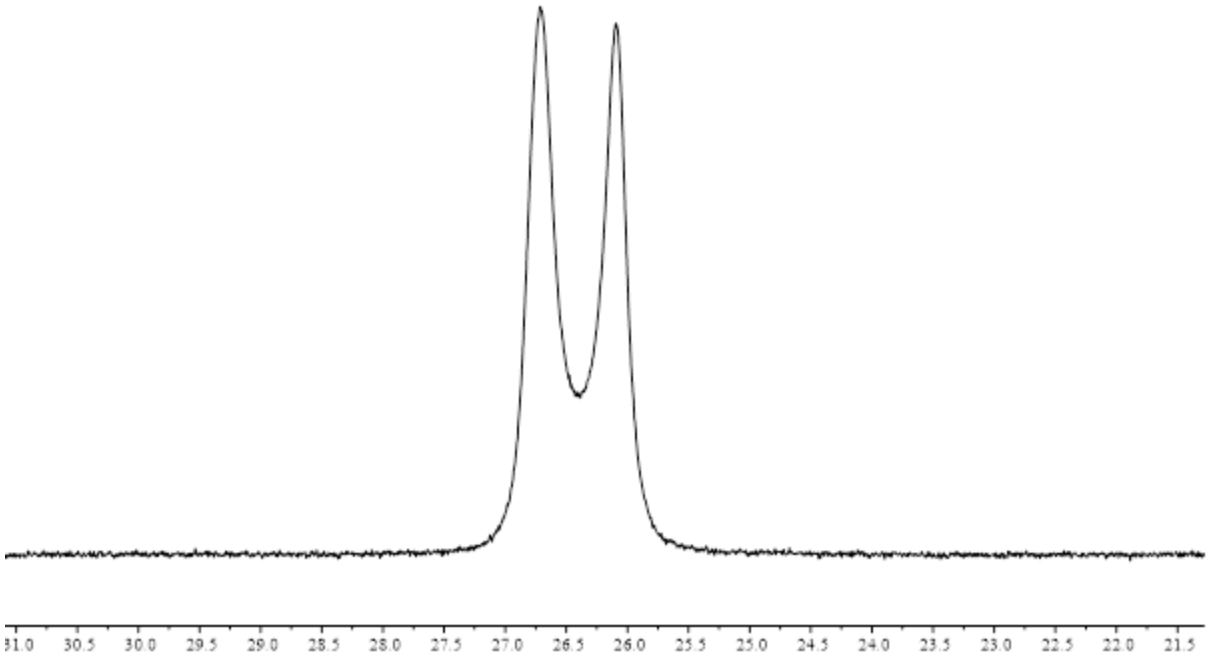


Figure S17. ^{31}P spectrum of **57** at –80 °C, referenced to external HMPA (0.5 M in THF, 26.1 ppm).

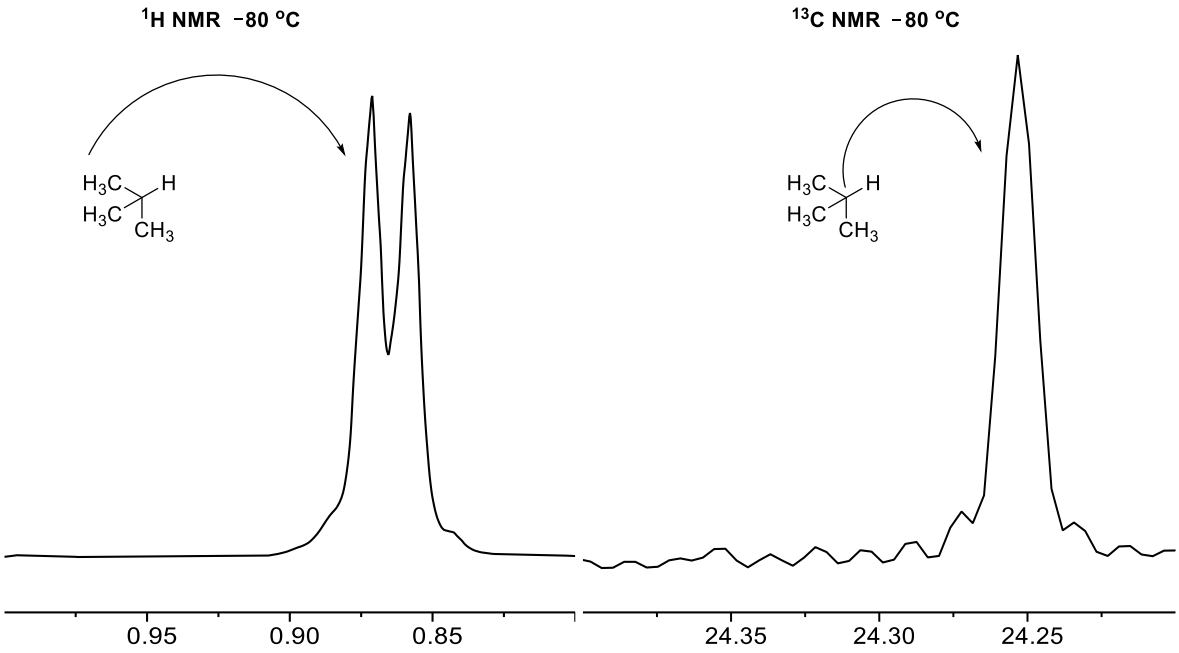


Figure S18. ^{1}H and ^{13}C spectra of **57** at –80 °C zoomed in on the isobutane product, referenced to THF-d_8 (1.72 and 67.21 ppm).

Preparation of 4-lithiochromane 57 for collection of low temperature lithium and phosphorous spectra: An oven-dried 5 mm NMR tube was placed under argon using a septum capped NMR tube adapter. To this tube was added *tert*-butyllithium (25 µL, 42 µmol, 1.2 equiv, 1.66 M in pentane). The tube was placed under vacuum for 5 min to remove the pentane solvent. After refilling with argon, the tube was capped with an NMR tube septum and cooled to –78 °C. Freshly distilled (NaK) THF (400 µL) was then added and the solid *tert*-butyllithium was dissolved by mixing on a vortexer in 1-2 s bursts. HMPA (36 µL, 210 µmol, 6.0 equiv) and chromane (4.3 µL, 35 µmol, 1.0 equiv) were dissolved in THF (200 µL). This solution was then added to the *tert*-butyllithium solution and mixed in a vortexer in 1-2 s bursts. The tube was maintained in the –78 °C bath until it was placed into the NMR spectrometer that was precooled to –80 °C. The sample was then cooled in 5-degree intervals down to –115 °C.

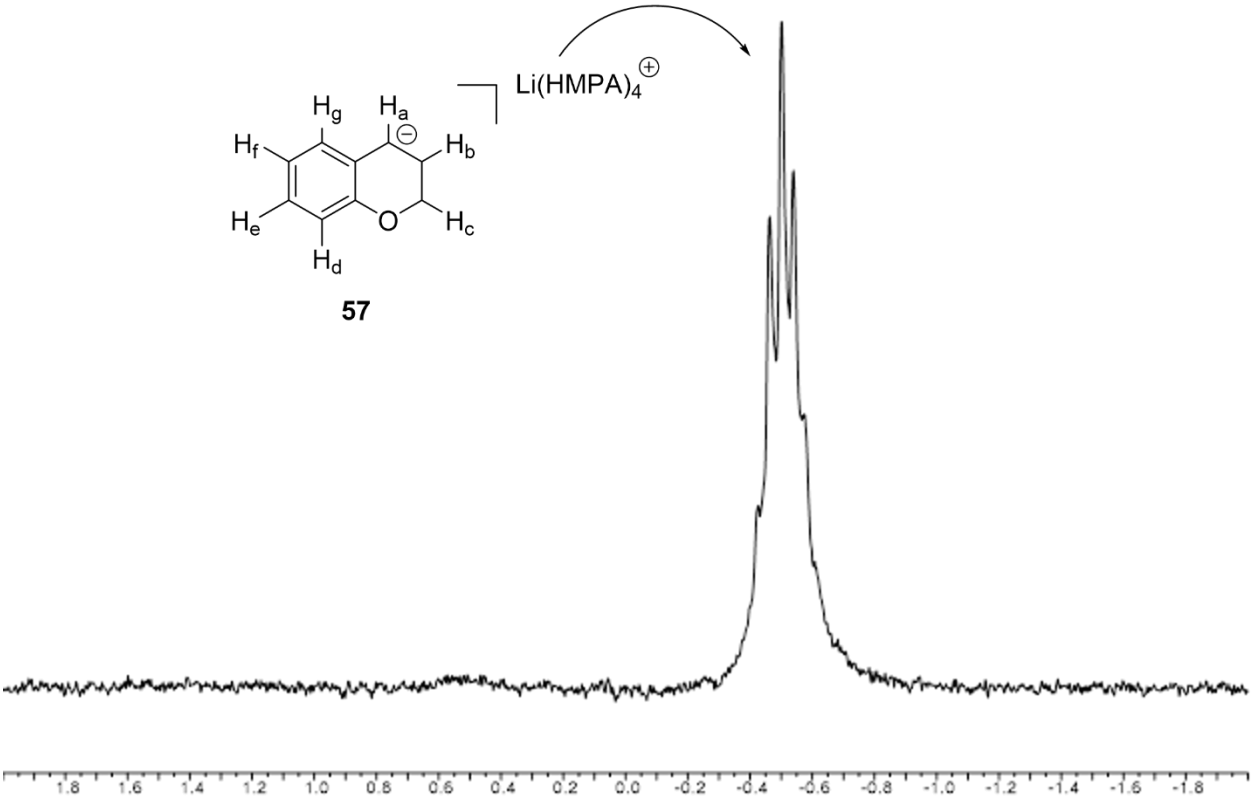


Figure S19. ^{7}Li spectrum of **57** at –115 °C, referenced to external LiCl (0.5 M in THF, 0.0 ppm).

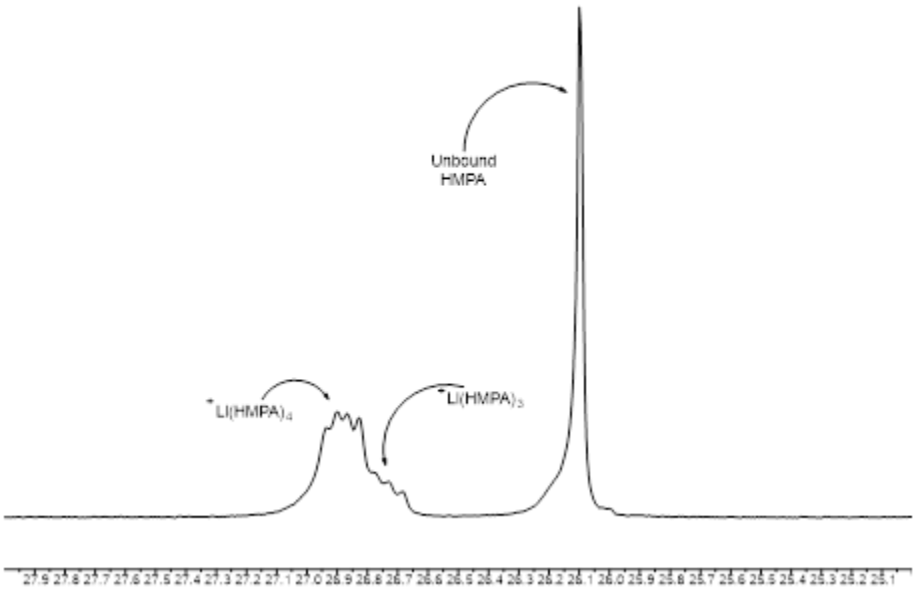


Figure S20. ^{31}P spectrum of **57** at –115 °C, referenced to external HMPA (0.5 M in THF, 26.1 ppm).

2.4. Procedure for Rapid Injection NMR (RI-NMR) Experiments

An oven-dried 5 mm NMR tube was placed under argon using a septum capped NMR tube adapter. To this tube was added *tert*-butyllithium (16 µL, 25 µmol, 1.25 equiv, 1.56 M in pentane). The tube was placed under vacuum for 5 min to remove the pentane solvent. After refilling with argon the tube was capped with an NMR tube septum and cooled to –78 °C. Freshly distilled (NaK) THF-d_8 (300 µL) was then added and the solid *tert*-butyllithium was dissolved by mixing on a vortexer in 1-2 s bursts. Freshly distilled (CaH_2) HMPA-d_{18} (21 µL, 120 µmol, 6.0 equiv) and chromane (2.5 µL, 20 µmol, 1.0 equiv) were dissolved in THF-d_8 (200 µL). This solution was then added to the *tert*-butyllithium solution and mixed in a vortexer in 1-2 s bursts. The tube was maintained in the –78 °C bath until it was placed into the NMR spectrometer that was precooled to –80 °C. The injector apparatus was loaded with 1-bromooctane (6.9 µL, 40 µmol, 2.0 equiv) and then lowered into the instrument. After 5 min for temperature equilibration, data collection was started (at = 0.5 s, d1 = 0.5 s) and the 1-bromooctane solution was injected. The consumption of the lithiated chromane was instantaneous (<1s) as can be seen from the spectra below.

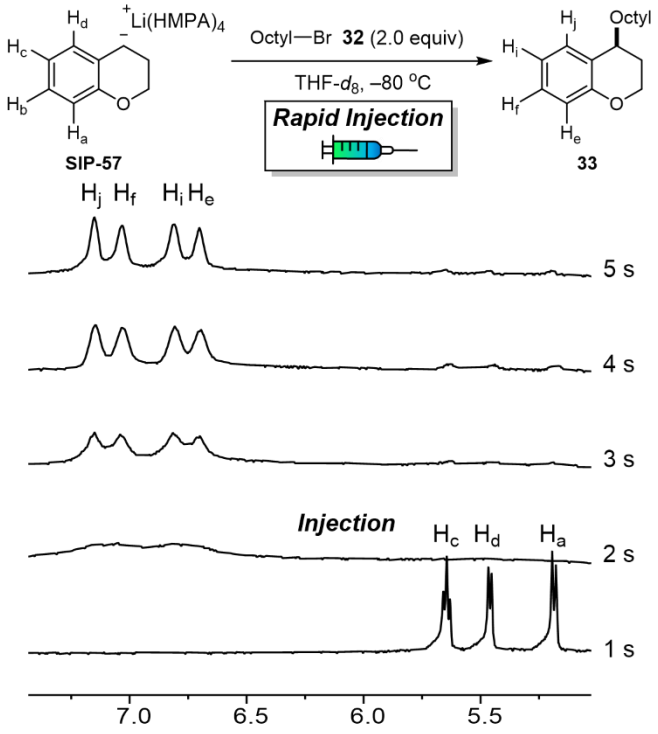
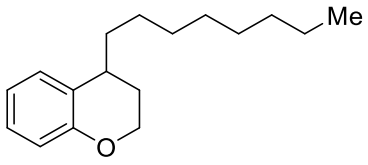


Figure S21. ^{1}H NMR spectra (RI-NMR) of the injection of 1-bromooctane into **57** at –80 °C, referenced to THF-d_8 (1.72 ppm).

2.5. Experimental Data for Alkylated Chromanes

4-octylchromane 33



33

Chromane **33** was prepared according to General Procedure A using chromane (63 µL, 0.50 mmol, 1.0 equiv) and 1-bromooctane (95 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (100 % hexanes to 10 % EtOAc in hexanes) to yield chromane **33** (1st run: 115 mg, 93 %; 2nd run: 120 mg, 97 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8 Hz, 1H), 7.08 (t, *J* = 8 Hz, 1H), 6.85 (t, *J* = 7 Hz, 1H), 6.79 (d, *J* = 8 Hz, 1H), 4.24-4.10 (m, 2H), 2.78 (dq, *J* = 10.3, 5.3 Hz, 1H), 2.11-2.01 (m, 1H), 1.86-1.74 (m, 2H), 1.60-1.22 (m, 13H), 0.89 (t, *J* = 7 Hz, 3H).

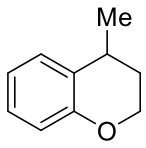
^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 129.2, 127.3, 127.0, 120.2, 116.9, 63.7, 36.6, 33.7, 32.0, 29.9, 29.7, 29.5, 27.1, 27.0, 22.8, 14.3.

HRMS: (APCI) calc. $C_{17}H_{27}O$ $[M+H]^+$: 247.2056. Found: 247.2052.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2924, 2852, 1580, 1487, 1452, 1223, 750 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.91** (UV)

4-MethylChromane 34



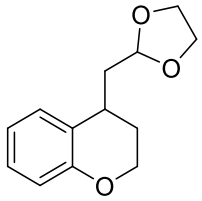
34

Chromane **34** was prepared according to General Procedure A using chromane (63 μL, 0.50 mmol, 1.0 equiv) and methyl iodide (34 μL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (100 % hexanes to 10 % EtOAc in hexanes) to yield chromane **34** (70 mg, 88 %) as a colorless oil containing ca 10 % of unreacted chromane. Spectral data are in accordance with literature reports.[2]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, J = 7.6 Hz, 1H), 7.09 (td, J = 8.0, 1.7 Hz, 1H), 6.87 (td, J = 7.4, 1.3 Hz, 1H), 6.80 (dd, J = 8.1, 1.3 Hz, 1H), 4.26 – 4.13 (m, 2H), 2.97 (h, J = 6.7 Hz, 1H), 2.10 (dddd, J = 13.5, 7.5, 5.8, 3.5 Hz, 1H), 1.79 – 1.68 (m, 1H), 1.34 (d, J = 7.0 Hz, 3H).

TLC (10 % EtOAc in hexanes): R_f **= 0.91** (UV)

4-((1,3-dioxolan-2-yl)methyl)chromane 35



35

Chromane **35** was prepared according to General Procedure A using chromane (63 µL, 0.50 mmol, 1.0 equiv) and 2-bromomethyl-1,3-dioxolane (57µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (100 % hexanes to 10 % EtOAc in hexanes) to yield chromane **35** (1^{st} run: 65 mg, 5 9%; 2^{nd} run: 69 mg, 63 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (ddd, J = 7.7, 1.8, 0.8 Hz, 1H), 7.09 (dddd, J = 8.0, 7.2, 1.7, 0.6 Hz, 1H), 6.86 (td, J = 7.5, 1.3 Hz, 1H), 6.80 (dd, J = 8.2, 1.3 Hz, 1H), 5.01 (t, J = 4.9 Hz, 1H), 4.24 – 4.14 (m, 2H), 4.07 – 3.98 (m, 2H), 3.94 – 3.83 (m, 2H), 3.09 (dq, J = 10.0, 5.1 Hz, 1H), 2.21 – 2.08 (m, 2H), 2.00 – 1.88 (m, 2H).

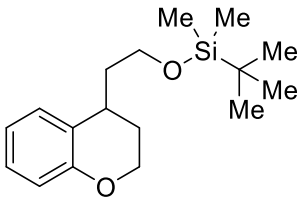
^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7, 129.3, 127.6, 125.9, 120.3, 117.0, 103.4, 65.1, 64.8, 63.4, 40.5, 30.0, 27.5.

HRMS: (APCI) calc. $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1172. Found: 221.1172.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2926, 2878, 1607, 1580, 1489, 1223, 1140, 1038, 1024, 941, 752 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.17** (UV)

tert-butyl(2-(chroman-4-yl)ethoxy)dimethylsilane 36



36

Chromane **36** was prepared according to General Procedure A using chromane (63 µL, 0.50 mmol, 1.0 equiv) and (2-bromoethoxy)-tert-butyldimethylsilane (118 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (100 % hexanes to 10 % EtOAc in hexanes) to yield chromane **36** (1^{st} run: 119 mg, 81 %; 2^{nd} run: 120 mg, 82 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 7.7 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.86 (t, J = 7.4 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 4.22 – 4.14 (m, 2H), 3.75 (dd, J = 6.8, 5.7 Hz, 2H), 3.01 (dq, J = 10.1, 5.2 Hz, 1H), 2.15 – 1.96 (m, 2H), 1.88 – 1.67 (m, 2H), 0.92 (s, 9H), 0.08 (d, J = 4.1 Hz, 6H).

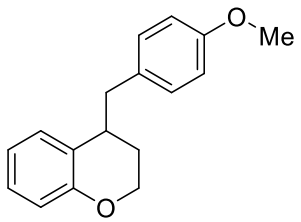
^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7, 129.4, 127.4, 126.5, 120.2, 116.9, 63.5, 60.7, 39.6, 30.3, 27.0, 26.1, 18.4, –5.11.

HRMS: (APCI) calc. $C_{17}H_{29}O_2Si$ $[M+H]^+$: 293.1931. Found: 293.1932.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2951, 2858, 1581, 1489, 1254, 1223, 1096, 841, 750 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.91** (UV)

4-*p*-methoxybenzylchromane 37



37

Chromane **37** was prepared according to General Procedure A using chromane (63 µL, 0.50 mmol, 1.0 equiv) and *p*-methoxybenzyl chloride (118 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (100 % hexanes to 10 % EtOAc in hexanes) to yield chromane **37** (1st run: 99 mg, 78 %; 2nd run: 96 mg, 75 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 – 7.08 (m, 4H), 6.91 – 6.79 (m, 4H), 4.25 – 4.11 (m, 2H), 3.82 (s, 3H), 3.17 (ddd, J = 13.7, 5.1, 1.8 Hz, 1H), 3.04 (dq, J = 10.4, 5.2 Hz, 1H), 2.72 – 2.62 (m, 1H), 1.91 (ddt, J = 14.1, 9.3, 4.8 Hz, 1H), 1.75 (ddt, J = 14.1, 5.3, 2.8 Hz, 1H).

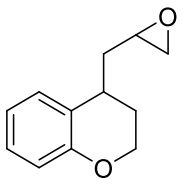
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.3, 154.7, 132.0, 130.3, 129.3, 127.6, 126.0, 120.2, 117.0, 114.0, 63.4, 55.4, 42.1, 35.7, 26.3.

HRMS: (APCI) calc. $C_{17}H_{19}O_2$ $[M+H]^+$: 255.1380. Found: 255.1376.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2941, 1609, 1582, 1510, 1489, 1449, 1238, 1225, 1026, 841, 754 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.45** (UV)

4-(oxiran-2-ylmethyl)chromane 38



38

Chromane **38** was prepared according to General Procedure A using chromane (63 µL, 0.50 mmol, 1.0 equiv) and epichlorohydrin (43 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (20 % EtOAc in hexanes to 40 % EtOAc in hexanes) to yield chromane **38** (1^{st} run: 52 mg, 55 %; 2^{nd} run: 50 mg, 53 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 – 7.07 (m, 2H), 6.90 – 6.81 (m, 2H), 4.30 – 4.16 (m, 2H), 3.20 – 3.01 (m, 2H), 2.90 – 2.77 (m, 1H), 2.64 – 2.44 (m, 1H), 2.31 – 1.83 (m, 3H), 1.74 – 1.62 (m, 1H).

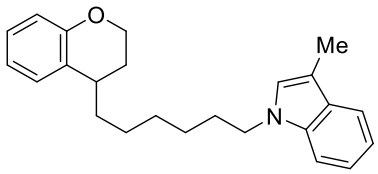
^{13}C NMR (101 MHz, $CDCl_3$): Major diast. δ 154.6, 129.3, 127.8, 125.2, 120.2, 117.1, 63.2, 51.3, 46.8, 39.6, 32.4, 27.5. Minor diast. δ 154.8, 128.8, 127.7, 125.4, 120.4, 117.1, 63.7, 50.3, 47.7, 39.2, 31.5, 27.3.

HRMS: (APCI) calc. $C_{12}H_{15}O_2$ $[M+H]^+$: 191.1067. Found: 191.1065.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 3040, 2924, 1605, 1578, 1489, 1450, 1223, 833, 750 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.35** (UV)

1-(6-(chroman-4-yl)hexyl)-3-methyl-1H-indole 39



39

Chromane **39** was prepared according to General Procedure A using chromane (63 μL, 0.50 mmol, 1.0 equiv) and 1-(6-bromohexyl)-3-methyl-1H-indole (152 μL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (10 % DCM in hexanes then 10 % EtOAc in hexanes) to provide compound **39** (1st run: 156.2 mg, 90 %; 2nd run: 154.2 mg, 89 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (d, *J* = 8 Hz, 1H), 7.30 (d, *J* = 8 Hz, 1H), 7.21 (t, *J* = 8 Hz, 1H), 7.11 (q, *J* = 7 Hz, 3H), 6.90-6.83 (m, 2H), 6.80 (d, *J* = 8 Hz, 1H), 4.26-4.10 (m, 2H), 4.07 (t, *J* = 7 Hz, 2H), 2.75 (dq, *J* = 4 Hz, *J* = 5 Hz, 1H), 2.34 (s, 3H), 2.09-1.99 (m, 1H), 1.89-1.70 (m, 4H), 1.58-1.25 (m, 7H).

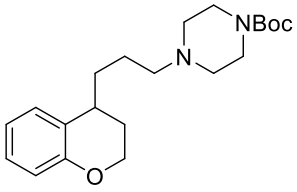
^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 136.4, 129.2, 128.8, 127.3, 126.8, 125.6, 121.4, 120.2, 119.1, 118.5, 116.9, 110.2, 109.3, 63.7, 46.2, 36.4, 33.6, 30.5, 29.6, 27.1, 27.0, 26.9, 9.7.

HRMS: (+ESI) calc. $C_{24}H_{30}NO$ $[M+H]^+$: 348.2322. Found: 348.2320.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2926, 2855, 1580, 1487, 1466, 1452, 1385, 1360, 1331, 1308, 1267, 1258, 1223, 1198, 1117, 1069, 1057, 1036, 1013, 810, 752 cm^{-1}.

TLC (10 % DCM in hexanes): R_f **= 0.10** (UV)

tert-butyl 4-(3-(chroman-4-yl)propyl)piperazine-1-carboxylate 40



40

Chromane **40** was prepared according to General Procedure A using chromane (63 μL, 0.50 mmol, 1.0 equiv) and a solution of tert-butyl 4-(3-bromopropyl)piperazine-1-carboxylate (169 mg, 0.55 mmol, 1.1 equiv) in THF (0.5 mL). After standard work-up the residue was purified by flash-column chromatography on silica gel (20 % to 50 % EtOAc in hexanes) to provide compound **40** (144 mg, 80 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 – 7.03 (m, 2H), 6.84 (td, *J* = 7.4, 1.3 Hz, 1H), 6.78 (dd, *J* = 8.1, 1.3 Hz, 1H), 4.21 – 4.10 (m, 2H), 3.43 (t, *J* = 5.1 Hz, 4H), 2.79 (dq, *J* = 10.5, 5.4 Hz, 1H), 2.44 – 2.31 (m, 6H), 2.06 (dddd, *J* = 13.8, 8.2, 5.7, 4.2 Hz, 1H), 1.86 – 1.75 (m, 2H), 1.69 – 1.50 (m, 3H), 1.45 (s, 9H).

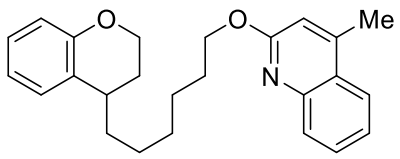
^{13}C NMR (101 MHz, $CDCl_3$): δ 154.8, 154.6, 129.1, 127.4, 126.4, 120.2, 116.9, 79.7, 63.6, 58.7, 53.2, 44.2 (br), 34.1, 33.5, 28.5, 27.0, 24.3.

HRMS: (+ESI) calc. $C_{21}H_{33}N_2O_3$ $[M+H]^+$: 361.2486. Found: 361.2480.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2950, 1695, 1489, 1456, 1418, 1364, 1244, 1223, 1169, 1003, 752 cm^{-1}.

TLC (50 % EtOAc in hexanes): R_f **= 0.14** (UV)

2-((6-bromohexyl)oxy)-4-methylquinoline 41



41

Chromane **41** was prepared according to General Procedure A using chromane (63 μL, 0.50 mmol, 1.0 equiv) and a solution of 2-((6-bromohexyl)oxy)-4-methylquinoline (191.1 mg, 0.55 mmol, 1.1 equiv) in THF (0.5 mL). After standard work-up the residue was purified by flash-column chromatography on silica gel (5 % EtOAc in hexanes) to provide compound **41** (1st run: 99.6 mg, 52 %; 2nd run: 103.6 mg, 55 %) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3): 7.87 (ddt, *J* = 12, 8, 1 Hz, 2H), 7.63 (ddt, *J* = 9, 7, 2 Hz, 1H), 7.41 (ddt, *J* = 8, 7, 1 Hz, 1H), 7.20 – 7.06 (m, 2H), 6.88 (ddt, *J* = 9, 8, 1 Hz, 1H), 6.86 – 6.75 (m, 2H), 4.49 (ddt, *J* = 7 Hz, 2H), 4.27 – 4.13 (m, 2H), 2.81 (dq, *J* = 10, 5 Hz, 1H), 2.64 (s, 3H), 2.13-2.04 (m, 1H), 1.91-1.78 (m, *4*H), 1.65 – 1.40 (m, 7H).

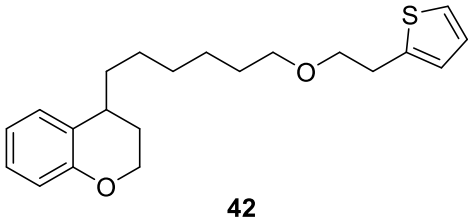
^{13}C NMR (101 MHz, CDCl3): δ 162.3, 154.6, 146.8, 146.7, 129.3, 129.2, 127.8, 127.3, 126.9, 125.5, 123.8, 123.8, 120.2, 116.9, 113.3, 65.7, 63.7, 36.5, 33.7, 29.7, 29.2, 27.1, 27.0, 26.3, 18.8.

HRMS: (ESI) calc. $C_{25}H_{29}NO_2$ $[M+H]^+$: 376.2271. Found: 376.2257.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2930, 2855, 1609, 1572, 1514, 1487, 1466, 1450, 1400, 1381, 1375, 1331, 1310,, 1267, 1258, 1236, 1223, 1186, 1161, 1130, 1119, 1049, 1020, 853, 729, 687 cm^{-1}.

TLC (5 % EtOAc in hexanes): R_f **= 0.43** (UV)

4-(6-(2-(thiophen-2-yl)ethoxy)hexyl)chromane 42



42

Chromane **42** was prepared according to General Procedure A using chromane (63 μL, 0.50 mmol, 1.0 equiv) and a solution of 2-(2-((6-bromohexyl)oxy)ethyl)thiophene (160 mg, 0.55 mmol, 1.1 equiv) in THF (0.5 mL). After standard work-up the residue was purified by flash-column chromatography on silica gel (10 % EtOAc in hexanes to 20 % EtOAc in hexanes) to provide compound **42** (1^{st} run: 71 mg, 41 %; 2^{nd} run: 75 mg, 44 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.11 (m, 2H), 7.11 – 7.06 (m, 1H), 6.93 (dd, *J* = 5.1, 3.3 Hz, 1H), 6.89 – 6.83 (m, 2H), 6.79 (dd, *J* = 8.1, 1.3 Hz, 1H), 4.24 – 4.13 (m, 2H), 3.66 (t, *J* = 6.9 Hz, 2H), 3.47 (td, *J* = 6.6, 1.7 Hz, 2H), 3.10 (td, *J* = 6.9, 1.0 Hz, 2H), 2.78 (dq, *J* = 10.3, 5.3 Hz, 1H), 2.06 (dddd, *J* = 13.7, 8.1, 5.7, 4.2 Hz, 1H), 1.88 – 1.74 (m, 2H), 1.67 – 1.32 (m, 9H).

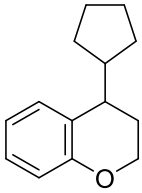
^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 141.6, 129.2, 127.3, 126.9, 126.8, 125.2, 123.7, 120.2, 116.9, 71.5, 71.2, 63.7, 36.5, 33.7, 30.7, 29.8, 29.7, 27.1, 27.0, 26.3.

HRMS: (APCI) calc. $C_{21}H_{29}O_2S$ $[M+H]^+$: 345.1883. Found: 345.1879.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2928, 2855, 1609, 1582, 1489, 1454, 1223, 1115, 826, 752, 694 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.42** (UV)

4-cyclopentylchromane 43



43

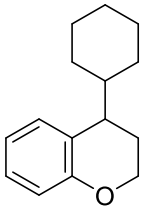
Chromane **43** was prepared according to General Procedure C using chromane (63 μL, 0.50 mmol, 1.0 equiv) and bromocyclopentane (56 μL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (2 % EtOAc in hexanes) to provide compound **43** (71 mg, 70 %) as a colorless oil containing ca 5 % of an inseparable isomer. Spectral data are in accordance with literature reports.[3]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 – 7.00 (m, 2H), 6.88 – 6.74 (m, 2H), 4.35 – 4.14 (m, 2H), 2.65 (dt, J = 9.2, 4.8 Hz, 1H), 2.23 – 1.90 (m, 3H), 1.90 – 1.32 (m, 7H), 1.32 – 1.08 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.4, 130.0, 127.5, 126.4, 119.6, 116.8, 63.5, 45.1, 38.9, 31.9, 29.8, 25.8, 25.5, 24.9.

TLC (2 % EtOAc in hexanes): R_f **= 0.69** (UV)

4-cyclohexylchromane 44



44

Chromane **44** was prepared according to General Procedure C using chromane (63 µL, 0.50 mmol, 1.0 equiv) and bromocyclohexane (68 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (10 % EtOAc in hexanes) to provide compound **44** (68 mg, 63 %) as a colorless oil containing ca 5 % of an inseparable isomer.

^{1}H NMR (400 MHz, $CDCl_3$): 7.16 – 7.06 (m, 2H), 6.89 – 6.77 (m, 2H), 4.25 (ddd, J = 11, 8, 4 Hz, 1H), 4.13 (ddd, J = 11, 7, 4 Hz, 1H), 2.69 (q, J = 6 Hz, 1H), 2.04 – 1.86 (m, 2H), 1.85 – 1.64 (m, 5H), 1.64 – 1.55 (m, 1H), 1.35 – 1.09 (m, 4H), 0.97 (qd, J = 12, 3 Hz, 1H).

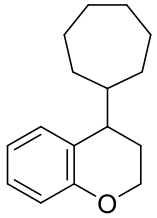
^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 129.3, 127.2, 125.3, 119.9, 116.9, 64.8, 41.3, 39.4, 31.8, 28.5, 27.0, 26.8, 26.8, 23.9.

HRMS: (APCl) calc. $C_{15}H_{20}O$ $[M+H]^+$: 217.1587 Found: 217.1587.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2920, 2851, 1582, 1489, 1450, 1319, 1304, 1269, 1254, 1238, 1223, 1200, 1119, 1069, 1049, 1030, 1015, 907, 826, 818, 749 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.90** (UV)

4-cycloheptylchromane 45



45

Chromane **45** was prepared according to General Procedure A using chromane (63 µL, 0.50 mmol, 1.0 equiv) and bromocycloheptane (76 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (10 % EtOAc in hexanes) to provide compound **45** (1st run: 83 mg, 72 %; 2nd run: 83 mg, 72 %) as a colorless oil containing ca 5 % of an inseparable isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, J = 7.8 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.87 (td, J = 7.5, 1.3 Hz, 1H), 6.79 (dd, J = 8.1, 1.3 Hz, 1H), 4.29 (dt, J = 10.8, 4.2 Hz, 1H), 4.04 (ddd, J = 10.8, 8.6, 4.2 Hz, 1H), 2.92 – 2.82 (m, 1H), 2.18 – 2.07 (m, 1H), 1.97 – 1.85 (m, 2H), 1.84 – 1.40 (m, 10H), 1.38 – 1.26 (m, 1H), 1.21 – 1.08 (m, 1H).

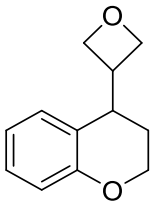
^{13}C NMR (101 MHz, $CDCl_3$): δ 155.76, 128.22, 127.07, 125.97, 120.34, 116.99, 65.85, 41.89, 40.52, 33.71, 29.03, 28.46, 27.93, 27.82, 27.43, 23.57.

HRMS: (APCI) calc. $C_{16}H_{23}O$ $[M+H]^+$: 231.1743. Found: 231.1740.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2920, 2851, 1605, 1578, 1485, 1450, 1219, 1061, 907, 752 cm^{-1}.

TLC (5 % EtOAc in hexanes): R_f **= 0.75** (UV)

4-(oxetan-3-yl)chromane 47



47

Chromane **47** was prepared according to General Procedure A using chromane (63 µL, 0.50 mmol, 1.0 equiv) and 3-bromooxetane (46 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (10 % EtOAc in hexanes to 25 % EtOAc in hexanes) to provide compound **47** (1^{st} run: 70 mg, 74 %; 2^{nd} run: 68 mg, 71 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.06 (m, 1H), 6.88 – 6.77 (m, 3H), 4.88 (dq, *J* = 7.8, 6.0 Hz, 2H), 4.75 (dd, *J* = 7.9, 6.0 Hz, 1H), 4.62 (dd, *J* = 7.2, 6.0 Hz, 1H), 4.24 – 4.13 (m, 2H), 3.41 – 3.27 (m, 1H), 3.23 (dt, *J* = 10.3, 6.0 Hz, 1H), 2.05 (dddd, *J* = 13.8, 7.4, 5.4, 3.9 Hz, 1H), 1.67 (dtd, *J* = 13.6, 6.6, 3.7 Hz, 1H).

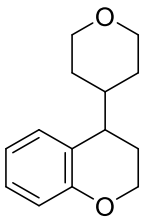
^{13}C NMR (101 MHz, $CDCl_3$): δ 154.4, 128.2, 128.0, 124.2, 120.4, 117.2, 76.9, 75.8, 63.9, 40.3, 37.3, 25.1.

HRMS: (APCI) calc. $C_{12}H_{15}O_2$ $[M+H]^+$: 191.1067. Found: 191.1064.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2951, 2866, 1605, 1578, 1489, 1450, 1304, 1223, 976, 918, 752, 729 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.09** (UV)

4-(tetrahydro-2H-pyran-4-yl)chromane 48



48

Chromane **48** was prepared according to General Procedure A using chromane (63 µL, 0.50 mmol, 1.0 equiv) and 4-bromotetrahydropyran (62 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (10 % EtOAc in hexanes to 25 % EtOAc in hexanes) to provide compound **48** (64.6 mg, 60 %) as a colorless oil that contained 5 % of an inseparable isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 – 7.05 (m, 2H), 6.89 – 6.76 (m, 2H), 4.29 – 4.13 (m, 2H), 4.06 – 3.94 (m, 2H), 3.44 – 3.29 (m, 2H), 2.68 (q, *J* = 6.1 Hz, 1H), 2.09 – 1.85 (m, 3H), 1.69 – 1.47 (m, 3H), 1.46 – 1.29 (m, 1H).

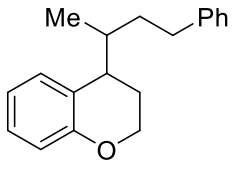
^{13}C NMR (101 MHz, CDCl3): δ 155.0, 129.6, 127.7, 124.2, 119.9, 117.1, 68.5, 68.4, 64.1, 38.9, 38.7, 31.7, 29.0, 23.6.

HRMS: (APCl) calc. $C_{14}H_{19}O_2$ $[M+H]^+$: 219.1380 Found: 219.1376.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2936, 2932, 2839, 1580, 1489, 1450, 1219, 1013, 752 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.14** (UV)

4-(4-phenylbutan-2-yl)chromane 49



49

Chromane **49** was prepared according to General Procedure A using chromane (63 µL, 0.50 mmol, 1.0 equiv) and 3-bromo-1-phenylbutane (95 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (100 % hexanes to 10 % EtOAc in hexanes) to provide compound **49** (1^{st} run: 109 mg, 66:34 d.r., 82 %; 2^{nd} run: 110 mg, 66:34 d.r., 83 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): Unresolved diastereomers δ 7.38 – 6.93 (m, 7H), 6.90 – 6.72 (m, 2H), 4.34 – 4.17 (m, 1H), 4.05 (ddd, J = 10.6, 8.8, 3.3 Hz, 1H), 3.04 – 2.78 (m, 1H), 2.78 – 2.40 (m, 2H), 2.25 – 2.03 (m, 1H), 1.99 – 1.82 (m, 2H), 1.82 – 1.27 (m, 2H), 1.11 (d, J = 6.7 Hz, 2H), 0.78 (d, J = 6.8 Hz, 1H).

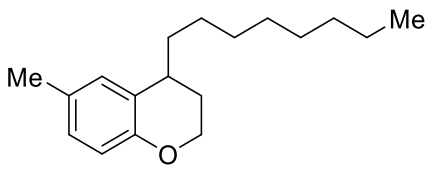
^{13}C NMR (101 MHz, $CDCl_3$): Major diast: δ 155.5, 142.5, 128.6, 128.5, 128.4, 127.2, 125.8, 125.3, 120.2, 116.9, 65.4, 39.6, 34.7, 34.0, 33.3, 23.5, 17.9. Minor diast: δ 155.8, 142.6, 128.5, 128.5, 128.1, 127.1, 125.9, 125.6, 120.5, 117.0, 65.6, 37.7, 37.0, 35.2, 34.2, 22.6, 14.6.

HRMS: (APCI) calc. $C_{19}H_{23}O$ $[M+H]^+$: 267.1743. Found: 267.1740.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2951, 2870, 1605, 1578, 1489, 1450, 1223, 1065, 752, 698 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.61** (UV)

6-methyl-4-*n*-octylChromane 50



50

Chromane **50** was prepared according to General Procedure A using 6-methylchromane (74 mg, 0.50 mmol, 1.0 equiv) and 1-bromooctane (95 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (100 % hexanes to 10 % EtOAc in hexanes) to provide compound **50** (1st run: 109 mg, 84 %; 2nd run: 108 mg, 83 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, *J* = 2.1 Hz, 1H), 6.88 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 4.20 – 4.08 (m, 2H), 2.73 (dq, *J* = 10.1, 5.2 Hz, 1H), 2.26 (s, 3H), 2.04 (dddd, *J* = 13.9, 8.3, 5.7, 4.1 Hz, 1H), 1.79 (dtd, *J* = 16.0, 5.3, 2.5 Hz, 2H), 1.59 – 1.22 (m, 13H), 0.94 – 0.83 (m, 3H).

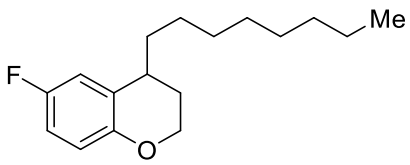
^{13}C NMR (101 MHz, $CDCl_3$): δ 152.4, 129.6, 129.3, 127.9, 126.7, 116.6, 63.6, 36.7, 33.7, 32.0, 29.9, 29.7, 29.5, 27.2, 27.1, 22.8, 20.8, 14.3.

HRMS: (APCI) calc. $C_{18}H_{29}O$ $[M+H]^+$: 261.2213. Found: 261.2213.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2924, 2855, 1616, 1585, 1499, 1465, 1230, 1037, 804, 737 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.90** (UV)

6-fluoro-4-octylchromane 51



51

Chromane **51** was prepared according to General Procedure B using 6-fluorochromane (76 mg, 0.50 mmol, 1.0 equiv) and 1-bromooctane (95 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (100 % hexanes to 5 % EtOAc in hexanes) to provide compound **51** (1st run: 116 mg, 88 %; 2nd run: 114 mg, 86 %) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3): δ 6.90 – 6.67 (m, 3H), 4.15 (qdd, *J* = 10.8, 7.2, 3.4 Hz, 2H), 2.76 (dq, *J* = 10.3, 5.3 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.79 (dddd, *J* = 14.7, 11.4, 7.4, 4.3 Hz, 2H), 1.62 – 1.21 (m, 13H), 0.91 (t, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, CDCl3): δ 158.1, 155.7, 150.7, 128.1, 128.1, 117.7, 117.6, 115.0, 114.8, 114.1, 113.9, 63.9, 36.4, 33.9, 32.0, 29.9, 29.7, 29.5, 27.0, 26.8, 22.8, 14.2.

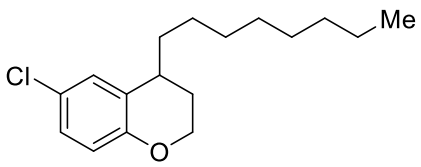
^{19}F NMR (470 MHz, CDCl3) δ –124.99.

HRMS: (APCI) calc. $C_{17}H_{25}FO$ $[M+H]^+$: 265.1962. Found: 265.1961.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2951, 2924, 2855, 1493, 1466, 1427, 1258, 1120, 934, 864, 810, 741, 729 cm^{-1}.

TLC (5 % EtOAc in hexanes): R_f **= 0.50** (UV)

6-chloro-4-octylchromane 52



52

Chromane **52** was prepared according to General Procedure B using 6-chlorochromane (69 µL, 0.50 mmol, 1.0 equiv) and 1-bromooctane (95 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified by flash-column chromatography on silica gel (100 % hexanes to 20 % EtOAc in hexanes) to provide compound **52** (1st run: 111 mg, 79 %; 2nd run: 118 mg, 84 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 – 6.95 (m, 2H), 6.71 (d, *J* = 8.6 Hz, 1H), 4.25 – 4.08 (m, 2H), 2.74 (dq, *J* = 10.2, 5.3 Hz, 1H), 2.03 (dddd, *J* = 13.8, 8.1, 5.7, 4.2 Hz, 1H), 1.85 – 1.69 (m, 2H), 1.58 – 1.21 (m, 14H), 0.92 – 0.81 (m, 3H).

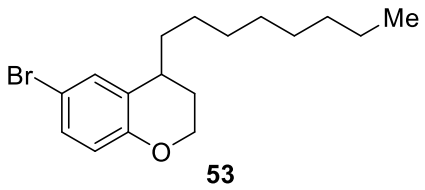
^{13}C NMR (101 MHz, $CDCl_3$): δ 153.3, 128.8, 128.6, 127.2, 124.9, 118.2, 63.9, 36.4, 33.8, 32.0, 29.9, 29.7, 29.5, 27.0, 26.6, 22.8, 14.3.

HRMS: (APCI) calc. $C_{17}H_{25}ClO$ $[M+H]^+$: 281.1662. Found: 281.1667.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2924, 2855, 1485, 1466, 1261, 1227, 876, 814 cm^{-1}.

TLC (20 % EtOAc in hexanes): R_f **= 0.89** (UV)

6-bromo-4-octylchromane 53



53

Chromane **53** was prepared according to General Procedure B using 6-chlorochromane (73 µL, 0.50 mmol, 1.0 equiv) and 1-bromooctane (95 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified via column chromatography on silica gel (10 % EtOAc in hexanes) to provide compound **53** as a mixture of isomers with dehalogenated products. The desired isomer was separated on preparatory HPLC (C18 Column, 99 % CH_3CN/1 % methanol). (1^{st} run: 40 mg, 25 %; 2^{nd} run: 41 mg, 26 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 2.4 Hz, 1H), 7.16 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 1H), 4.20 – 4.11 (m, 2H), 2.74 (dq, *J* = 10.2, 5.3 Hz, 1H), 2.02 (dddd, *J* = 13.9, 8.3, 5.7, 4.2 Hz, 1H), 1.82 – 1.71 (m, 2H), 1.54 – 1.39 (m, 2H), 1.39 – 1.23 (m, 11H), 0.89 (t, *J* = 6.8 Hz, 3H).

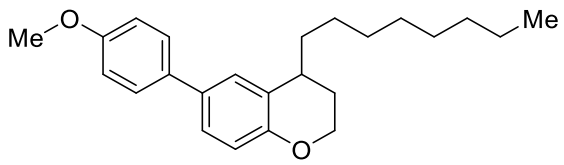
^{13}C NMR (101 MHz, $CDCl_3$): δ 153.8, 131.7, 130.1, 129.2, 118.7, 112.2, 63.8, 36.4, 33.7, 32.0, 29.8, 29.7, 29.4, 27.0, 26.5, 22.8, 14.3.

HRMS: (APCI) calc. $C_{27}H_{26}OBr$ $[M+H]^+$: 325.1162. Found: 325.0981.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2924, 2855, 1491, 1408, 1261, 1227, 1126, 814 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.74** (UV)

6-(4-methoxyphenyl)-4-octylchromane 54



54

Chromane **54** was prepared according to General Procedure B using 6-(4-methoxyphenyl)chromane (120.2 mg, 0.50 mmol, 1.0 equiv) and 1-bromooctane (95 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified via column chromatography on silica gel (50 % hexanes DCM) to provide compound **54** (100 mg, 57 %) as a crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.42 (m, 2H), 7.32 – 7.23 (m, 3H), 7.01 – 6.80 (m, 3H), 4.26 – 4.12 (m, 2H), 3.84 (s, 3H), 2.82 (dq, J = 10.2, 5.2 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.90 – 1.78 (m, 2H), 1.62 – 1.22 (m, 15H), 0.94 – 0.82 (m, 4H).

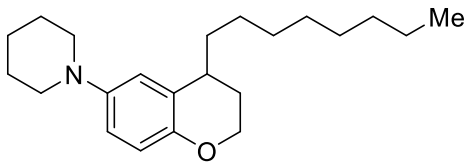
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7, 153.8, 134.1, 133.0, 127.9, 127.6, 127.2, 125.8, 117.2, 114.3, 63.8, 55.5, 36.7, 33.9, 32.0, 29.9, 29.7, 29.5, 27.2, 27.0s, 22.8, 14.3.

HRMS: (APCI) calc. $C_{24}H_{32}O_2$ $[M+H]^+$: 353.2472. Found: 353.2475.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2955, 2920, 2851, 1609, 1489, 1465, 1438, 1273, 1250, 1231, 118, 1134, 1088, 1042, 1018, 891, 810, 794, 764, 721 cm^{-1}.

TLC (50 % DCM in hexanes): R_f **= 0.67** (UV)

1-(4-octylchroman-6-yl)piperidine 55



55

Chromane **55** was prepared according to General Procedure B using 1-(chroman-6-yl)piperidine (108 mg, 0.50 mmol, 1.0 equiv) and 1-bromooctane (95 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified via column chromatography on silica gel (20 % EtOAc in hexanes) to provide compound **55** (1^{st} run: 138.3 mg, 84 %; 2^{nd} run: 147.2 mg, 89 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 – 6.68 (m, 3H), 4.19 – 4.05 (m, 2H), 3.04 – 2.96 (m, 4H), 2.73 (dq, J = 10.1, 5.2 Hz, 1H), 2.09 – 1.98 (m, 1H), 1.83 – 1.66 (m, 6H), 1.62 – 1.47 (m, 3H), 1.47 – 1.21 (m, 12H), 0.94 – 0.84 (m, 3H).

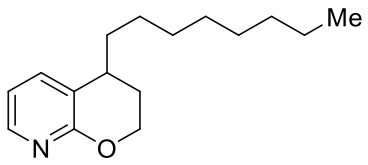
^{13}C NMR (101 MHz, $CDCl_3$): δ 148.7, 146.6, 127.1, 118.5, 117.5, 116.9, 63.6, 52.7, 36.7, 34.1, 32.0, 29.9, 29.7, 29.5, 27.2, 27.2, 26.4, 24.4, 22.8, 14.3.

HRMS: (APCI) calc. $C_{22}H_{35}NO$ $[M+H]^+$:3 30.2791. Found: 330.2782.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2924, 2853, 1497, 1219, 1134, 953, 808 cm^{-1}.

TLC (20 % EtOAc in hexanes): R_f **= 0.80** (UV)

4-octyl-3,4-dihydro-2H-pyrano[2,3-b]pyridine 56



56

Chromane **56** was prepared according to General Procedure B using 3,4-dihydro-2H-pyrano[2,3-b]pyridine (63 µL, 0.50 mmol, 1.0 equiv) and 1-bromooctane (95 µL, 0.55 mmol, 1.1 equiv). After standard work-up the residue was purified via column chromatography on silica gel (50 % EtOAc in hexanes) to provide compound **56** (1^{st} run: 61 mg, 49 %; 2^{nd} run: 64 mg, 52 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.46 (ddd, *J* = 7.4, 1.9, 0.9 Hz, 1H), 6.85 (dd, *J* = 7.4, 4.8 Hz, 1H), 4.42 – 4.25 (m, 2H), 2.80 (dq, *J* = 10.7, 5.5 Hz, 1H), 2.06 (dddd, *J* = 13.9, 8.3, 5.6, 3.9 Hz, 1H), 1.85 – 1.70 (m, 2H), 1.57 – 1.21 (m, 13H), 0.91 – 0.84 (m, 3H).

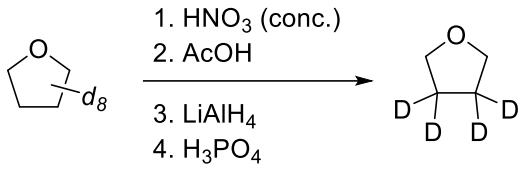
^{13}C NMR (101 MHz, $CDCl_3$): δ 161.1, 146.4, 138.1, 122.0, 117.2, 64.5, 35.9, 34.0, 32.0, 29.8, 29.7, 29.4, 27.0, 26.5, 22.8, 14.2.

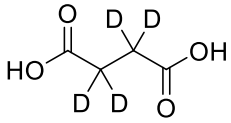
HRMS: (APCI) calc. $C_{16}H_{26}NO$ $[M+H]^+$: 248.2009. Found: 248.2006.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2916, 2851, 1578, 1472, 1429, 1275, 1231, 772 cm^{-1}.

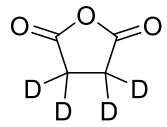
TLC (50 % EtOAc in hexanes): R_f **= 0.50** (UV)

2.6. Synthesis of THF-d_4

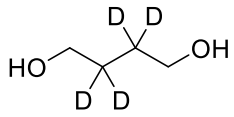




Step 1: A 125 mL Erlenmeyer flask was equipped with a magnetic stir bar and charged with HNO_3 (47.7 mL, 0.75 mol, 6.0 equiv). THF-d_8 (10.0 g, 125 mmol, 1.0 equiv) was then added in 0.50 mL portions once every 15 minutes. Each addition led to copious evolution of nitrogen oxides. The reaction has an initial induction period of ~ 10 minutes and additional THF should not be added until initiation is evident. After complete addition (ca 3 h) the flask was stirred for an additional 1 h. The mixture was cooled to 0 °C and held for 30 minutes. The white precipitate that formed was then filtered, washed with ice-water (2 x 10 mL), and dried under vacuum yielding the crude succinic acid-d_4 (9.27g, 60.8 %). This material was used without further purification.

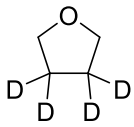


Step 2: A 50 mL round bottom flask was equipped with a magnetic stir bar and charged with the crude product from the first step. The flask was equipped with a reflux condenser (ice water). Acetyl chloride (16.27 ml, 228 mmol, 3.0 equiv) was added via syringe and the mixture bubbled vigorously. After the initial exotherm, the mixture was heated to 80 °C for 2 h. During this time, the succinic acid dissolved completely. The mixture was cooled to 0 °C, and the anhydride product crystallized from the mixture. The product was collected on a Büchner funnel and dried under vacuum to afford the crude product as a white solid (6.96 g, 88 %). This material was used without further purification.



Step 3: A 500 mL 3-neck flask was equipped with a magnetic stir bar and charge with $LiAlH_4$ (16 g, 400 mmol, 6.0 equiv, pellets). THF (300 mL) was added, and the mixture was stirred for 30 min as the pellets dissolved. The crude product from step 2 was then added in portions as a solid. The flask was equipped with a reflux condenser and heated to reflux overnight (ca 12 h). The mixture was cooled to 0 °C and water (16.0 mL) was added slowly over 1.5 h. A solution of NaOH (16.0 mL, 4 M) was added over 30 minutes followed by water (50 mL) over 15 minutes. The mixture was then

filtered through celite to remove the aluminum salts and washed with Et_2O (200 mL). The combined organic components were concentrated under vacuum to yield the crude 1,4-butanediol as a pale-yellow oil (5.3 g, 84 %). This material was used without further purification.



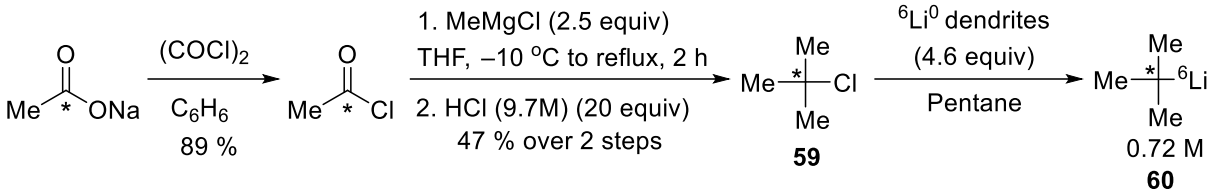
Step 4: A 25 mL round bottom flask was equipped with a magnetic stir bar, the crude butane diol, and phosphoric acid (1.6 mL, 26.7 mmol, 0.5 equiv). The flask was equipped with a short path distillation head and a preweighed receiving flask. The mixture was heated to 160 °C for 3 h at which point the distillation had stopped. 4.13 g of material was collected initially. NaK (ca 1 g) was added, and the product was transferred to a new flask with the aid of vacuum. The product was collected as a colorless liquid (2.18 g, 50 %). Spectral Data are in accordance with the literature.[4]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74.

^{2}H NMR (77 MHz, $CHCl_3$): δ 1.69.

2.7. Synthesis of Isotopically Enriched *tert*-Butyllithium

Synthesis of ^{13}C and ^{6}Li Labelled *tert*-butyllithium



59 **60**

Step 1 – Synthesis of acetyl chloride: An oven-dried, 250 ml 3-neck round bottom flask was placed under argon and charged with sodium acetate (99 % ^{13}C, 10.0g, 121 mmol, 1.0 equiv). The flask was equipped with a short-path distillation head and a 200 mL receiving flask. The condenser on the short-path was cooled with ice water and the receiving flask cooled to –78 °C in a dry-ice acetone bath to ensure full recovery of the product. Benzene (55 mL) was added *via* syringe and the flask was lowered into a water bath at rt to control the exotherm. Oxalyl chloride (11.5 mL, 128 mmol, 1.05 equiv) was added dropwise *via* syringe while stirring. Immediate evolution of gas was evident. The full addition took ca 15 min. After stirring at rt for 30 min the bubbling had slowed significantly. The reaction was heated to 70 °C for 1 h to ensure full conversion of the starting sodium acetate. The volatile components were then distilled at 110 °C. The contents of the receiving flask were analyzed by NMR as a neat solution. Analysis of this spectrum revealed 108 mmol (89 % yield) of acetyl chloride as a solution in benzene. This solution was used directly in the next step.

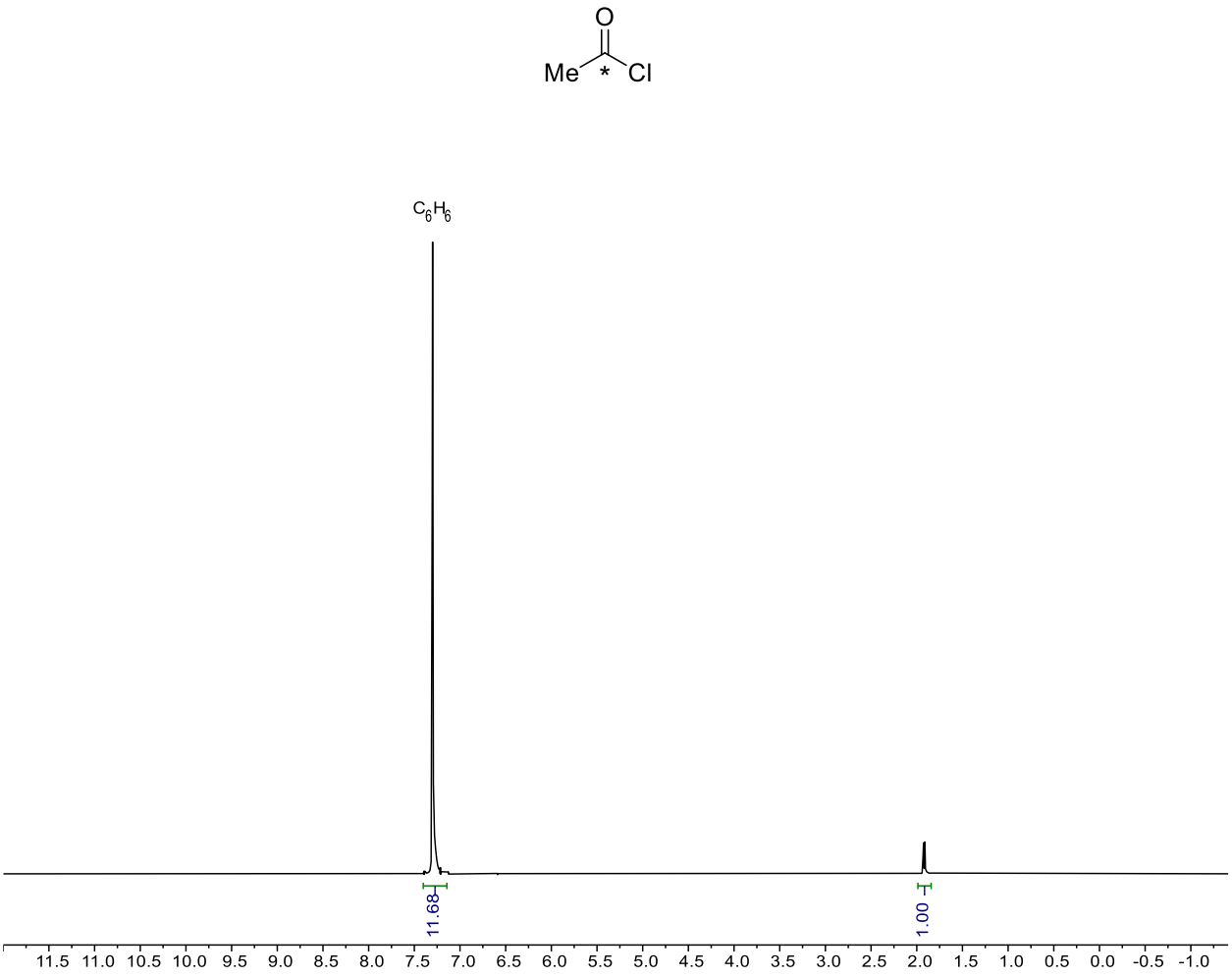


Figure S22. ^{1}H NMR spectrum of the acetyl chloride solution neat in benzene, referenced to C_6H_6 (7.30 ppm).

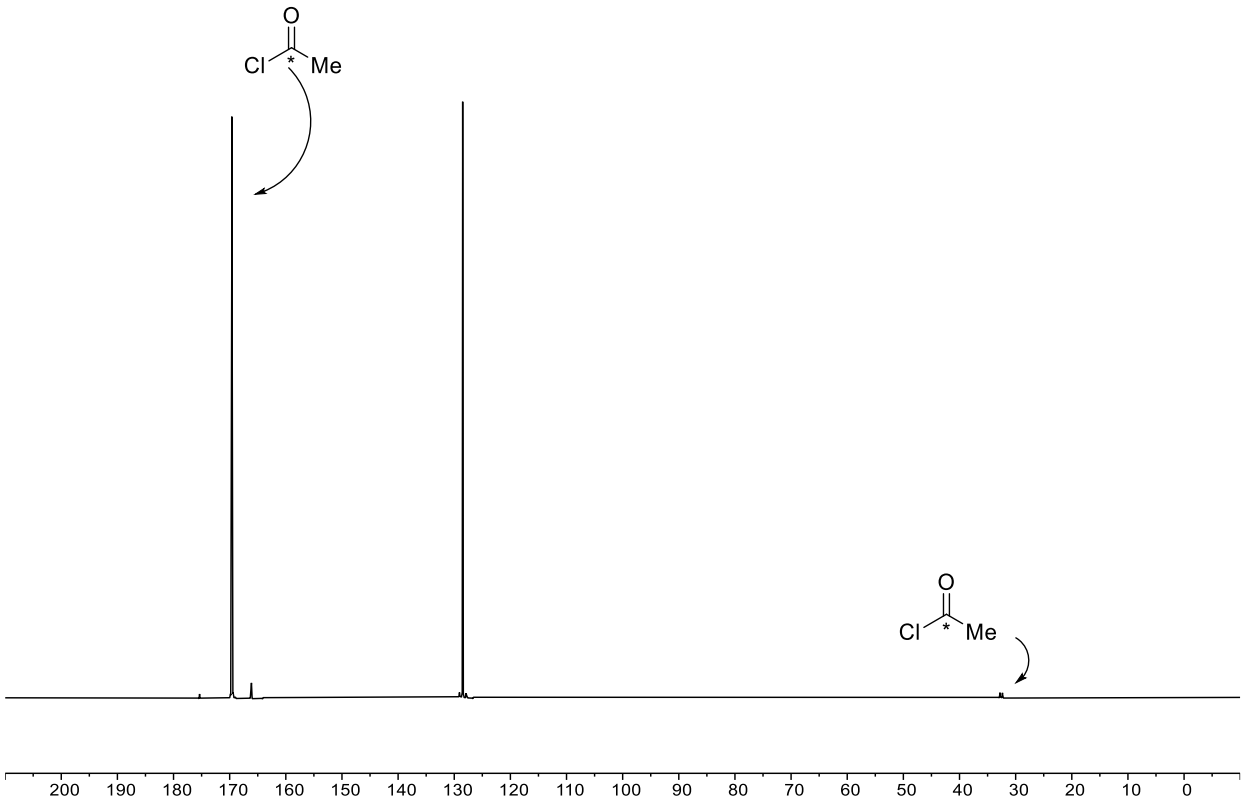
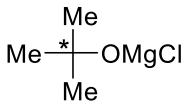
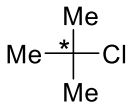


Figure S23. ^{13}C NMR spectrum of the acetyl chloride solution neat in benzene, referenced to C_6H_6 (128.50 ppm).



Step 2 – Synthesis of chloromagnesium tert-butoxide: An oven-dried 500 mL 3-neck flask was placed under argon and charged with methyl magnesium chloride solution (90 mL, 3.0 M in THF, 240 mmol, 2.22 equiv) and diluted with THF (150 mL). The flask was equipped with a reflux condenser, and the flask cooled to –10 °C. The acetyl chloride solution was then transferred in via cannula over the course of 30 min. As the addition proceeded, the solution became cloudy and began to reflux. After addition was completed, the solution was maintained at –10 °C until the reflux had concluded (ca 10 min). The mixture was then heated to reflux for 1 h. NMR of the neat solution at this time showed only the tert-butyl signal and ~ 10 % remaining Grignard reagent. This was deemed to be complete. The volatile components were then removed by rotary evaporation and subsequent heating to 100 °C under high vacuum for 2 h. The resulting white solid was used in the next step without further purification.



Step 3 – Synthesis of *t*-butyl chloride 59: The salts from the previous step were cooled to –10 °C and then hydrochloric acid (250 mL, 9.7 M, 20 equiv) was added. The addition was slow at first as any residual Grignard reagent was quenched and was accelerated after the first 30 mL were added. The salts were maintained at –10 °C until bubbling through an oil bubbler had slowed. The mixture was then cautiously heated to rt and the flask was equipped with a short path distillation head. The receiving flask was cooled to –78 °C and the flask was warmed to 90 °C. The flask was maintained at the final temperature for 30 min at which point all desired product had distilled. The material in the receiving flask was washed twice with cold water, dried with sodium sulfate and analyzed by NMR. To this material was added CaH_2 (2.0 g) and stirred overnight. Distillation of the product afforded the tert-butyl chloride (4.65 g, 47 % yield) at a suitable level of purity for the next step. Critically, this material contained ca 1 % of MTBE presumably from methanol form from an oxidation of the Grignard reagent. The MTBE is critical to the success of the subsequent step.

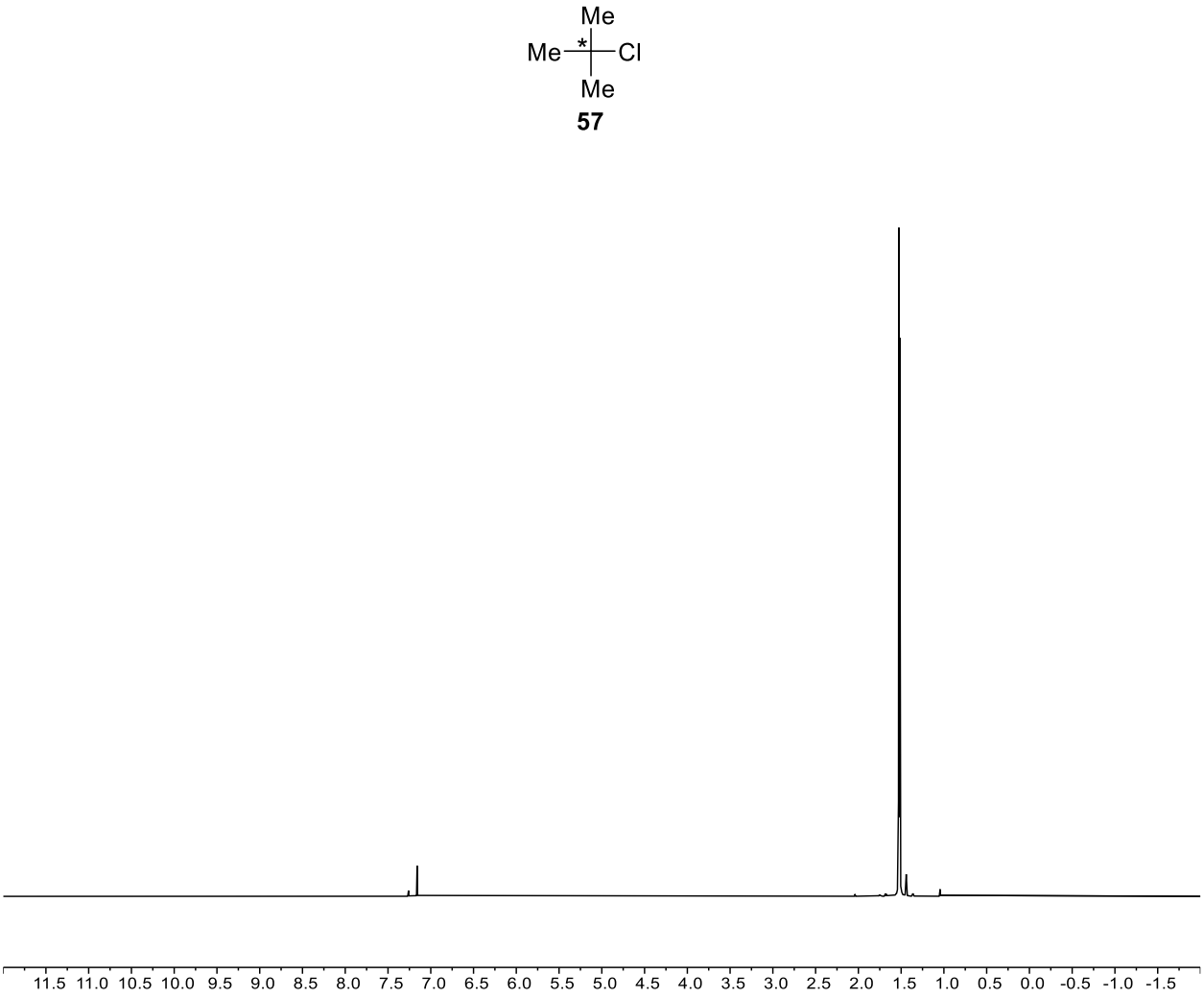
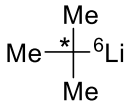
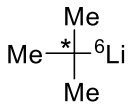


Figure S24. ^{1}H NMR spectrum of the *t*-BuCl in $CDCl_3$, referenced to $CDCl_3$ (7.26 ppm).



Step 4 – Synthesis of tert-butyl lithium 60: Prepared according to a recently developed protocol.[5] In the glovebox, a 50-mL Schlenk flask was equipped with a glass-coated stir bar, lithium (95% ^{6}Li, 276 mg, 45.6 mmol, 4.56 equiv), sodium (5.8 mg, 0.3 mmol, 0.03 equiv) and capped with a septum. The flask was removed from the glovebox and freshly condensed NH_3 (8.0 mL, 5 M) was added at –78 °C *via* cannula. After 5 min, the lithium bronze solution was warmed to rt over 20 min where ammonia ca 2 mL boiled off slowly. The vessel was placed under vacuum (0.05 torr) to remove the remainder of ammonia over 30 min providing lithium dendrites. The flask was backfilled with argon and the septum was removed briefly ca 10 s followed by carefully scraping the lithium dendrites off the walls to the bottom of the vessel with a metal spatula. Pentane (10 mL) was added *via* syringe. The labelled *tert*-butyl chloride (1.1 mL, 10 mmol, 1.0 equiv) was then added dropwise while stirring rapidly. After the first 200 µL of *tert*-butyl chloride were added, the addition was paused until the initiation was evident. The pentane quickly began to reflux, and the temperature was controlled by the rate of addition of the *tert*-butyl chloride. 1 h after the addition the purple/black heterogenous mixture was then withdrawn with a syringe and the remaining solids were washed with pentane (2 x 2.0 mL). The combined pentane solution was filtered through a Teflon syringe filter (PALL PN#4927, 25 mm, 0.2 µm). The resulting solution was titrated by modifying a known procedure by Gilman.[6]

A scintillon vial was charged with DI water (10 mL) and a magnetic stir bar followed by sparging with argon for 10 min. The vial was fitted with a septum and an aliquot of the organolithium reagent (0.50 mL) was added in one portion. The solution was titrated with standard acid (HCl, 0.242 M) using phenolphthalein as indicator (2-3 drops) to give the total base. A 5 mL flask was equipped with a magnetic stir bar, capped with a septum, and purged with argon. The flask was charged with diethyl ether (3.0 mL) and 1,2-dibromoethane (200 µL). An aliquot of organolithium reagent (0.50 mL) was added dropwise with vigorous stirring. After 5 min, DI water (2.0 mL) was added, and the solution was titrated with standard acid (HCl, 0.242 M) using phenolphthalein as indicator (2-3 drops) to give the residual base. The active base of the organolithium reagent was then calculated by subtracting the residual base from the total base. The final solution was determined to be 0.72 M in *tert*-butyllithium. This solution contained a small amount of the *tert*-butyl dimer ca 1 % by integration of the ^{13}C NMR.



58

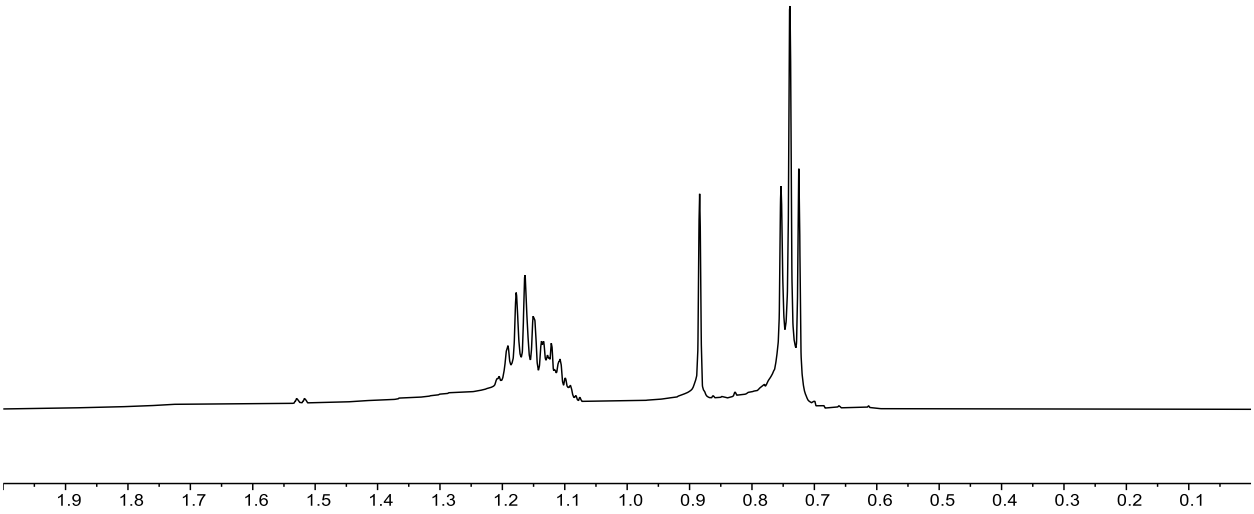
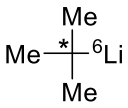


Figure S25. ^{1}H NMR spectrum of the *t*-BuLi in pentane, referenced to C*H*$_3$ of pentane (0.82 ppm).



60

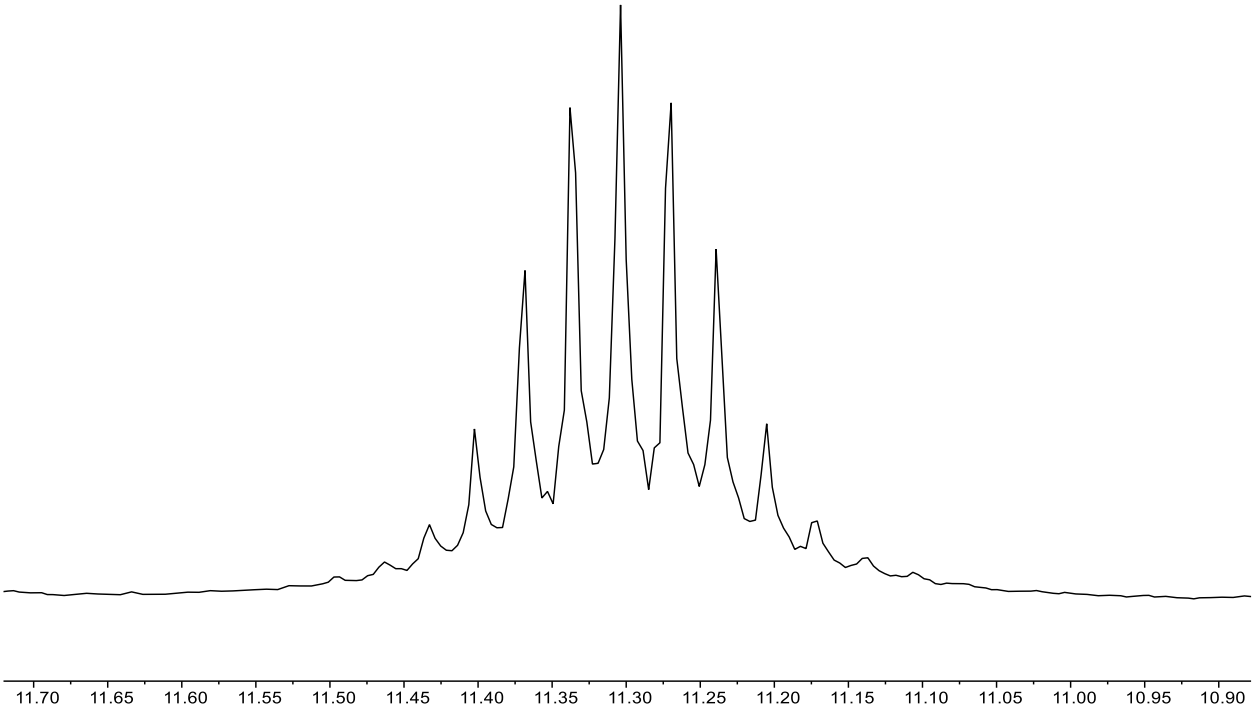
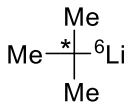


Figure S26. ^{13}C NMR spectrum of the *t*-BuLi in pentane zoomed on the Me_3CLi signal so that coupling to ^{6}Li can be observed, referenced to CH_3 of pentane (14.10 ppm).



60

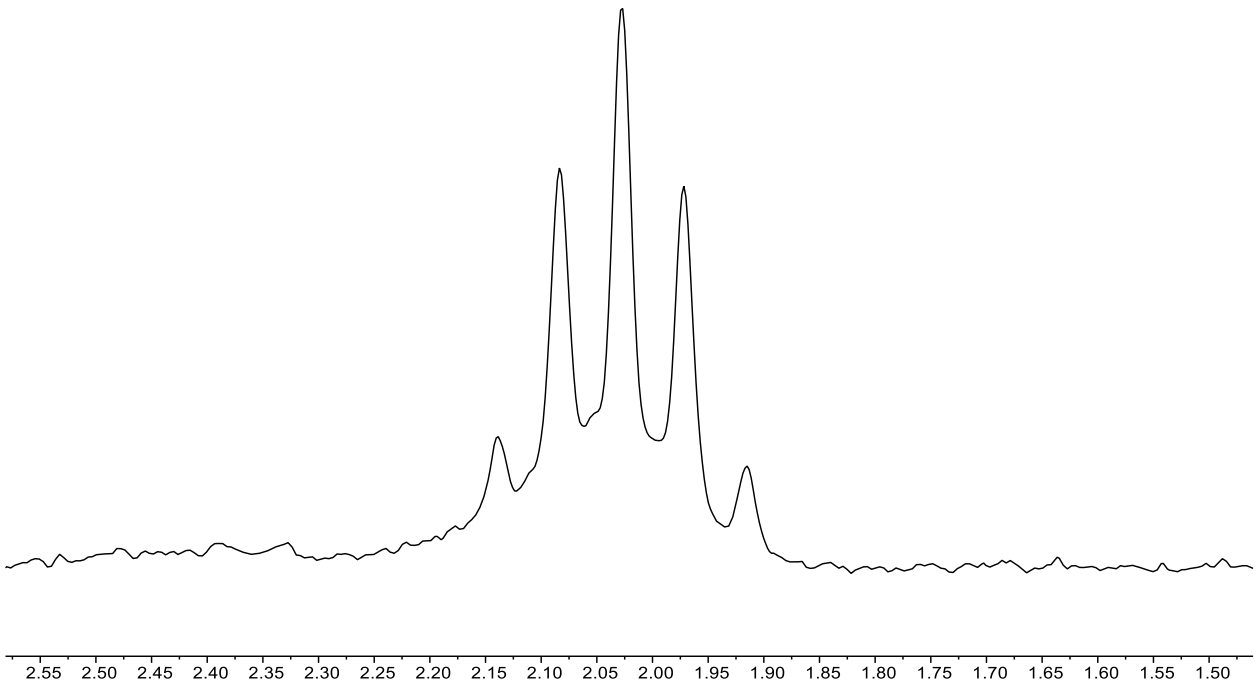
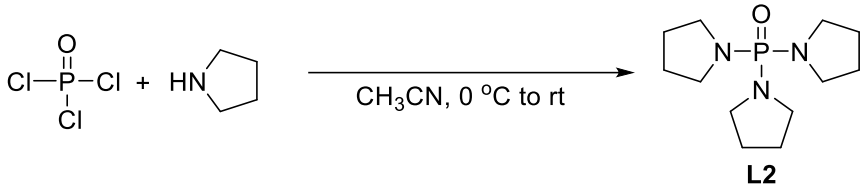


Figure S27. ^{6}Li spectrum of *t*-BuLi in pentane, referenced to external LiCl (0.5 M in THF, 0.0 ppm).

2.8. Synthesis of Starting Materials

Tris(pyrrolidine)phosphoramide (TPPA) L2



L2

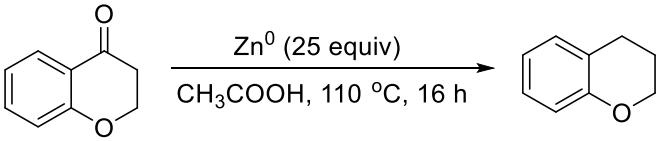
Prepared according to a literature procedure.[7]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.19 – 3.09 (m, 4H), 1.83 – 1.74 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 46.4 (d, J = 4.5 Hz), 26.5 (d, J = 8.1 Hz).

^{31}P NMR (202 MHz, $CDCl_3$) δ 15.58.

Chromane 29



1.0 equiv **29**

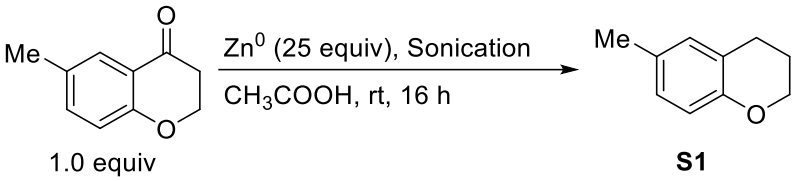
Prepared according to a literature procedure.[8]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 – 7.00 (m, 1H), 6.82 (dddd, J = 16.4, 8.3, 3.7, 1.4 Hz, 1H), 4.23 – 4.15 (m, 1H), 2.80 (td, J = 6.6, 2.1 Hz, 1H), 2.07 – 1.96 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 130.0, 127.3, 122.4, 120.2, 116.8, 66.6, 25.0, 22.5.

TLC (10 % EtOAc in hexanes): R_f **= 0.90** (UV)

6-methylchromane S1



1.0 equiv **S1**

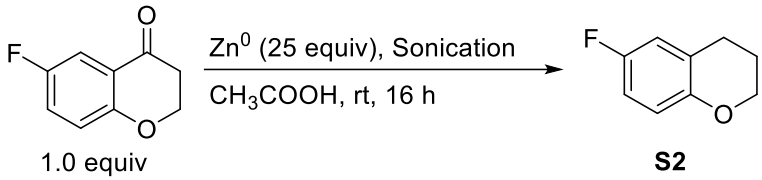
An oven dried 50 mL round bottom flask equipped with stir bar was charged with zinc powder (8.54 g, 125 mmol, 25 equiv), acetic acid (25 mL) and 6-methyl-4-chromanone (0.90 g, 5.5 mmol, 1.0 equiv). This mixture was then sonicated for 30 min at rt. The mixture was stirred at rt for 16 h at which point TLC indicated completion of the reaction. The mixture was poured onto a celite filter pad and rinsed with EtOAc (150 mL). The organic components were washed with sat. $NaHCO_3$ (4 x 150 mL), water (150 mL) and brine (150 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude products were purified by flash-column chromatography on silica gel (10 % EtOAc in hexanes) to afford the desired product **S1** (756 mg, 93 %). Spectral data matched previously reported values.[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 – 6.82 (m, 2H), 6.69 (d, *J* = 8.2 Hz, 1H), 4.20 – 4.12 (m, 2H), 2.76 (t, *J* = 6.5 Hz, 2H), 2.25 (s, 3H), 1.99 (dt, *J* = 10.5, 6.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.8, 130.3, 129.4, 127.9, 122.0, 116.6, 66.5, 25.0, 22.7, 20.6.

TLC (10 % EtOAc in hexanes): R_f **= 0.90** (UV)

6-fluorochromane S2



1.0 equiv **S2**

An oven dried 50 mL round bottom flask equipped with stir bar was charged with zinc powder (8.58 g, 135 mmol, 25 equiv), acetic acid (25 mL) and 6-fluoro-4-chromanone (0.90 g, 5.4 mmol, 1.0 equiv). This mixture was then sonicated for 30 min at rt. The mixture was stirred at rt for 16 h at which point TLC indicated completion of the reaction. The mixture was poured onto a celite filter pad and rinsed with EtOAc (150 mL). The organic components were washed with sat. $NaHCO_3$ (4 x 150 mL), water (150 mL) and brine (150 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude products were purified by flash-column chromatography on silica gel (10 % EtOAc in hexanes) to afford the desired product **S2** as a colorless oil (601 mg, 73 %). Spectral data matched previously reported values.[9]

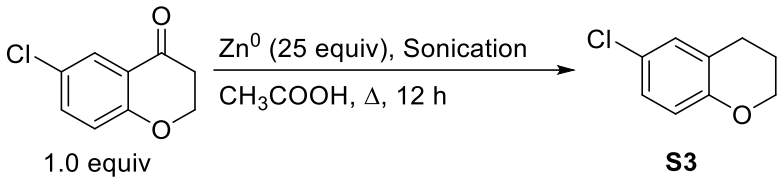
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 – 6.64 (m, 3H), 4.20 – 4.08 (m, 2H), 2.77 (t, *J* = 6.5 Hz, 2H), 1.99 (dt, *J* = 11.6, 6.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.8 (d, *J* = 237.5 Hz), 151.0 (d, *J* = 2.0 Hz), 123.4 (d, *J* = 7.3 Hz), 117.6 (d, *J* = 8.0 Hz), 115.7 (d, *J* = 22.5 Hz), 114.0 (d, *J* = 23.1 Hz), 66.5, 25.2, 22.2.

^{19}F NMR (377 MHz, CDCl3): δ –124.73.

TLC (10 % EtOAc in hexanes): R_f **= 0.90** (UV)

6-chlorochromane S3



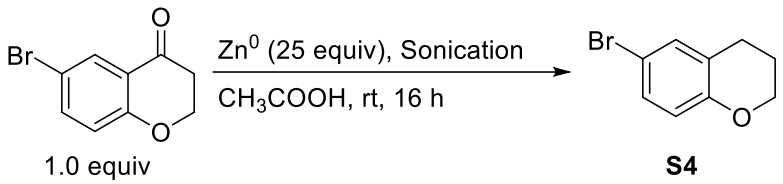
An oven dried 50 mL round bottom flask equipped with stir bar was charged with zinc powder (11.75 g, 123 mmol, 25 equiv), acetic acid (40 mL) and 6-chloro-4-chromanone (0.90 g, 4.93 mmol, 1.0 equiv). This mixture was then sonicated for 30 min at rt. The mixture was heated to reflux for 12 h at which point TLC indicated completion of the reaction. The mixture was poured onto a celite filter pad and rinsed with EtOAc (150 mL). The organic components were washed with sat. $NaHCO_3$ (4 x 150 mL), water (150 mL) and brine (150 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude products were purified by flash-column chromatography on silica gel (10 % EtOAc in hexanes) to afford the desired product **S3** as a colorless oil (677 mg, 81 %). Spectral data matched previously reported values.[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (m, 2H), 6.71 (d, *J* = 7.9 Hz, 1H), 4.19 – 4.13 (m, 2H), 2.76 (t, *J* = 6.5 Hz, 2H), 2.03 – 1.94 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 153.7, 129.4, 127.3, 124.8, 123.9, 118.1, 66.6, 24.9, 22.1.

TLC (10 % EtOAc in hexanes): R_f **= 0.90** (UV)

6-bromochromane S4



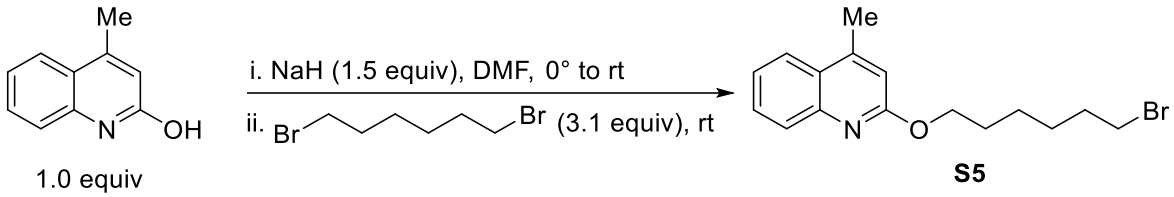
An oven dried 50 mL round bottom flask equipped with stir bar was charged with zinc powder (8.54 g, 125 mmol, 25 equiv), acetic acid (25 mL) and 6-bromo-4-chromanone (1.14 g, 5 mmol, 1.0 equiv). This mixture was then sonicated for 30 min at rt. The mixture was stirred at rt for 16 h at which point TLC indicated completion of the reaction. The mixture was poured onto a celite filter pad and rinsed with EtOAc (150 mL). The organic components were washed with sat. $NaHCO_3$ (4 x 150 mL), water (150 mL) and brine (150 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude products were purified by flash-column chromatography on silica gel (10 % EtOAc in hexanes) to afford the desired product **S4** (879 mg, 83 %). Spectral data matched previous reports.[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 – 7.13 (m, 2H), 6.69 – 6.65 (m, 1H), 4.19 – 4.13 (m, 2H), 2.76 (t, *J* = 6.5 Hz, 2H), 2.03 – 1.94 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.2, 132.4, 130.2, 124.5, 118.6, 112.2, 66.6, 24.9, 22.1.

TLC (10 % EtOAc in hexanes): R_f **= 0.90** (UV)

2-((6-bromohexyl)oxy)-4-methylquinoline S5



A 500 mL round bottom flask was placed under nitrogen, lowered into an ice water bath, and charged with NaH (940 mg, 39.2 mmol, 1.5 equiv) and DMF (100 mL). The flask was removed from the ice bath and 4-methylquinolin-2-ol (4.188 g, 26.3 mmol, 1.0 equiv) was added dropwise as a solution in DMF (30 mL). after 45 min, neat 1,6-dibromohexane (12.72 mL, 82.7 mmol, 3.1 equiv) was added *via* syringe. After 90 min, the mixture was poured into DCM (140 mL) and the organic components were washed with saturated aqueous $NaHCO_3$ (140 mL). The organic layer was separated and washed with a 50:50 solution saturated NaCl and water (3 x 140 mL). The combined organic extract was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The resulting clear, colorless oil was further dried (1 torr, 80 °C) to remove residual 1,6-dibromohexane. The remaining oil was purified via column chromatography on silica gel (gradient from 1 % EtOAc in hexanes to 50 % EtOAc in hexanes). The resulting almost pure oil was recrystallized from hexanes to provide compound **S5** (2.268 g, 27 %) as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): 7.89 – 7.79 (m, 2H), 7.60 (ddd, *J* = 8, 7, 1 Hz, 1H), 7.38 (ddd, *J* = 8, 7, 1 Hz, 1H), 6.75 (d, *J* = 1 Hz, 1H), 4.46 (t, *J* = 7 Hz, 2H), 3.43 (t, *J* = 7 Hz, 2H), 2.62 (d, *J* = 1 Hz, 3H), 1.96 – 1.78 (m, 4H), 1.62 – 1.47 (m, 4H).

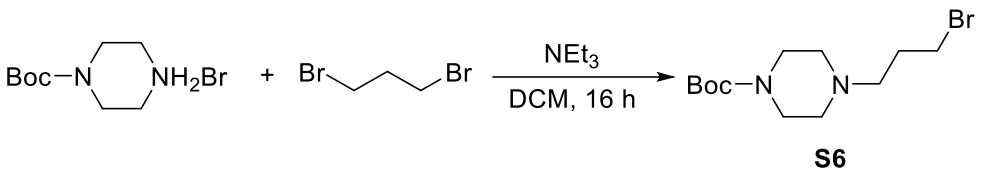
^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2, 146.8, 146.8, 129.3, 127.8, 125.5, 123.8, 123.8, 113.3, 65.5, 34.0, 32.9, 29.0, 28.1, 25.5, 18.8.

HRMS: (+ESI) calc. $C_{16}H_{20}ONBr$ $[M+H]^+$: 322.0801. Found: 322.0795.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2961, 2945, 2862, 1611, 1570, 1514, 1466, 1450, 1435, 1429, 1404, 1379, 1369, 1348, 1337, 1329, 1306, 1290, 1271, 1236, 1190, 1155, 1132, 1125, 1059, 11041, 1022, 1014, 1006, 981, 962, 939, 866, 852, 732 cm^{-1}.

TLC (5 % EtOAc in hexanes): R_f **= 0.61** (UV)

tert-butyl 4-(3-bromopropyl)piperazine-1-carboxylate S6



S6

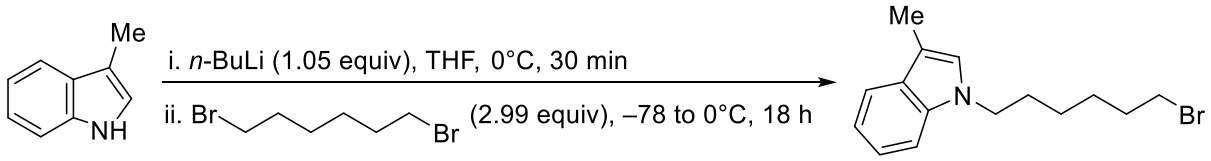
Prepared according to a literature procedure.[12]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 (t, *J* = 6.6 Hz, 2H), 3.41 (t, *J* = 5.1 Hz, 4H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.37 (t, *J* = 5.1 Hz, 4H), 2.02 (p, *J* = 6.7 Hz, 2H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 79.8, 56.6, 53.2, 31.8, 30.0, 28.6.

TLC (20 % EtOAc in hexanes): R_f **= 0.33** ($KMnO_4$)

1-(6-bromohexyl)-3-methyl-1H-indole S7



1.0 equiv

S7

A flame dried, 100 mL round bottom flask was placed under nitrogen and charged with a stir bar, 3-methyl-1H-indole (1.005 g, 7.66 mmol, 1.0 equiv) and freshly distilled (Na/Ph_2CO) THF (47 mL). The flask was placed in an ice bath. After 5 min, *n*-BuLi (2.81 mL, 8.01 mmol, 1.05 equiv, 2.85 M) was added dropwise. After 30 min, flask was transferred to a dry ice/acetone bath and chilled to an external temperature of –78 °C. The neat 1,6-dibromopropane (3.67 mL, 22.9 mmol, 2.99 equiv) was added dropwise *via* syringe. The flask was returned to the ice bath and allowed to warm to rt over 18 h. DI water (2 mL) was added, and the volatile components were removed *in vacuo*. The resulting residue was suspended in water and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica gel (100 % hexanes to 5 % EtOAc in hexanes). 1.65 g of material was recovered which contained 1,6-bis(3-methyl-1H-indol-1-yl)hexane (5 mol%) as an impurity.

Analytically pure samples were prepared by preparatory HPLC (Agilent 5 Prep-C18 50 x 50.0 mm (L x ID), 1 % methanol in acetonitrile, flow rate: 40 mL/min) to give 1-(6-bromohexyl)-3-methyl-1H-indole **S7** as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8 Hz, 1H), 7.31 (dt, *J* = 8 Hz, 1H), 7.28 (s, 1H), 7.22 (ddd, *J* = 8, 7, Hz, 1H), 7.12 (ddd, *J* = 8, 7 Hz, 1H), 6.88 (d, *J* = 1 Hz, 1H), 4.09 (t, *J* = 7 Hz, 2H), 3.40 (t, *J* = 7 Hz, 2H), 2.35 (d, *J* = 1 Hz, 3H), 1.91 – 1.79 (m, 4H), 1.55 – 1.43 (m, 2H), 1.43 – 1.26 (m, 2H).

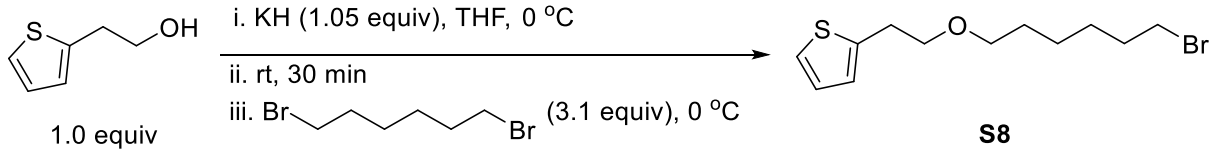
^{13}C NMR (101 MHz, $CDCl_3$): δ 136.4, 128.8, 125.5, 121.4, 119.2, 118.6, 110.3, 109.2, 46.0, 33.9, 32.7, 30.3, 27.9, 26.3, 9.7.

HRMS: (APCI) calc. $C_{15}H_{20}BrN$ $[M+H]^+$: 294.0852, Found: 294.0845.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 2932, 2859, 1481, 1466, 1385, 1360, 1331, 1263, 1244, 1196, 1161, 1013, 791, 730 cm^{-1}.

TLC (5 % EtOAc in hexanes): R_f = **0.61** (UV)

2-(2-((6-bromohexyl)oxy)ethyl)thiophene S8



A flame dried, 100 mL round bottom flask was placed under nitrogen and charged with KH (164.0 mg, 4.10 mmol, 1.05 equiv), and freshly distilled (NaK) THF (20 mL). The flask was lowered into an ice bath and 2-(thiophen-2-yl)ethan-1-ol (435.0 µL, 3.913 mmol, 1.0 equiv) was added dropwise *via* syringe. The flask was removed from the ice bath and allowed to warm to rt over 30 min. The flask placed into an ice bath and 1,6-dibromohexane (1.24 mL, 12.21 mmol, 3.1 equiv) was added in one portion. The flask was allowed to warm to rt over 8 h. The mixture was poured into water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica gel (100 % hexanes to

20 % EtOAc in hexanes). The resulting oil was purified further by bulb-to-bulb distillation to provide **S8** (333 mg, 29 %) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3): 7.14 (dd, *J* = 5, 1 Hz, 1H), 6.93 (dd, *J* = 5, 3 Hz, 1H), 6.84 (dq, *J* = 3.3, 1 Hz, 1H), 3.65 (t, *J* = 7 Hz, 2H), 3.43 (dt, *J* = 22, 7 Hz, 4H), 3.09 (td, *J* = 7, 1 Hz, 2H), 1.92 – 1.81 (m, 2H), 1.66 – 1.53 (m, 2H), 1.52 – 1.32 (m, 4H).

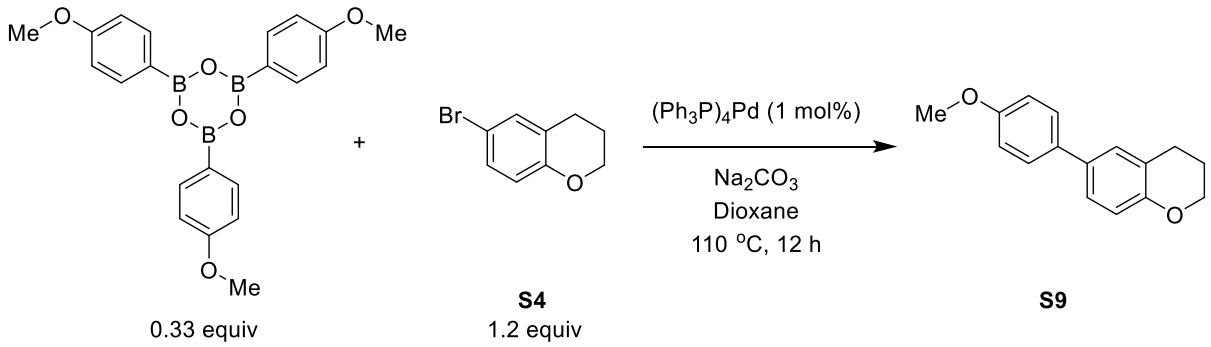
^{13}C NMR (101 MHz, CDCl3): δ 141.6, 126.8, 125.2, 123.7, 71.6, 71.0, 34.0, 32.9, 30.7, 29.6, 28.1, 25.5.

HRMS: (+APCl) calc. $C_{12}H_{19}BrOS$ $[M+H]^+$: 291.0413. Found: 291.0408.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 3071, 2932, 2859, 2793, 1458, 1439, 1358, 1323, 1300, 1261, 1242, 1204, 1111, 1057, 1049, 849, 826, 694, 644, 559, 505, 455 cm^{-1}.

TLC (20 % EtOAc in hexanes): R_f **= 0.90** (UV)

6-(4-methoxyphenyl)chromane S9



An oven dried 50-mL round bottom flask was placed under nitrogen and charged with tris(4-methoxyphenyl)boroxine (334.8 mg, 0.833 mmol, 0.33 equiv), and bis(tri-tert-butylphosphine)palladium (12.8 mg, 0.025 mmol, 1 mol%). Anhydrous dioxane (18 mL) was added *via* syringe. Sodium carbonate (1.908 g, 18 mmol, 18 equiv) was dissolved in degassed water (9.0 mL) and the solution was added in one portion. 6-bromochromane, **S4**, (639 mg, 3.0 mmol, 1.0 equiv) was added quickly to the flask *via* syringe. The flask was equipped with a reflux condenser and the flask was heated to 150 °C for 16 h until the starting material was consumed as determined by GC-MS. The reaction was cooled to rt and pouring into a separatory funnel containing ethyl acetate (50 mL) and 1 M HCl (50 mL). The layers were separated and

the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica gel (100 % hexanes to 10 % EtOAc in hexanes) to provide compound **S9** as a white crystalline solid (415 mg, 69 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.41 (m, 2H), 7.30 – 7.18 (m, 2H), 6.98 – 6.90 (m, 2H), 6.84 (d, J = 8.4 Hz, 1H), 4.27 – 4.14 (m, 2H), 3.84 (s, 3H), 2.85 (t, J = 6.5 Hz, 2H), 2.09 – 1.99 (m, 2H).

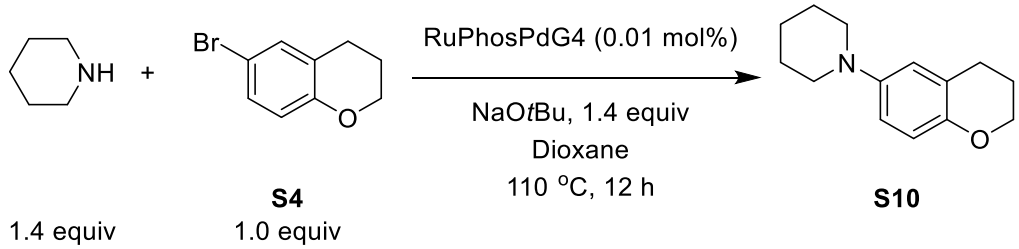
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7, 154.2, 133.7, 133.0, 128.1, 127.7, 125.7, 122.4, 117.1, 114.2, 66.6, 55.4, 25.1, 22.5.

HRMS: (APCI) calc. $C_{16}H_{16}O_2$ $[M+H]^+$: 241.1223 Found: 241.1223.

IR: (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$: 1605, 1489, 1466, 1443, 1431, 1273, 1231, 1188, 1134, 1065, 1038, 1022, 1003, 899, 880, 791, 745 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.16** (UV)

1-(chroman-6-yl)piperidine S10



In an argon atmosphere glovebox, a scintillation vial was charged with a stir bar, sodium *tert*-butoxide (336 mg, 3.5 mmol, 1.4 equiv), and RuPhosPdG4 (2 mg, 0.002 mmol, 0.01 mol%). The vial was capped with a Teflon cap and removed from the glovebox. Dioxane (Sigma, anhydrous, 2.0 mL), 6-bromochromane, **S4**, (363 µL, 2.5 mmol, 1.0 equiv), and piperidine (345 µL, 3.5 mmol, 1.4 equiv) were each added *via* syringe. The mixture was heated to 110 °C for 12 h at which time GC/MS indicated completion of the reaction. The mixture was poured into water (10 mL) and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The

resulting residue was purified via column chromatography on silica gel (10 % EtOAc in hexanes to 20 % EtOAc in hexanes) to provide compound **S10** (280 mg, 52 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 – 6.69 (m, 2H), 6.65 (d, *J* = 2.8 Hz, 1H), 4.17 – 4.10 (m, 2H), 3.03 – 2.96 (m, 4H), 2.76 (t, *J* = 6.5 Hz, 2H), 2.03 – 1.93 (m, 2H), 1.71 (p, *J* = 5.7 Hz, 4H), 1.53 (dtd, *J* = 9.0, 5.3, 2.2 Hz, 2H).

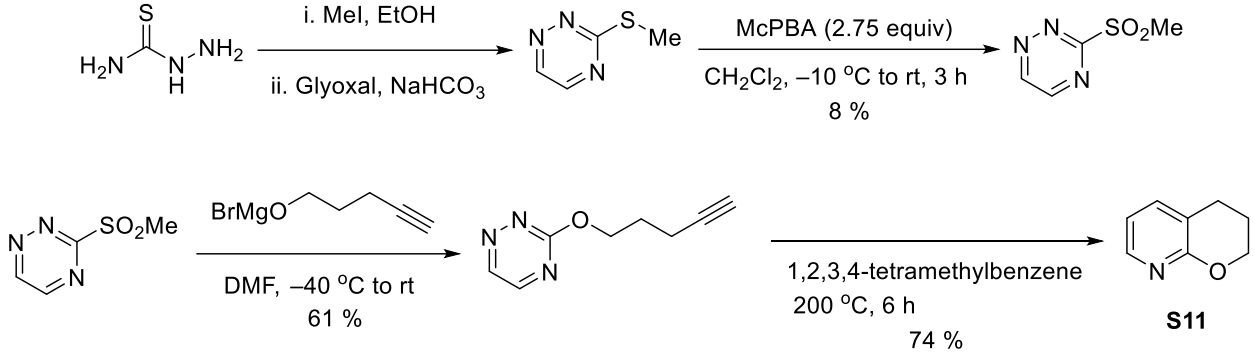
^{13}C NMR (101 MHz, $CDCl_3$): δ 149.0, 146.6, 122.3, 118.9, 117.6, 117.0, 66.5, 52.6, 26.3, 25.4, 24.4, 22.8.

HRMS: (APCI) calc. $C_{14}H_{20}NO$ $[M+H]^+$: 218.1539 Found: 218.1536.

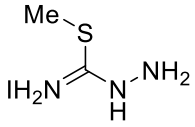
IR:(Diamond-ATR, neat):$\tilde{\upsilon}_{max}$:2926, 1497, 1445, 1223, 1200, 1059, 1001, 953, 881, 745 cm^{-1}.

TLC (10 % EtOAc in hexanes): R_f **= 0.34** (UV)

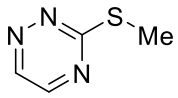
3,4-dihydro-2H-pyrano[2,3-b]pyridine S11



3,4-dihydro-2H-pyrano[2,3-b]pyridine was prepared according to a 5-step procedure that has been published previously.[1314]

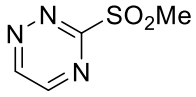


Step 1: Synthesis of S-methylthiosemicarbazide HI salt: Prepared according to a modified literature procedure. A 100 mL round bottom flask was charged with thiosemicarbazide (4.56 g, 50 mmol, 1.0 equiv), ethanol (50 mL), and methyl iodide (3.1 mL , 50 mmol, 1.0 equiv). The mixture was heated to reflux for 3 h. The mixture was cooled and the resulting dense white precipitate was filtered, washed with cold ethanol (2 x 10 mL), and dried. The solid (11.3 g, 97 %) was used without further purification.



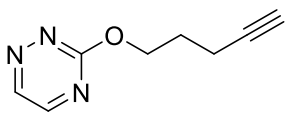
Step 2: Synthesis of 3-(methylthio)-1,2,4-triazine: Prepared according to a modified literature procedure. A 500 mL round bottom flask was charged with S-methylthiosemicarbazide HI salt (11.3 g, 48.5 mmol, 1.0 equiv), sodium bicarbonate (8.1 g, 97 mmol, 2.0 equiv), a stir bar, and ice water (300 mL). A solution of glyoxal (11.1 mL, 40 % aqueous, 97 mmol, 2.0 equiv) was added and the mixture was maintained at 0 °C for 5 h. The mixture was poured into a separatory funnel and extracted with chloroform (5 x 150 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. This provided the desired 3-(methylthio)-1,2,4-triazine as a yellow oil (5.2 g, 84 %) that solidified on standing.

Spectral data matched the previously reported values.[11]



Step 3: Synthesis of 3-(methylsulfonyl)-1,2,4-triazine: Prepared according to a modified literature procedure. A 500 mL round bottom flask was charged with a stir bar, 3-(methylthio)-1,2,4-triazine (5.0 g, 39.3 mmol, 1.0 equiv), and dichloromethane (30 ml). The flask was equipped with an addition funnel and placed under nitrogen. A 300 mL beaker was charged with McPBA (25 g, 75 %, 108 mmol, 2.75 equiv), $MgSO_4$ (20 g), and dichloromethane (200 mL). This solution was stirred for 15 min before being transferred into the addition funnel. The flask was cooled to –10 °C and the McPBA solution was added over the course of 1 h. The flask was warmed to rt and stirring was continued for 3 h. The resulting solution was filtered through a sintered glass frit, rinsed with dichloromethane (50 mL), and concentrated *in vacuo*. The residue was suspended on silica gel (20 g) and loaded directly onto a silica gel column and the product was eluted with 75 % EtOAc in hexanes. This provided the desired 3-(methylsulfonyl)-1,2,4-triazine as a white solid (474 mg, 8 %).

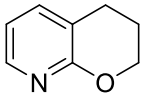
Spectral data matched the previously reported values.[11]



Step 4: Synthesis of 3-(pent-4-yn-1-yloxy)-1,2,4-triazine: Prepared according to a modified literature procedure. A 10 mL round bottom flask was charged with a stir bar, diethyl ether (3.0 mL), and MeMgBr (1.03 mL, 3.0 M, 3.1 mmol, 1.04 equiv). The mixture was cooled to –10 °C and the neat 4-pentynol (381 µL, 4.1 mmol, 1.37 equiv) was added dropwise. The flask was warmed to rt and the mixture was stirred for 45 min. The solution was then concentrated *in vacuo* to obtain a

foamy semisolid. DMF (3.0 mL) was added *via* syringe and the mixture was cooled to –40 °C. 3-(methylsulfonyl)-1,2,4-triazine (474 mg, 2.98 mmol, 1.0 equiv) was added and the mixture was allowed to warm to rt. After 4 h, TLC indicated full conversion of the starting material. The mixture was concentrated *in vacuo* and dissolved in water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified on silica gel to obtain the product as a colorless oil (300 mg, 61 %).

Spectral data matched the previously reported values.[12]



S11

Step 5: Synthesis of 3,4-dihydro-2H-pyrano[2,3-b]pyridine S11: Prepared according to a modified literature procedure. A 25 mL round bottom flask was charged with a stir bar, 3-(pent-4-yn-1-yloxy)-1,2,4-triazine (300 mg, 1.8 mmol, 1.0 equiv) and 1,2,3,4-tetramethylbenzene (10 mL). The flask was lowered into a preheated oil bath at 200 °C and monitored by TLC. After 6 h the reaction was complete and the entire mixture was purified by column chromatography on silica gel (10 % ethyl acetate in hexanes to 75 % ethyl acetate in hexanes) to afford the product as a colorless semisolid **S11** (180 mg, 74 %).

Spectral data matched the previously reported values.[12]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 4.9 Hz, 1H), 7.38 (d, J = 7.1 Hz, 1H), 6.83 (t, J = 6.4 Hz, 1H), 4.35 (t, J = 5.2 Hz, 2H), 2.81 (t, J = 6.5 Hz, 2H), 2.02 (p, J = 5.9 Hz, 2H).

TLC (50 % EtOAc in hexanes): R_f **= 0.45** (UV)

2.9. Substrates that did not work.

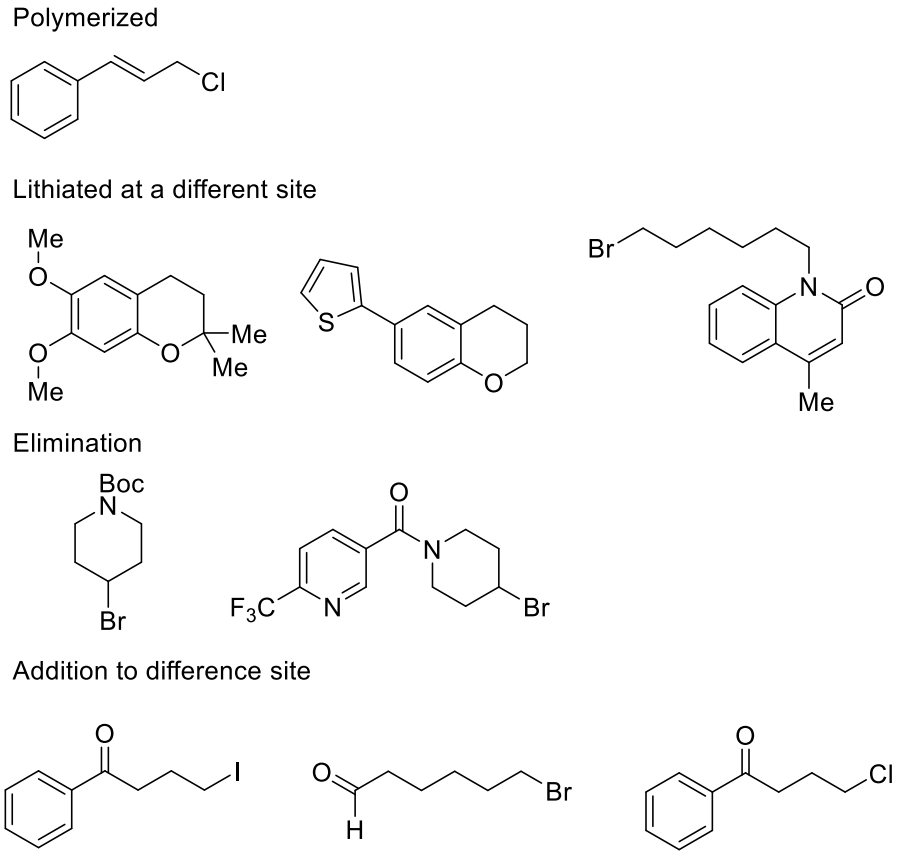
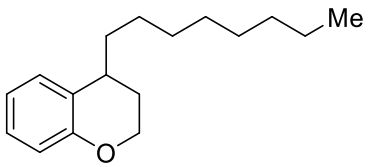


Figure S28. Substrates that did not work and a general reason for why they did not work.

3. NMR Spectra



33

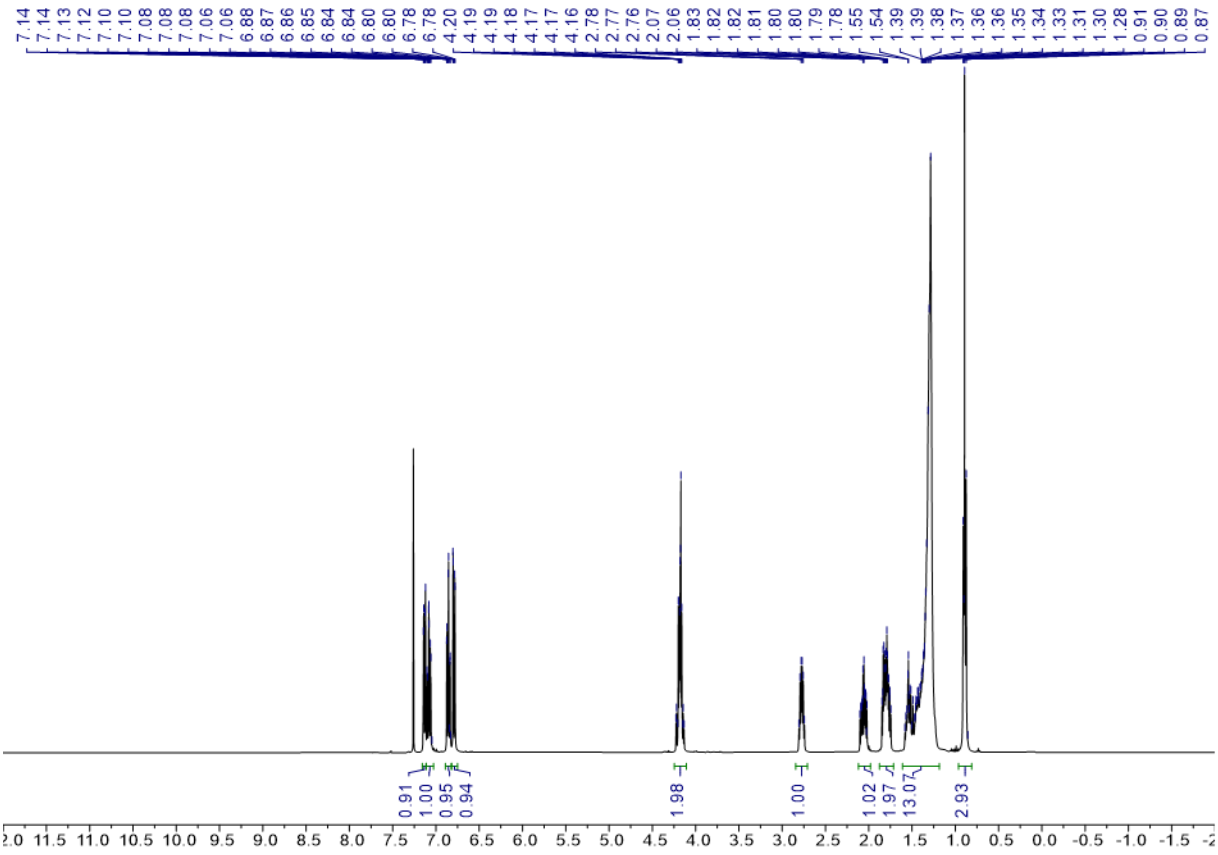


Figure S29. ^{1}H NMR spectrum of **33**, referenced to $CDCl_3$ (7.26 ppm).

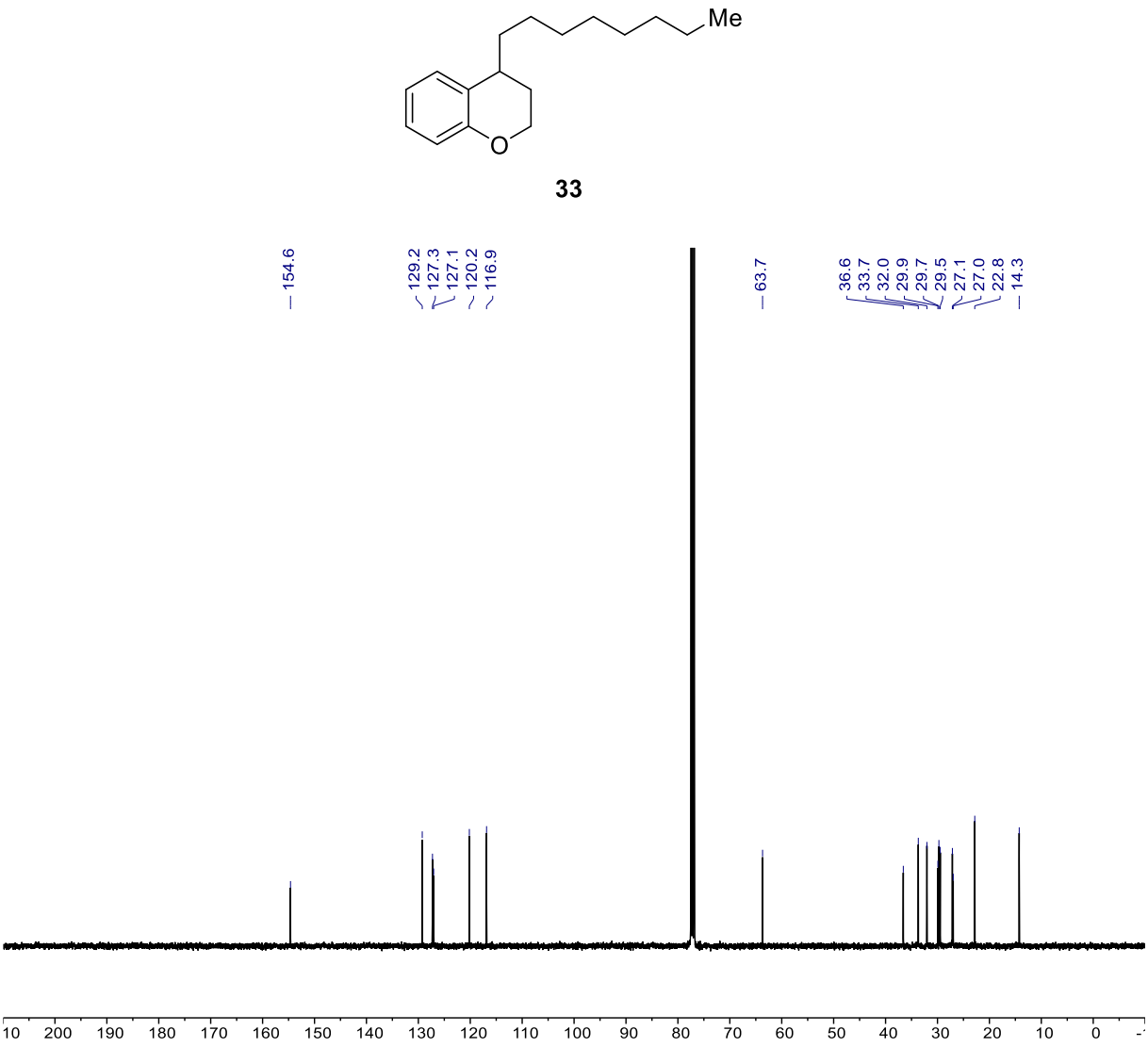


Figure S30. ^{13}C NMR spectrum of **33**, referenced to $CDCl_3$ (77.16 ppm).

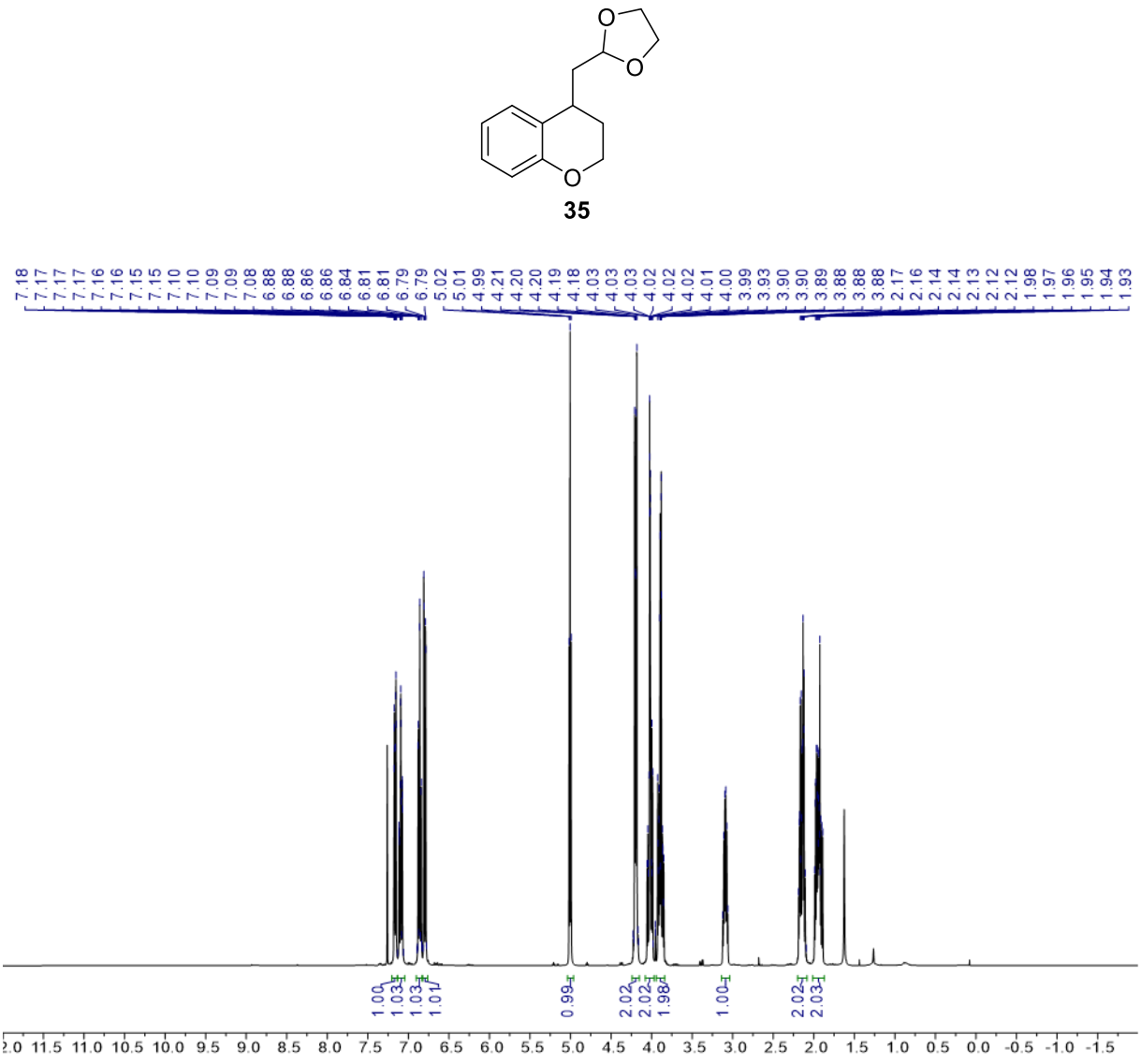


Figure S31. ^{1}H NMR spectrum of **35**, referenced to $CDCl_3$ (7.26 ppm).

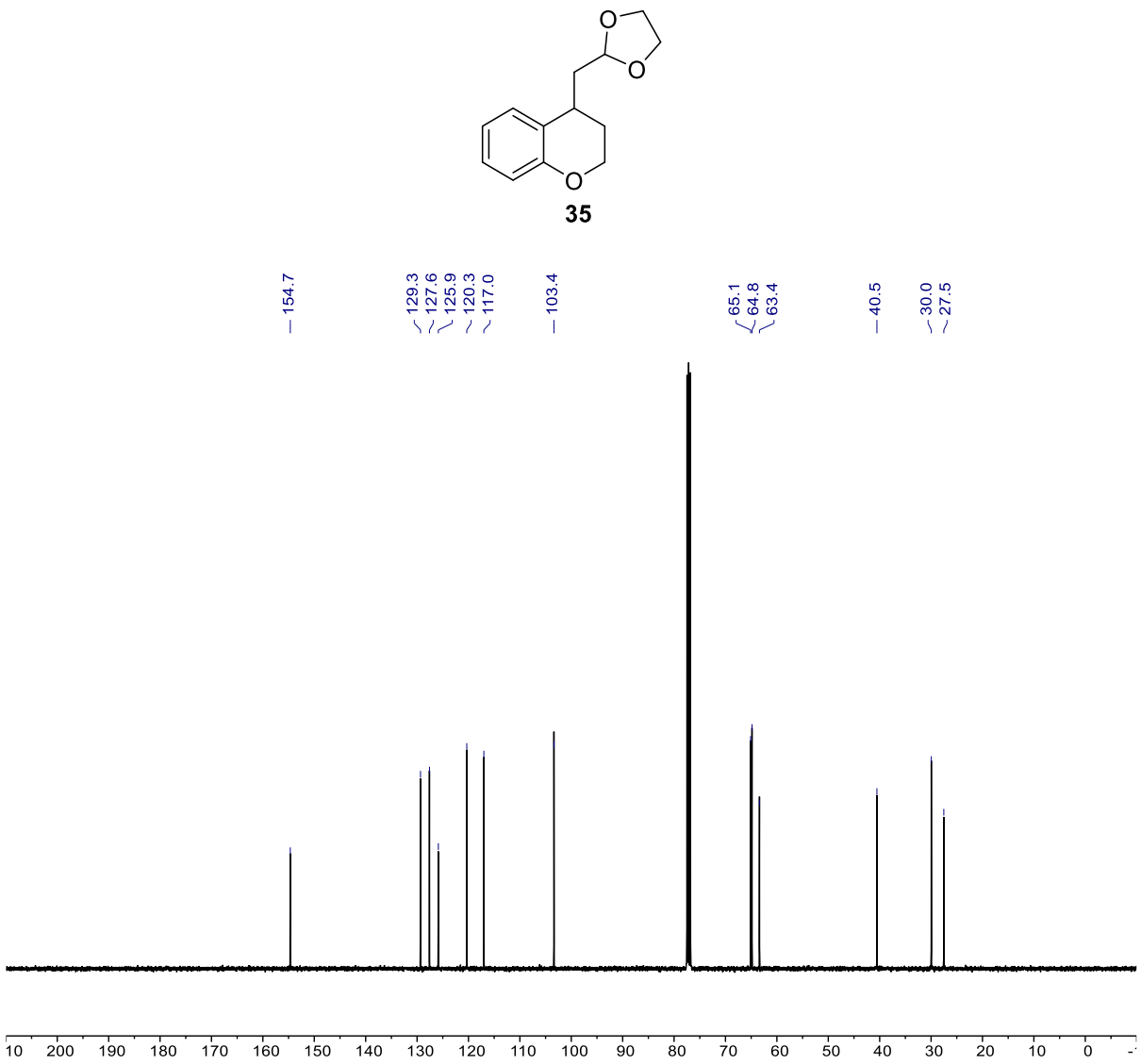


Figure S32. ^{13}C NMR spectrum of **35**, referenced to $CDCl_3$ (77.16 ppm).

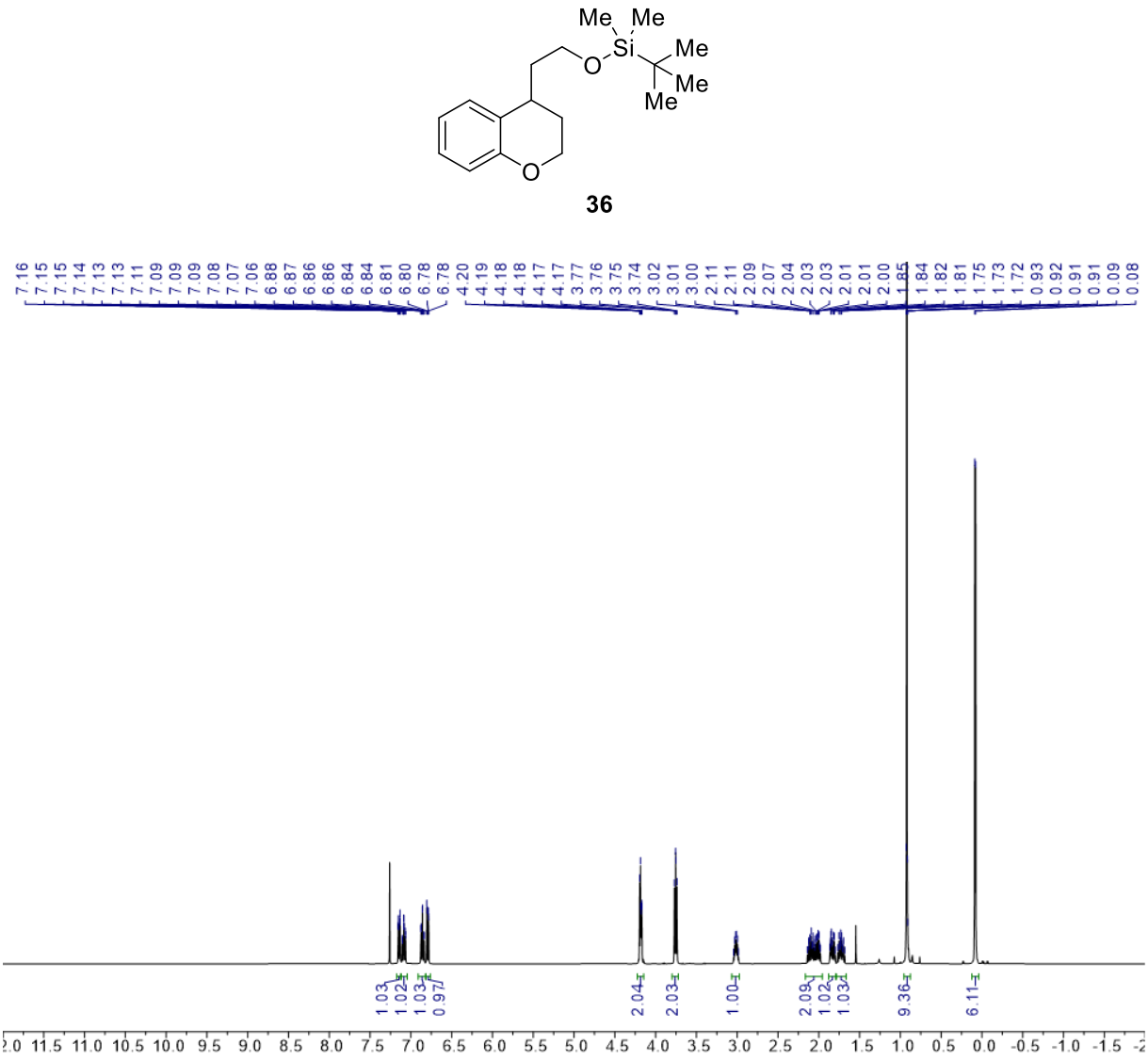


Figure S33. ^{1}H NMR spectrum of **36**, referenced to $CDCl_3$ (7.26 ppm).

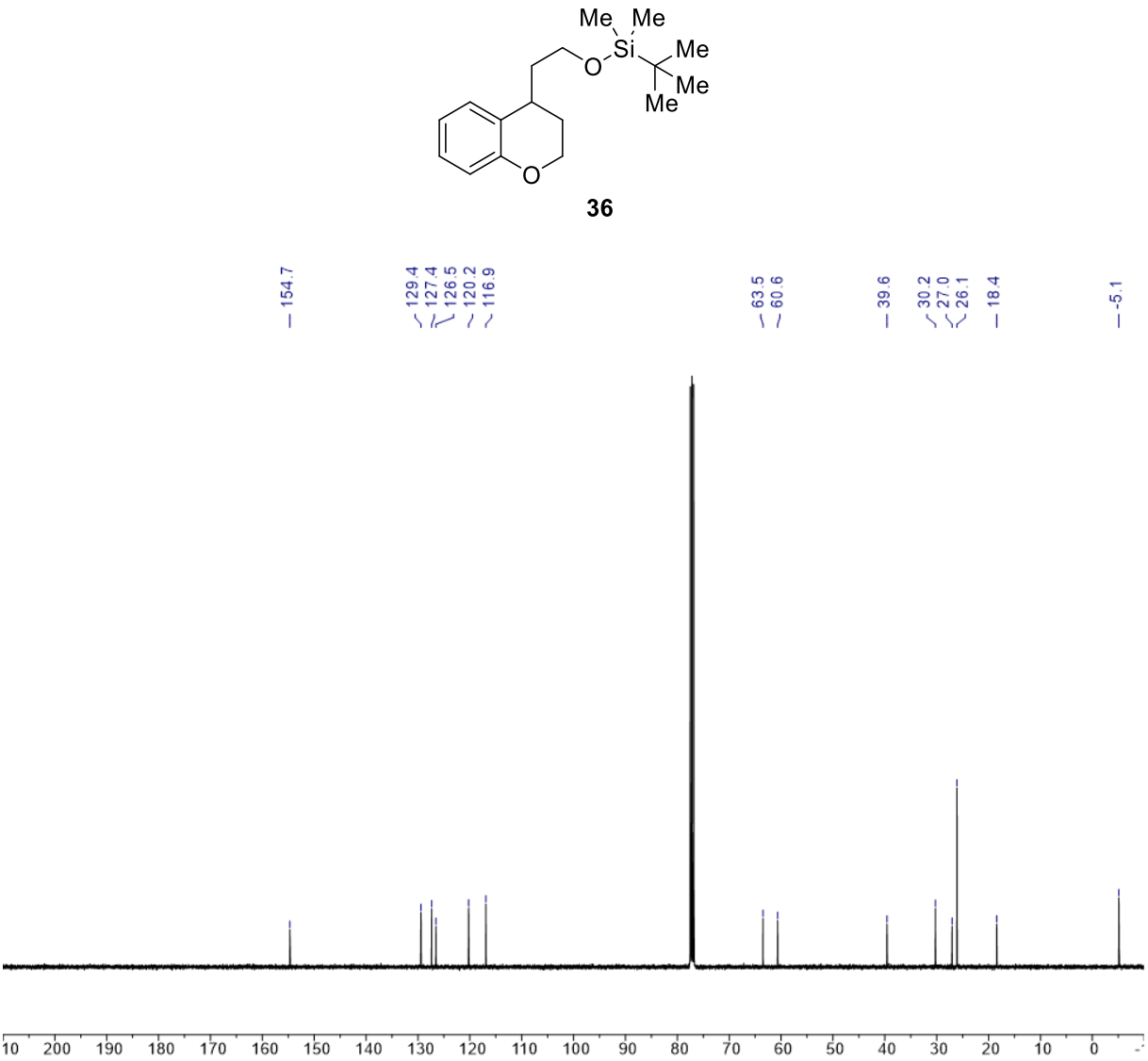
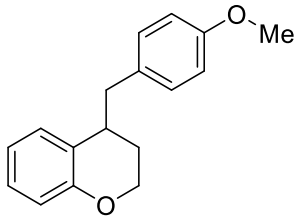


Figure S34. ^{13}C NMR spectrum of **36**, referenced to $CDCl_3$ (77.16 ppm).



37

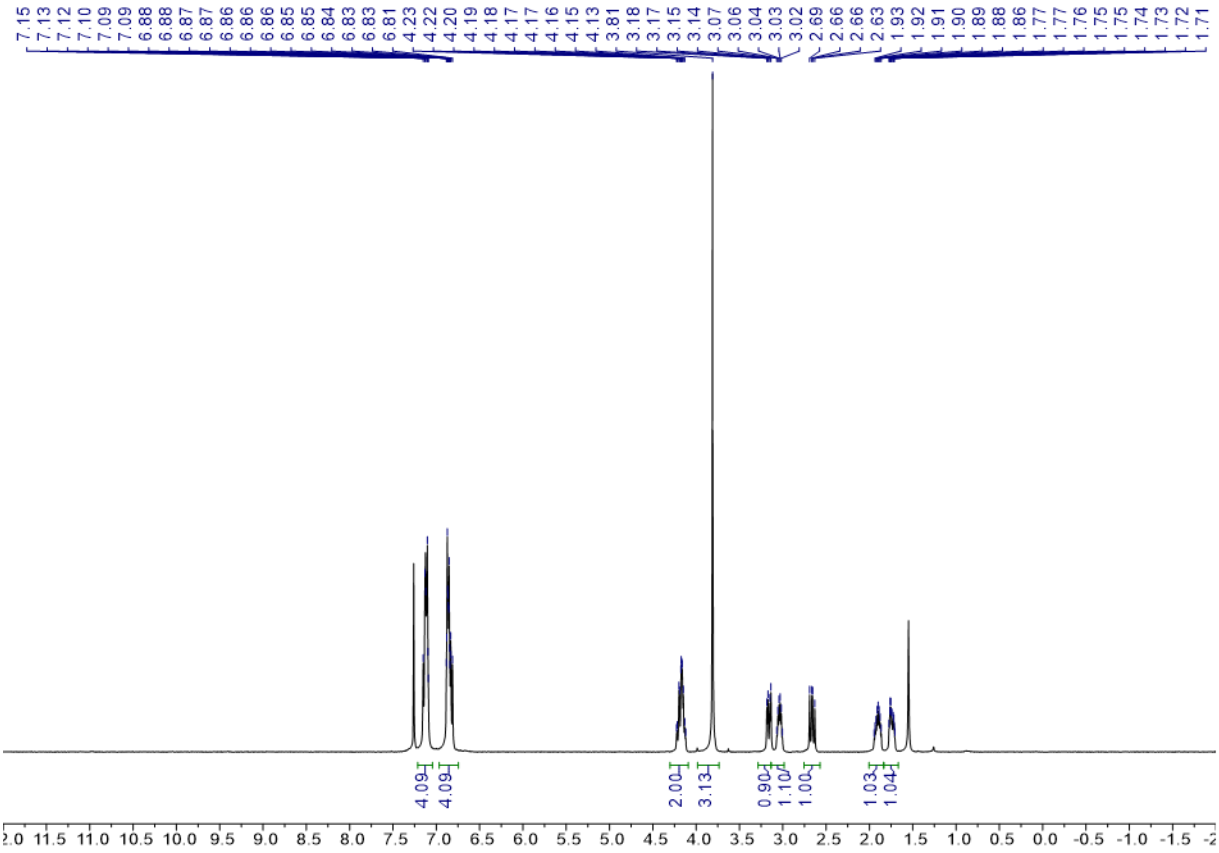


Figure S35. ^{1}H NMR spectrum of **37**, referenced to $CDCl_3$ (7.26 ppm).

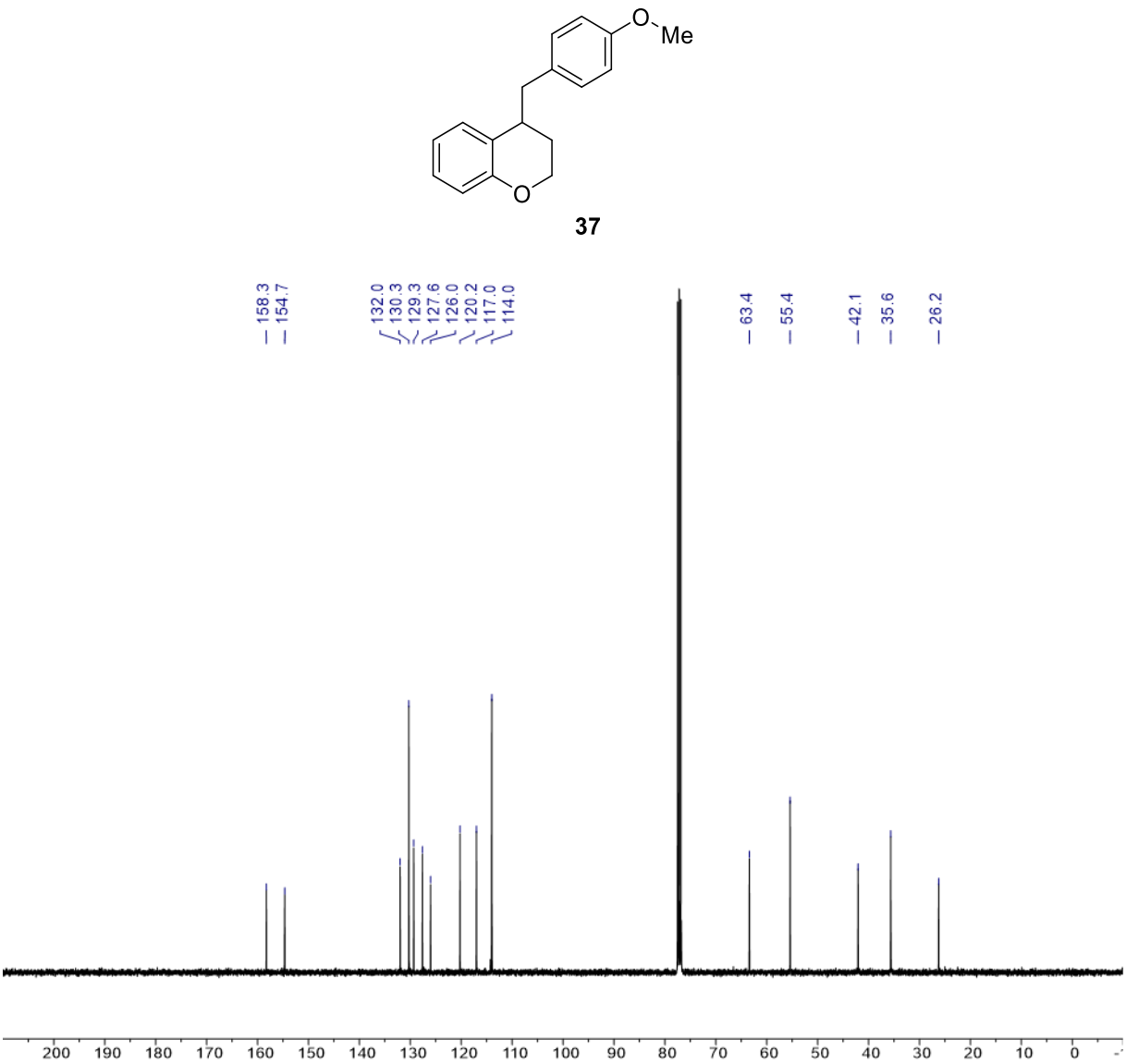


Figure S36. ^{13}C NMR spectrum of **37**, referenced to $CDCl_3$ (77.16 ppm).

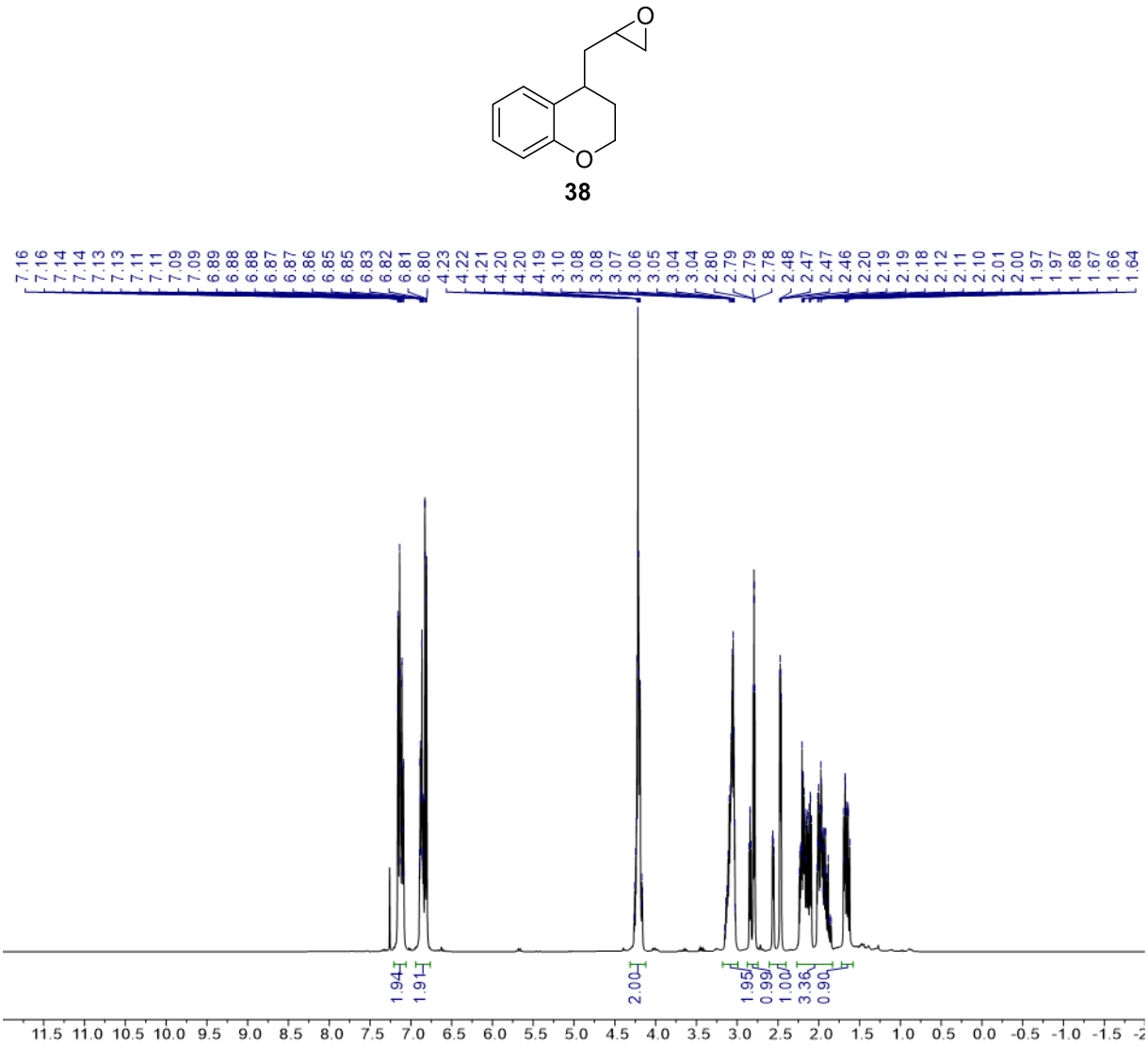


Figure S37. ^{1}H NMR spectrum of **38**, referenced to $CDCl_3$ (7.26 ppm).

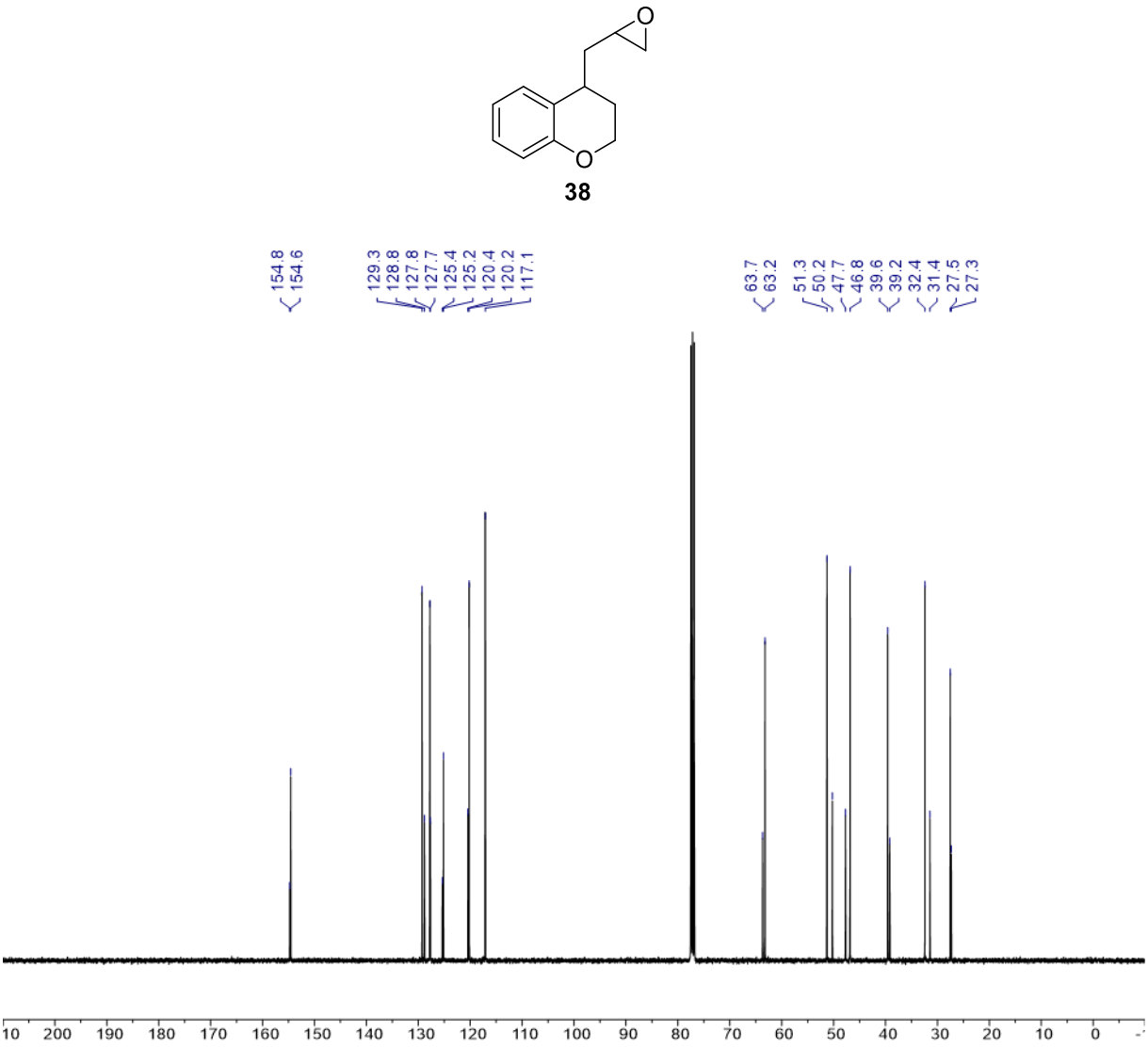


Figure S38. ^{13}C NMR spectrum of **38**, referenced to $CDCl_3$ (77.16 ppm).

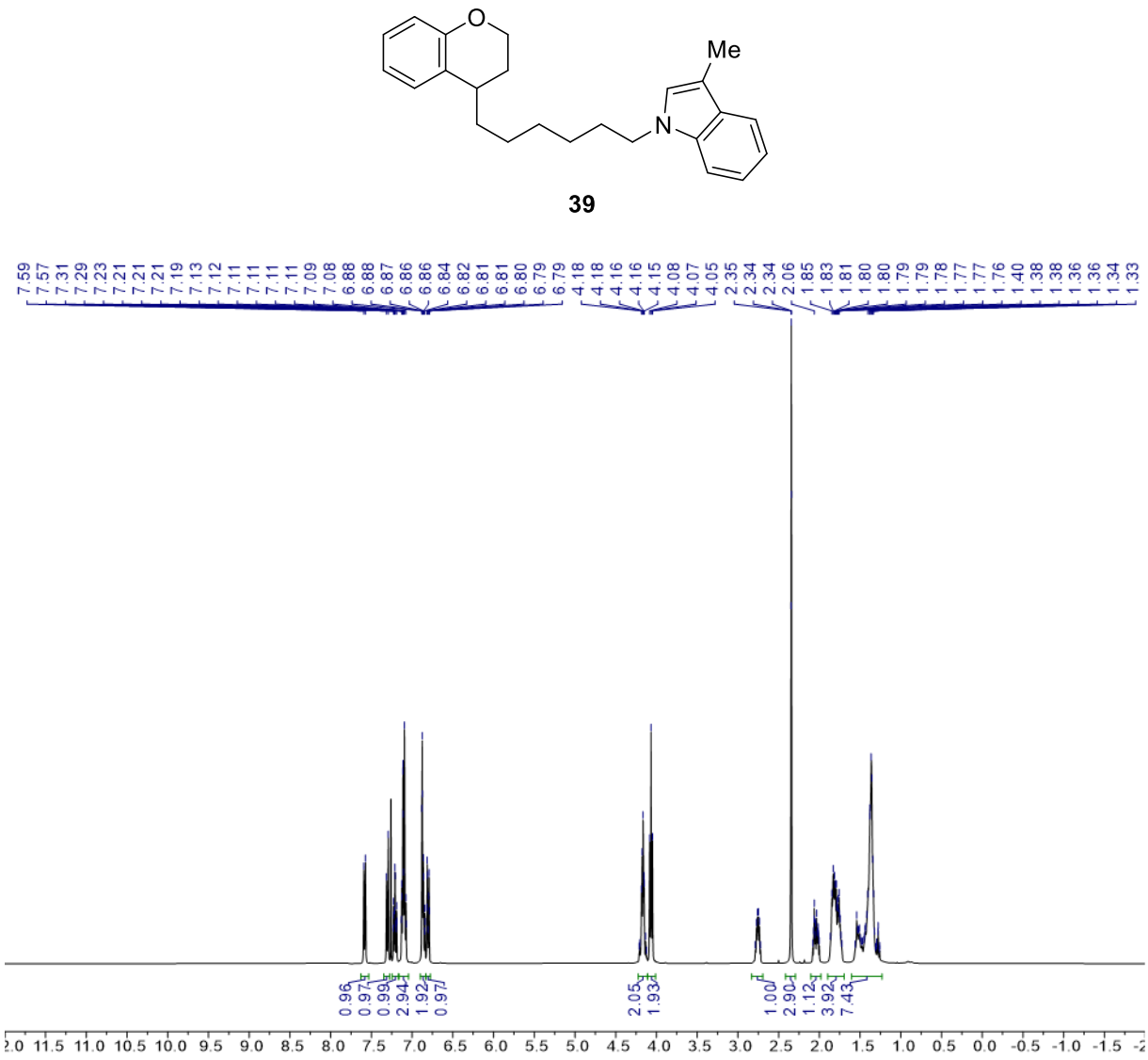


Figure S39. ^{1}H NMR spectrum of **39**, referenced to $CDCl_3$ (7.26 ppm).

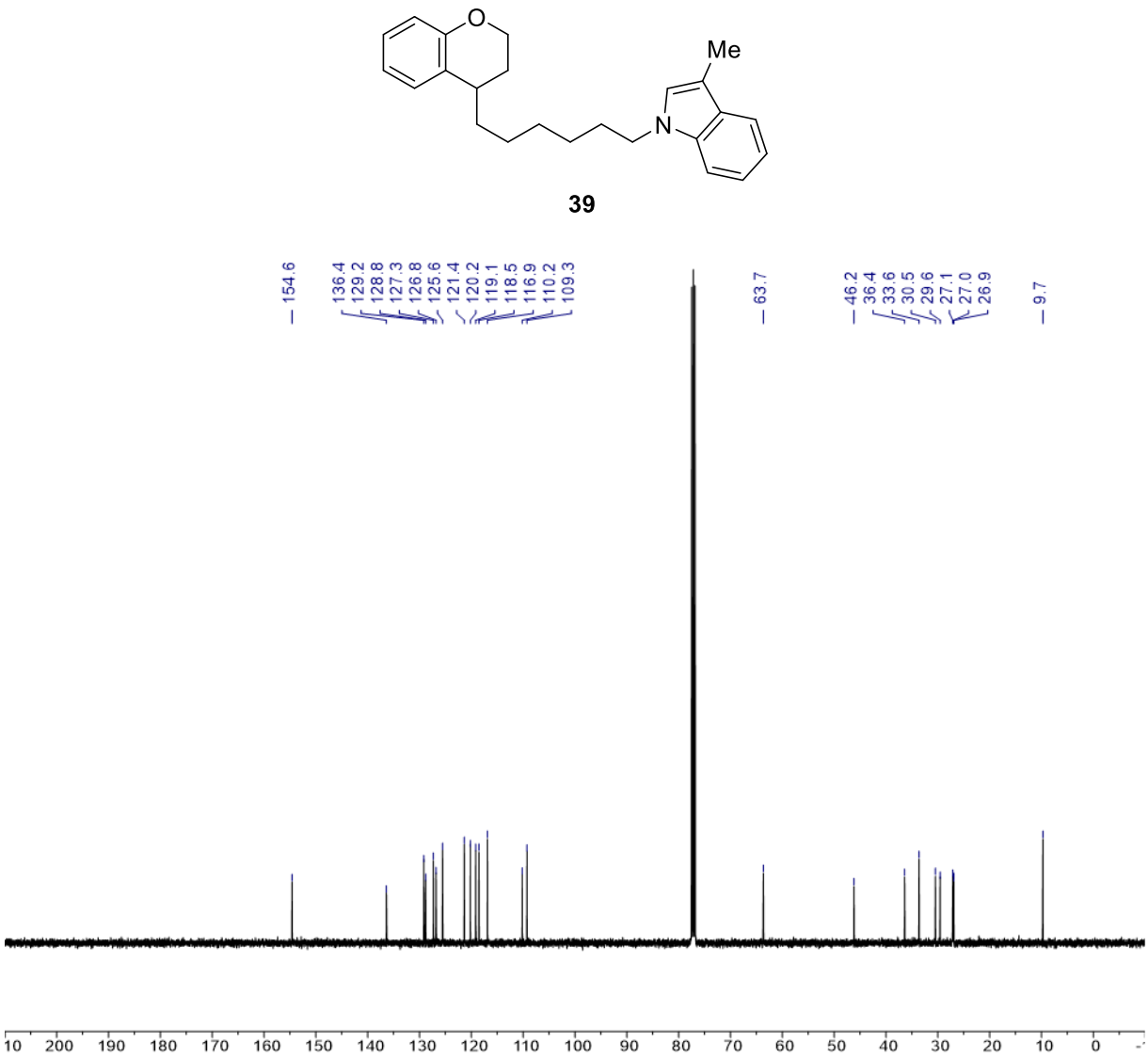


Figure S40. ^{13}C NMR spectrum of **39**, referenced to $CDCl_3$ (77.16 ppm).

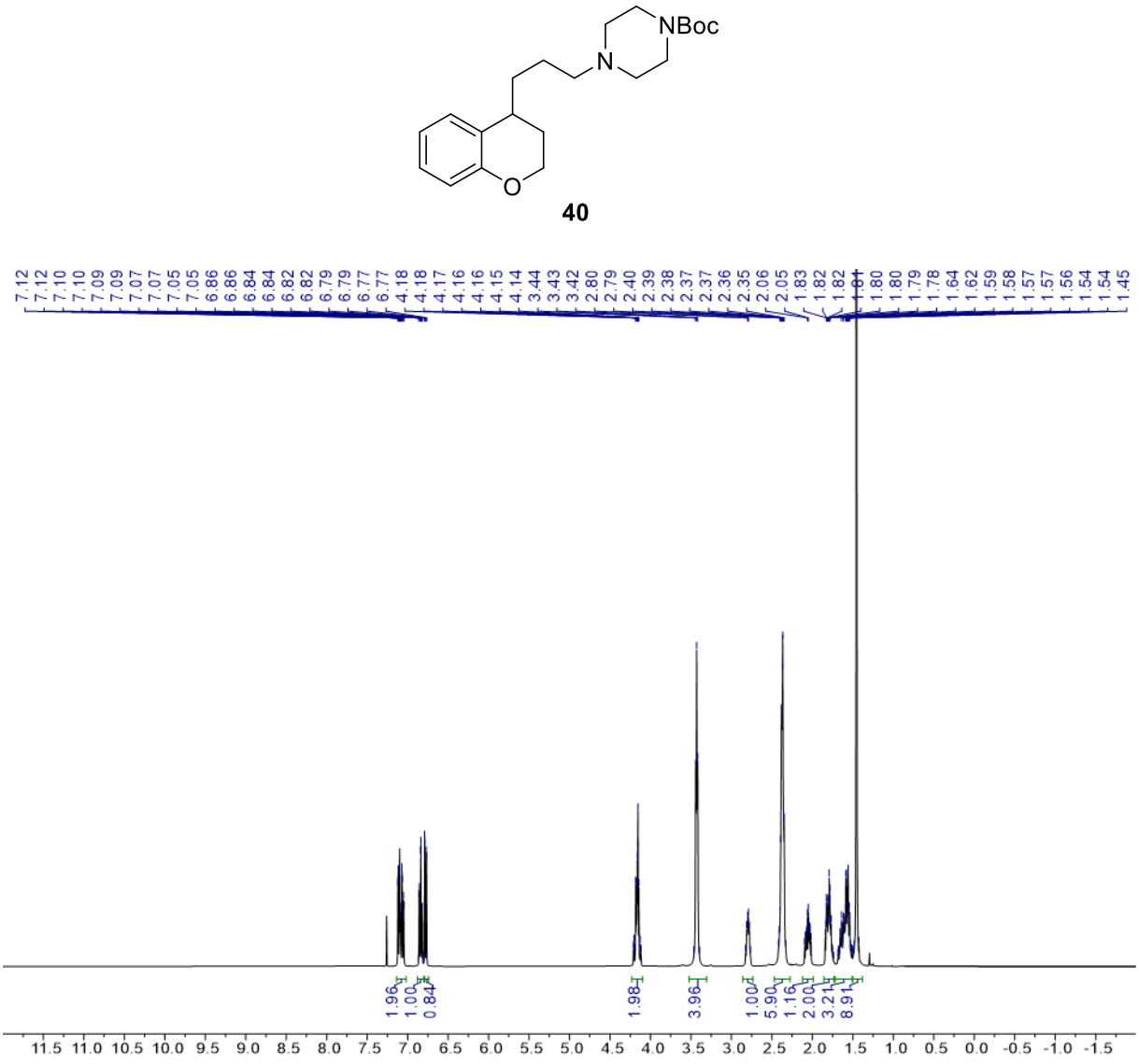


Figure S41. ^{1}H NMR spectrum of **40**, referenced to $CDCl_3$ (7.26 ppm).

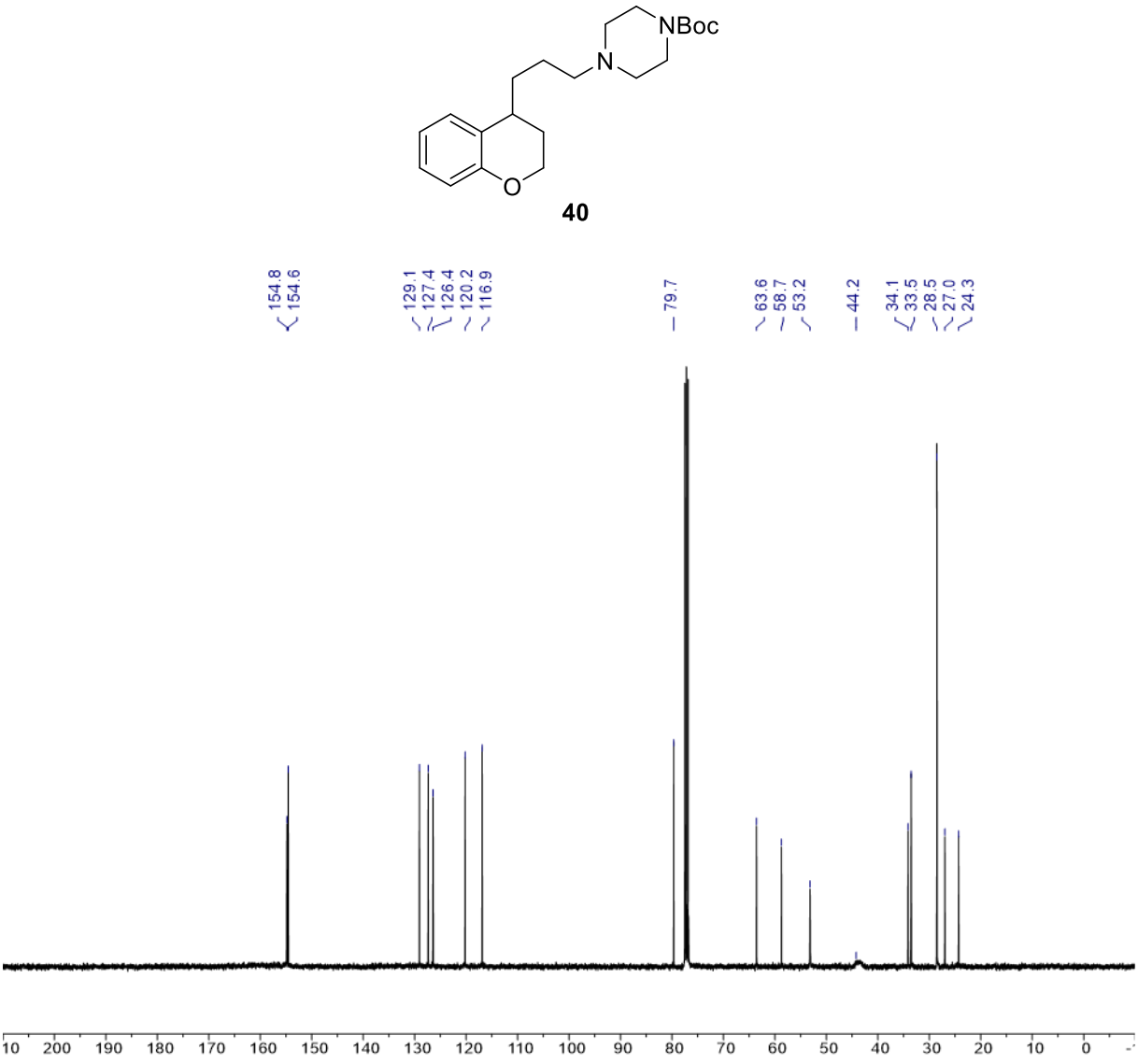
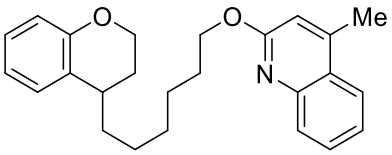


Figure S42. ^{13}C NMR spectrum of **40**, referenced to $CDCl_3$ (77.16 ppm).



41

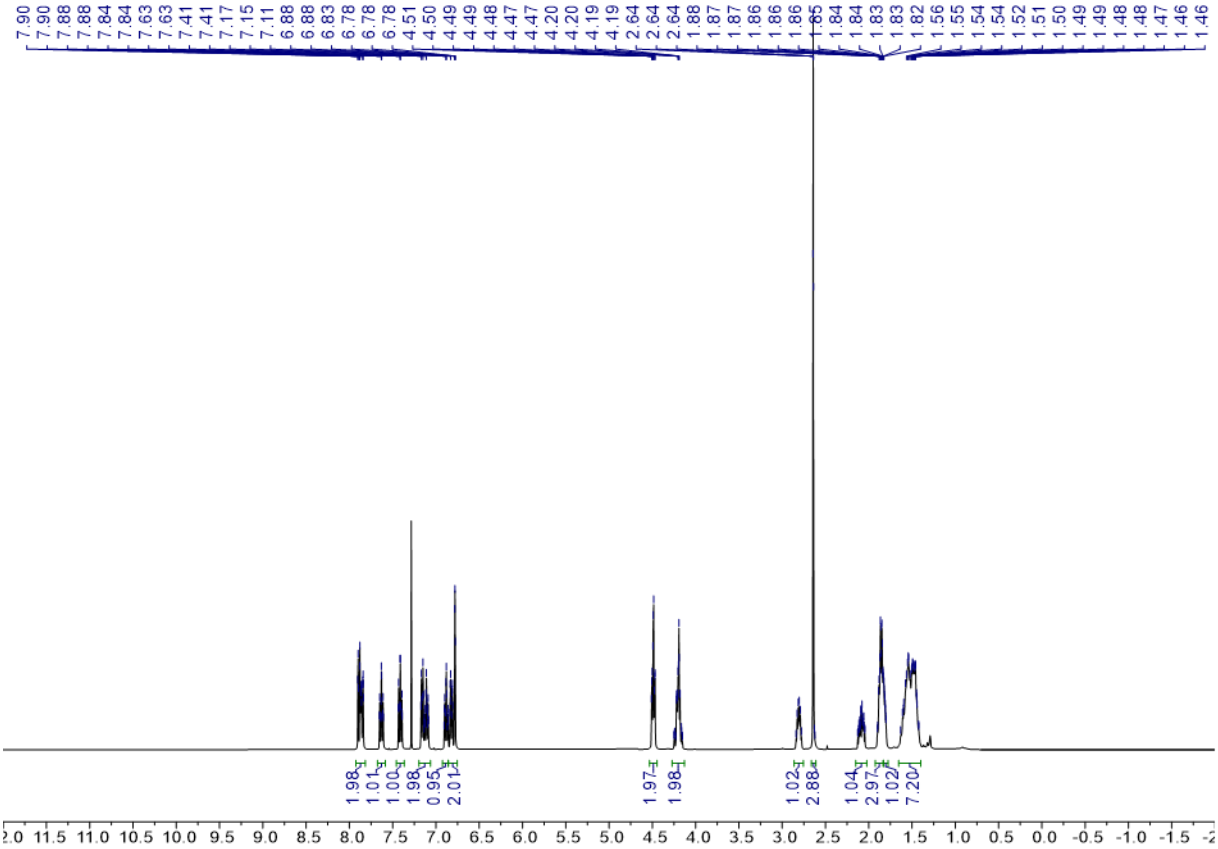
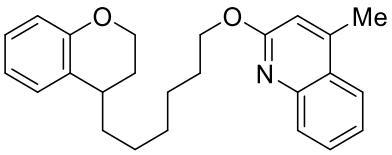


Figure S43. ^{1}H NMR spectrum of **41**, referenced to $CDCl_3$ (7.26 ppm).



41

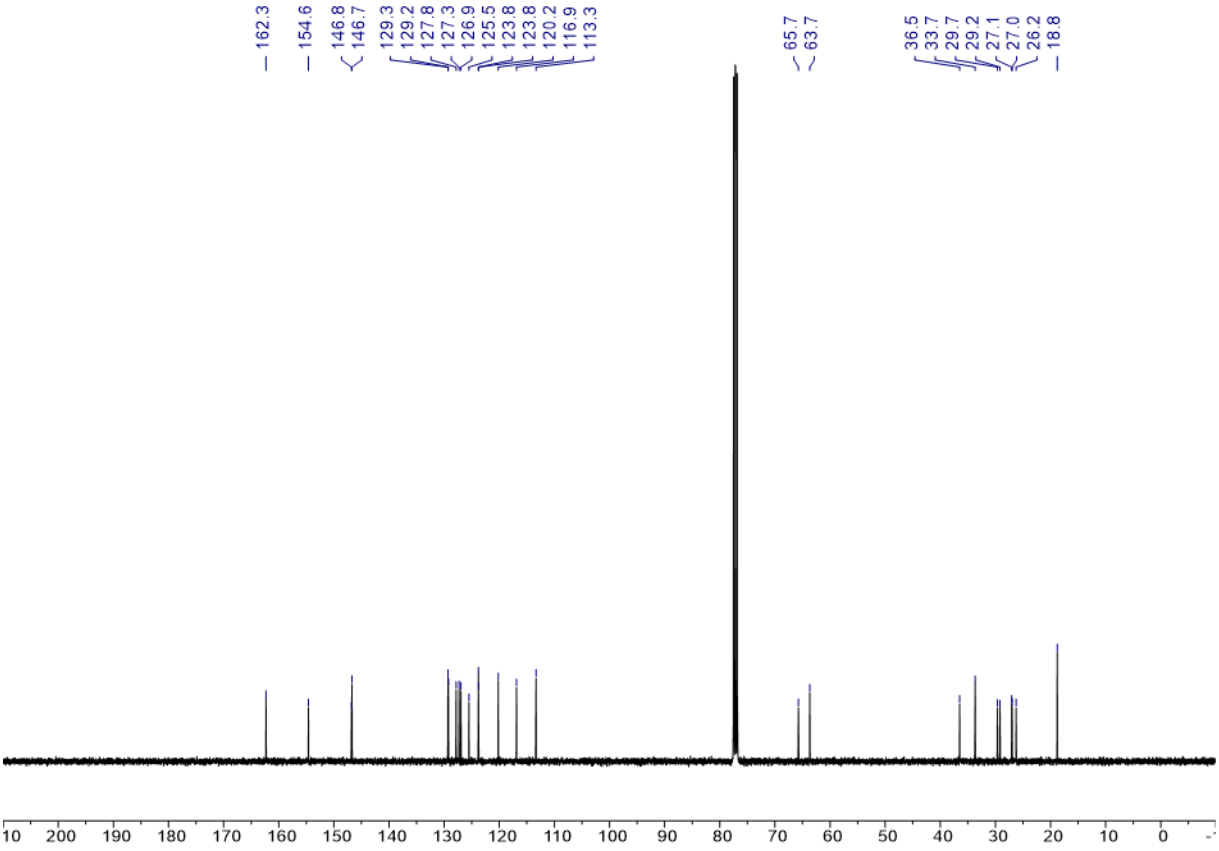


Figure S44. ^{13}C NMR spectrum of **41**, referenced to $CDCl_3$ (77.16 ppm).

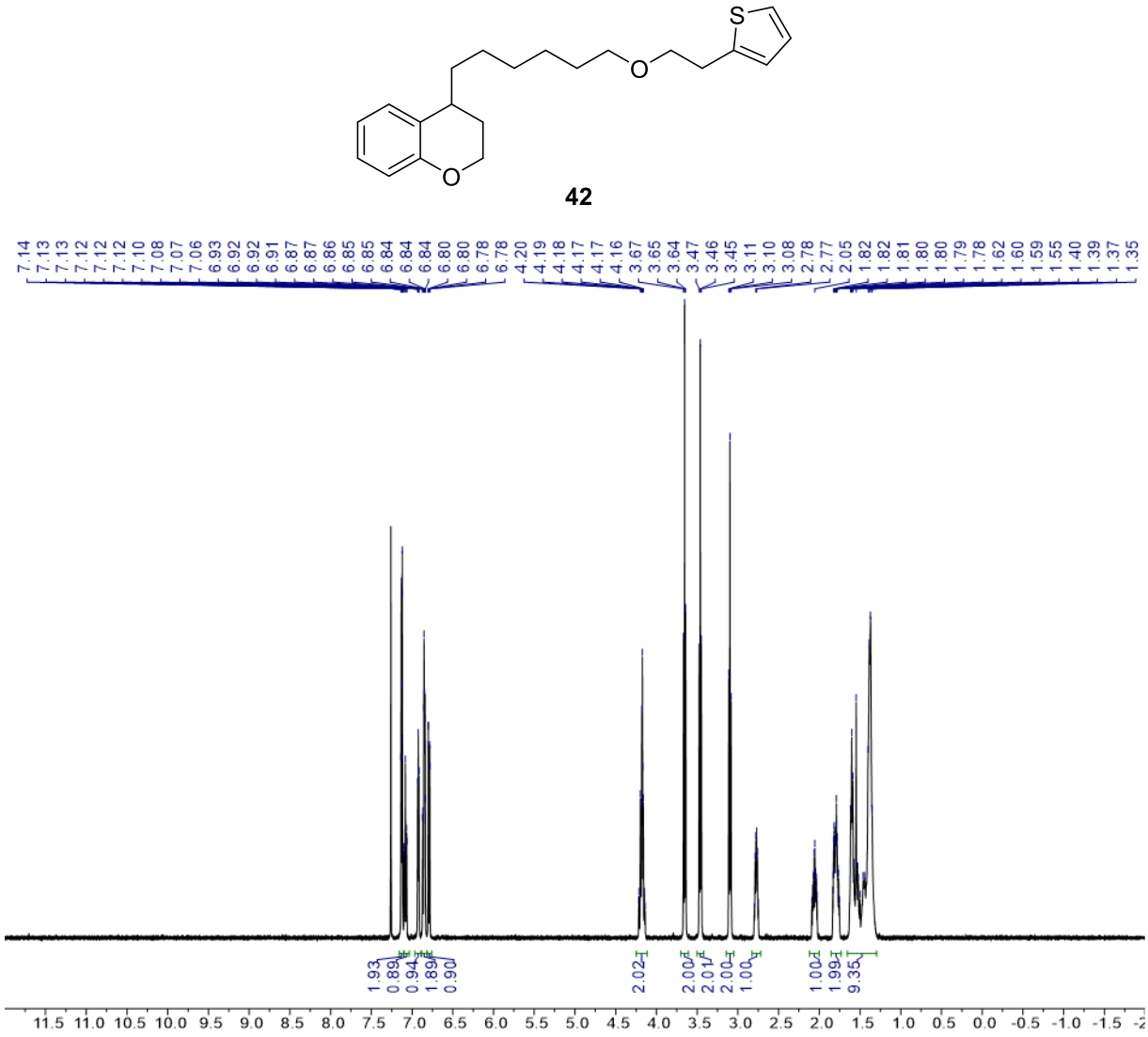


Figure S45. ^{1}H NMR spectrum of **42**, referenced to $CDCl_3$ (7.26 ppm).

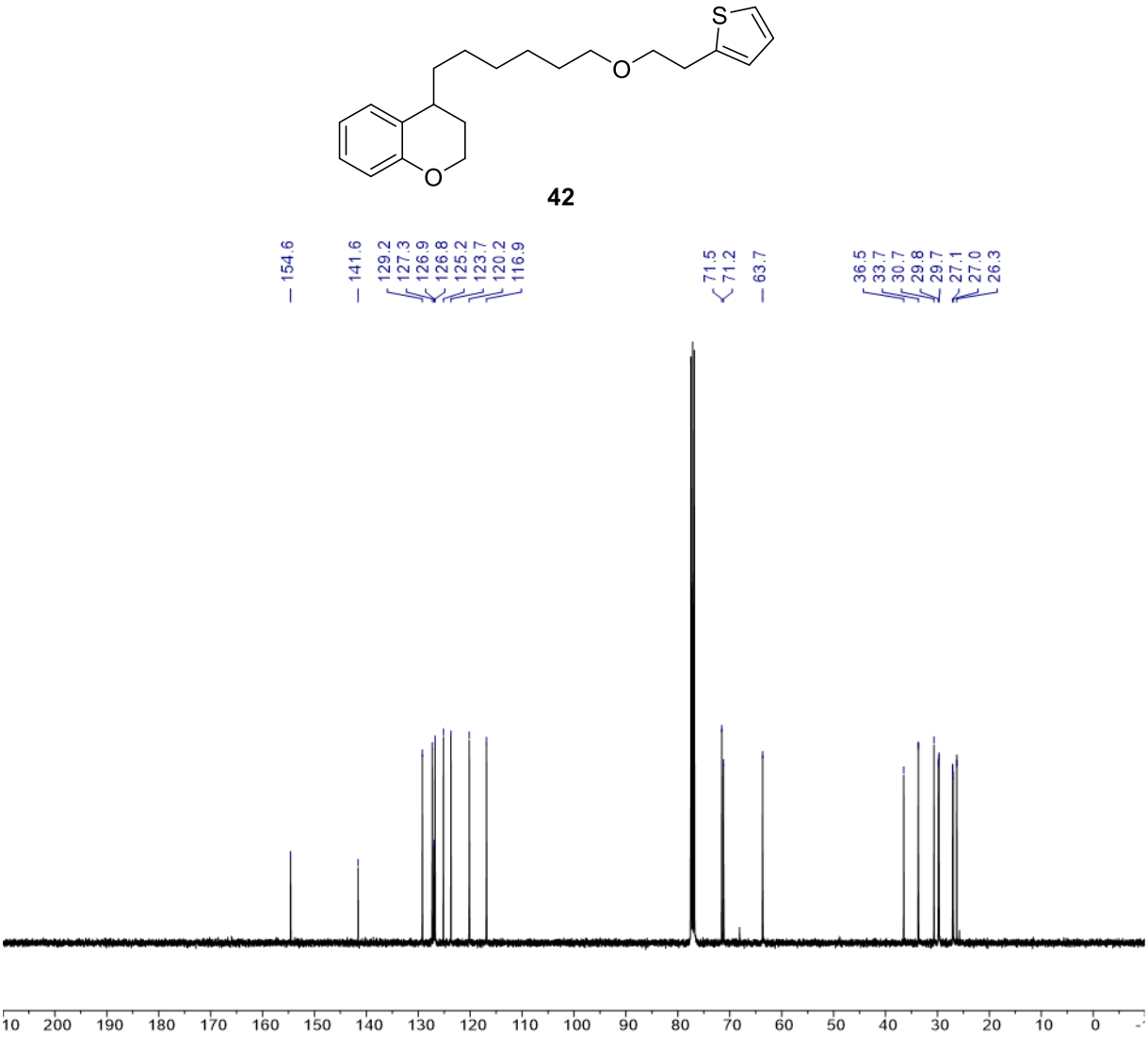


Figure S46. ^{13}C NMR spectrum of **42**, referenced to $CDCl_3$ (77.16 ppm).

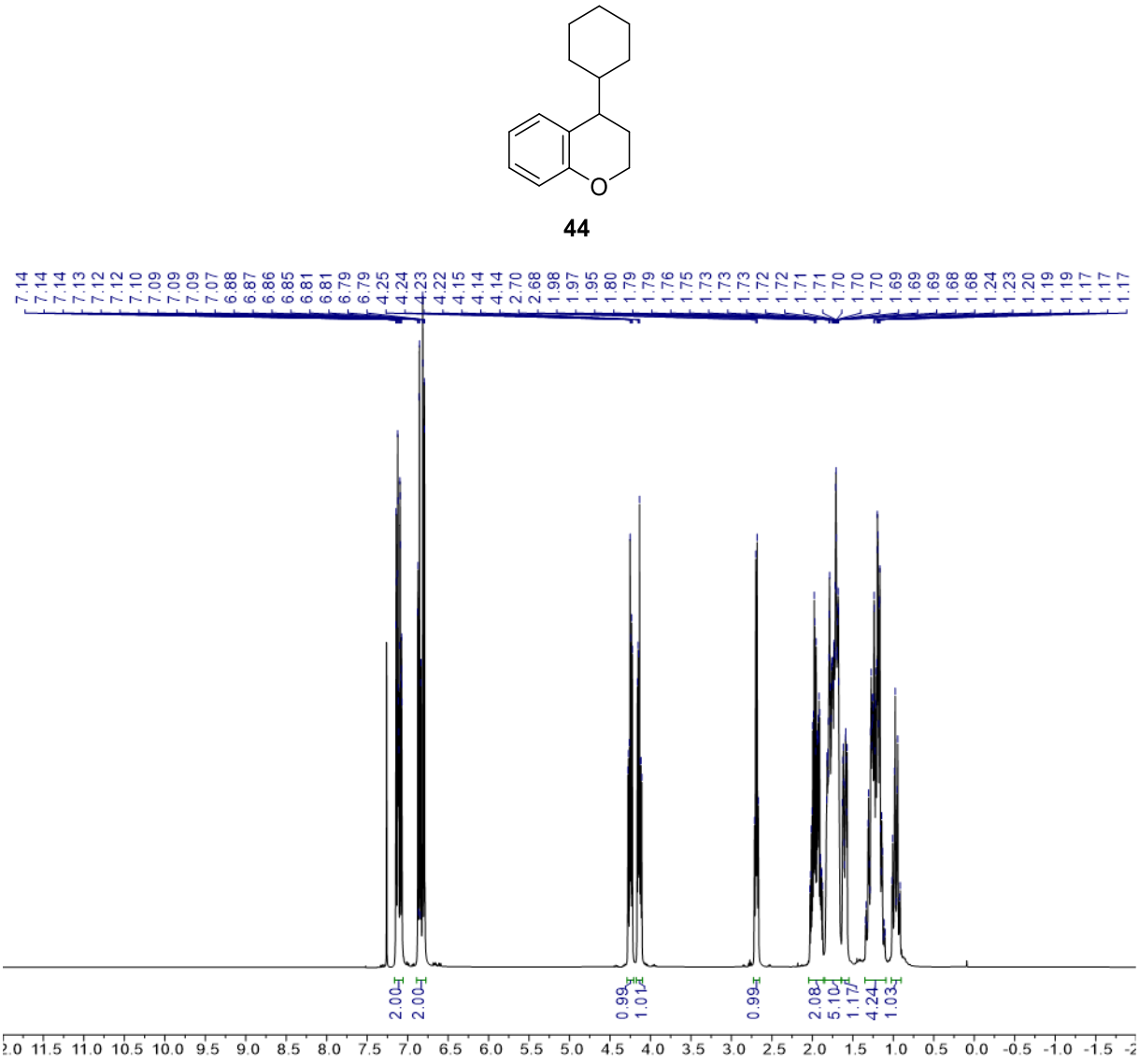


Figure S47. ^{1}H NMR spectrum of **44**, referenced to $CDCl_3$ (7.26 ppm).

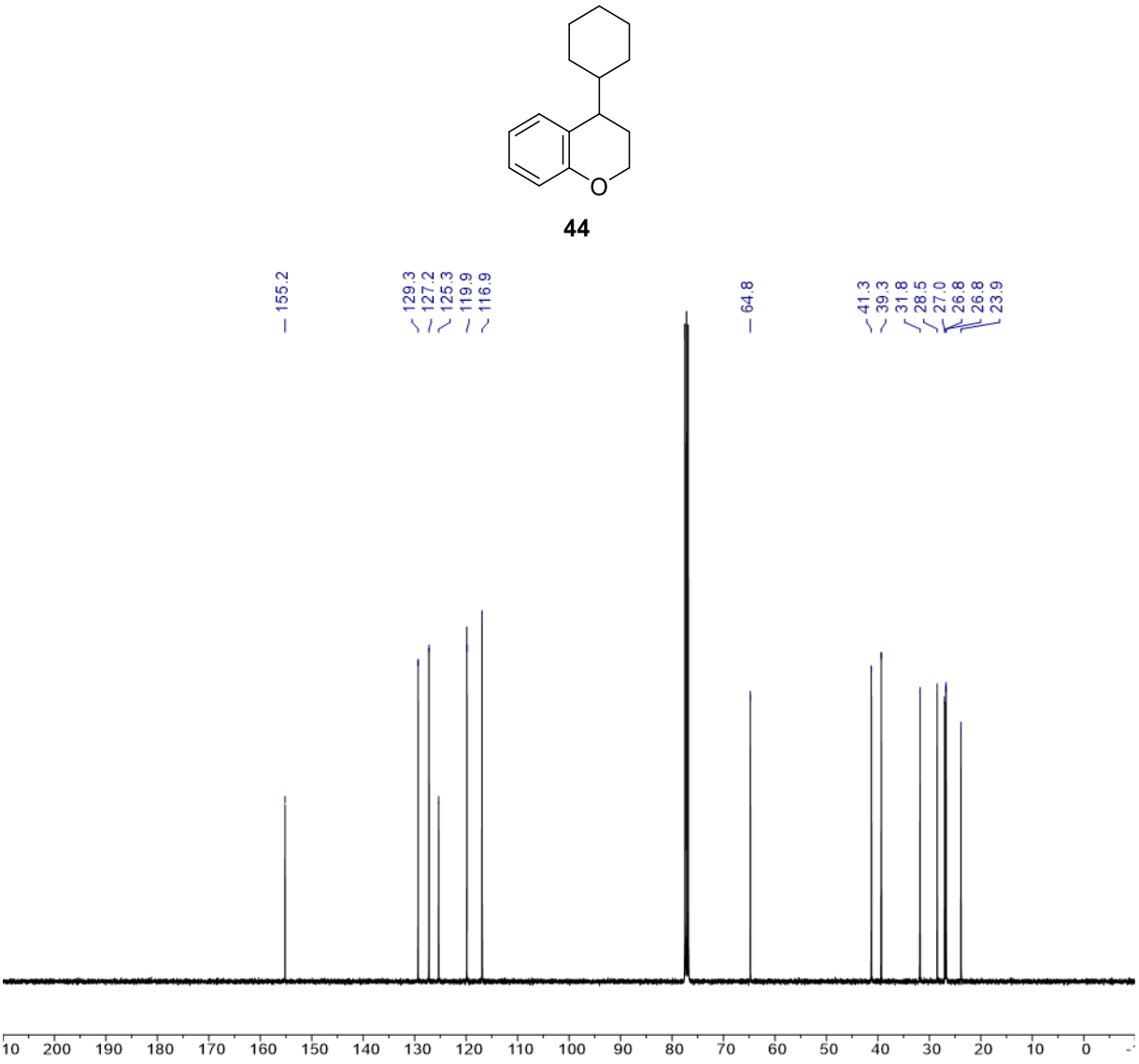


Figure S48. ^{13}C NMR spectrum of **44**, referenced to $CDCl_3$ (77.16 ppm).

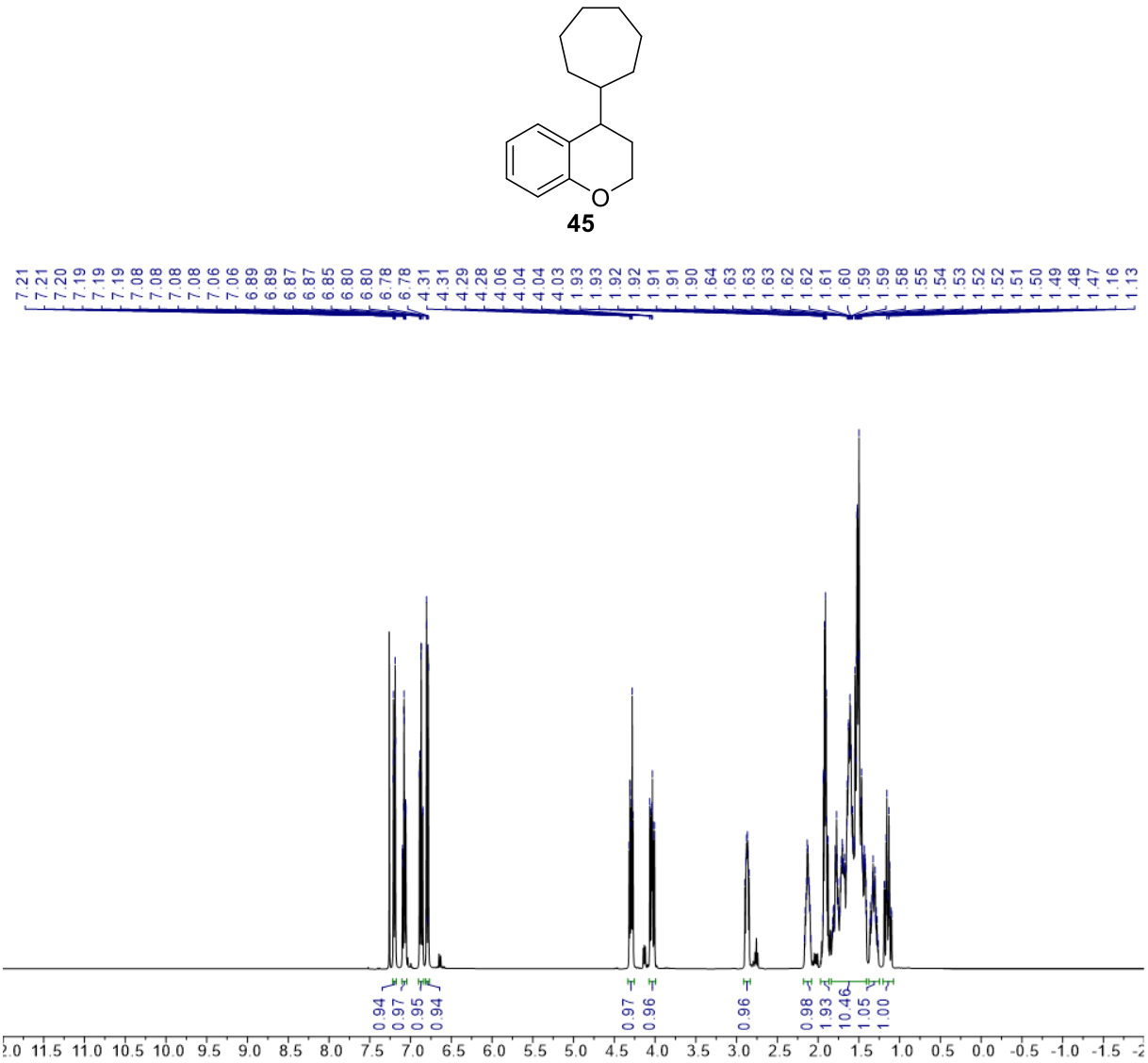


Figure S49. ^{1}H NMR spectrum of **45**, referenced to $CDCl_3$ (7.26 ppm).

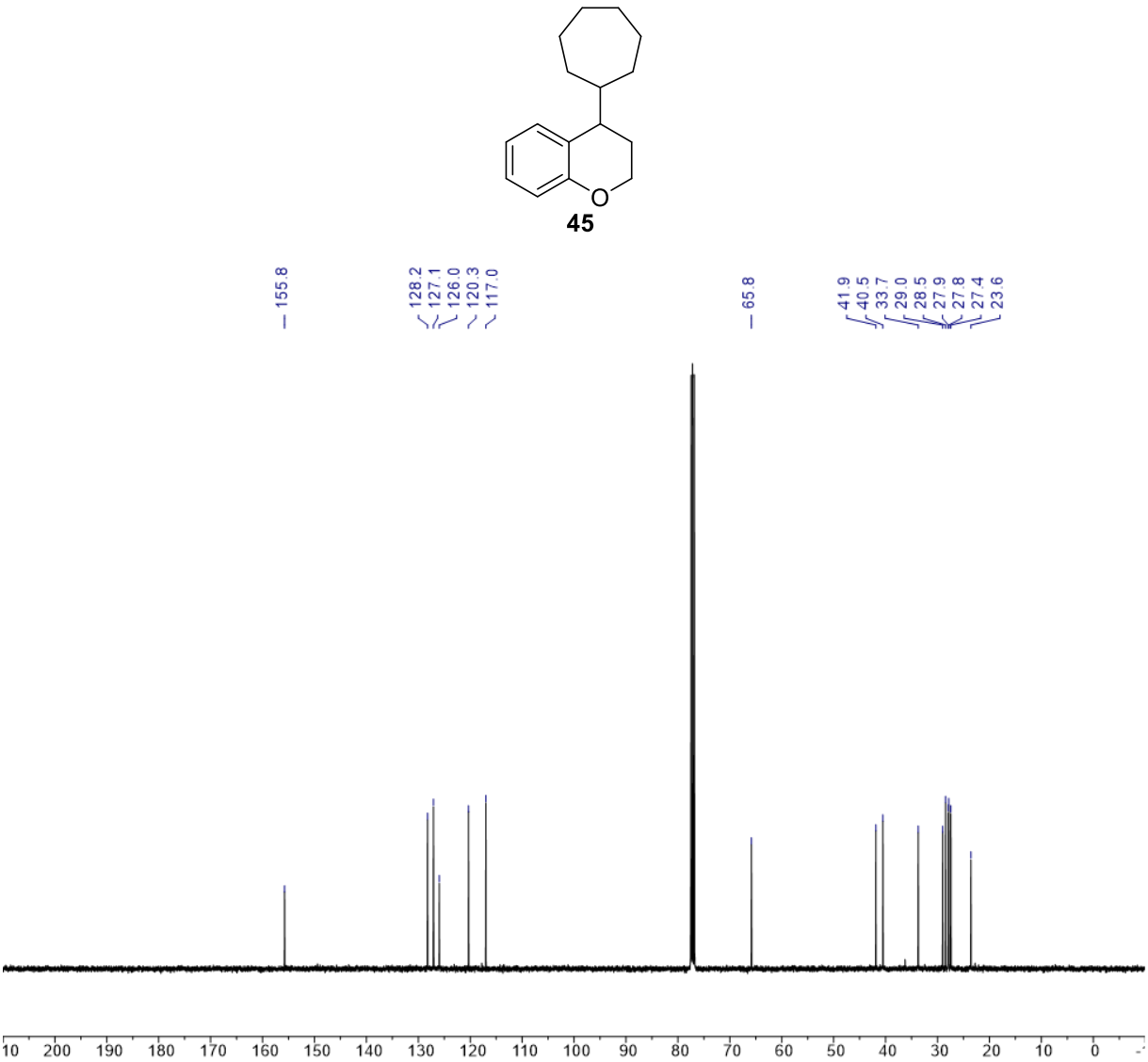


Figure S50. ^{13}C NMR spectrum of **45**, referenced to $CDCl_3$ (77.16 ppm).

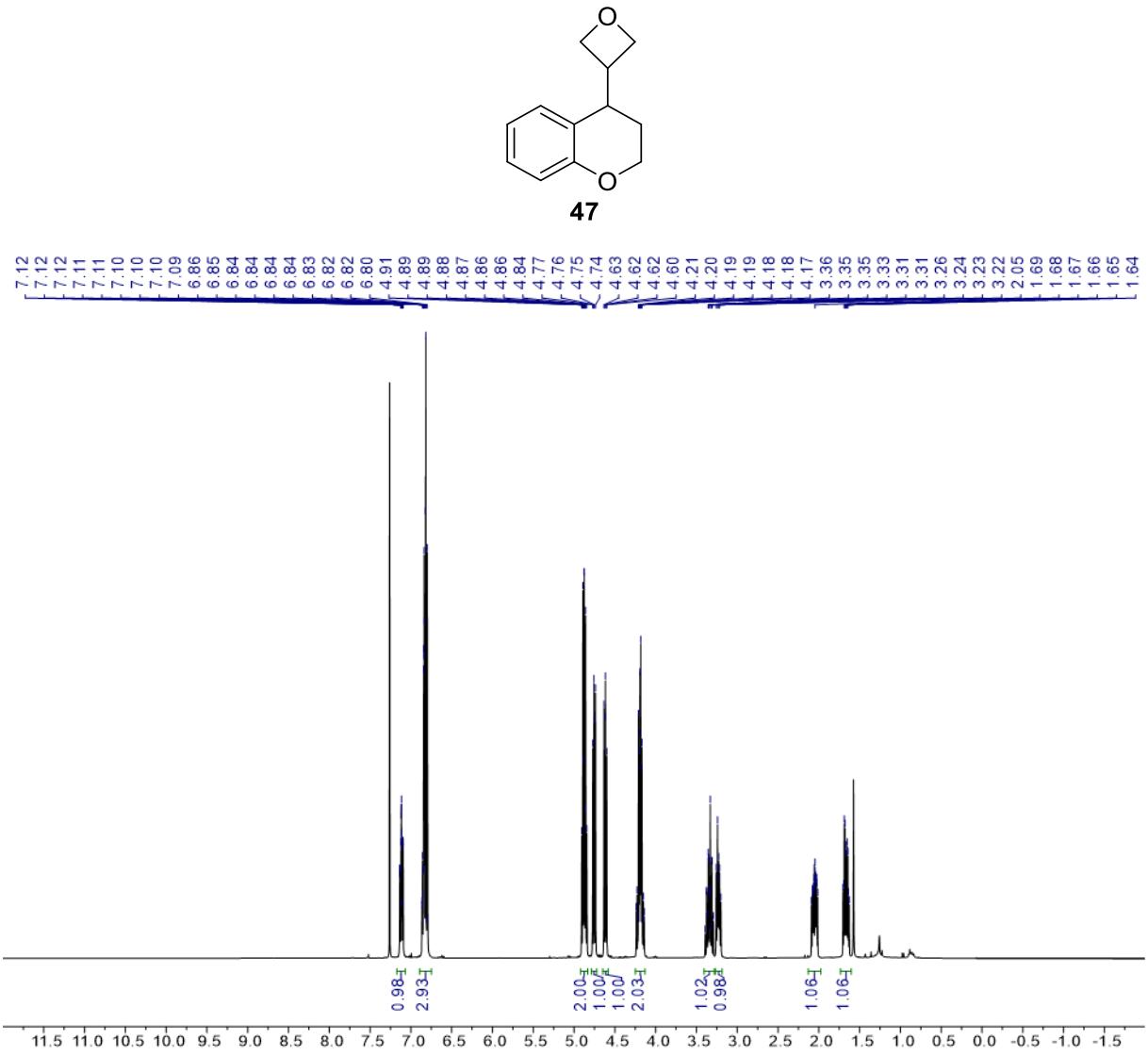


Figure S51. ^{1}H NMR spectrum of **47**, referenced to $CDCl_3$ (7.26 ppm).

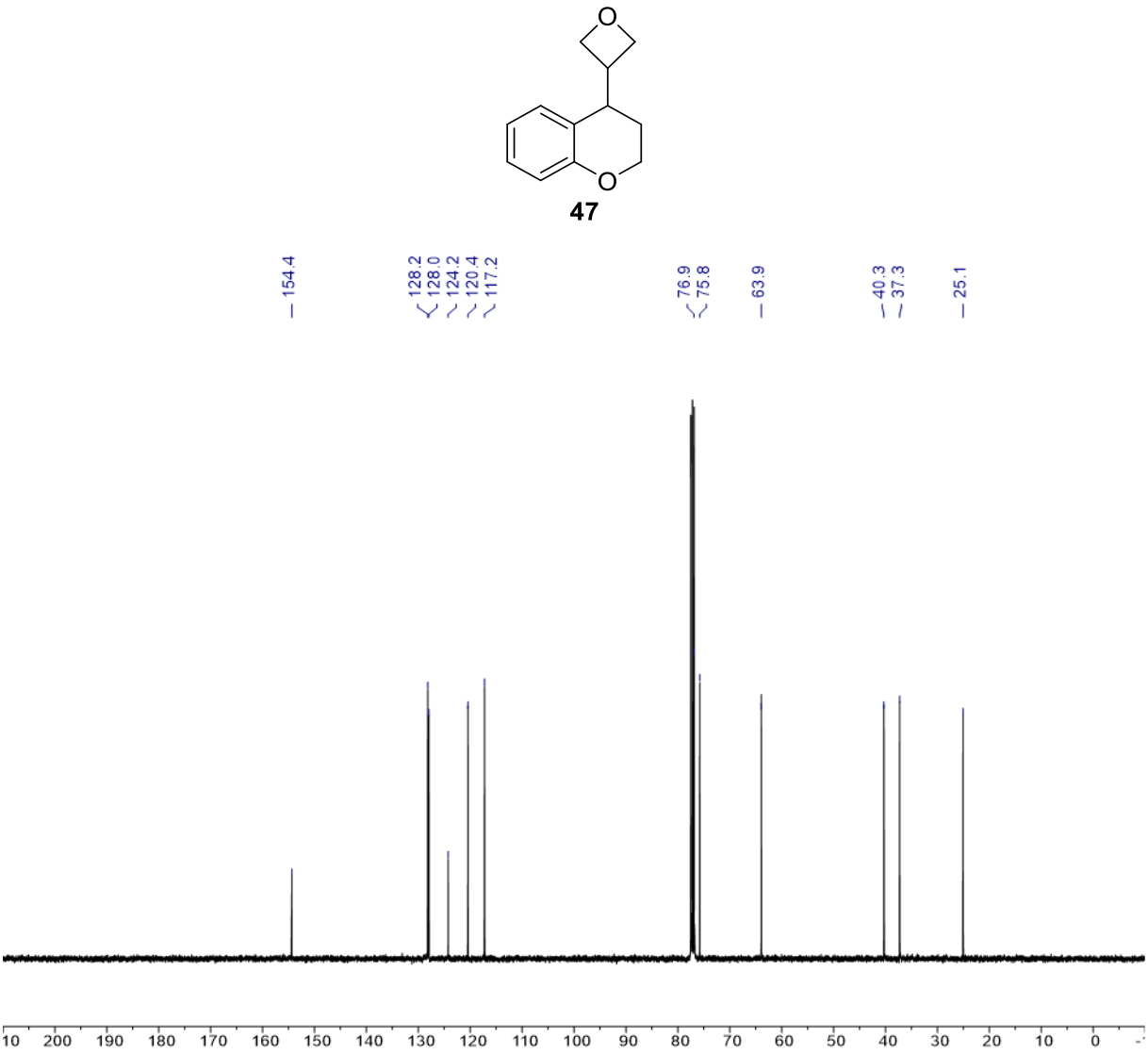


Figure S52. ^{13}C NMR spectrum of **47**, referenced to $CDCl_3$ (77.16 ppm).

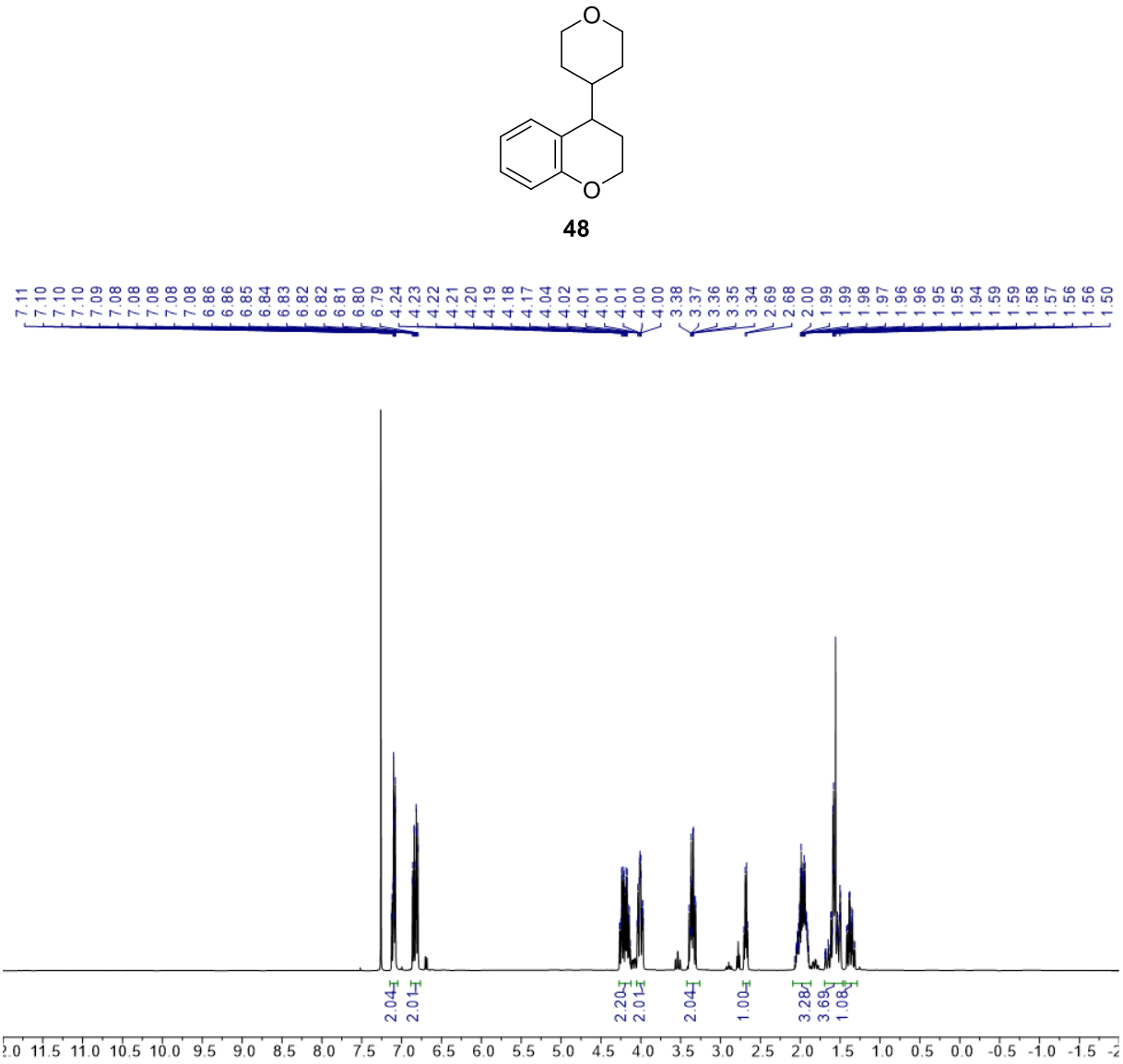


Figure S53. ^{1}H NMR spectrum of **48**, referenced to $CDCl_3$ (7.26 ppm).

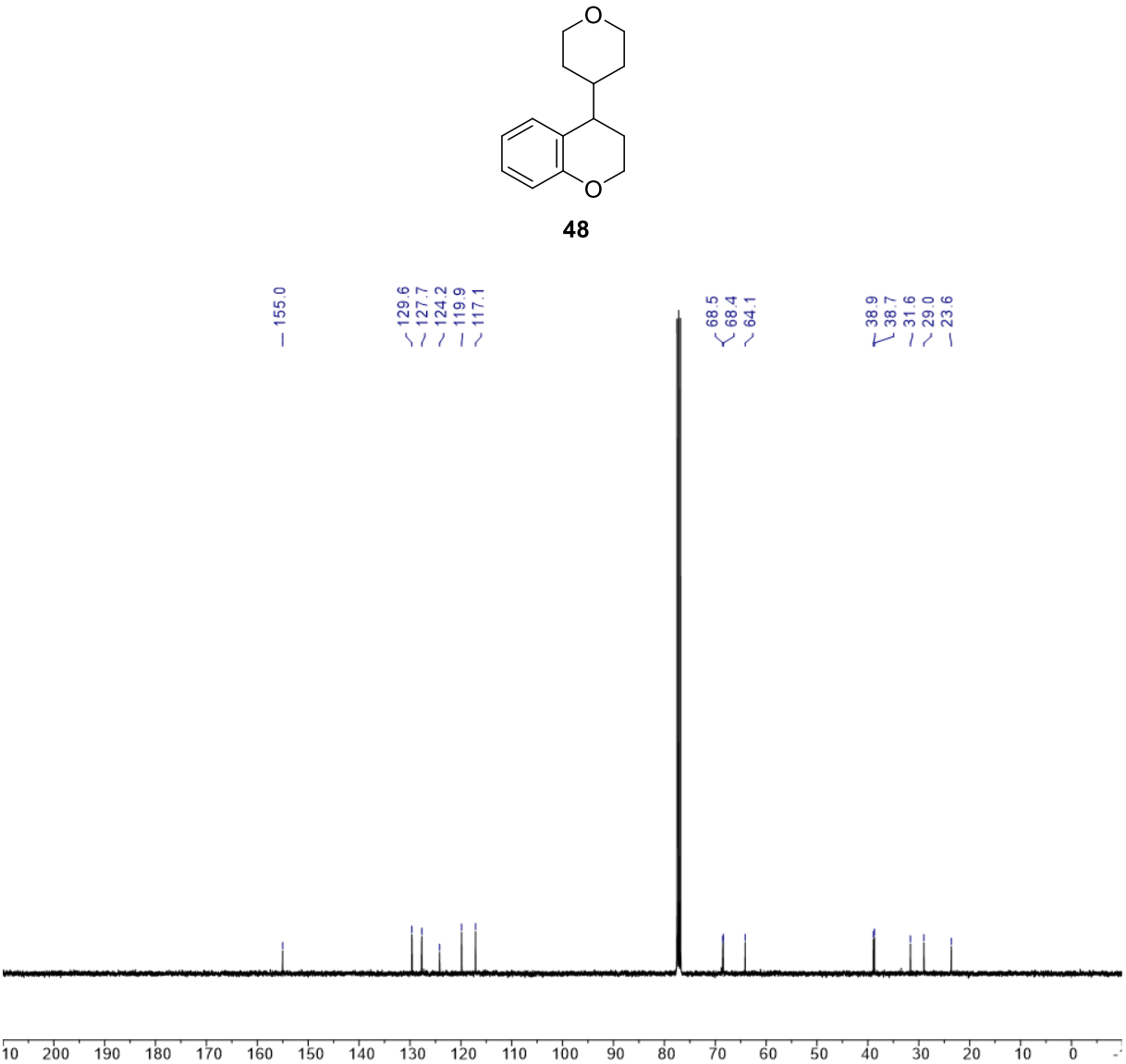


Figure S54. ^{13}C NMR spectrum of **48**, referenced to $CDCl_3$ (77.16 ppm).

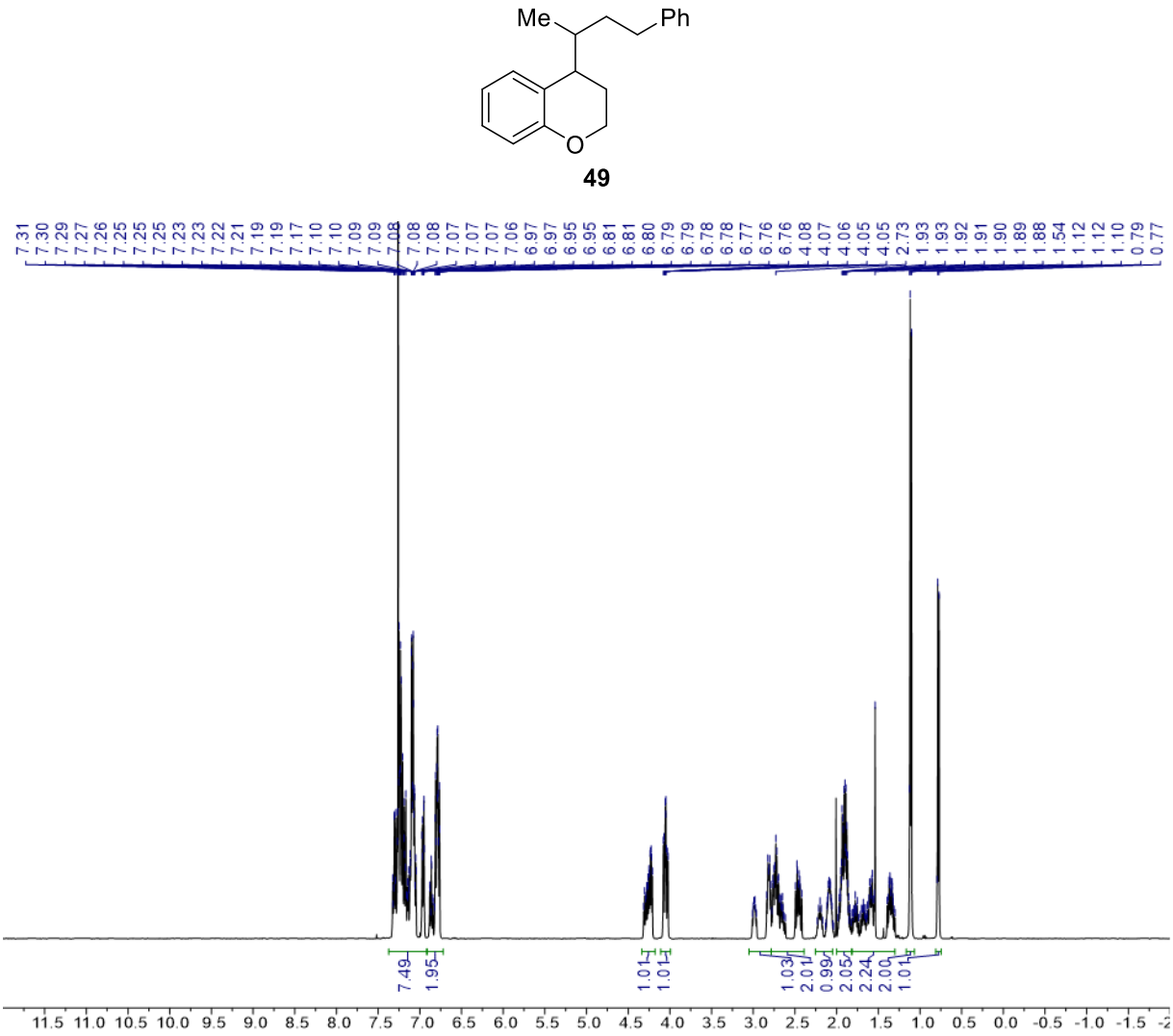


Figure S55. ^{1}H NMR spectrum of **49**, referenced to $CDCl_3$ (7.26 ppm).

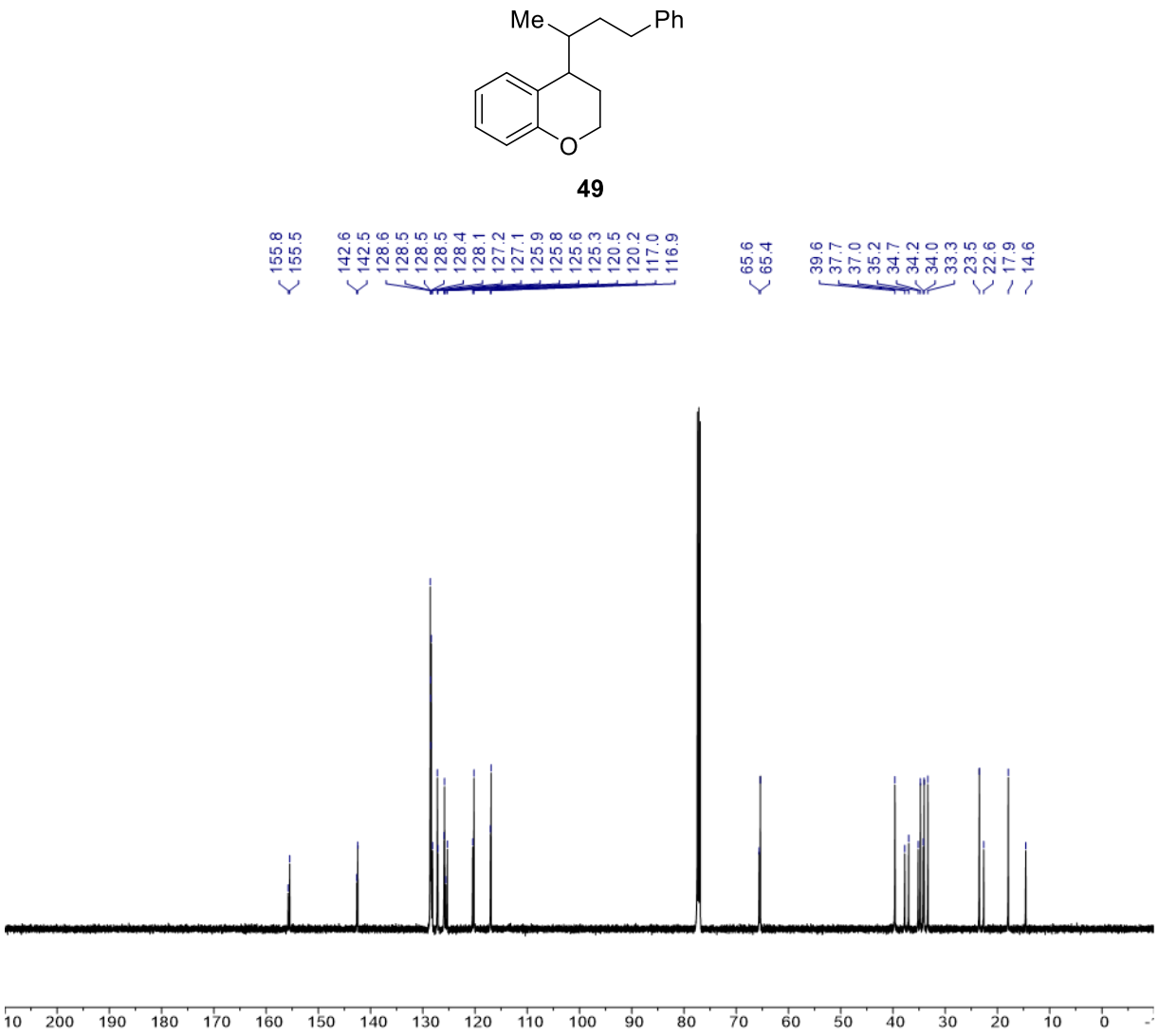


Figure S56. ^{13}C NMR spectrum of **49**, referenced to $CDCl_3$ (77.16 ppm).

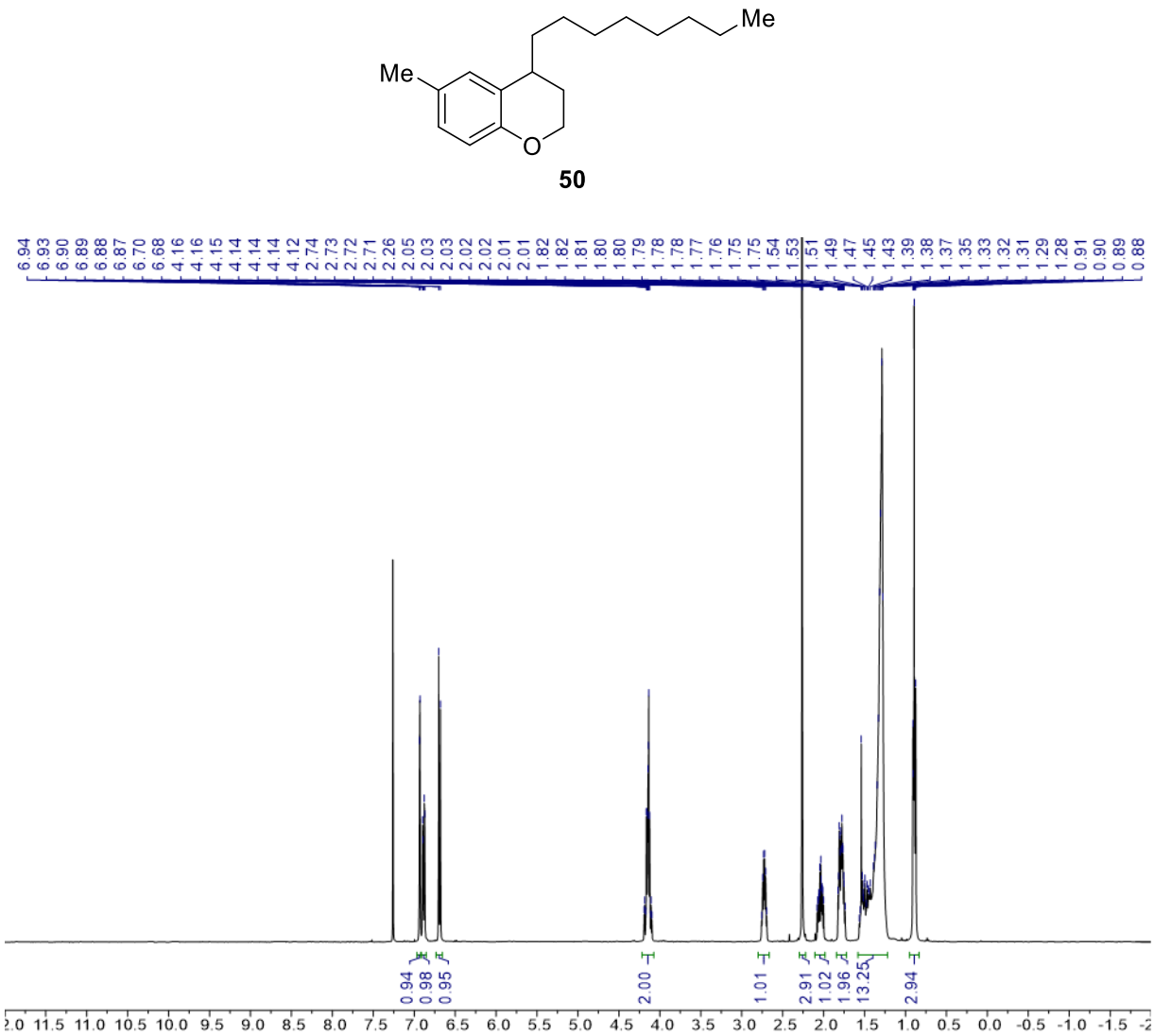


Figure S57. ^{1}H NMR spectrum of **50**, referenced to $CDCl_3$ (7.26 ppm).

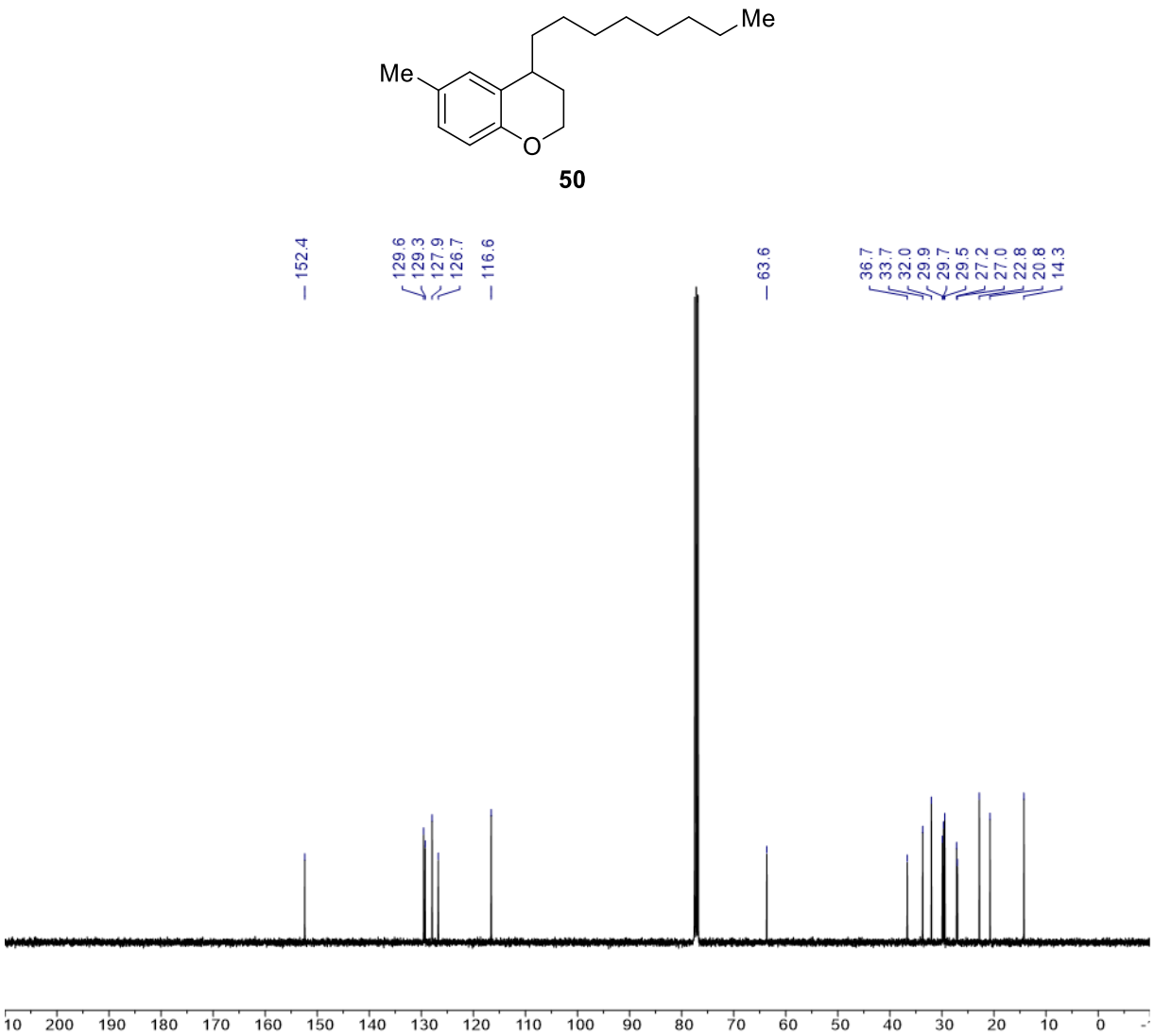


Figure S58. ^{13}C NMR spectrum of **50**, referenced to $CDCl_3$ (77.16 ppm).

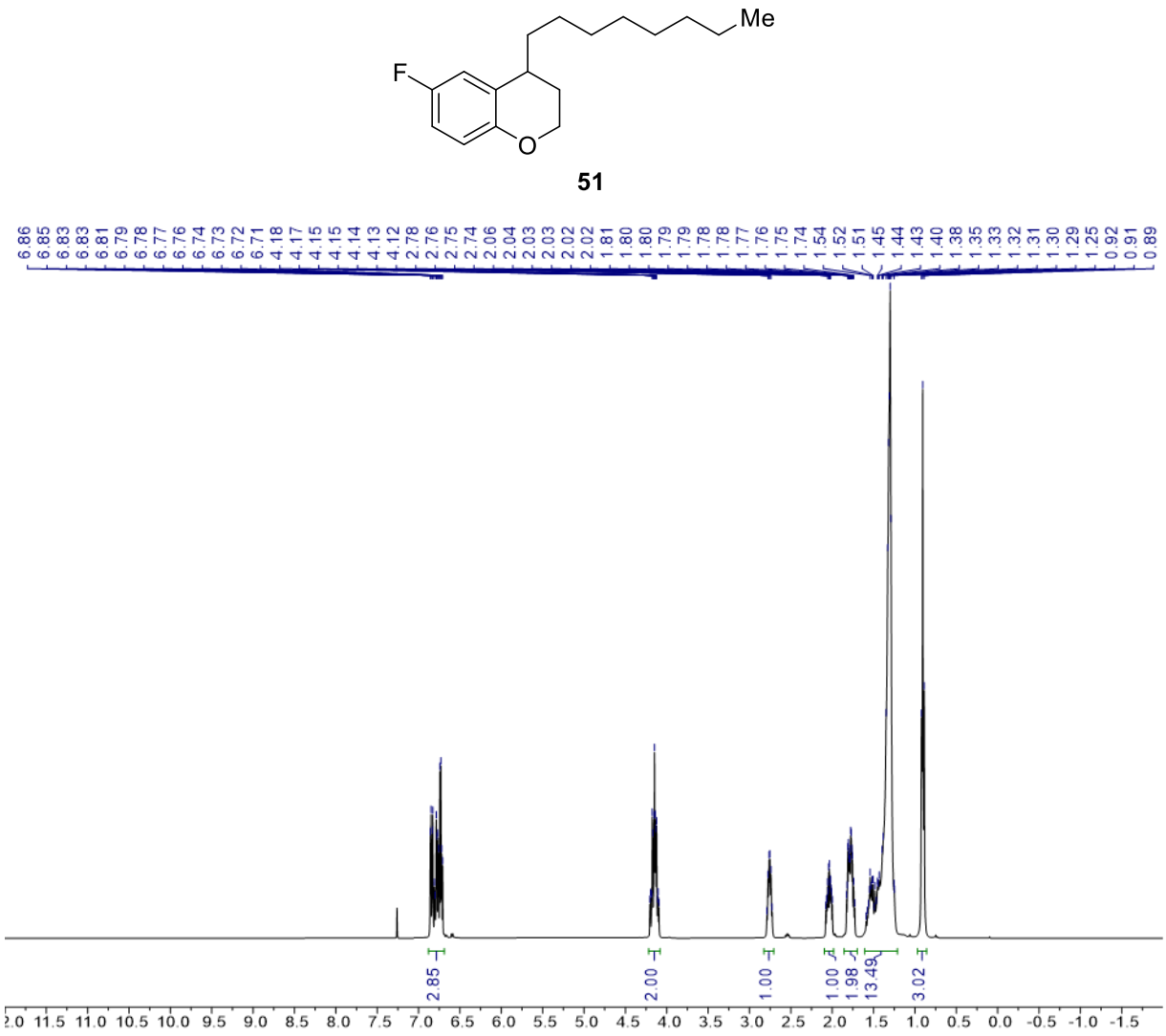


Figure S59. ^{1}H NMR spectrum of **51**, referenced to $CDCl_3$ (7.26 ppm).

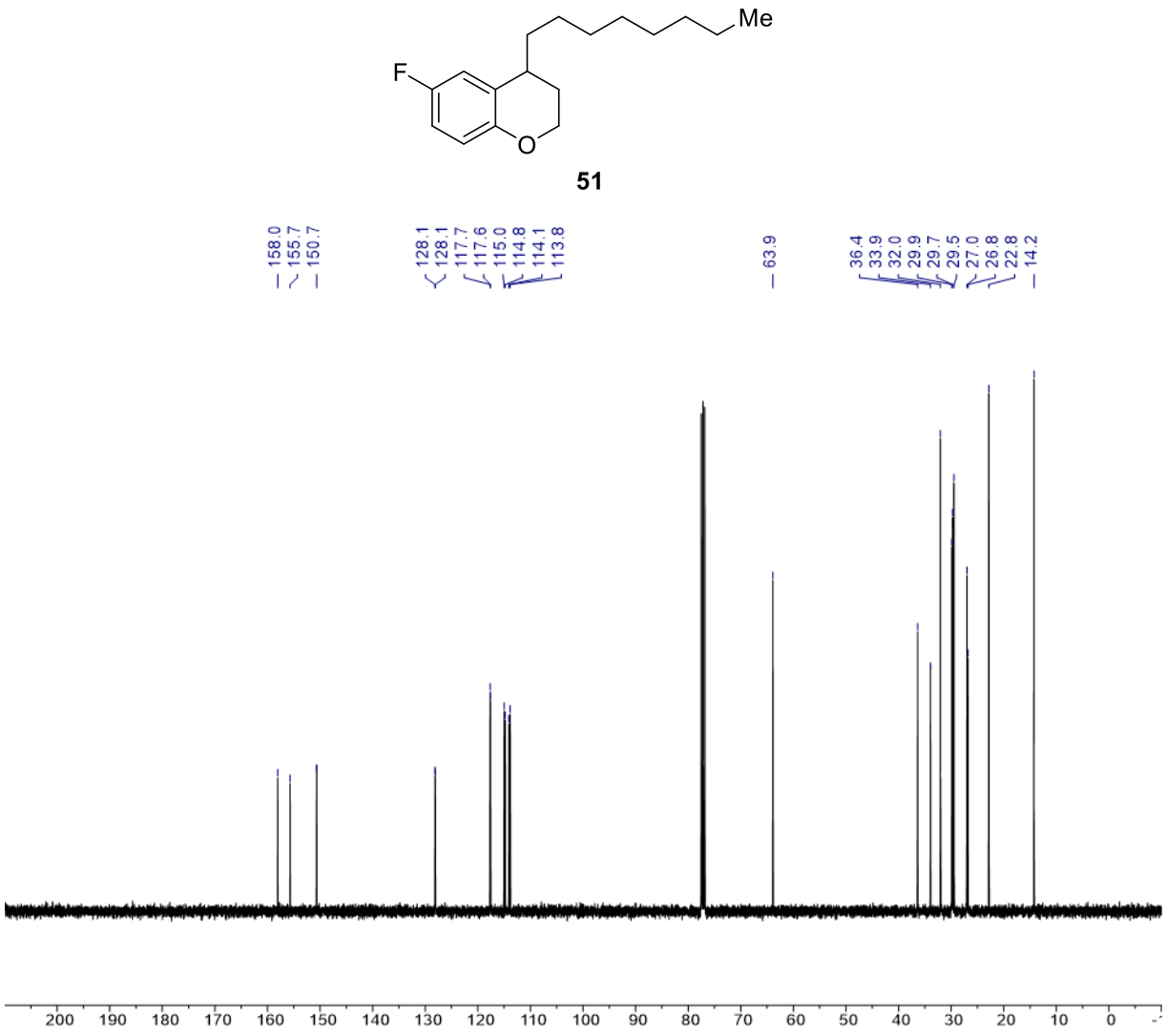


Figure S60. ^{13}C NMR spectrum of **51**, referenced to $CDCl_3$ (77.16 ppm).

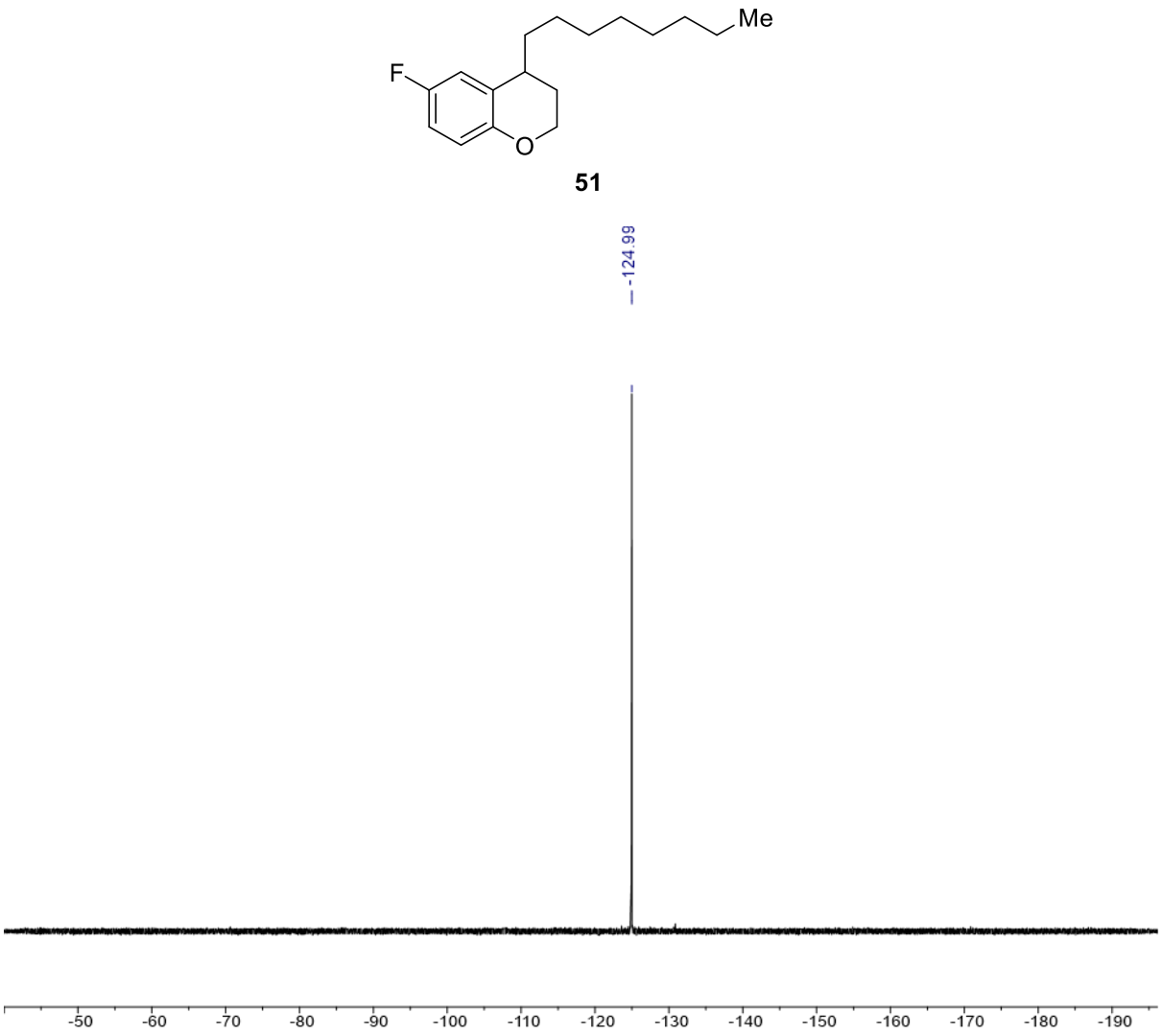


Figure S61. ^{19}F NMR spectrum of **51**, referenced to external trifluorotoluene (-63.72 ppm).

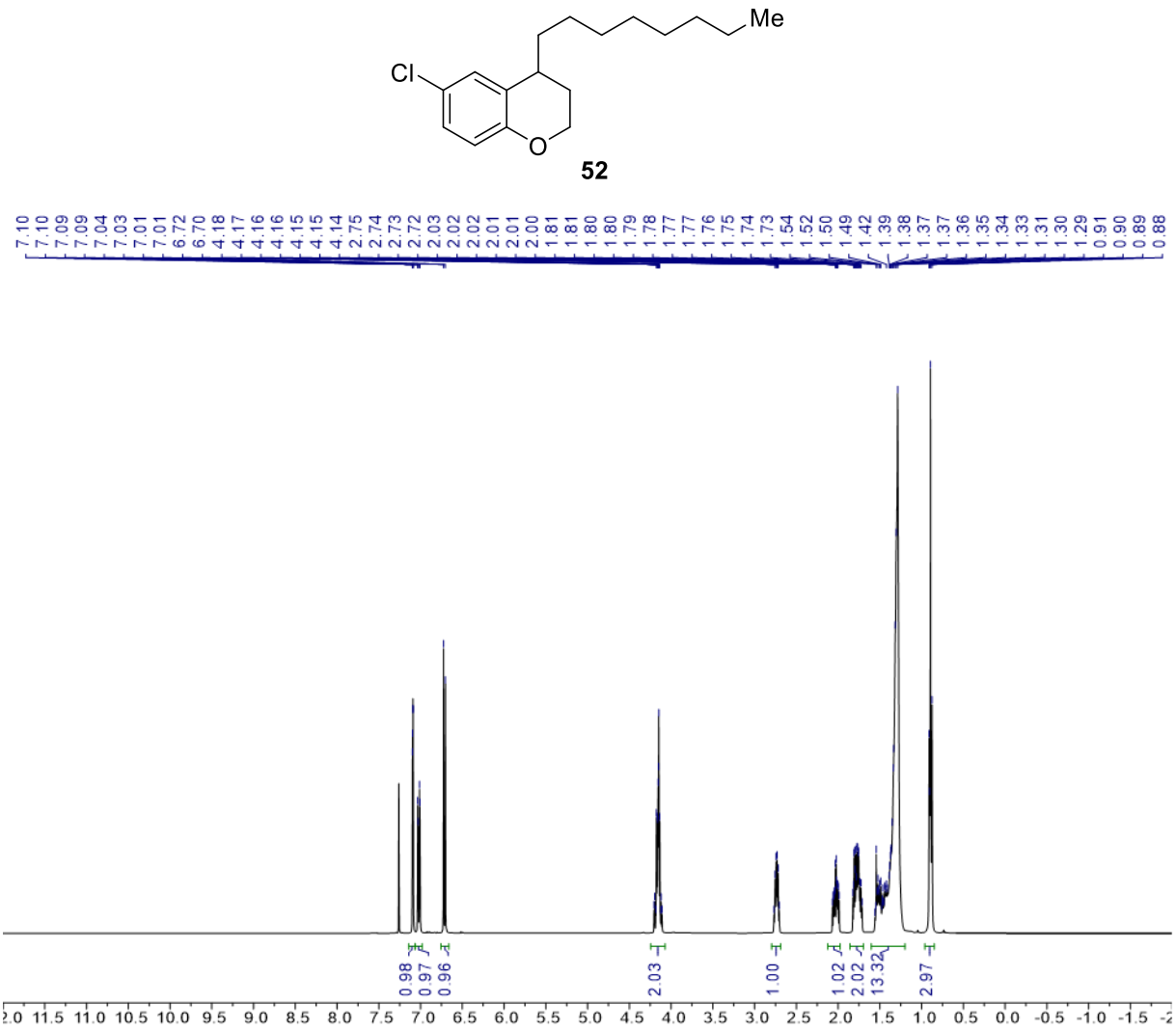


Figure S62. ^{1}H NMR spectrum of **52**, referenced to $CDCl_3$ (7.26 ppm).

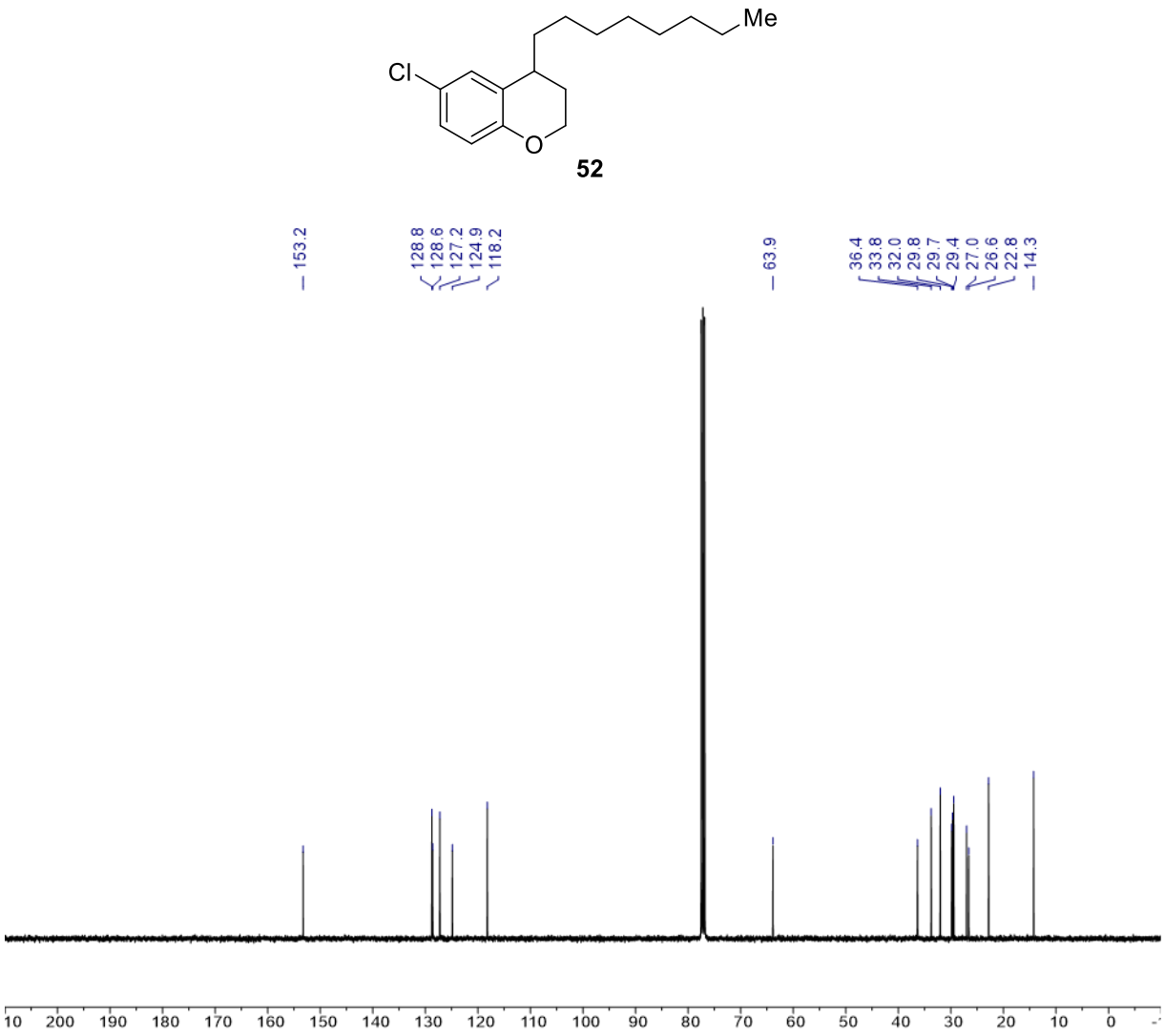


Figure S63. ^{13}C NMR spectrum of **52**, referenced to $CDCl_3$ (77.16 ppm).

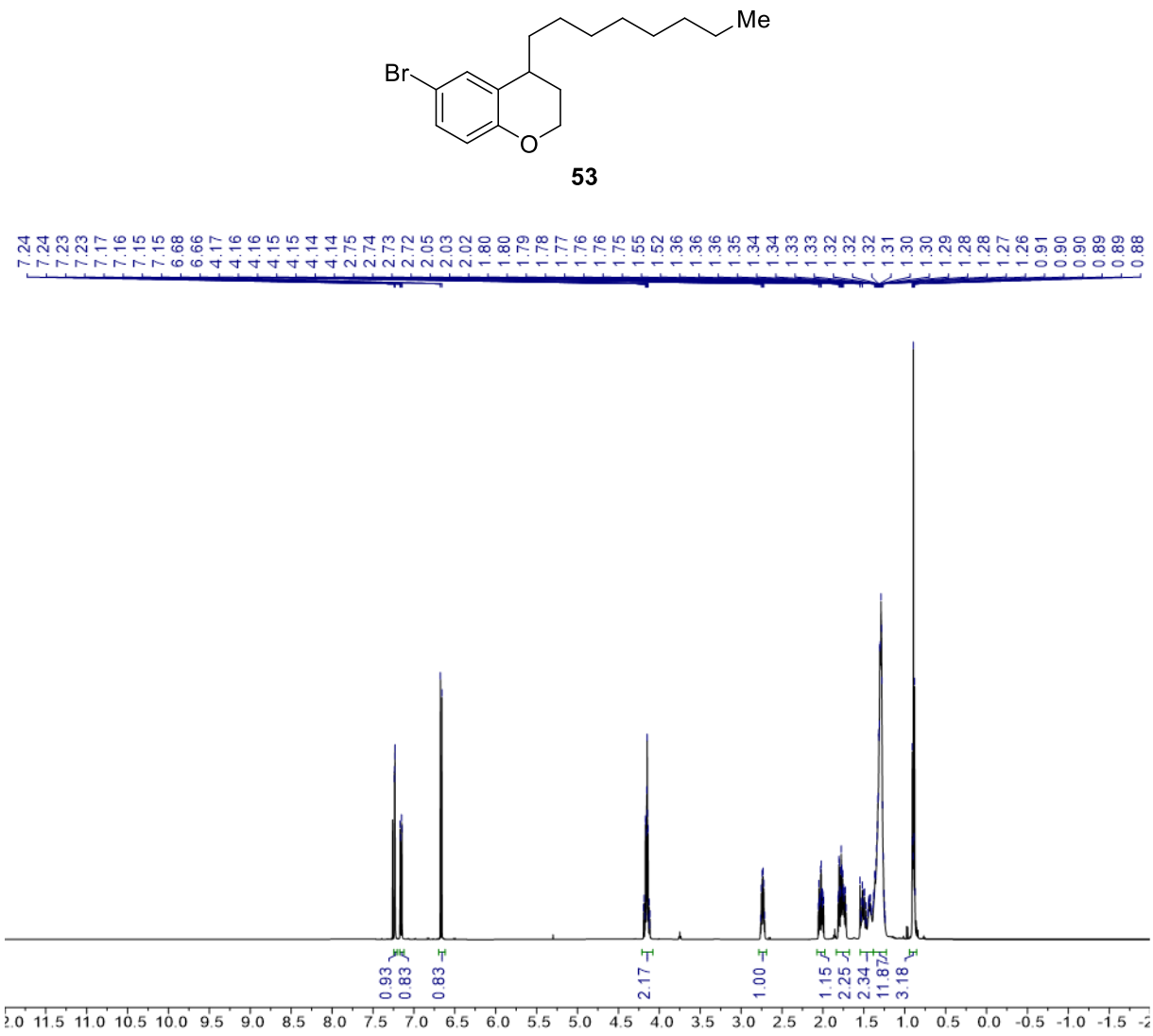


Figure S64. ^{1}H NMR spectrum of **53**, referenced to $CDCl_3$ (7.26 ppm).

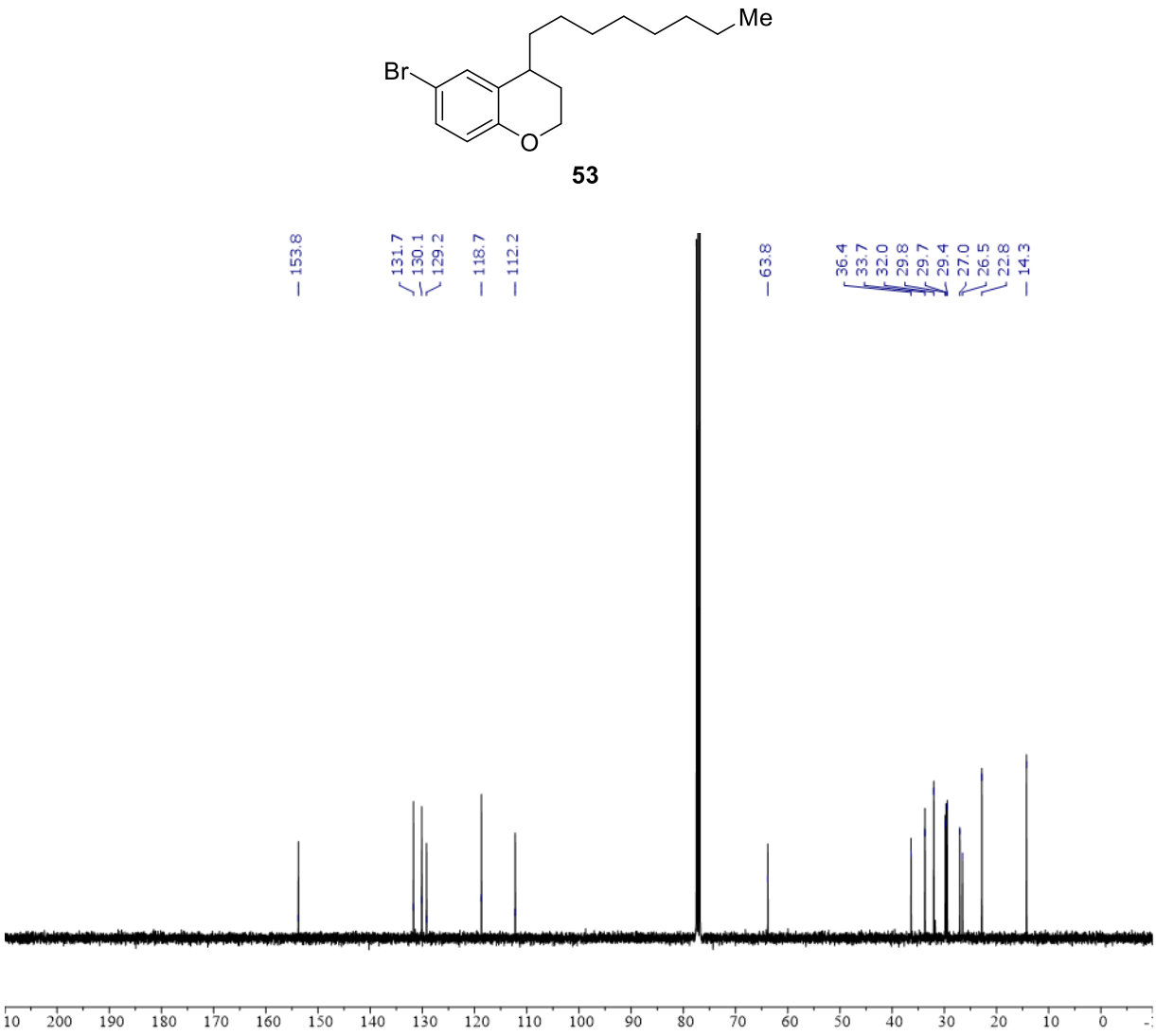


Figure S65. ^{13}C NMR spectrum of **53**, referenced to $CDCl_3$ (77.16 ppm).

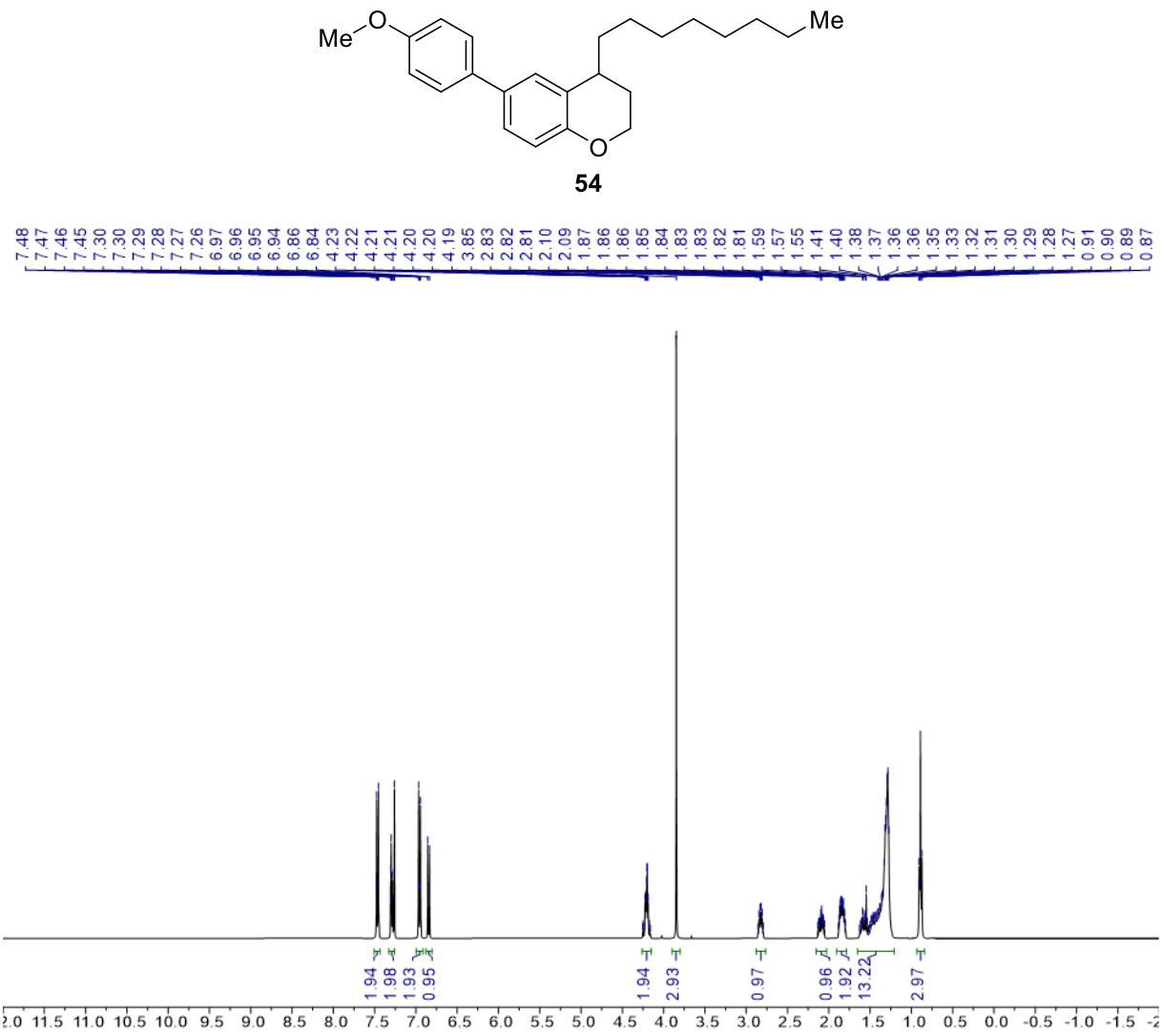


Figure S66. ^{1}H NMR spectrum of **54**, referenced to $CDCl_3$ (7.26 ppm).

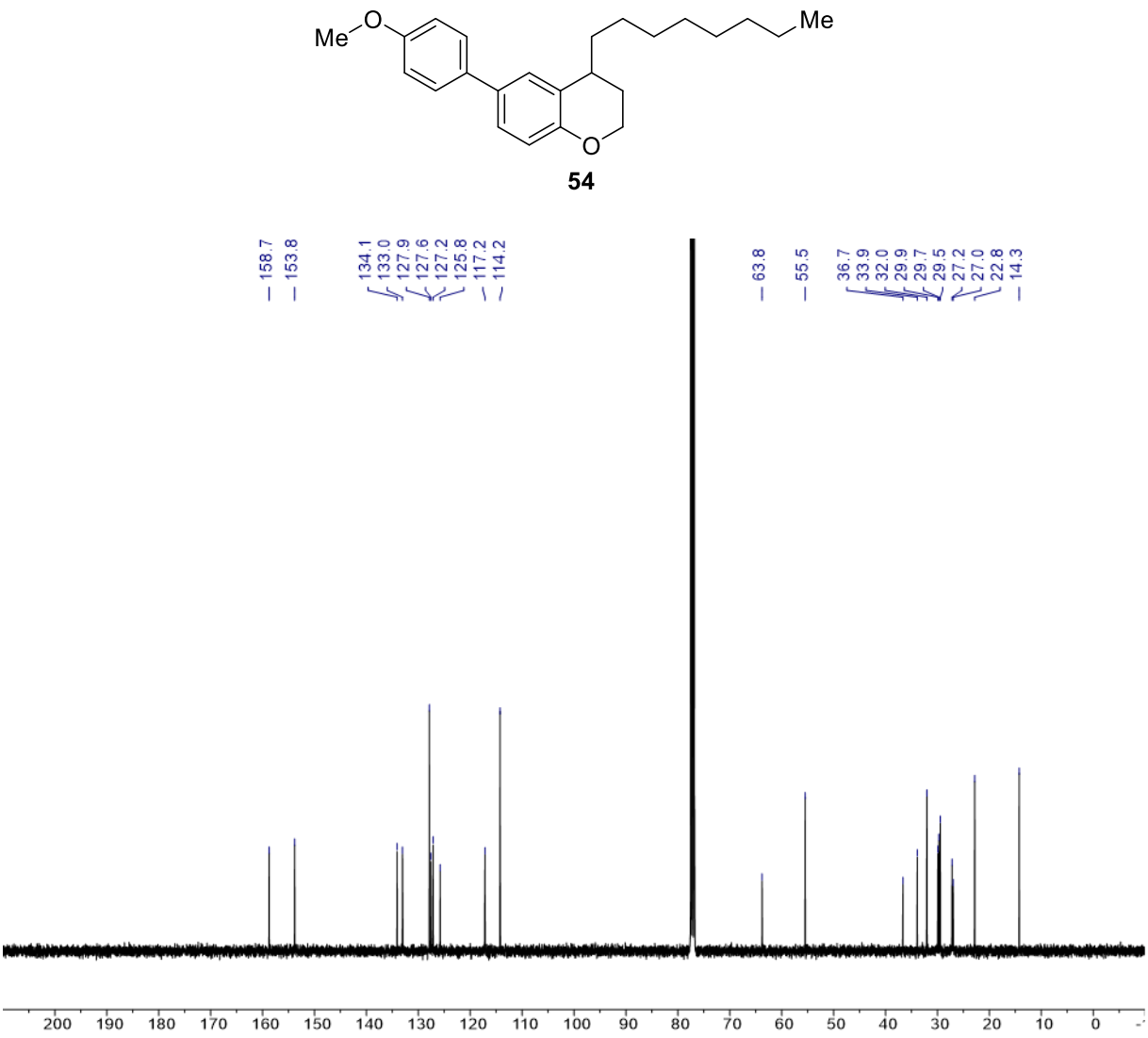


Figure S67. ^{13}C NMR spectrum of **54**, referenced to $CDCl_3$ (77.16 ppm).

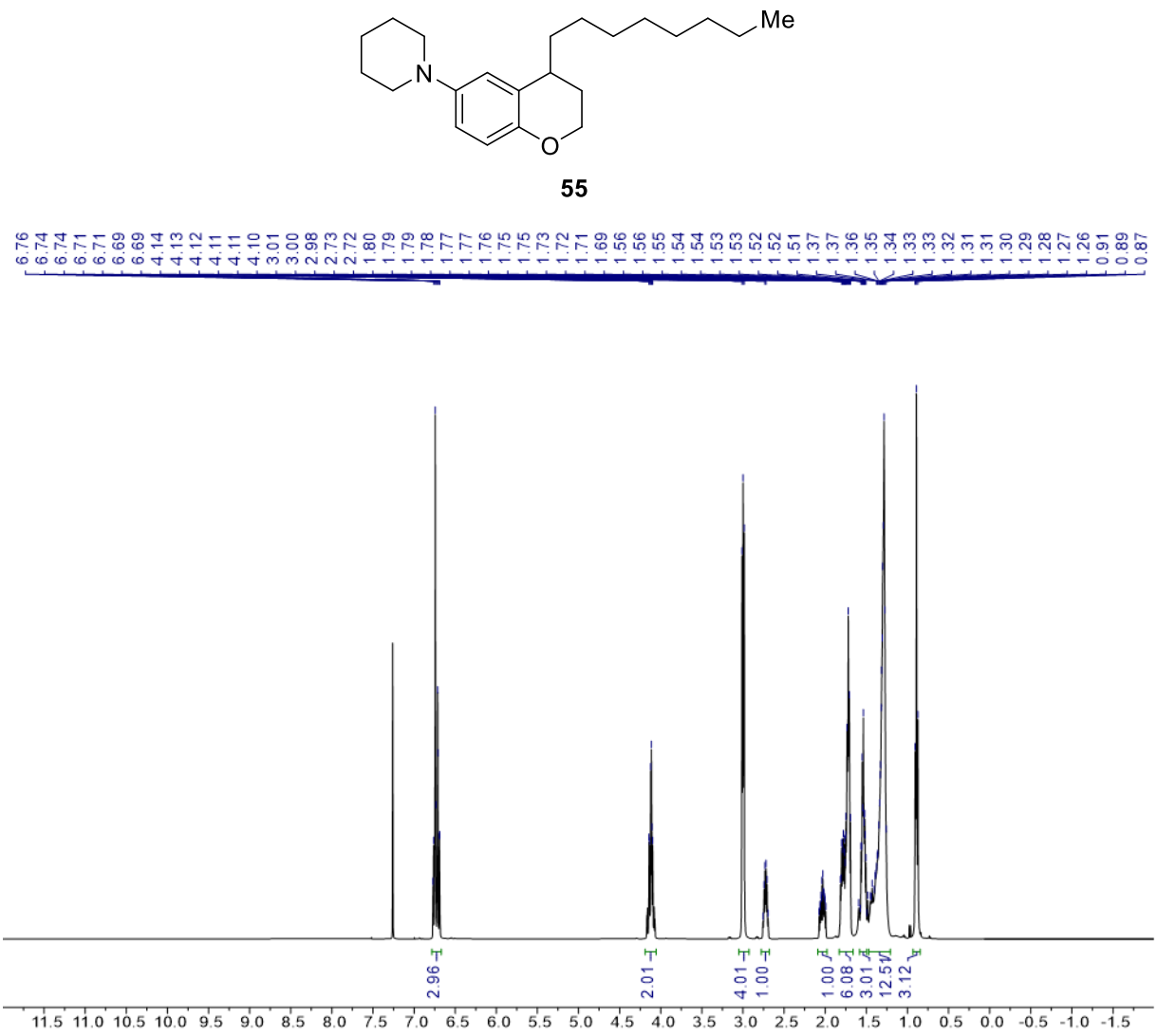


Figure S68. ^{1}H NMR spectrum of **55**, referenced to $CDCl_3$ (7.26 ppm).

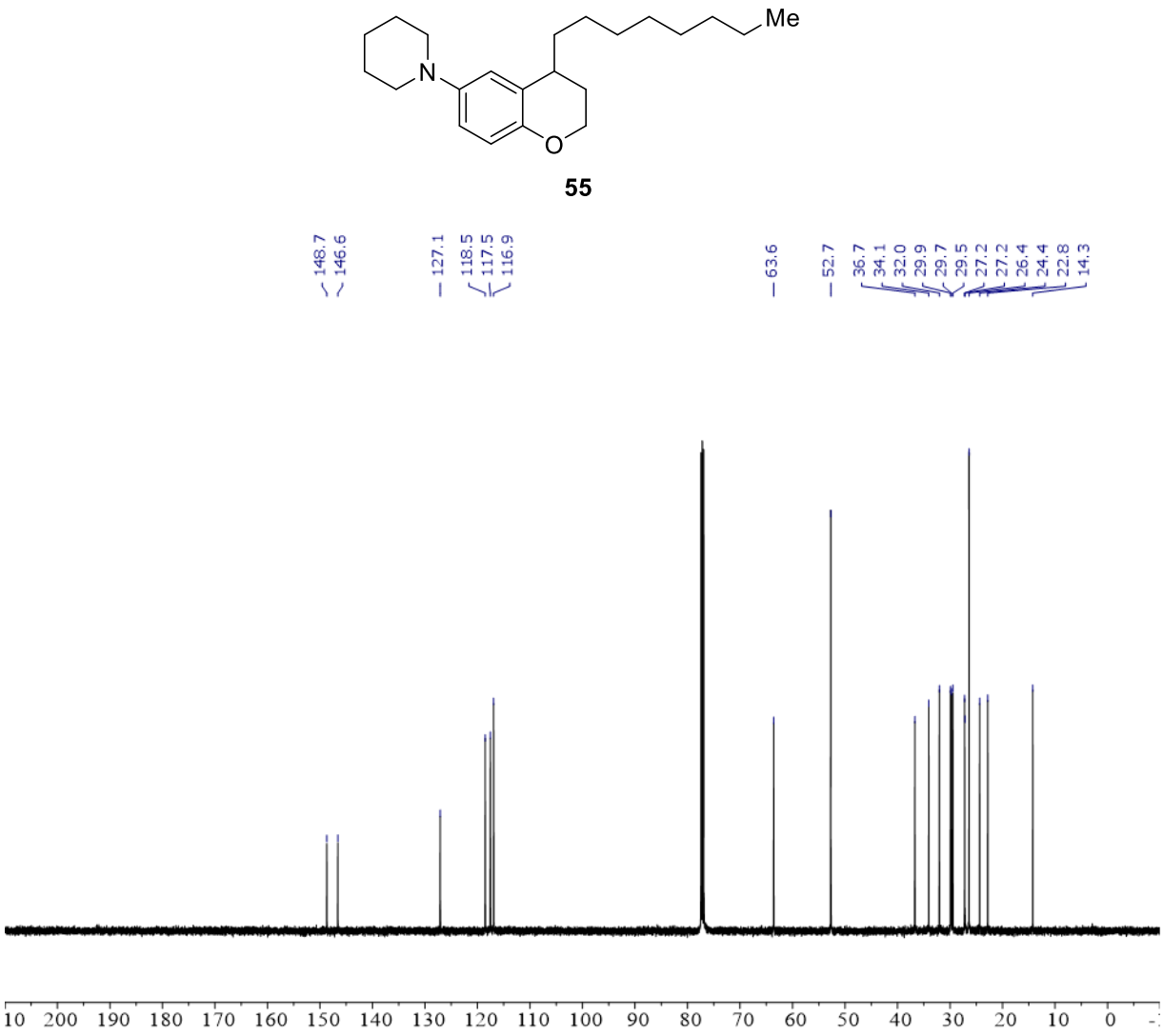


Figure S69. ^{13}C NMR spectrum of **55**, referenced to $CDCl_3$ (77.16 ppm).

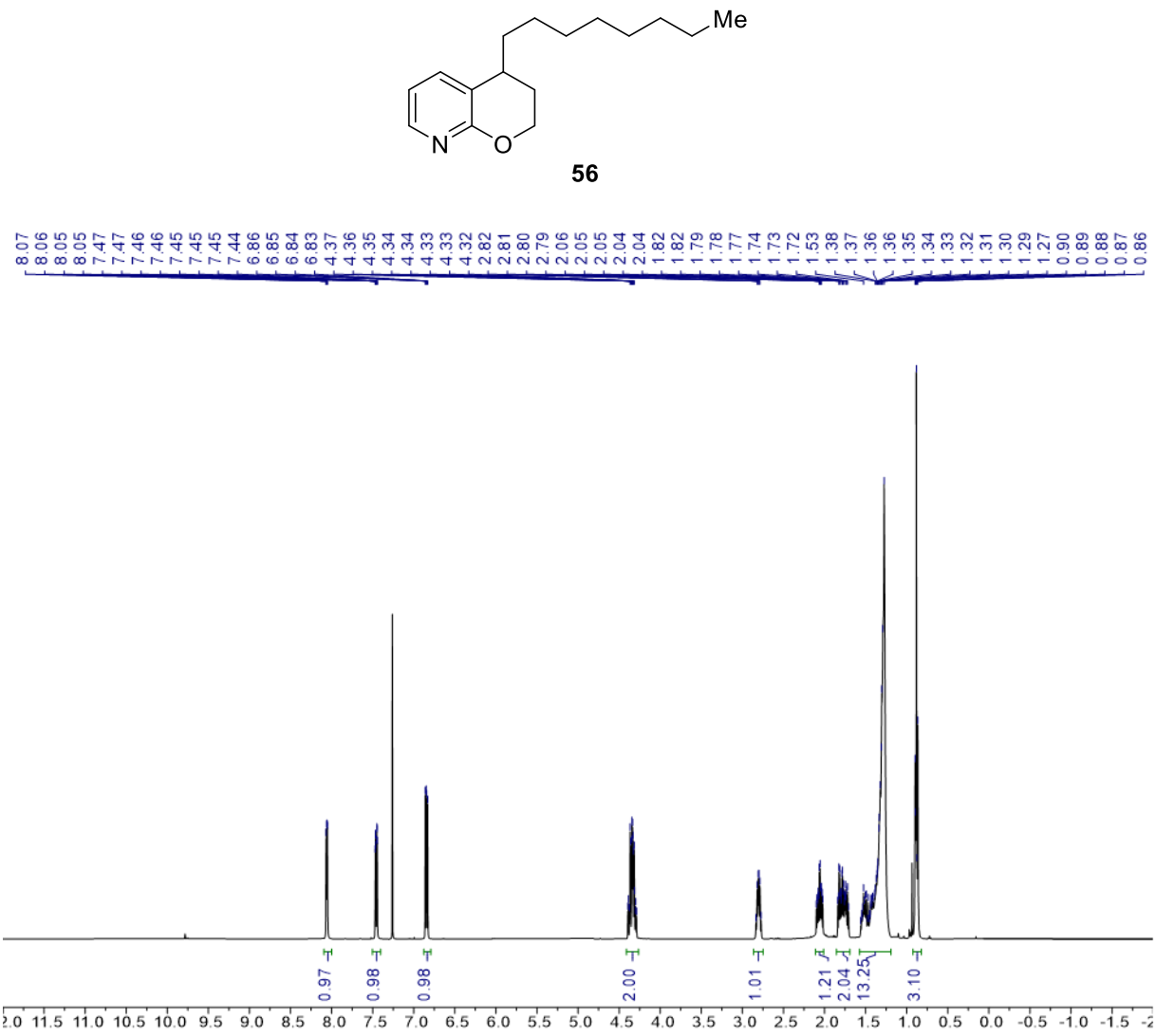


Figure S70. ^{1}H NMR spectrum of **56**, referenced to $CDCl_3$ (7.26 ppm).

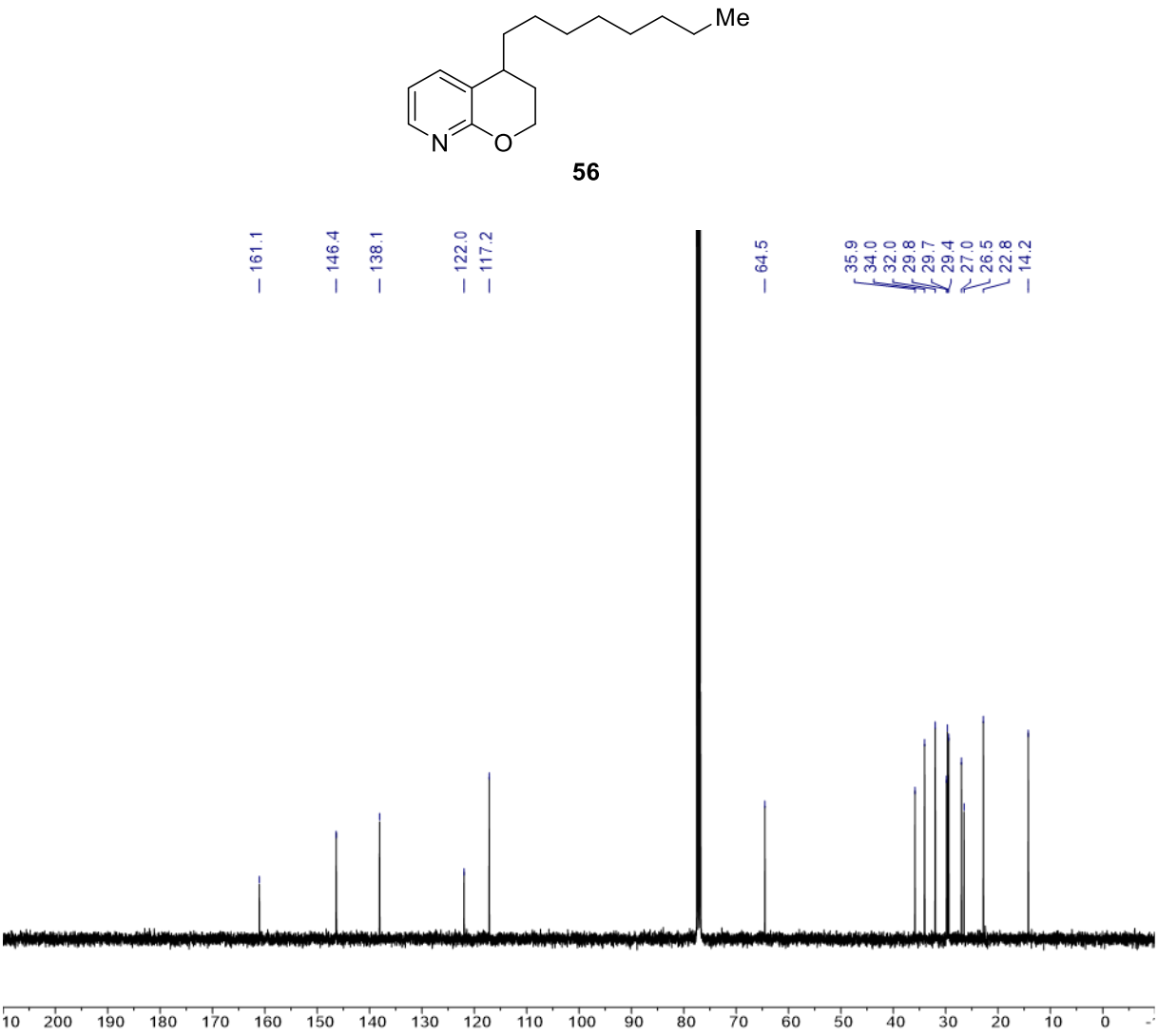


Figure S71. ^{13}C NMR spectrum of **56**, referenced to $CDCl_3$ (77.16 ppm).

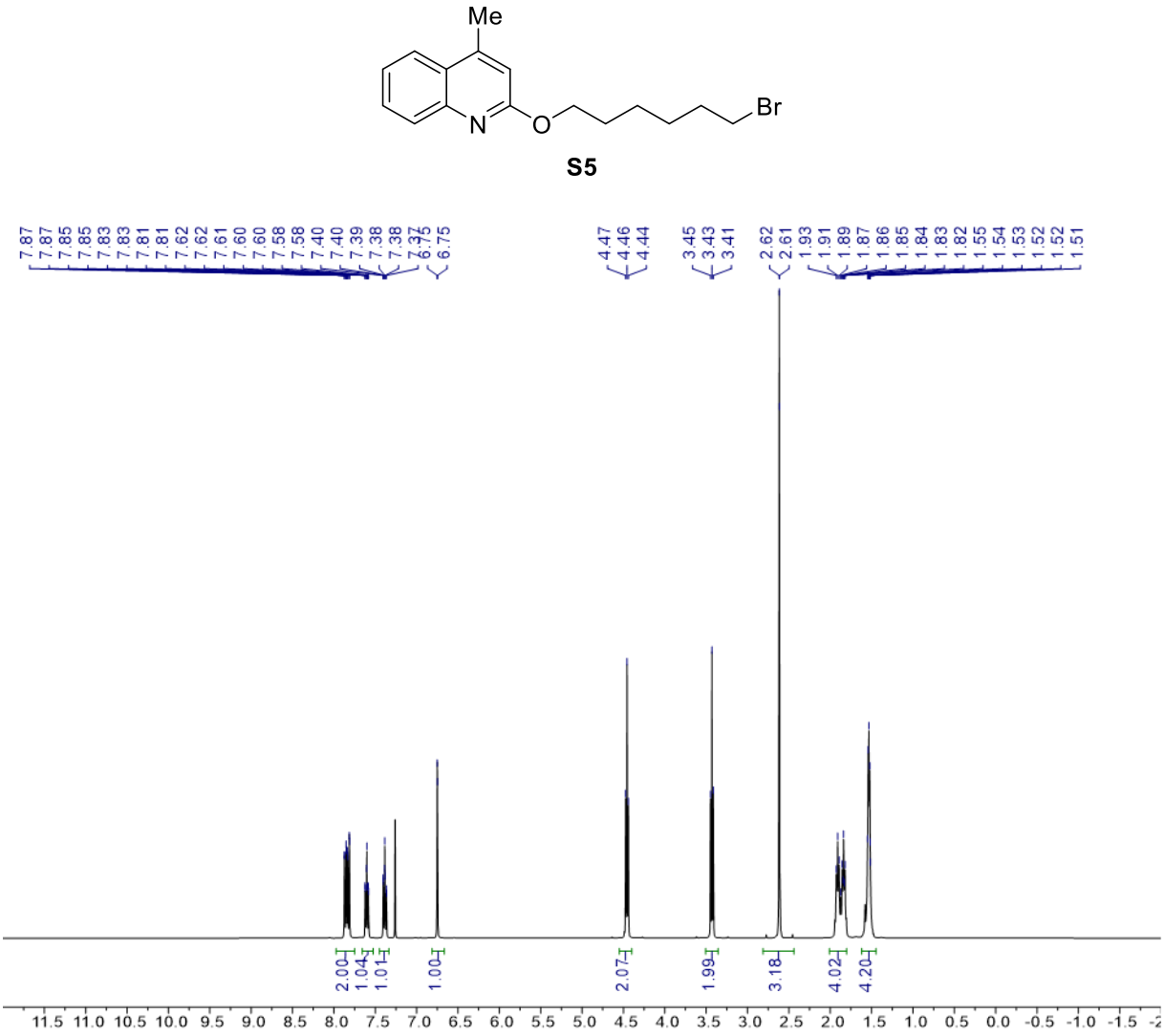


Figure S72. ^{1}H NMR spectrum of **S5**, referenced to $CDCl_3$ (7.26 ppm).

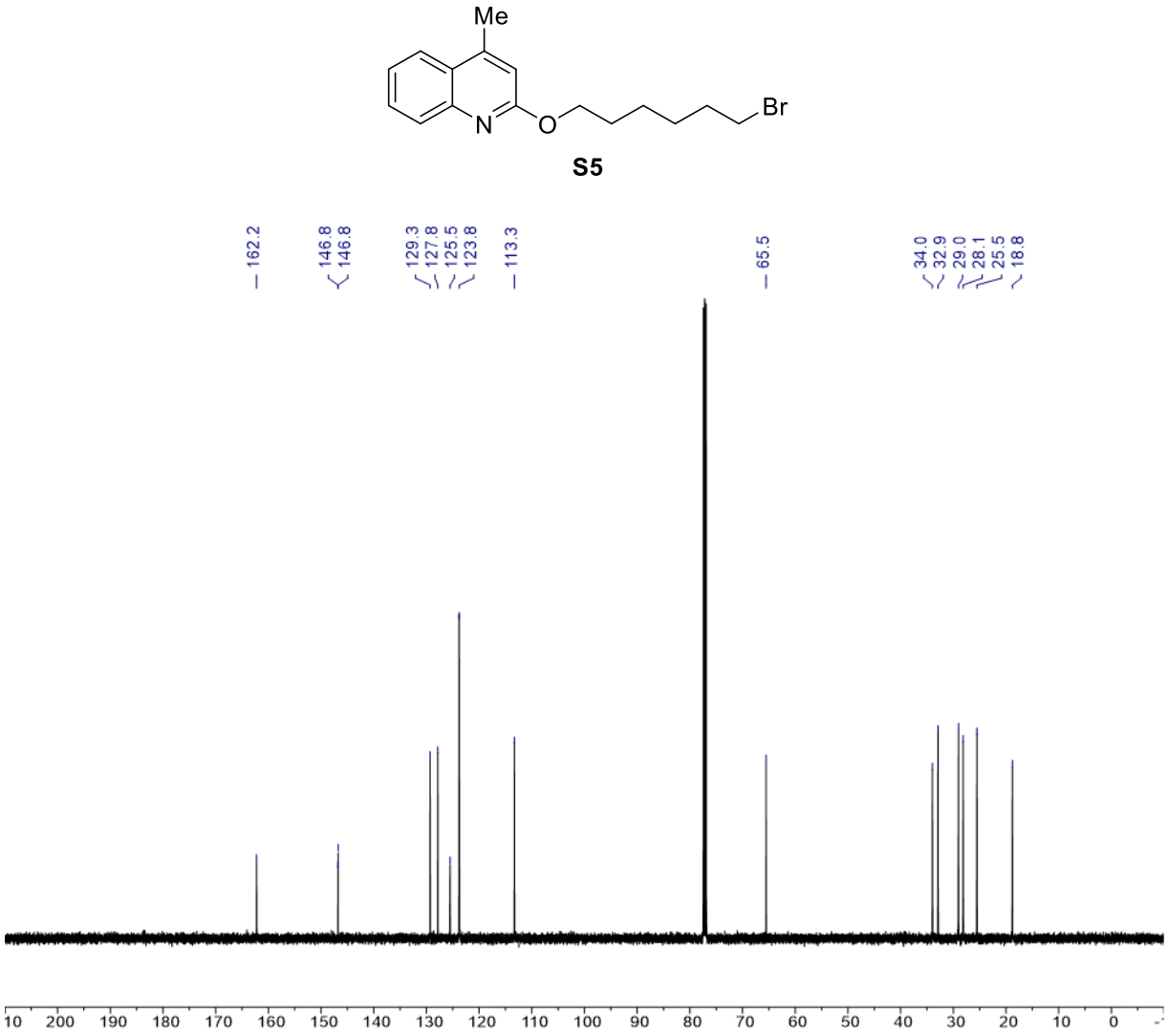


Figure S73. ^{13}C NMR spectrum of **S5**, referenced to $CDCl_3$ (77.16 ppm).

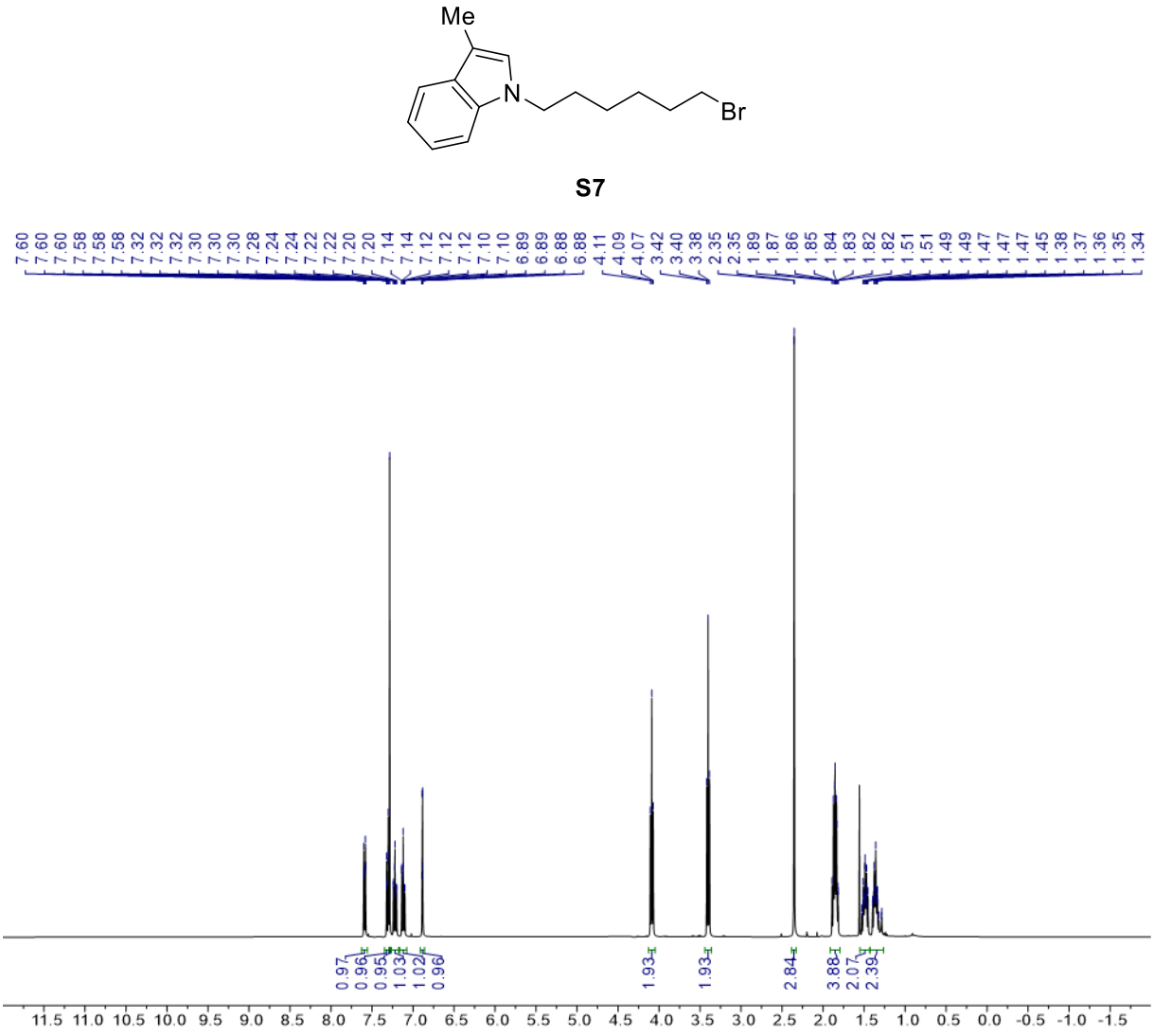
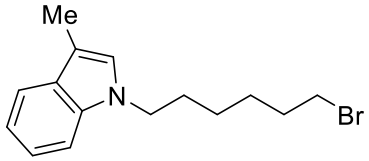


Figure S74. ^{1}H NMR spectrum of **S7**, referenced to $CDCl_3$ (7.26 ppm).



S7

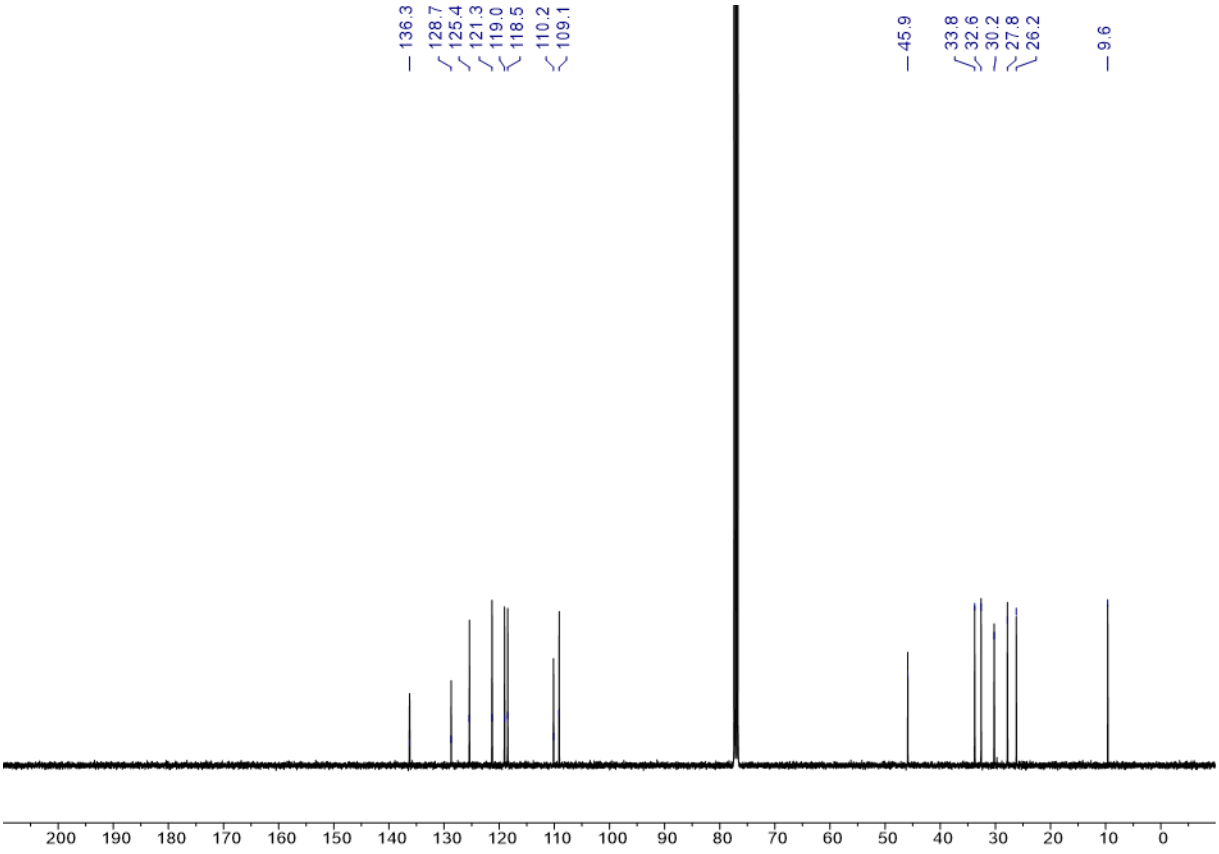


Figure S75. ^{13}C NMR spectrum of **S7**, referenced to $CDCl_3$ (77.16 ppm).

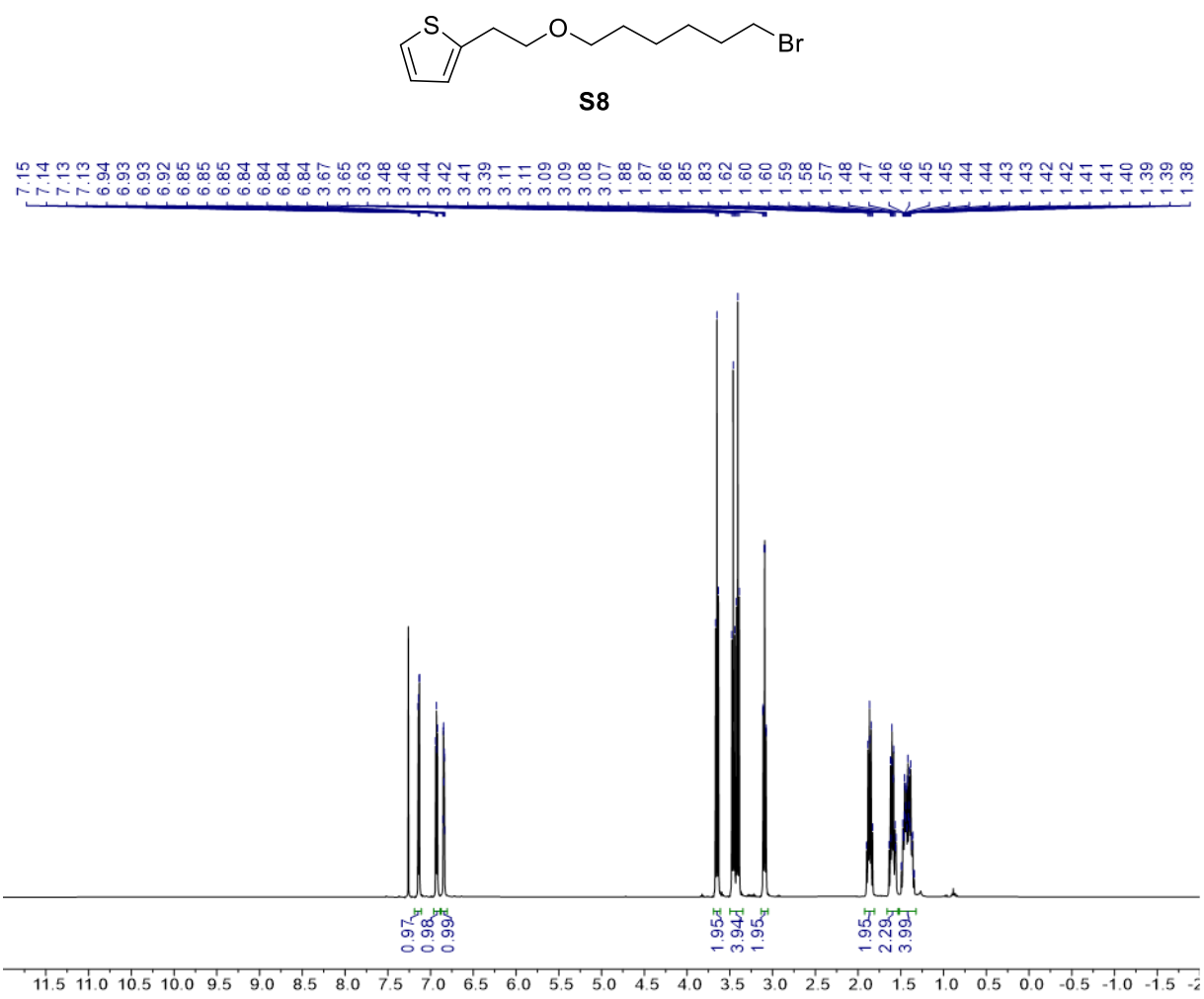


Figure S76. ^{1}H NMR spectrum of **S8**, referenced to $CDCl_3$ (7.26 ppm).

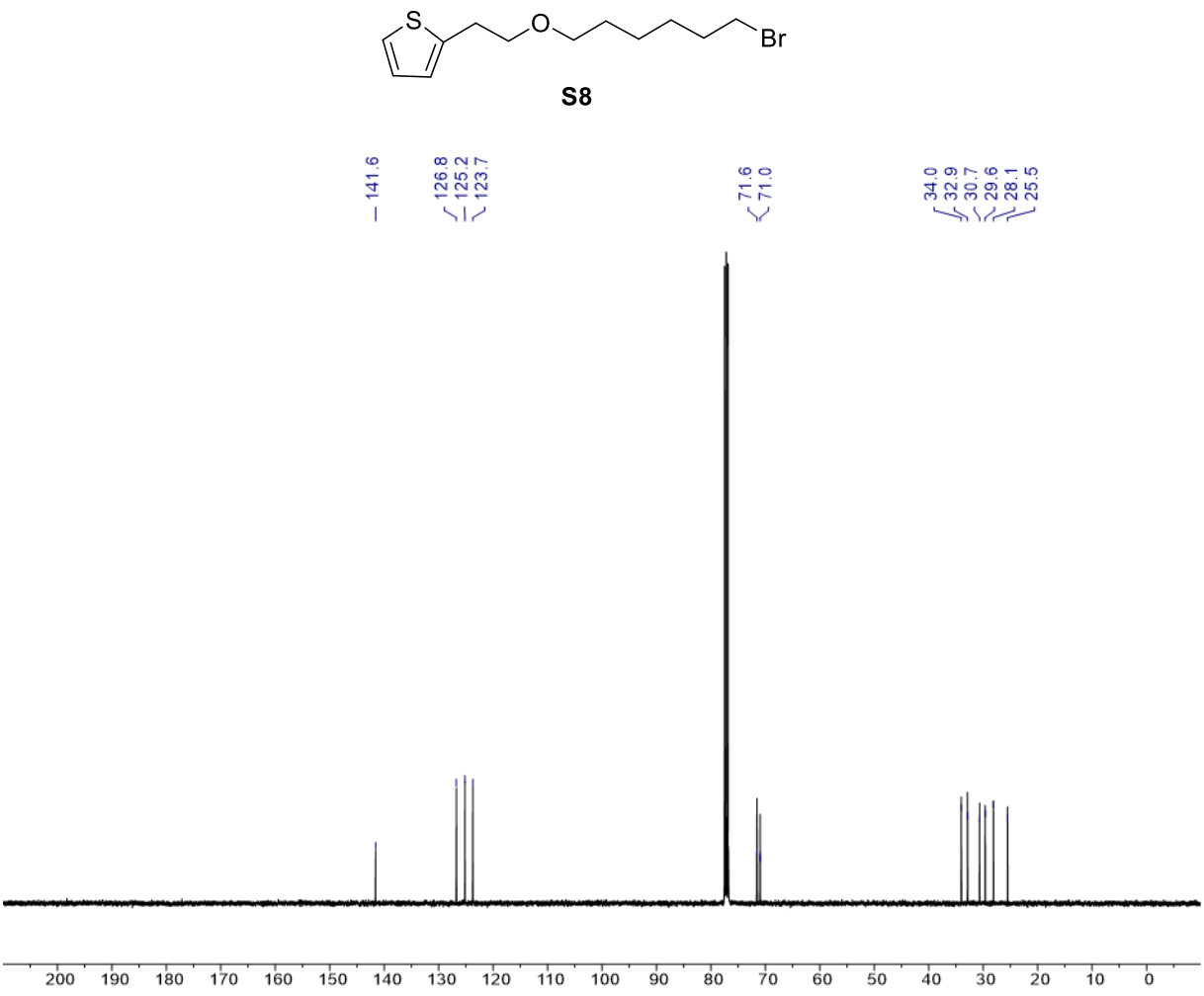


Figure S77. ^{13}C NMR spectrum of **S8**, referenced to $CDCl_3$ (77.16 ppm).

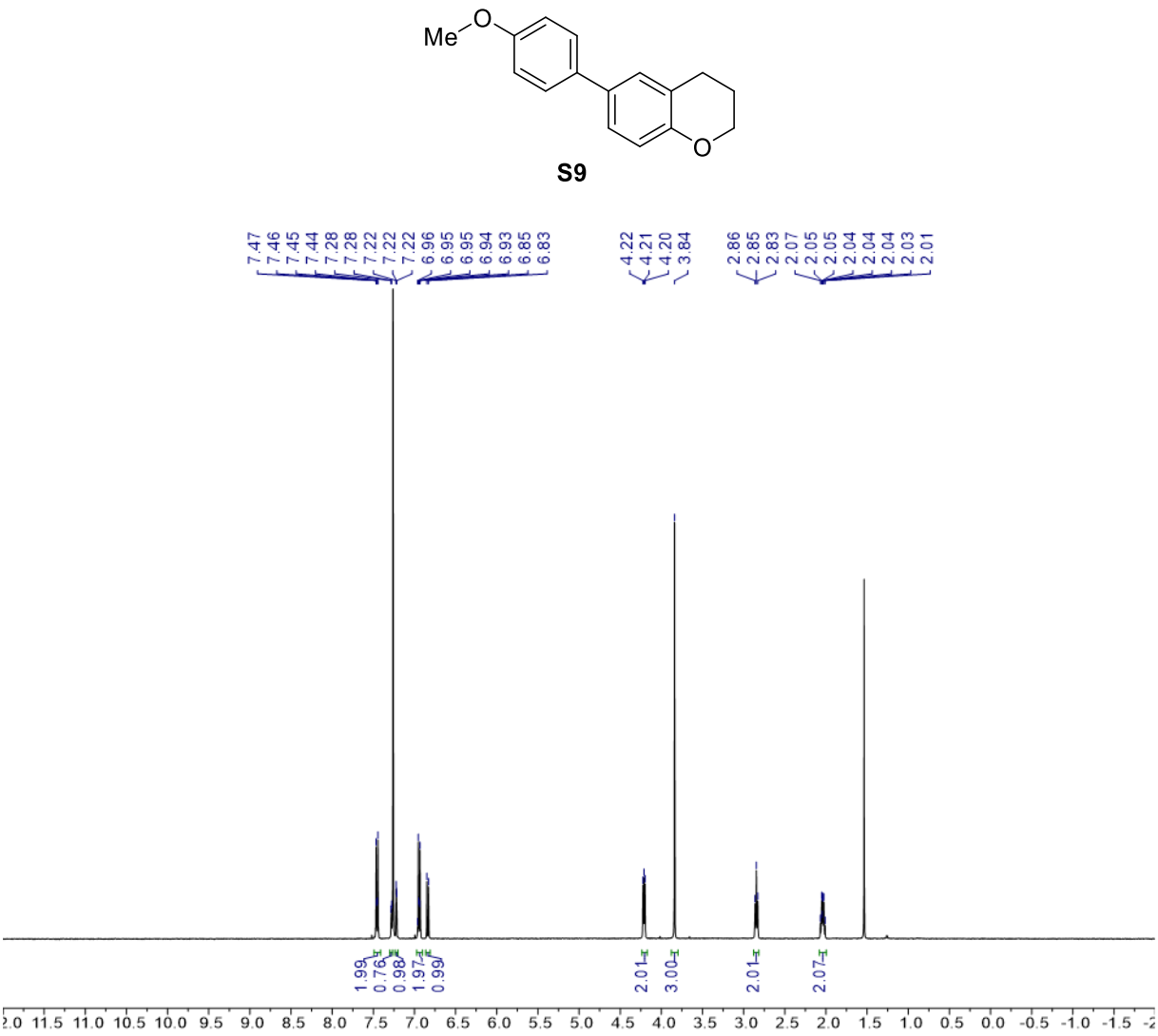


Figure S78. ^{1}H NMR spectrum of **S9**, referenced to $CDCl_3$ (7.26 ppm).

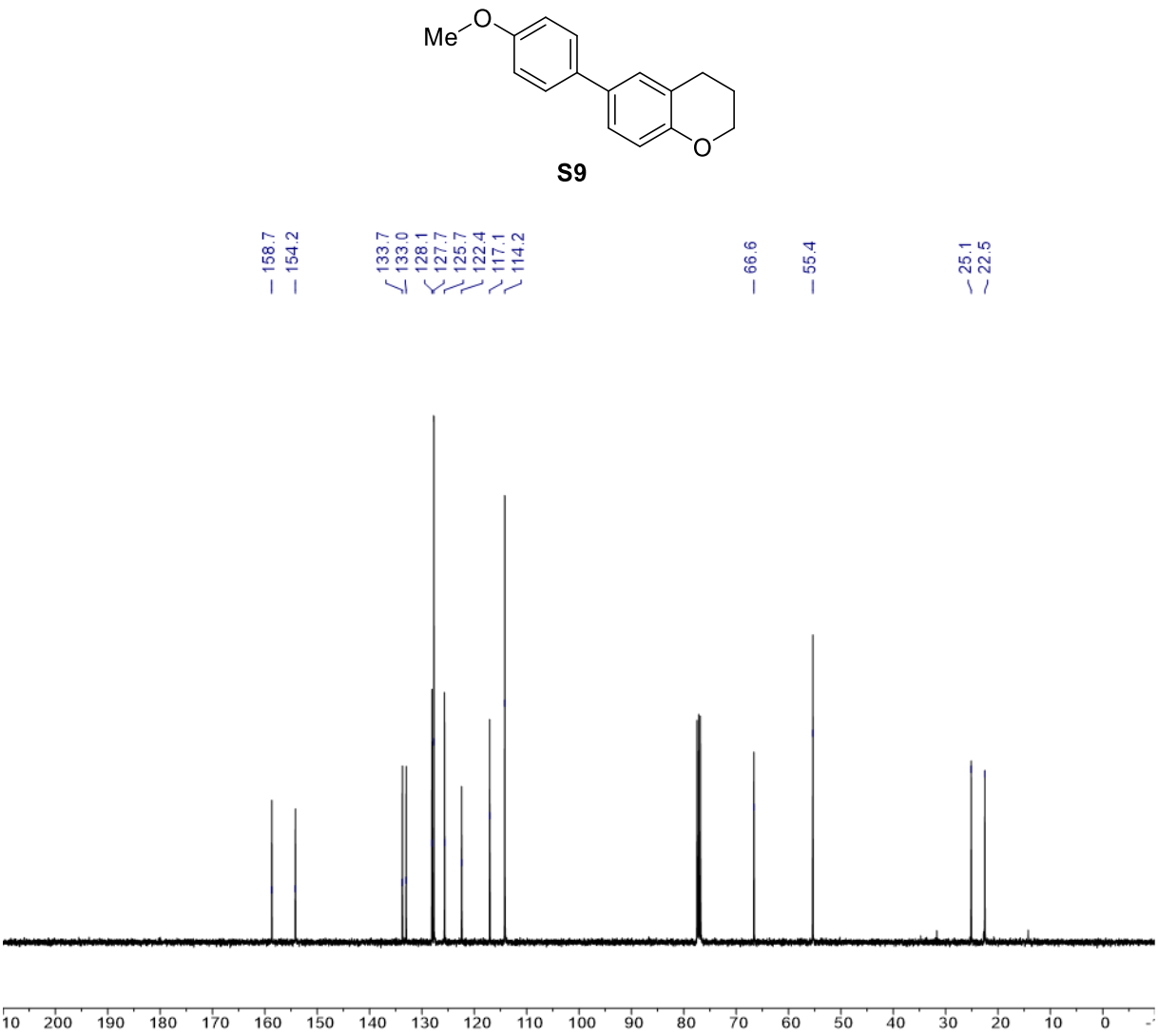


Figure S79. ^{13}C NMR spectrum of **S9**, referenced to $CDCl_3$ (77.16 ppm).

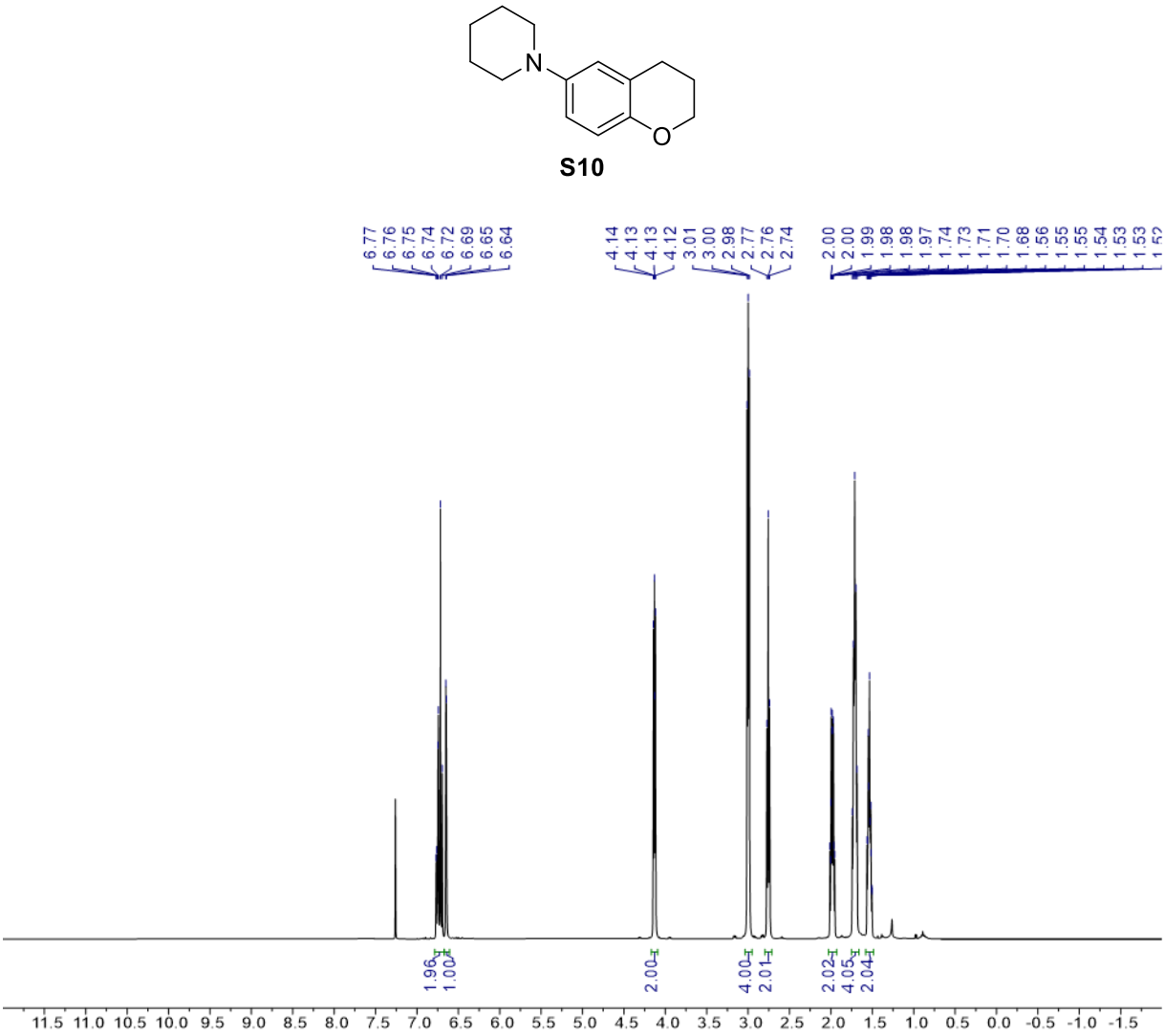


Figure S80. ^{1}H NMR spectrum of **S10**, referenced to $CDCl_3$ (7.26 ppm).

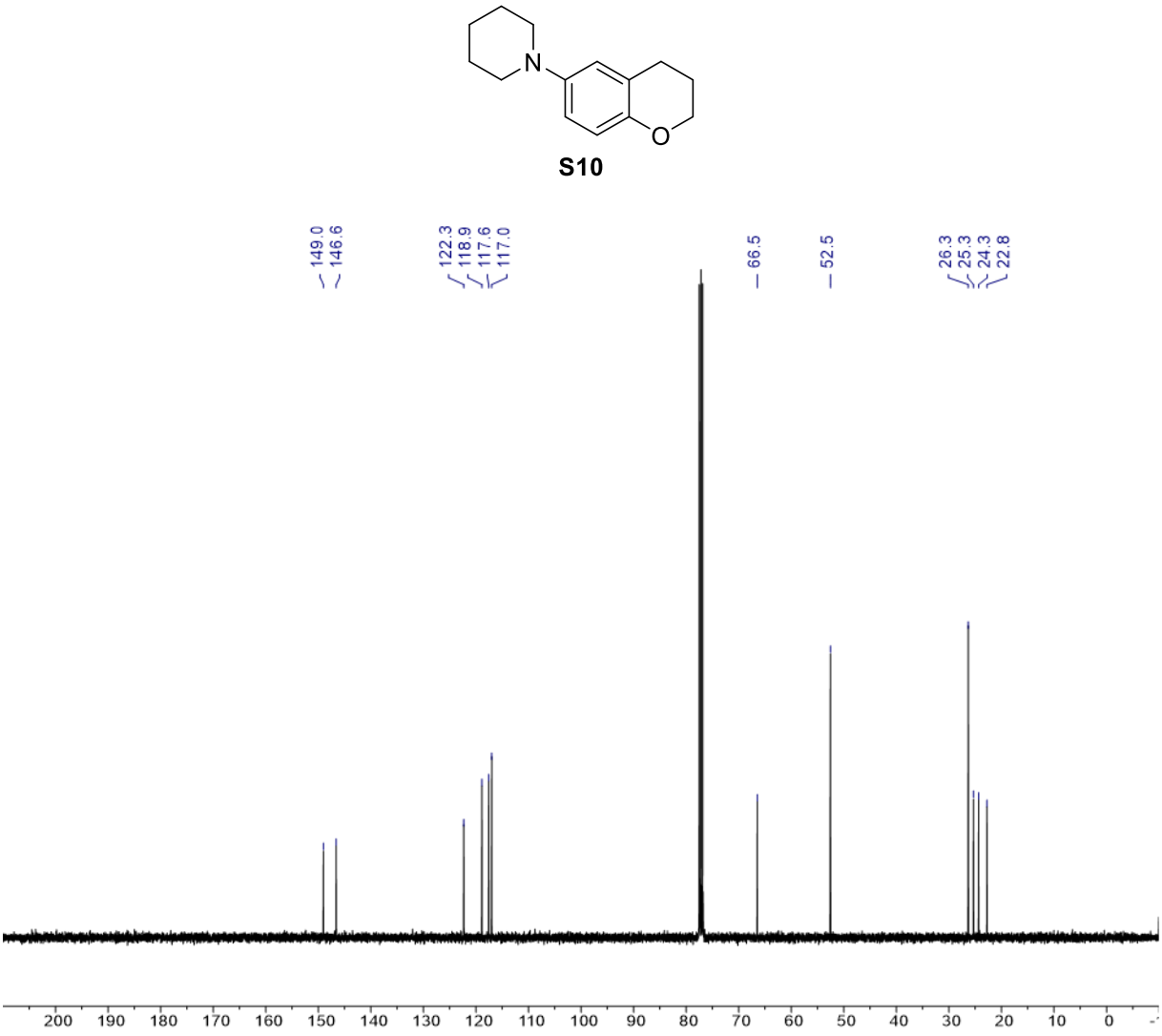


Figure S81. ^{13}C NMR spectrum of **S10**, referenced to $CDCl_3$ (77.16 ppm).

4. References

[1] Thomas, A. A.; Wang, H.; Zahrt, A. F.; Denmark, S. E. Structural, Kinetic, and Computational Characterization of the Elusive Arylpalladium(II)boronate Complexes in the Suzuki-Miyaura Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 3805-3821.

[2] Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K. Trialkylmanganate-Induced Cyclization of Allyl 2-Iodophenyl Ether, *N*,*N*-Diallyl-2-iodoaniline, and α-Iodo Acetal. *J. Org. Chem.* **1997**, *62*, 1910–1911.

[3] Binder, J. T.; Cordier, C. J.; Fu, G. C. Catalytic Enantioselective Cross-Couplings of Secondary Alkyl Electrophiles with Secondary Alkylmetal Nucleophiles: Negishi Reactions of Racemic Benzylic Bromides with Achiral Alkylzinc Reagents. *J. Am. Chem. Soc.* **2012**, *134*, 17003–17006.

[4] Bissel, E. R.; Finger, M. Organic Deuterium Compounds. II. Some Deuterated Tetrahydrofurans[1]. *J. Org. Chem.* **1959**, *24*, 1259–1261.

[5] Crockett, M. P.; Aguirre, L. S.; Jimenez, L. B.; Hsu, H.-H.; Thomas, A. A. Preparation of Highly Reactive Lithium Metal Dendrites for the Synthesis of Organolithium Reagents. *J.Am. Chem. Soc.* DOI: 10.1021/jacs.2c07207.

[6] Gilman, H.; Cartledge, F. K. THE ANALYSIS OF ORGANOLITHIUM COMPOUNDS. *J. Organomet. Chem.* **1964,** *2*, 447-454.

[7] Wilson, S. R.; Misra, R. N.; Georgiadis, G. M. Alkoxide-Promoted [1,3] Rearrangements of 1,3-Dithianes. *J. Org. Chem.* **1980**, *45*, 2460–2468.

[8] McManus, J. B.; Nicewicz, D. A. Direct C–H Cyanation of Arenes via Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 2880–2883.

[9] Li, Z.; Sun, H.-M.; Shen, Q. Iron-mediated inter- and intramolecular reductive cross-coupling of unactivated alkyl chlorides with aryl bromides. *Org. Biomol. Chem.* **2016,** *14*, 3314-3321.

[10] Bradsher, C. K.; Reames, D. C. Oxygen Heterocycles by the Parham Cyclialkylation. *J. Org. Chem.* **1981,** *46*, 1384-1388.

[11] Schmidt, B.; Krehl, S.; Sotelo-Meza, V. Synthesis of Chromanes through RCM–Transfer Hydrogenation. *Synthesis* **2012**, *44*, 1603-1613.

[12] Baraldi, P. G.; Romagnoli, R.; Nuñez, M. d. C.; Perretti, M.; Paul-Clark, M. J.; Ferrario, M.; Govoni, M.; Benedini, F.; Ongini, E. Synthesis of Nitro Esters of Prednisolone, New Compounds Combining Pharmacological Properties of Both Glucocorticoids and Nitric Oxide. *J. Med. Chem.* **2004**, *47*, 711–719.

[13] Shi, D.-H.; Harjani, J. R.; Gable, R. W.; Baell, J. B. Synthesis of 3-(Alkylamino)-, 3-(Alkoxy)-, 3-(Aryloxy)-, 3-(Alkylthio)-, and 3-(Arylthio)-1,2,4-triazines by Using a Unified Route with 3-(Methylsulfonyl)-1,2,4-triazine. *Eur. J. Org. Chem.*, **2016**, 2842-2850.

[14] Taylor, E. C.; Macor, J. E.; Pont, J. L. INTRAMOLECULAR DIELS-ALDER REACTIONS OF 1,2,4-TRIAZINES. A GENERAL SYNTHESIS OF FURO[2,3-b]PYRIDINES, 2,3-DIHYDROPYRANO[2,3-b]PYRIDINES, AND PYRROLO[2,3-b]PYRIDINES[1]. *TETRAHEDRON*, **1987**, *43*, 5145-5158.