Supporting Information

Facile Synthesis of Diiodoheteroindenes and Understanding Their Sonogashira Cross-Coupling Selectivity for the Construction of Unsymmetrical Enediynes

Alexander V. Ponomarev,[a] Natalia A. Danilkina,[a] Julia S. Okuneva,[a] Aleksandra A. Vidyakina,[a] Ekaterina A. Khmelevskaya,[a] Alexander S. Bunev[b], Andrey M. Rumyantsev,[c] Anastasia I. Govdi,[a] Thomas Suarez[d], Igor V. Alabugin*[d], Irina A. Balova*[a]

[a]Institute of Chemistry, Saint Petersburg State University (SPbU), Saint Petersburg, 199034, Russia, E-mail: i.balova@spbu.ru

[b]Medicinal Chemistry Center, Tolyatti State University, Tolyatti, 445020, Russia

[c]Department of Genetics and Biotechnology, Saint Petersburg State University (SPbU), Saint Petersburg, 199034, Russia,

[d]Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306, USA. E-mail: alabugin@chem.fsu.edu

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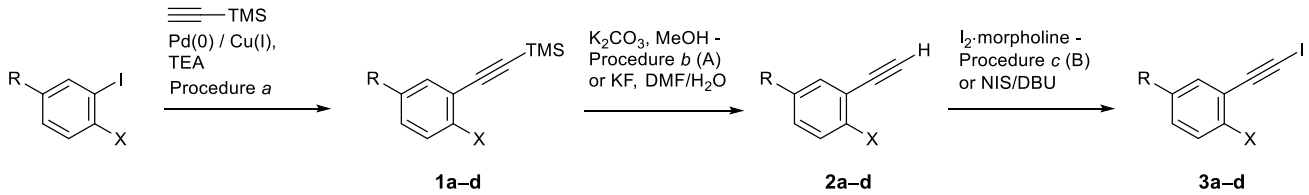
1 General Information and Methods

Reagents and solvents (absolute DMF) purchased from commercial suppliers were used without further purification. Other solvents were purified using standard techniques. Catalysts: $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ were purchased from Sigma-Aldrich. Starting alkynes **9a**,[1] **9d**,[2] **9f**,[3] **9g**,[4] were synthesized by known procedures. Unsymmetrical enediynes for biological studies **19f–h**[5] and **20**[6] were obtained as described earlier.

Synthesis of iodoalkynes and the Sonogashira coupling were carried out under argon in oven-dried glassware. Other reactions were carried out under air unless stated otherwise. Evaporation of solvents and concentration of reaction mixtures were performed under vacuum at 35 °C (25 °C for iodoalkynes) on a rotary evaporator. TLC was carried out on silica gel plates (Silica gel 60, UV 254) with detection by UV or staining with a basic aqueous solution of $KMnO_4$. A normal-phase silica gel (Silica gel 60, 230−400 mesh) was used for column chromatography. ^1H, $^{13}C\{^1H\}$ and DEPT and NOESY NMR spectra were recorded at 400 and 101 MHz, respectively, at 25 °C in $CDCl_3$, acetone-d_6, or DMSO-d_6 without an internal standard. The ^1H NMR data are reported as chemical shifts (δ), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants (*J*, given in Hz), and the H atom type. The $^{13}C\{^1H\}$ NMR data are reported as chemical shifts (δ) the C atom type. Chemical shifts for ^1H and ^{13}C are reported as δ values (ppm) and referenced to residual solvents (δ = 7.26 ppm for ^1H; δ = 77.16 ppm for ^{13}C for spectra recorded in $CDCl_3$, δ = 2.05 ppm for ^1H; δ = 29.84 ppm for ^{13}C for spectra recorded in acetone-d_6, and δ = 2.50 ppm for ^1H; δ = 39.52 ppm for ^{13}C for spectra in DMSO-d_6). High-resolution mass spectra were determined for solutions of all compounds in MeCN or MeOH using ESI in the mode of positive ion registration with a TOF mass analyzer.

2 Synthetic Procedure

2.1 Synthesis of Functionalized Iodoalkynes 3a–d

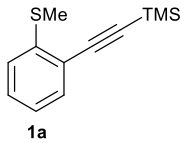


X = SMe, R = H (a); X = NMe_2, R = COOEt (b); X = OMe, R = H (c); X = OH, R = H (d)

General procedure *a* for the synthesis of *ortho*-(TMS-ethynyl) functionalized arenes 1a–d

A solution of *ortho*-iodoarene (1.00 equiv) in trimethylamine (c = 0.200 – 0.500 M) was degassed by bubbling argon through the reaction mixture for 10 min. Then, Pd catalyst ($PdCl_2(PPh_3)_2$ (2.00 mol%) or $Pd(PPh_3)_4$ (5.00 mol%)) followed by CuI (1.00 mol% – 10.0 mol%) was added under argon. The reaction mixture was stirred under argon for several 3–5 minutes and ethynyltrimethylsilane (1.20–1.50 equiv) was added to the reaction mixture. The reaction mixture was stirred under argon at the appropriate temperature for the appropriate time (TLC monitoring), then it was cooled to room temperature, if necessary, and passed through a short pad of silica gel, eluting with EtOAc. Volatiles were removed under reduced pressure. The crude product was purified by column chromatography on silica gel.

Trimethyl((2-(methylsulfanyl)phenyl)ethynyl)silane (1a)

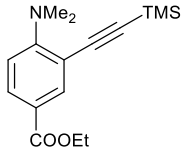


1a

Compound **1a** was obtained according to General procedure *a* from 2-iodothioanisole (3.50 g, 14.0 mmol, 1.00 equiv), ethynyltrimethylsilane (1.65 g, 2.33 mL, 16.8 mmol, 1.20 equiv), $PdCl_2(PPh_3)_2$ (196 mg, 0.280

mmol, 2.00 mol%), CuI (26.7 mg, 0.140 mmol, 1.00 mol%) in trimethylamine (70.0 mL, c = 0.200 M) at room temperature. Reaction time – 1.5 h. The crude product was purified by column chromatography on silica gel using hexane as the eluent to give alkyne **1a** as a yellow oil (2.99 g, 97 %). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.42 (dd, 1H, ^3J = 7.6, ^4J = 1.3 Hz, H-Ar), 7.30–7.26 (m, 1H, H-Ar), 7.13 (d, 1H, ^3J = 7.9 Hz, H-Ar), 7.08–7.04 (m, 1H, H-Ar), 2.48 (s, 3H, SCH_3), 0.28 (s, 9H, TMS). ^{1}H NMR spectrum corresponds to the previously reported data.[7]

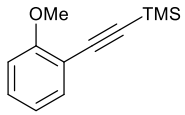
Ethyl 4-(dimethylamino)-3-((trimethylsilyl)ethynyl)benzoate (1b)



1b

Compound **1b** was obtained according to General procedure *a* from ethyl 4-(dimethylamino)-3-iodobenzoate (500 mg, 1.57 mmol, 1.00 equiv), ethynyltrimethylsilane (185 mg, 0.260 mL, 1.88 mmol, 1.20 equiv), $PdCl_2(PPh_3)_2$ (22.0 mg, 0.0313 mmol, 2.00 mol%), CuI (2.98 mg, 0.0157mmol, 1.00 mol%) in trimethylamine (7.83 mL, c = 0.200 M) at room temperature. Reaction time – 1.5 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (20:1) as the eluent to give alkyne **1b** as a brown oil (432 mg, 95 %). ^{1}H NMR spectrum (400 Hz, $CDCl_3$, δ): 8.07 (d, 1H, ^4J = 2.3 Hz, H-Ar), 7.84 (dd, 1 H, ^3J = 8.8 Hz, ^4J = 2.3 Hz, H-Ar), 6.78 (d, 1H, ^3J = 8.8 Hz, H-Ar), 4.32 (c, 2H, ^3J = 8.8 Hz, CH_2CH_3), 3.08 (s, 6H, $N(CH_3)_2$), 1.36 (t, 3H, ^3J = 8.8 Hz, CH_2CH_3), 0.25 (s, 9H,TMS). ^{13}C NMR spectrum (101 Hz, $CDCl_3$), δ, ppm: 166.0 (C=O), 157.4 (C-Ar), 137.2 (CH-Ar), 130.9 (CH-Ar), 120.7 (C-Ar), 115.3 (CH-Ar), 111.8 (C-Ar), 104.2 (C≡), 99.8 (C≡), 60.5 (OCH_2CH_3), 42.7 ($N(CH_3)_2$), 14.4 (OCH_2CH_3), –0.2 (TMS). HRMS ESI: $[M+Na]^+$ calculated for $C_{16}H_{23}NNaO_2Si$: 312.1390; found 312.1395.

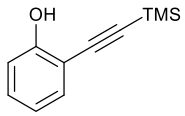
((2-Methoxyphenyl)ethynyl)trimethylsilane (1c)



1c

Compound **1c** was obtained according to General procedure *a* from ethyl 2-iodoanisole (750 mg, 3.20 mmol, 1.00 equiv), ethynyltrimethylsilane (409 mg, 0.576 mL, 4.17 mmol, 1.30 equiv), $Pd(PPh_3)_4$ (185 mg, 0.160 mmol, 5.00 mol%), CuI (61.0 mg, 0.320 mmol, 10.0 mol%) in trimethylamine (16.0 mL, c = 0.200 M) at 55 °C. Reaction time – 1 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (20:1) as the eluent to give alkyne **1c** as a yellow oil (564 mg, 86 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, 1H, ^3J = 7.5, ^4J = 1.3 Hz, H-Ar), 7.32 – 7.22 (m, 1H, H-Ar, overlaps with the solvent signal), 6.90 – 6.84 (m, 2H, H-Ar) 3.88 (s, 3H, OCH_3), 0.27 (s, 9H, TMS). ^{1}H NMR spectrum corresponds to the previously reported data.[8]

2-((Trimethylsilyl)ethynyl)phenol (1d)



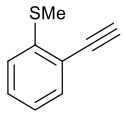
1d

Compound **1d** was obtained according to General procedure *a* from ethyl 2-iodophenol (2.00 g, 9.09 mmol, 1.00 equiv), ethynyltrimethylsilane (1.34 g, 1.91 mL, 13.6 mmol, 1.50 equiv), $Pd(PPh_3)_4$ (525 mg, 0.454 mmol, 5.00 mol%), CuI (173.0 mg, 0.909 mmol, 10.0 mol%) in trimethylamine (18.0 mL, c = 0.500 M) at room temperature. Reaction time – 2 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (7:1→3:1) as the eluent to give alkyne **1d** as a yellow oil (1.64 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 7.7, 1.5 Hz, 1H, CH-Ar), 7.27 – 7.21 (m, 1H, CH-Ar, overlaps with $CHCl_3$ signal), 6.94 (dd, *J* = 8.3, 0.6 Hz, 1H, CH-Ar), 6.87 – 6.83 (m, 1H, CH-Ar), 5.83 (s, 1H, OH), 0.28 (s, 9H, TMS). ^{1}H NMR spectrum corresponds to the previously reported data.[9]

General procedure *b* for the synthesis of *ortho*-ethynyl functionalized arenes 2a–d

To a stirred solution of a TMS-protected alkyne **1** (1.00 equiv) in MeOH or EtOH (c = 0.100 M) K_2CO_3 (2.00 equiv) was added. The resulting suspension was stirred until full disappearance of starting alkyne (TLC control). Upon completion, the solid was filtered and washed with MeOH or EtOH, respectively. Filtrate was concentrated under reduced pressure (30 °C bath temperature). The resulting suspension was dissolved in DCM and washed with water. Combined aqueous layers were extracted with DCM. Combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. After filtration, volatiles were removed under reduced pressure (28 °C bath temperature), and the crude product was purified by column chromatography on silica gel or used at the next step without purification.

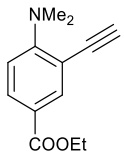
1-Ethynyl-2-(methylsulfanyl)benzene (2a)



2a

Compound **2a** was synthesized from TMS-alkyne **1a** (2.00 g, 9.07 mmol, 1.00 equiv) and K_2CO_3 (2.51 g, 18.1 mmol, 2.00 equiv) in MeOH (90.7 mL) using General procedure *b*. Reaction time – 3 h. The crude product **2a** was obtained as dark-yellow oil (1.34 g, 99 %) and was used at the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, 1H, ^3J = 7.6, ^4J = 1.4 Hz, H-Ar), 7.36 – 7.29 (m, 1H, H-Ar), 7.17 (d, ^3J = 8.0 Hz, 1H, H-Ar), 7.13 – 7.05 (m, 1H, H-Ar), 3.47 (s, 1H, CC-H), 2.50 (s, 3H, SCH_3). ^{1}H NMR spectrum corresponds to the previously reported data.[10]

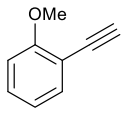
Ethyl 4-(dimethylamino)-3-ethynylbenzoate (2b)



2b

The alkyne **2b** was synthesized from TMS-alkyne **1b** (579 mg, 2.00 mmol, 1.00 equiv) and K_2CO_3 (553 mg, 4.00 mmol, 2.00 equiv) in EtOH (20.0 mL) using General procedure *b*. Reaction time – 19 hours. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (10:1) as the eluent to give terminal alkyne **2b** as a yellow oil (413 mg, 95 %). ^{1}H NMR (400.13 MHz, $CDCl_3$, δ) 8.11 (d, 1H, ^4J = 2.1 Hz, H-Ar), 7.88 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.1 Hz, H-Ar), 6.82 (d, 1H, ^3J = 8.8 Hz, H-Ar), 4.33 (q, 2 H, ^3J = 7.2 Hz, CH_2CH_3), 3.40 (s, 1H, CC-H), 3.07 (s, 6H, $N(CH_3)_2$), 1.37 (t, 3 H, ^3J = 7.2 Hz, CH_2CH_3). ^{13}C{^{1}H} NMR (101.6 MHz, $CDCl_3$, δ) 165.9 (C=O), 157.9 (C-Ar), 137.4 (CH-Ar), 131.1 (CH-Ar), 121.0 (C-Ar), 115.6 (CH-Ar), 111.2 (C-Ar), 82.7 (C≡), 82.6 (C≡), 60.6 (OCH_2CH_3), 42.9 ($N(CH_3)_2$), 14.4 (OCH_2CH_3). HRMS ESI $[M + H]^+$ calcd for $C_{13}H_{16}NO_2^+$ 218.1176, found 218.1184.

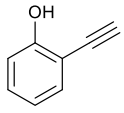
1-Ethynyl-2-methoxybenzene (2c)



2c

The alkyne **2c** was synthesized from 2-([2-Trimethylsilyl]ethynyl)anisole (**1c**) (0.512 g, 2.51 mmol) and K_2CO_3 (0.693 g, 5.01 mmol) in MeOH (25 mL) using General procedure *b*. Reaction time – 3 hours. The crude product was obtained as brown oil (0.298 g, 90 %) and used at the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, 1H, ^3J = 7.5, ^4J = 1.7 Hz, H-Ar), 7.32 (ddd, 1H, ^3J = 8.4, ^3J = 7.5, ^4J = 1.7 Hz, H-Ar), 6.93 – 6.88 (m, 2H, H-Ar), 3.90 (s, 3H, OCH_3), 3.31 (s, 1H, CC-H). ^{1}H NMR spectrum corresponds to the previously reported data.[8]

2-Ethynylphenol (2d)



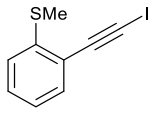
2d

2-Ethynylphenol (**2d**) was synthesized using KF/DMF/H_2O TMS-deprotection procedure.[11] To a stirred solution of TMS-alkyne **1d** (800 mg, 4.20 mmol, 1.00 equv) in a mixture of DMF/H_2O (9:1, v/v; 4.20 mL) potassium fluoride (366 mg, 6.31 mmol, 1.50 equiv) was added. The reaction mixture was stirred for 10 min at room temperature (TLC control), than the mixture was poured into the aqueous solution of NH_4Cl (200 mL) and extracted with ethyl acetate (3×50). The combined organic layers were washed with brain (3×150) and dried over anhydrous Na_2SO_4. After filtration, volatiles were removed under reduced pressure. Crude product was purified by column chromatography on silica gel using hexane : ethyl acetate (7:1→3:1) as the eluent to give alkyne **2d** as a yellow oil (402 mg, 81 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 7.7, 1.6 Hz, 1H, CH-Ar), 7.34 – 7.22 (m, 1H, CH-Ar, overlaps with $CHCl_3$ signal), 6.95 (dd, J = 8.3, 0.6 Hz, 1H, CH-Ar), 6.90 – 6.86 (m, 1H, CH-Ar), 5.80 (s, 1H, OH), 3.46 (s, 1H, CC-H). ^{1}H NMR spectrum corresponds to the previously reported data.[12] HRMS ESI $[M - H]^+$ calcd for $C_8H_5O^-$ 117.0346, found 117.0342.

General procedure *c* for the synthesis of 1-iodoalkynes 3a,b

A solution of terminal alkyne **2** (1.00 equiv) in dry THF (c = 0.100 M) was degassed by bubbling of argon through the solution within 10 – 15 min. Then to the degassed stirring and cooled to the corresponding temperature solution of alkyne **2** *N*-iodomorpholine hydroiodide (1.80–3.00 equiv) followed by CuI (15 mol. %) was added. The reaction mixture was stirred at the corresponding temperature under argon until full disappearance of starting alkyne (TLC control). Upon completion of the reaction, the mixture was diluted with ethyl acetate and washed with saturated aqueous solution of $Na_2S_2O_3$, then NH_4Cl and water. Combined aqueous phase was extracted with ethyl acetate three times and combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration, volatiles were removed under reduced pressure. Crude product was purified by column chromatography on silica gel

1-(Iodoethynyl)-2-(methylsulfanyl)benzene (3a)

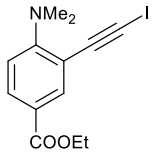


3a

Iodoalkyne **3a** was synthesized from 2-ethynylthioanisole (**2a**) (990 mg, 6.68 mmol, 1.00 equiv), *N*-iodomorpholine hydroiodide (6.83 g, 20.0 mmol, 3.00 equiv) and CuI (0.191 g, 1.00 mmol, 15.0 mol%) in

THF (67.0 mL) at 0–5 °C using General procedure *c*. Reaction time – 1.5 hours. The crude product was purified by column chromatography on silica gel using hexane : acetone (50:1) as the eluent to give iodoalkyne **3a** as a yellow-ginger oil (1.72 g, 94 %). ^{1}H NMR (400.13 MHz, $CDCl_3$, δ) 7.39 (dd, 1H, ^{3}J = 7.7 Hz, ^{4}J = 1.4 Hz, H-Ar), 7.29 (td, 1H, ^{3}J = 7.7 Hz, ^{4}J = 1.4 Hz, H-Ar), 7.15 (d, 1H, ^{3}J = 7.7 Hz, H-Ar), 7.07 (td, 1 H, ^{3}J = 7.7, ^{4}J = 1.1, H-Ar), 2.49 (s, 3H, SCH_3). ^{13}C{^{1}H} NMR (101.6 MHz, $CDCl_3$, δ) 142.5 (C-Ar), 133.3 (CH-Ar), 129.2 (CH-Ar), 124.17 (CH-Ar), 124.15 (CH-Ar), 121.6 (C-Ar), 91.7 (C≡), 15.1 (SCH_3), 12.9 (≡CI). HRMS ESI $[M + Na]^+$ calcd for $C_9H_7INaS^+$ 296.9205, found 296.9218.

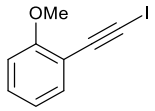
Ethyl 4-(dimethylamino)-3-(iodoethynyl)benzoate (3b)



3b

Iodoalkyne **3b** was synthesized from ethyl 4-(dimethylamino)-3-ethynylbenzoate (**2b**) (140 mg, 0.644 mmol, 1.00 equiv), *N*-iodomorpholine hydroiodide (659 mg, 1.93 mmol, 3.00 equiv) and CuI (18.0 mg, 0.097 mmol, 15 mol%) in THF (6.44 mL) at –5 °C using General procedure *b*. Reaction time – 1.5 hours. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (10:1) as the eluent to give alkyne **3b** as a light-yellow solid (0.188 g, 85 %). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.05 (d, 1H, ^{4}J = 2.1 Hz, H-Ar), 7.84 (dd, 1H, ^{3}J = 8.9 Hz, ^{4}J = 2.1 Hz, H-Ar), 6.78 (d, 1H, ^{3}J = 8.9 Hz, H-Ar), 4.32 (q, 2H, ^{3}J = 7.1 Hz, CH_2CH$_3$), 3.07 (s, 6H, N(CH$_3$)$_3$), 1.36 (t, 3H, ^{3}J = 7.1 Hz, OCH$_2$CH_3). ^{13}C{^{1}H} NMR (101.6 MHz, $CDCl_3$, δ) 165.9 (C=O), 157.8 (C-Ar), 137.6 (CH-Ar), 131.1 (CH-Ar), 120.6 (C-Ar), 115.3 (CH-Ar), 111.9 (C-Ar), 92.9 (C≡), 60.6 (OCH_2CH$_3$), 42.8 (N(CH$_3$)$_2$), 14.4 (OCH$_2$$CH_3$), 10.5 (≡CI). HRMS ESI $[M + H]^+$ calcd for $C_{13}H_{15}INO_2^+$ 344.0142, found 344.0134.

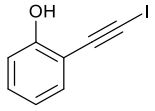
1-(Iodoethynyl)-2-methoxybenzene (3c)



3c

To a stirred solution of 2-ethynylarene **2c** (30.0 mg, 0.227 mmol, 1.00 equiv) in acetonitrile (0.900 mL, c = 0.250 M) DBU (38.0 mg, 37.3 μL, 0.250 mmol, 1.10 equiv) followed by NIS (56.0 mg, 0.250 mmol, 1.10 equiv) was added at room temperature. The reaction mixture was stirred for the corresponding time (TLC control), then it was diluted with DCM (15.0 mL) and washed three times with water. Combined aqueous layers were extracted with DCM (10.0 mL), combined with the first DCM portion and dried over anhydrous Na_2SO_4. After filtration, volatiles were removed under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (20:1) as the eluent gave product **3c** as a yellow oil (50 mg, 85 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, 1H, ^{3}J = 7.6, ^{4}J = 1.6 Hz, CH-Ar), 7.32 – 7.27 (m, 1H, CH-Ar), 6.91 – 6.86 (m, 2H, CH-Ar), 3.88 (s, 3H, OCH_3). ^{1}H NMR spectrum corresponds to the previously reported data.[13]

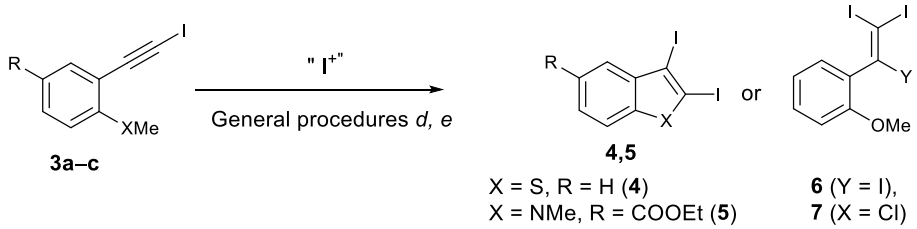
2-(Iodoethynyl)phenol (3d)



3d

To a stirred solution of alkyne **2d** (335 mg, 2.84 mmol, 1.00 equv) in acetonitrile (18.9 mL, c = 0.15 M) DBU (475 mg, 0.467 mL, 3.12 mmol, 1.10 equv) was added under an argon atmosphere. The reaction mixture was cooled to 0 °C, and the solution of NIS (702 mg, 3,12 mmol, 1.10 equv) in acetonitrile (3.5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and then was stirred at this temperature for 20 min (TLC control). The reaction mixture was quenched with aqueous 0.5 M solution of HCl (50.0 mL) and extracted with ethyl acetate (2×50.0 mL). The combined organic layers were washed with brine (100 mL), and dried over anhydrous Na_2SO_4. After filtration, volatiles were removed under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (7:1→4:1) as the eluent gave product **3d** as a yellow oil (610 mg, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.7, 1.5 Hz, 1H, CH-Ar), 7.28 – 7.21 (m, 1H, CH-Ar, overlaps with $CHCl_3$ signal), 6.94 (dd, *J* = 8.3, 0.7 Hz, 1H, CH-Ar), 6.88 – 6.84 (m, 1H, CH-Ar), 5.72 (s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.0, 132.4, 131.0, 120.4, 115.0, 110.0, 88.8, 13.32. HRMS ESI [M – H]$^+$ calcd for $C_8H_4IO^-$ 242.9312, found 242.9214.

2.2 Reaction of Iodoalkynes 3a–d with Electrophiles (Electrophile-Promoted Cyclization or Electrophilic Addition)



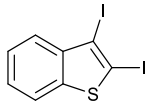
General procedure *d*

To a stirred solution of iodoalkyne **3** (1.00 equiv) in DCM (c = 0.100 M) a solution of electrophilic agent (I_2 or ICl, 1.00 – 1.40 equiv) in DCM (c = 0.100 M) was added dropwise at room temperature. The reaction mixture was stirred at a corresponding temperature until full disappearance of iodoalkyne (TLC control). Upon completion, the reaction mixture was diluted with DCM and washed with saturated solution of $Na_2S_2O_3$. The organic layers was separated, and the aqueous layer was extracted with DCM. Combined organic layers were dried over anhydrous Na_2SO_4. After filtration, volatiles were removed under reduced pressure and the crude product was purified by column chromatography on silica gel.

General procedure *e*

To a stirred solution of iodoalkyne **3** (1.00 equiv) in DCM (c = 0.100 M) NIS (1.10 equiv) was added. The reaction mixture was stirred for the corresponding time at room temperature (TLC control). Upon completion, the reaction mixture was diluted with DCM and washed with saturated solution of $Na_2S_2O_3$. The organic layers was separated, and the aqueous layer was extracted with DCM. Combined organic layers were dried over anhydrous Na_2SO_4. After filtration, volatiles were removed under reduced pressure, and the crude product was purified by column chromatography on silica gel.

2,3-Diiodobenzo[*b*]thiophene (4)

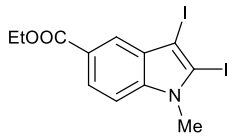


4

Diiodobenzothiophene **4** was synthesized from 2-(2-iodoethynyl)thioanisole (**3a**) (895 mg, 3.26 mmol, 1.00 equiv) in DCM (32.6 mL) and iodine (0.870 g, 3.43 mmol, 1.05 equiv) in DCM (34.3 mL) at room

temperature using General procedure *d*. Reaction time – 1.5 h. The crude product was purified by column chromatography on silica gel using pentane as the eluent to give diiodide **4** as a light-beige solid (1.22 g, 97 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 1H, ^3J = 7.8 Hz, CH-Ar), 7.69 (d, 1H, ^3J = 7.8 Hz,), 7.38 (td, 1H, ^3J = 7.8, ^4J = 1.1 Hz, CH-Ar), 7.32 (td, 1H, J = 7.8, ^4J = 1.1 Hz, CH-Ar). ^{1}H NMR spectrum corresponds to the previously reported data.[14]

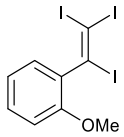
Ethyl 2,3-diiodo-1-methyl-1*H*-indole-5-carboxylate (5)



5

Diiodoindole **5** was synthesized from ethyl 4-(dimethylamino)-3-(iodoethynyl)benzoate (**3b**) (240 mg, 0.714 mmol, 1.00 equiv) in DCM (7.14 mL) and NIS (177 mg, 0.785 mmol, 1.10 equiv) using General procedure *e*. Reaction time – 26 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (7:1) as the eluent to give diiodide **5** as a light-yellow solid (278 mg, 86 %). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.14 (d, 1H, ^4J = 2.1 Hz, H-Ar), 7.90 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.1 Hz, H-Ar), 7.28 (d, 1H, ^3J = 8.7 Hz, H-Ar), 4.42 (q, 2H, ^3J = 7.1 Hz, CH_2CH$_3$), 3.90 (s, 3H, N(CH$_3$)), 1.44 (t, 3H, ^3J = 7.1 Hz, CH$_2$CH_3). ^{13}C{^{1}H} NMR (101.6 MHz, $CDCl_3$) δ 167.0 (C=O), 140.4 (C-Ar), 131.1 (C-Ar), 124.1 (CH-Ar), 124.0 (CH-Ar), 123.3 (C-Ar), 109.7 (CH-Ar), 98.0 (C-I), 73.1 (C-I), 60.8 (OCH_2CH$_3$), 36.3 (N(CH$_3$)), 14.4 (OCH$_2$$CH_3$). HRMS ESI [M + Na]$^+$ calcd for $C_{12}H_{11}I_2NNaO_2^+$ 477.8771, found 477.8778.

2-(1,2,2-Triiodovinyl)anisole (6)



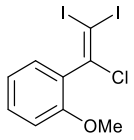
6

a) Triiodide **6** was synthesized from 2-(2-iodoethynyl)anisole (**3c**) (26.0 mg, 0.101 mmol, 1.00 equiv) in DCM (1.01 mL) and iodine (51.0 mg, 0.151 mmol, 1.5 equiv) in DCM (1.51 mL) using General procedure *d* at room temperature. Reaction time – 24 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (30:1) as the eluent to give triiodide **6** as a white solid (39.0 mg, 76 %). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 1H, H-Ar), 7.13 (dd, 1 H, ^3J = 7.4 Hz, ^4J = 1.8 Hz, H-Ar), 6.96 (td, 1 H, ^3J = 7.4 Hz, ^4J = 1.1 Hz, H-Ar), 6.88 (d, 1H, ^3J = 8.0 Hz, H-Ar), 3.90 (s, 3H, OCH$_3$). ^{13}C{^{1}H} NMR (101.6 MHz, $CDCl_3$) δ 154.5 (C-Ar), 136.1 (C-Ar), 130.4 (CH-Ar), 128.6 (CH-Ar), 120.7 (CH-Ar), 111.8 (CH-Ar), 109.2 (C-I), 55.8 (OCH$_3$), 24.1 (CI$_2$). HRMS ESI [M + H]$^+$ calcd for $C_9H_8I_3O^+$ 512.7704, found 512.7699.

b) Triiodide **6** was synthesized from 2-(2-iodoethynyl)anisole (**3c**) (20.0 mg, 0.0775 mmol, 1.00 equiv) in DCM (0.775 mL) and iodine (59.0 mg, 0.233 mmol, 3.0 equiv) in DCM (2.33 mL) using General procedure *d* at 40 °C. Reaction time – 24 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (30:1) as the eluent to give triiodide **6** as a white solid (39.2 mg, 99 %).

c) Triiodide **6** was synthesized from 2-(2-iodoethynyl)anisole (**3c**) (20.0 mg, 0.0775 mmol, 1.00 equiv) in DCE (0.775 mL) and iodine (59.0 mg, 0.233 mmol, 3.0 equiv) in DCE (2.33 mL) using General procedure *d* at 80 °C. Reaction time – 24 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (30:1) as the eluent to give triiodide **6** as a white solid (30.5 mg, 77 %).

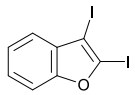
2-(1-chloro-2,2-diiodovinyl)anisole (7)



7

Iodochlorinated product **7** was synthesized from 2-(2-iodoethynyl)anisole (**3c**) (30.0 mg, 0.116 mmol, 1.00 equiv) in DCM (1.16 mL) and ICl (23.0 mg, 0.140 mmol, 1.20 equiv) in DCM (1.40 mL) using General procedure *d* at room temperature. Reaction time – 0.5 hours. The crude product was purified by column chromatography on silica gel (eluting system: EtOAc/hexane = 1:30) to give product **7** as white-off solid (40.0 mg, 82 %): ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 1H, H-Ar), 7.20 (dd, 1H, ^{3}J = 7.5 Hz, ^{4}J = 1.7 Hz, H-Ar), 6.98 (td, 1H, ^{3}J = 7.5 Hz, ^{4}J = 0.9 Hz, H-Ar), 6.93 (d, 1H, ^{3}J = 8.4 Hz, H-Ar), 3.89 (s, 3H, OCH_3); ^{13}C{^{1}H} NMR (101.6 MHz, $CDCl_3$) δ 155.6 (C-Ar), 138.5 (C-Ar), 131.1 (CH-Ar), 129.8 (CH-Ar), 128.6 (C-Cl), 120.6 (CH-Ar), 111.6 (CH-Ar), 55.8 (OCH_3), 17.0 (CI_2). ESI technique is not applicable for the measurement of HRMS for product **7**.

2,3-Diiodobenzofuran (8)



8

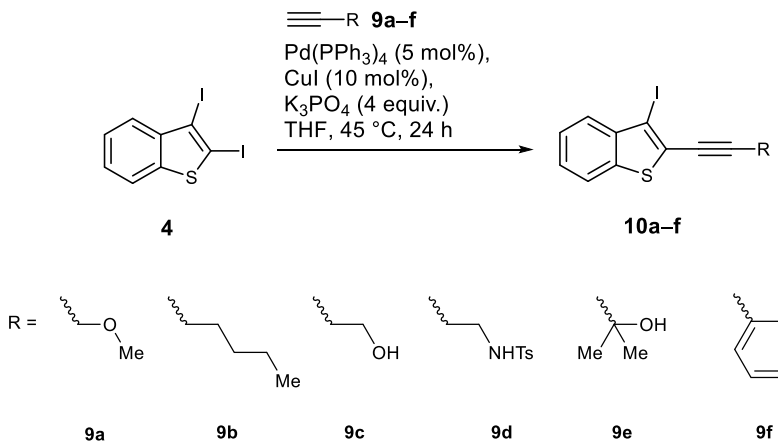
Method 1

To a cooled to 0 °C solution of TMS-alkyne **1d** (100 mg, 0.525 mmol, 1 equiv) in acetonitrile (10.5 mL, c = 0.05 M) water (18.9 mg, 1.05 mmol, 2.00 eqiv) was added. A stream of argon was bubbled through the reaction mixture. Then AgF (140 mg, 1.10 mmol, 2.10 equv) was added, and the reaction mixture was stirred at 0 °C for 20 min. Then NIS (284 mg, 1.26 mmol, 2.40 equv) was added and the reaction mixture was stirred at 0 °C for 1 h (TLC control). The reaction was quenched with aqueous solution of $Na_2S_2O_3$ (50.0 mL) and extracted with ethyl acetate (3×50.0 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4. After filtration, volatiles were removed under reduced pressure, and the crude product was purified by column chromatography on silica gel using hexane as the eluent to give diodide **8** as a white solid (25.0 mg, 13 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.40 (m, 1H), 7.36 – 7.34 (m, 1H), 7.30 – 7.20 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.0, 131.5, 125.5, 124.1, 121.3, 111.2, 106.4, 80.1. HRMS ESI $[M]^+$ calcd for $C_8H_4I_2O^+$ 369.8346, found 369.8345; MS EI $[M]^+$ calcd for $C_8H_4I_2O^+$ 369.0, found 370, $[M-I]^+$ (243); $[M-I-CO]^+$ (215).

Method 2

To a solution of iodoalkyne **3d** (400 mg, 1.64 mmol, 1 equiv) in DCM distilled over $CaCl_2$ (16.4 mL, c = 0.1 M) NIS (738 mg, 3.28 mmol,) followed by PPh_3 (43.0 mg, 0.164 mmol, 10 mol%) was added in one portion at room temperature. The reaction mixture was stirred for 30 min (TLC control), then it was quenched with aqueous solution of $Na_2S_2O_3$ (50.0 mL), extracted with DCM (30.0 mL). The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, volatiles were removed under reduced pressure, and the crude product was purified by column chromatography on silica gel using hexane → hexane / ethyl acetate (60:1) as the eluent to give diodide **8** as a white solid (223 mg, 37 %).

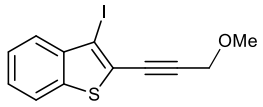
2.3 Regioselective C2 Sonogashira Coupling for 2,3-Diiodobenzo[*b*]thiophene (4)



Optimized General Procedure *f* for the Sonogashira coupling

To a solution of 2,3-diiodobenzo[*b*]thiophene (**4**) (1.00 equiv) in dry THF (c = 0.100 M) in a vial with a stirring bar $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), and K_3PO_4 (4.00 equiv) were added subsequently under argon atmosphere. Then the vial was sealed and the resulting mixture was degassed by bubbling of an Ar stream directly through the mixture. Then an alkyne **9** (1.20 equiv) was added. The vial with the reaction mixture was placed into preheated to 45 °C aluminum vial block and stirred for 24 hours. The reaction mixture was cooled to room temperature and passed through a short pad of silica gel eluting with EtOAc. The volatiles were removed under reduced pressure. The crude product was purified by column chromatography on silica gel.

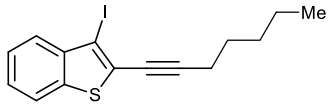
3-Iodo-2-(3-methoxyprop-1-yn-1-yl)benzo[*b*]thiophene (10a)



10a

2-Ethynylbenzothiophene **10a** was synthesized from 2,3-diiodobenzo[*b*]thiophene (**4**) (96.0 mg, 0.250 mmol, 1.00 equiv), 3-methoxyprop-1-yne (**9a**) (21.0 mg, 25.2 μL, 0.300 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (14.5 mg, 0.0125 mmol, 5 mol%), CuI (4.74 mg, 0.0250 mmol, 10 mol%), and K_3PO_4 (213 mg, 1.00 mmol, 4.00 equiv) in THF (2.50 mL) using General procedure *f*. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (30:1) as the to give 2-ethynylbenzothiophene **10a** as light-yellow solid (65.0 mg, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.70 (m, 2H, CH-Ar), 7.49 – 7.38 (m, 2H, CH-Ar), 4.44 (s, 2H, CH_2OCH_3), 3.53 (s, 3H, CH_2OCH_3). ^{1}H NMR spectrum corresponds to the previously reported data.[15]

2-(Hept-1-yn-1-yl)-3-iodobenzo[*b*]thiophene (10b)

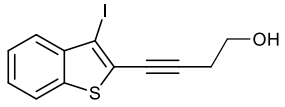


10b

2-Ethynylbenzothiophene **10b** was synthesized from 2,3-diiodobenzo[*b*]thiophene (**4**) (96.0 mg, 0.250 mmol, 1.00 equiv), hept-1-yne (**9b**) (29.0 mg, 39.6 μL, 0.300 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (14.5 mg, 0.0125 mmol, 5 mol%), CuI (4.74 mg, 0.0250 mmol, 10 mol%), and K_3PO_4 (213 mg, 1.00 mmol, 4.00 equiv) in THF (2.50 mL) using General procedure *f*. The crude product was purified by column chromatography on silica gel using hexane as the eluent to give 2-ethynylbenzothiophene **10b** as a yellow

oil (59.0 mg, 66 %): ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.71–7.67 (m, 2H, H-Ar), 7.46–7.36 (m, 2H, H-Ar), 2.54 (t, 2H, ^3J = 7.1 Hz, C≡C*C*H$_2$), 1.73–1.66 (m, 2H, C*H*$_2$), 1.56–1.49 (m, 2H, CH$_2$), 1.45–1.35 (m, 2H, CH$_2$), 0.95 (t, ^3J = 7.1 Hz, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101.6 MHz, $CDCl_3$) δ 140.6 (C-Ar), 138.7 (C-Ar), 126.3 (CH-Ar), 126.08 (CH-Ar), 126.02 (C-Ar), 125.7 (CH-Ar), 122.2 (CH-Ar), 101.3 (C-I), 86.6 (≡C), 75.4 (≡C), 31.3 (CH$_2$), 28.2 (CH$_2$), 22.4 (CH$_2$), 20.1 (CH$_2$), 14.2 (CH$_3$); HRMS ESI [M + Na]$^+$ calcd for $C_{15}H_{15}INaS^+$ 376.9831, found 376.9838.

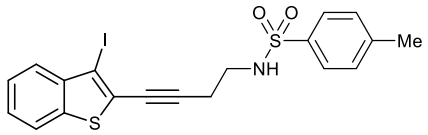
4-(3-Iodobenzo[*b*]thiophen-2-yl)but-3-yn-1-ol (10c)



10c

2-Ethynylbenzothiophene **10c** was synthesized from 2,3-diiodobenzo[*b*]thiophene (**4**) (96.0 mg, 0.250 mmol, 1.00 equiv), but-3-yn-1-ol (**9c**) (21.0 mg, 22.6 μL, 0.300 mmol, 1.20 equiv), Pd(PPh$_3$)$_4$ (14.5 mg, 0.0125 mmol, 5 mol%), CuI (4.74 mg, 0.0250 mmol, 10 mol%), and K_3PO_4 (213 mg, 1.00 mmol, 4.00 equiv) in THF (2.50 mL) using General procedure *f*. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (5:1) as the eluent to give 2-ethynylbenzothiophene **10c** as light-yellow solid (65.0 mg, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.63 (m, 2H, CH-Ar), 7.46 – 7.38 (m, 2H, CH-Ar), 3.93 – 3.88 (m, 2H, *CH*$_2$OH), 2.83 (t, 2H ^3J = 6.1 Hz,≡C-CH$_2$), 2.01 (t, ^3J = 6.5 Hz, 1H, OH). ^{1}H NMR spectrum corresponds to the previously reported data.[16]

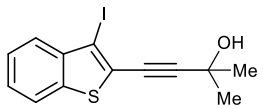
***N*-(4-(3-Iodobenzo[*b*]thiophen-2-yl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (10d)**



10d

2-Ethynylbenzothiophene **10d** was synthesized from 2,3-diiodobenzo[*b*]thiophene (**4**) (96.0 mg, 0.250 mmol, 1.00 equiv), *N*-(but-3-yn-1-yl)-4-methylbenzenesulfonamide (**9d**) (67.0 mg, 0.300 mmol, 1.20 equiv), Pd(PPh$_3$)$_4$ (14.5 mg, 0.0125 mmol, 5 mol%), CuI (4.74 mg, 0.0250 mmol, 10 mol%), and K_3PO_4 (213 mg, 1.00 mmol, 4.00 equiv) in THF (2.50 mL) using General procedure *f*. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) as the eluent to give 2-ethynylbenzothiophene **10d** as ginger solid (84.0 mg, 70 %). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.81 (d, 1 H, ^3J = 8.2 Hz, H-Ar), 7.72–7.67 (m, 2 H, H-Ar), 7.47–7.39 (m, 2 H, H-Ar), 7.29 (d, 1 H, ^3J = 8.0 Hz, H-Ar), 5.09 (t, 1 H, ^3J = 6.2 Hz, N*H*Ts), 3.31 – 3.27 (m, 2H, *CH*$_2$NHTs), 2.69 (t, 2H, ^3J = 6.4 Hz, ≡CCH$_2$), 2.39 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101.6 MHz, $CDCl_3$) δ 143.6 (C-Ar), 140.2 (C-Ar), 138.6 (C-Ar), 137.0 (C-Ar), 129.8 (CH-Ar), 127.1 (CH-Ar), 126.5 (CH-Ar), 126.0 (CH-Ar), 125.7 (CH-Ar), 124.5 (C-Ar), 122.1 (CH-Ar), 95.9 (C-I), 87.9 (≡C), 77.7 (≡C), 41.6 (NCH$_2$), 21.5, 21.3 (≡C-*CH*$_2$, CH$_3$). HRMS ESI [M + Na]$^+$ calcd for $C_{19}H_{16}INNaO_2S_2^+$ 503.9559, found 503.9552.

4-(3-Iodobenzo[*b*]thiophen-2-yl)-2-methylbut-3-yn-2-ol (10e)

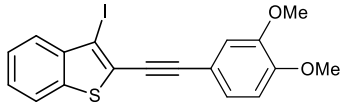


10e

2-Ethynylbenzothiophene **10e** was synthesized from 2,3-diiodobenzo[*b*]thiophene (**4**) (110 mg, 0.285 mmol), 2-methylbut-3-yn-2-ol (**9e**) (34.0 mg, 39.2 μL, 0.399 mmol, 1.4 equiv), Pd(PPh$_3$)$_4$ (16.5 mg, 0.0143 mmol, 5 mol%), CuI (5.43 mg, 0.0285 mmol, 10 mol%), and K_3PO_4 (242 mg, 1.14 mmol, 4.00 equiv) in

THF (2.85 mL) using General procedure *f*. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) as the eluent to give 2-ethynylbenzothiophene **10e** as a light-yellow solid (86.0 mg, 88 %). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.73–7.69 (m, 2H, H-Ar), 7.46–7.39 (m, 2H, H-Ar), 2.03 (br s, 1H, OH), 1.70 (s, 6H, $(CH_3)_2$). $^{13}C\{^{1}H\}$ NMR (101.6 MHz, $CDCl_3$, δ) 140.3 (C-Ar), 138.8 (C-Ar), 126.5 (CH-Ar), 126.1 (CH-Ar), 125.7 (CH-Ar), 124.3 (C-Ar), 122.1 (CH-Ar), 103.1 (C-I), 88.2 (≡C), 65.9 (*C*$(CH_3)_2$), 31.2 ($(CH_3)_2$); signal from one of (≡C) atoms overlaps with the solvent signal. HRMS ESI $[M + Na]^+$ calcd for $C_{13}H_{11}INNaOS^+$ 364.9467, found 364.9478.

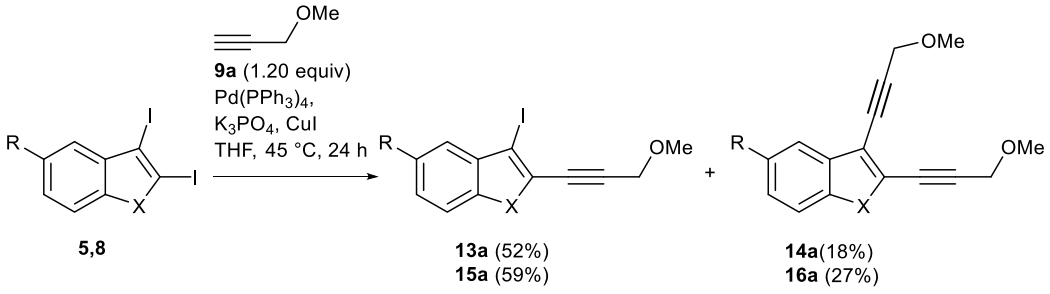
2-([3,4-Dimethoxyphenyl]ethynyl)-3-iodobenzo[*b*]thiophene (10f)



10f

2-Ethynylbenzothiophene **10f** The product was synthesized from 2,3-diiodobenzo[*b*]thiophene (**4**) (96.0 mg, 0.250 mmol, 1.00 equiv), 4-ethynyl-1,2-dimethoxybenzene **9f** (48.6 mg, 0.300 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (14.5 mg, 0.0125 mmol, 5 mol%), CuI (4.74 mg, 0.0250 mmol, 10 mol%), and K_3PO_4 (213 mg, 1.00 mmol, 4.00 equiv) in THF (2.50 mL) using General procedure *f*. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (10:1) as the eluent to give 2-ethynylbenzothiophene **10f** as a ginger solid (81.0 mg, 77 %): ^{1}H NMR (400.13 MHz, $CDCl_3$, δ) 7.74–7.71 (m, 2H, H-Ar), 7.47–7.41 (m, 2H, H-Ar), 7.26–7.24 (m, 1H, H-Ar, overlaps with $CHCl_3$ signal), 7.11 (d, 1H, ^{4}J = 2.0 Hz, H-Ar), 6.87 (d, 1H, ^{3}J = 8.4 Hz, H-Ar), 3.93 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3). $^{13}C\{^{1}H\}$ NMR (101.6 MHz, $CDCl_3$, δ) 150.4 (C-Ar), 148.9 (C-Ar), 140.7 (C-Ar), 139.1 (C-Ar), 126.5 (CH-Ar), 126.2 (CH-Ar), 125.8 (CH-Ar), 125.6 (CH-Ar), 125.4 (C-Ar), 122.2 (CH-Ar), 114.6 (C-Ar), 114.4 (CH-Ar), 111.3 (C-Ar), 99.1 (C-I), 87.5 (≡C), 82.8 (≡C), 56.2 (OCH_3), 56.1 (OCH_3). HRMS ESI $[M + Na]^+$ calcd for $C_{18}H_{13}INNaO_2S^+$ 442.9573, found 442.9555.

2.4 The Sonogashira Coupling with 2,3-Diiodoindole 5 and 2,3-Diiodobenzofuran 8



5,8

13a (52%)
15a (59%)

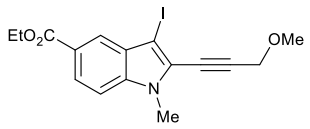
14a(18%)
16a (27%)

R = COOEt, X = NMe (**5, 13a, 14a**)
R = H, X = O (**8, 15a,16a**)

2.4.1 The Sonogashira Coupling with 2,3-diiodoindole 5

The reaction of 2,3-diiodindole **5** (114 mg, 0.250 mmol, 1.00 equiv) and 3-methoxyprop-1-yne **9a** (21.0 mg, 25.3 μL, 0.300 mmol, 1.20 equiv) was carried out with $Pd(PPh_3)_4$ (14.5 mg, 0.0125 mmol, 5 mol%), CuI (4.76 mg, 0.0250 mmol, 10 mol%), and K_3PO_4 (212 mg, 1.00 mmol, 4.00 equiv) in THF (2.50 mL) using General procedure *f*. Reaction time – 24 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) as the to give 2-ethynylindole **13a** as light-yellow solid (51.0 mg, 52 %, 59 % brsm), enediyne **14a** as a brown oil (15.0 mg, 18 %, 20 % brsm) and unrecovered starting diiodide **5** (15 mg, 87% conversion).

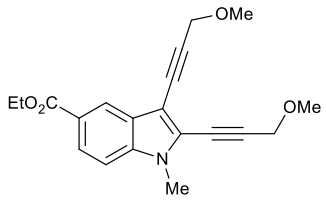
Ethyl 3-iodo-2-(3-methoxyprop-1-yn-1-yl)-1-methyl-1*H*-indole-5-carboxylate (13a)



13a

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.01 (d, 1H, *J* = 8.3 Hz,), 7.25 (d, 1H, overlaps with $CHCl_3$ signal), 4.49 (s, 2H, CH_2OCH_3), 4.42 (q, 2H, ^3J = 7.1 Hz, OCH_2CH_3), 3.88 (s, 3H, NCH_3), 3.54 (s, 3H, CH_2OCH_3), 1.44 (t, 3H, ^3J = 7.1 Hz, OCH_2CH_3). ^{1}H NMR spectrum corresponds to the previously reported data.[6]

Ethyl 2,3-bis(3-methoxyprop-1-yn-1-yl)-1-methyl-1*H*-indole-5-carboxylate (14a)



14a

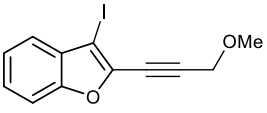
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, 1H, ^4J = 1.5 Hz, H-Ar), 8.00 (dd, ^3J = 8.7, ^4J =1.5 Hz, 1H, H-Ar), 7.27 (d, ^3J = 8.7 Hz, 1H, H-Ar), 4.47 (s, 2H, CH_2OCH_3), 4.46 (s, 2H, CH_2OCH_3), 4.41 (q, 2H, ^3J = 7.1 Hz, OCH_2CH_3), 3.51 (two s, 3H, CH_2OCH_3; 3H, NCH_3), 3.82 (s, 3H, CH_2OCH_3), 1.43 (t, 3H, ^3J = 7.1 Hz, OCH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4 (*C*OOEt), 138.7 (C-Ar), 127.6 (C-Ar), 126.7 (C-Ar), 125.5 (CH-Ar), 123.6 (C-Ar), 123.2 (CH-Ar), 109.5 (CH-Ar), 104.4 (C-Ar), 96.0 (≡C), 90.6 (≡C), 78.7 (≡C), 76.5 (≡C), 60.95 (OCH_2), 60.94 (OCH_2), 60.6 (OCH_2), 58.0 (OCH_3), 57.6 (OCH_3), 31.5 (N-CH_3), 14.6 (CH_2CH_3). HRMS ESI $[M + Na]^+$ calcd for $C_{20}H_{21}NNaO_4^+$363.1363, found 363.1366

2.4.2 The Sonogashira Coupling with 2,3-diiodobenzofuran 8

Reaction of 2,3-iodobenzofuran 8 with 3-methoxyprop-1-yne (9a)

The reaction was carried out according to the General procedure *f* from 2,3-iodobenzofuran (**8**) (52.0 mg, 0.141 mmol, 1.00 equiv), 3-methoxyprop-1-yne (**9a**) (21.0 mg, 16.1 µL, 0.169 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (8.12 mg, 0.00703 mmol, 5 mol%), CuI (2.68 mg, 0.0141 mmol, 10 mol%), and K_3PO_4 (119 mg, 0.562 mmol, 4.00 equiv) in THF (1.41 mL). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (30:1) as the eluent to give two products: 3-iodo-2-(3-methoxyprop-1-yn-1-yl)benzofuran (**15a**) as a yellow oil (28.0 mg, 64 %) and 2,3-bis(3-methoxyprop-1-yn-1-yl)benzofuran (**16a**) as a yellow oil (9.5 mg, 27 %).

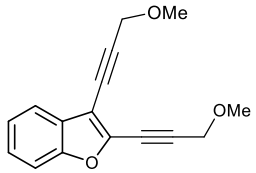
3-Iodo-2-(3-methoxyprop-1-yn-1-yl)benzofuran (**15a**)



15a

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.53 – 7.48 (m, 2H, H-Ar), 7.43 – 7.38 (m, 2H, H-Ar), 4.49 (s, 2H, CH_2), 3.46 (s, 3H, CH_3). ^{13}C NMR (101 МГц, Acetone-d_6) δ 155.1 (C-Ar), 141.6 (C-Ar), 131.1 (CH-Ar), 128.2 (CH-Ar), 125.2 (CH-Ar), 122.5 (CH-Ar), 112.3 (C-Ar), 96.2 (≡C), 76.5 (≡C or C-I), 73.4 (≡C or C-I), 60.4 (CH_2), 57.9 (CH_3). HRMS ESI $[M + H]^+$ calcd for $C_{12}H_{10}IO_2^+$ 312.9720, found 312.9726.

2,3-bis(3-methoxyprop-1-yn-1-yl)benzofuran (**16a**)



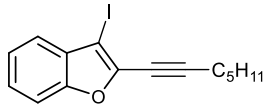
16a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 1H, H-Ar), 7.43 (d, *J* = 8.2 Hz, 1H, H-Ar), 7.41 – 7.35 (m, 1H, H-Ar), 7.30 (t, *J* = 7.4 Hz, 1H, H-Ar), 4.44 (s, 2H, CH_2), 4.43 (s, 2H CH_2), 3.50 (s, 3H, CH_3), 3.49 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.1 (C-Ar), 141.0 (C-Ar), 127.8 (CH-Ar), 126.7 (CH-Ar), 123.9 (CH-Ar), 120.7 (CH-Ar), 111.6 (C-Ar), 108.9 (C-Ar), 95.4 (≡C), 93.2 (≡C), 76.13 (≡C), 76.11 (≡C), 60.7 (CH_2), 60.4 (CH_2), 58.0 (CH_3), 57.8 (CH_3). HRMS ESI $[M + Na]^+$ calcd for $C_{16}H_{14}NaO_3^+$ 277.0835, found 277.0841.

Reaction of 2,3-iodobenzofuran 8 with hept-1-yne (9b)

The reaction was carried out according to the General procedure *f* from 2,3-iodobenzofuran (**8**) (68.0 mg, 0.183 mmol, 1.00 equiv), hept-1-yne (**9b**) (21.2 mg, 29.0 μL, 0.221 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (10.6 mg, 0.00919 mmol, 5 mol%), CuI (3.50 mg, 0.0183 mmol, 10 mol%), and K_3PO_4 (156 mg, 0.735 mmol, 4.00 equiv) in THF (1.83 mL). The crude product was purified by column chromatography on silica gel using pentane as the eluent to give two products: 2-(hept-1-yn-1-yl)-3-iodobenzofuran (**15b**) as a yellow oil (34.0 mg, 55 %) and 2,3-di(hept-1-yn-1-yl)benzofuran (**16b**) as a yellow oil (8.00 mg, 14%).

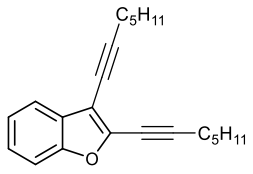
2-(Hept-1-yn-1-yl)-3-iodobenzofuran (15b)



15b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 4H, H-Ar), 2.56 (t, *J* = 7.1 Hz, 2H, CH_2), 1.76 – 1.64 (m, 2H, CH_2), 1.54 – 1.46 (m, 2H, CH_2), 1.44 – 1.35 (m, 2H, CH_2), 0.95 (t, *J* = 7.3 Hz, 1H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.0 (C-Ar), 141.9 (C-Ar), 130.6 (CH-Ar), 126.4 (CH-Ar), 123.9 (CH-Ar), 121.6 (C-Ar) (CH-Ar), 111.4 (C-Ar), 100.8 (≡C), 71.0 (≡C or C-I), 70.8 (≡C or C-I), 31.2 (CH_2), 28.0 (CH_2), 22.3 (CH_2), 19.9 (CH_2), 14.1 (CH_3). ESI technique is not applicable for the measurement of HRMS for product **15b**.

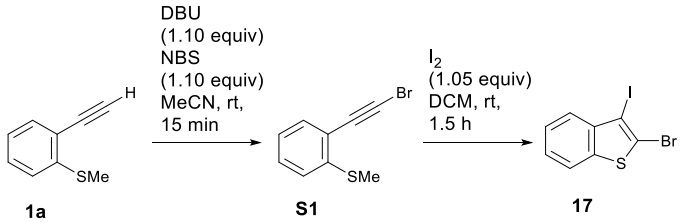
2,3-Di(hept-1-yn-1-yl)benzofuran (16b)



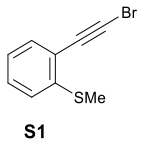
16b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.5 Hz, 1H, H-Ar), 7.39 (d, *J* = 8.0 Hz, 1H, H-Ar), 7.35 – 7.29 (m, 1H, H-Ar), 7.29 – 7.23 (m, 2H, H-Ar), 2.57 – 2.51 (m, 4H, 2×CH_2), 1.74 – 1.62 (m, 4H, 2×CH_2), 1.57 – 1.44 (m, 4H, 2×CH_2), 1.44 – 1.34 (m, 4H, 2×CH_2), 0.97 – 0.92 (m, 6H, 2×CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.8 (C-Ar), 141.4 (C-Ar), 128.5 (C-Ar), 125.9 (CH-Ar), 123.4 (CH-Ar), 120.5 (CH-Ar), 111.3 (CH-Ar), 108.3 (C-Ar), 101.0 (≡C), 98.3 (≡C), 70.9 (≡C), 70.4 (≡C), 31.2 (2×CH_2), 28.6 (CH_2), 28.1 (CH_2), 22.38 (CH_2), 22.35 (CH_2), 20.00 (CH_2), 19.99 (CH_2), 14.16 (CH_3), 14.10 (CH_3). HRMS ESI [M + H]$^+$ calcd for $C_{22}H_{27}O^+$ 307.2056, found 307.2060.

2.5 Synthesis of 2-Bromo-3-iodobenzo[*b*]thiophene (17)



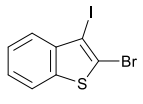
1-(Bromoethynyl)-2-(methylsulfanyl)benzene (S1)



S1

To a stirred solution of 2-ethynylthioanisole (**2a**) (158 mg, 1.07 mmol, 1.00 equiv) in acetonitrile (4.30 mL, c = 0.250 M) DBU (178 mg, 0.175 mL, 1.17 mmol, 1.10 equiv) followed by NBS (209 mg, 1.17 mmol, 1.10 equiv) was added. The reaction mixture was stirred for 15 minutes, then it was diluted with DCM (10.0 mL) and washed with water (3 × 10.0 mL). The combined aqueous layers were extracted with DCM (10.0 mL). Combined organic layers were dried over anhydrous Na_2SO_4. After filtration, volatiles were removed under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane : acetone (50:1) as the eluent to give bromoalkyne **S1** as yellow oil (211 mg, 87 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, 1H, ^3J = 7.6, ^4J =1.3 Hz, CH-Ar), 7.34 – 7.27 (m, 1H, CH-Ar), 7.15 (d, 1H, ^3J = 7.6 Hz, CH-Ar), 7.07 (td, 1H, ^3J = 7.6, ^4J = 1.1 Hz, CH-Ar), 2.49 (s, 3H, SCH_3). ^{1}H NMR spectrum corresponds to the previously reported data.[17] ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3 (C-Ar), 133.1 (CH-Ar), 129.3 (CH-Ar), 124.5 (CH-Ar), 124.4 (CH-Ar), 121.1 (C-Ar), 77.9 (C≡), 56.2 (≡CBr), 15.3 (OCH_3). HRMS ESI [M + H]$^+$ calcd for $C_9H_8BrS^+$ 226.9536, found 226.9525.

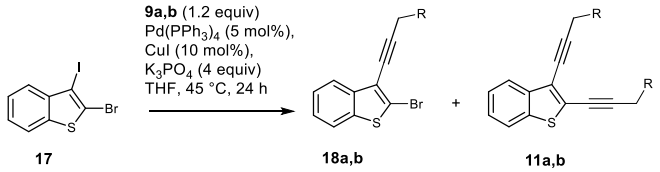
2-bromo-3-iodobenzo[*b*]thiophene (17)



17

2-Bromo-3-iodobenzothiophene **17** was synthesized from 2-(2-bromoethynyl)thioanisole (**S1**) (1.38 g, 6.08 mmol, 1.00 equiv) and iodine (1.57 g, 6.20 mmol, 1.02 equiv) using General procedure *d*. Reaction time – 1.5 hours. The crude product was purified by column chromatography on silica gel (eluting system: pentane) to give product **17** as light-grey solid (1.91 g, 93 %). NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.68 (m, 2H, CH-Ar), 7.43 – 7.39 (m, 1H, CH-Ar), 7.38 – 7.34 (m, 1H, CH-Ar). ^{1}H NMR spectrum corresponds to the previously reported data.[17] ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0 (C-Ar), 140.3 (CH-Ar), 126.2 (CH-Ar), 126.0 (CH-Ar), 125.8 (CH-Ar), 121.9 (CH-Ar), 119.6 (C-Br), 87.1 (C-I).

2.6 The Sonogashira Coupling of 2-Bromo-3-iodobenzo[b]thiophene 17



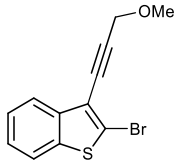
R = OMe (**9a, 11a, 18a**)
R = C_4H_9 (**9b, 11b, 18b**)

Reaction of 2-bromo-3-iodobenzo[*b*]thiophene 17 with 3-methoxyprop-1-yne (9a)

The reaction was carried out according to the General procedure *f* from 2-bromo-3-iodobenzo[*b*]thiophene (**17**) (85.0 mg, 0.250 mmol, 1.00 equiv), 3-methoxyprop-

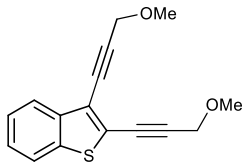
1-yne (**9a**) (21.0 mg, 25.3 µL, 0.300 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (14.5 mg, 0.0125 mmol, 5 mol%), CuI (4.74 mg, 0.025 mmol, 10 mol%), and K_3PO_4 (213 mg, 1.00 mmol, 4.00 equiv) in THF (2.50 mL). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (30:1) as the eluent to give two products: 2-bromo-3-(3-methoxyprop-1-yn-1-yl)benzo[*b*]thiophene (**18a**) as a yellow oil (34.0 mg, 41 % (58 % brsm)) and 2,3-bis(3-methoxyprop-1-yn-1-yl)benzo[*b*]thiophene (**11a**) as a brown oil (15.0 mg, 22 % (31 % brsm)) and unconverted starting material **17** (24.0 mg, conversion 72 %).

2-Bromo-3-(3-methoxyprop-1-yn-1-yl)benzo[*b*]thiophene (18a)



18a

^{1}H NMR (400.13 MHz, $CDCl_3$, δ) 7.84 (dd, 1 H, ^3J = 8.3 Hz, ^4J = 1.3 Hz, H-Ar), 7.70 (d, 1 H, ^3J = 8.3 Hz, ^4J = 1.3 Hz, H-Ar), 7.43–7.34 (m, 2 H, H-Ar), 4.46 (s, 2 H, CH_2O), 3.54 (s, 3 H, OCH_3); $^{13}C\{^1H\}$ NMR (101.6 MHz, $CDCl_3$, δ) 138.9 (C-Ar), 138.8 (C-Ar), 125.4 (CH-Ar), 125.3 (CH-Ar), 122.8 (CH-Ar), 121.7 (CH-Ar), 120.6 (C-Ar), 120.0 (C-Ar), 91.7 (≡C), 78.9 (≡C), 60.5 (CH_2), 57.7 (CH_3); HRMS ESI $[M + Na]^+$ calcd for $C_{12}H_{19}BrNaOS^+$ 302.9450, found 302.9460.



11a

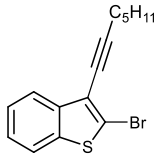
2,3-Bis(3-methoxyprop-1-yn-1-yl)benzo[*b*]thiophene (11a)

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.98 – 7.91 (m, 1H, CH-Ar), 7.91 – 7.83 (m, 1H, CH-Ar), 7.70 – 7.17 (m, 2H, CH-Ar), 4.48 (s, 2H, CH_2OCH_3), 4.45 (s, 2H, CH_2OCH_3), 3.47 (s, 3H, CH_2OCH_3), 3.44 (s, 3H, CH_2OCH_3). ^{13}C NMR (101 MHz, acetone-d_6) δ 139.3 (C-Ar), 139.1 (C-Ar), 127.7 (CH-Ar), 126.6 (CH-Ar), 126.5 (C-Ar), 124.0 (CH-Ar), 123.4 (CH-Ar), 123.3 (C-Ar), 97.0 (≡C), 93.7 (≡C), 79.4 (≡C), 79.2 (≡C), 60.67 (CH_2O), 60.65 (CH_2O), 57.7 (OCH_3), 57.6 (OCH_3). HRMS ESI $[M + Na]^+$ calcd for $C_{16}H_{14}NaO_2S^+$ 293.0607, found 293.0615.

Reaction of 2 Bromo-3-iodobenzo[*b*]thiophene 8 with Hept-1-yne (9b)

The reaction was carried out according to the General procedure *f* from 2-bromo-3-iodobenzo[*b*]thiophene (**17**) (85.0 mg, 0.250 mmol, 1.00 equiv), hept-1-yne (**9b**) (29.0 mg, 39.5 µL, 0.300 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (14.5 mg, 0.0125 mmol, 5 mol%), CuI (4.74 mg, 0.025 mmol, 10 mol%), and K_3PO_4 (213 mg, 1.00 mmol, 4.00 equiv) in THF (2.50 mL). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (60:1→20:1) as the eluent to give two products: 2-bromo-3-(hept-1-yn-1-yl)benzo[*b*]thiophene (**18b**) as a yellow oil (43.8 mg, 57 % (63 % brsm)) and 2,3-di(hept-1-yn-1-yl)benzo[*b*]thiophene (**11b**) as a brown oil (14.5 mg, 18 % (21 % brsm)) and unconverted starting material **17** (11.0 mg, conversion 87 %).

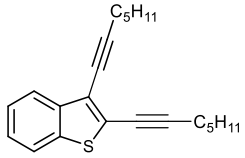
2-Bromo-3-(hept-1-yn-1-yl)benzo[*b*]thiophene (18b)



18b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 1H, CH-Ar), 7.69 (d, *J* = 7.5 Hz, 1H, CH-Ar), 7.41 – 7.32 (m, 2H, CH-Ar), 2.55 (t, *J* = 7.0 Hz, 2H, CH_2), 1.77 – 1.66 (m, 2H, CH_2), 1.58 – 1.51 (m, 2H, CH_2), 1.46 – 1.37 (m, 2H, CH_2), 0.96 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.3 (C-Ar), 139.0 (C-Ar), 125.3 (CH-Ar), 125.2 (CH-Ar), 123.0 (CH-Ar), 121.8 (CH-Ar), 121.4 (C-Ar), 118.7 (C-Ar), 97.7 (≡C), 73.2 (≡C), 31.2 (CH_2), 28.6 (CH_2), 22.4 (CH_2), 19.9 (CH_2), 14.2 (CH_3). HRMS ESI $[M + H]^+$ calcd for $C_{15}H_{16}BrS^+$ 307.0151, found 307.0149.

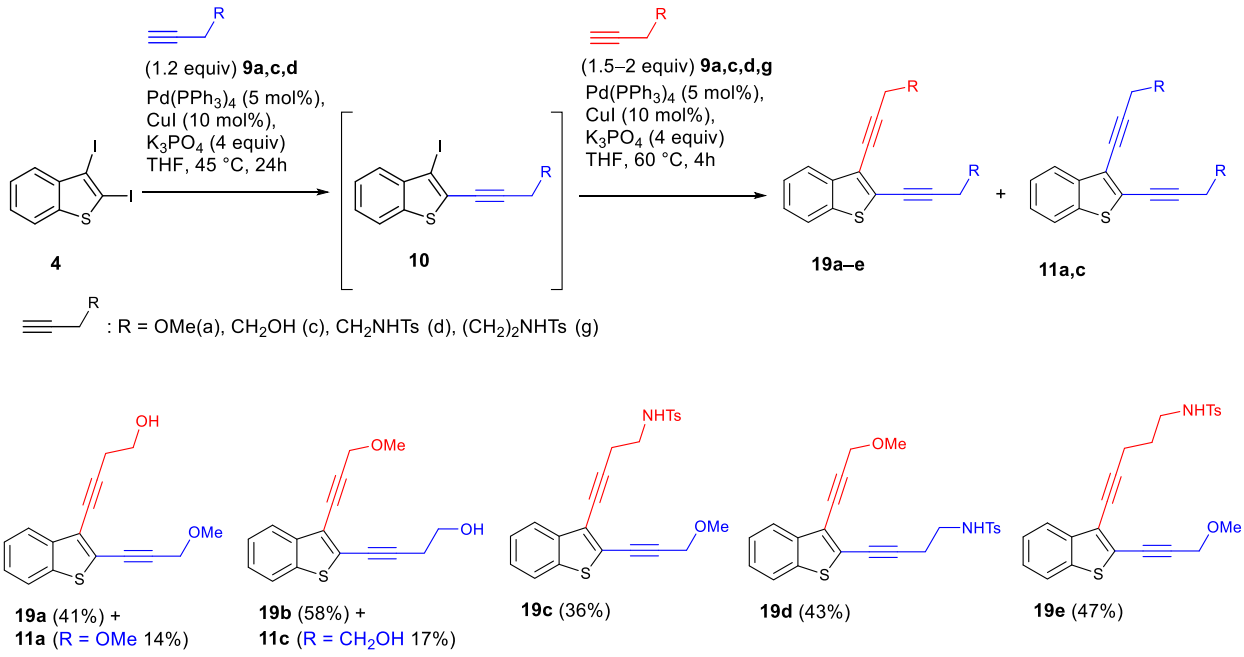
2,3-Di(hept-1-yn-1-yl)benzo[*b*]thiophene (11b)



11b

^{1}H NMR (400 MHz, $CDCl_3$) 7.81 – 7.81 (m, 1H, CH-Ar), 7.69 – 7.67 (m, 1H, CH-Ar), 7.41 – 7.33 (m, 2H, CH-Ar), 2.57 – 2.51 (m, 4H, 2×CH_2), 1.74 – 1.63 (m, 4H, 2×CH_2), 1.57 – 1.47 (m, 4H, 2×CH_2, overlaps with water signal), 0.97 – 0.92 (m, 6H, 2×CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 139.3 (C-Ar), 138.1 (C-Ar), 126.2 (C-Ar), 125.8 (CH-Ar), 124.9 (CH-Ar), 123.3 (CH-Ar), 122.6 (C-Ar), 122.1 (CH-Ar), 100.9 (≡C), 97.1 (≡C), 74.01 (≡C), 73.98 (≡C), 31.2 (two CH_2 signals overlap), 28.7 (CH_2), 28.3 (CH_2), 22.40 (CH_2), 22.38 (CH_2), 20.19 (CH_2), 19.94 (CH_2), 14.18 (CH_3), 14.15 (CH_3). HRMS ESI $[M + H]^+$ calcd for $C_{22}H_{27}S^+$ 323.1828, found 323.1825.

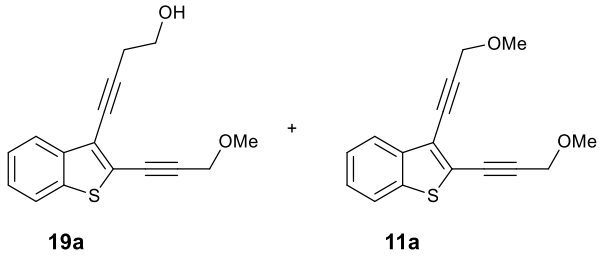
2.7 A Subsequent One-Pot Sonogashira Coupling for 2,3-Diiodobenzo[*b*]thiophene (4)



General Procedure *g*

To a solution of 2,3-diiodobenzo[*b*]thiophene (**4**) (100 mg, 0.259 mmol, 1.00 equiv) in dry THF (2.59 mL, c = 0.100 M) in a vial with a stirring bar $Pd(PPh_3)_4$ (15.0 mg, 0.0130 mmol, 5 mol%), CuI (4.53 mg, 0.0259 mmol, 10 mol%), and K_3PO_4 (220 mg, 1.04 mmol, 4 equiv) were added subsequently under argon atmosphere. Then the vial was sealed and the resulting mixture was degassed by bubbling of argon directly through the mixture. Then a first alkyne for C2-I coupling (1.00–1.20 equiv) was added. The vial with the reaction mixture was placed into preheated to 45 °C aluminum vial block and stirred for 24 hours. Then the reaction mixture was cooled and a second alkyne for C3-I coupling (1.00–2.50 equiv) was added to the mixture. The reaction mixture was heated with stirring at 60 °C for 4 hours. Then the reaction mixture was cooled to room temperature and passed through a short pad of silica gel eluting with ethyl acetate. The volatiles were removed under reduced pressure. The crude product was purified by column chromatography on silica gel. As a result of the synthesis of enediynes **19a** and **19b** corresponding symmetrical enediynes **11a** and **11c** were isolated. In all other cases the isolation of symmetrical byproducts was not performed.

4-(2-(3-Methoxyprop-1-yn-1-yl)benzo[*b*]thiophen-3-yl)but-3-yn-1-ol (19a) and enediyne 11a



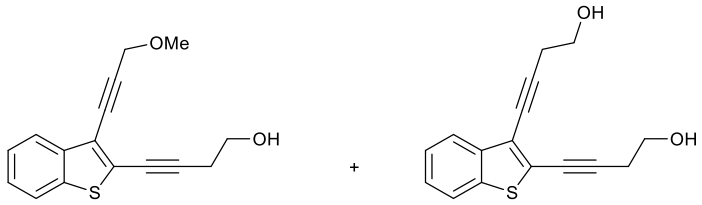
Endiyne **19a** and **11a** were synthesize according to General procedure *g* from 2,3-diiodobenzo[*b*]thiophene (**4**) (100 mg, 0.259 mmol, 1.00 equiv), first added alkyne was methyl propargyl ether **9a** (21.8 mg, 26.3 µL, 0.311 mmol, 1.20 equiv), second added alkyne was but-3-yn-1-ol **9c** (45.4 mg, 49.0 µL, 0.648 mmol, 2.50 equiv). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (10:1 → 1:1) as the eluent to give unsymmetrical enediyne **19a** as a yellow oil (29.0 mg, 41 %) and

symmetrical by-product **11a** as a brown oil (11.0 mg, 14 %). For the spectral data of enediyne **11a** see Section 2.6

4-(2-(3-methoxyprop-1-yn-1-yl)benzo[*b*]thiophen-3-yl)but-3-yn-1-ol (19a)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.79 (m, 1H, H-Ar), 7.74 – 7.71 (m, 1H, H-Ar), 7.46 – 7.33 (m, 2H, H-Ar), 4.43 (s, 2H, CH_2OCH_3), 3.89 (t, J = 6.1 Hz, 2H, CH_2OH), 3.50 (s, 3H, CH_2OCH_3), 2.84 (t, J = 6.1 Hz, 2H, $\equiv CCH_2$). OH signals overlaps with water signal. ^{1}H NMR spectrum corresponds to the previously reported data.[15]

4-(3-(3-Methoxyprop-1-yn-1-yl)benzo[*b*]thiophen-2-yl)but-3-yn-1-ol (19b) and 4,4'-(benzo[*b*]thiophene-2,3-diyl)bis(but-3-yn-1-ol) (11c)



19b **11c**

Endiynes **19b** and **11c** weresynthesize according to General procedure *g* from 2,3-diiodobenzo[*b*]thiophene (**4**) (100 mg, 0.259 mmol, 1.00 equiv), first added alkyne was but-3-yn-1-ol **9c** (21.8 mg, 26.3 μL, 0.311 mmol, 1.20 equiv), second added alkyne was methyl propargyl ether **9a** (45.4 mg, 49.0 μL, 0.648 mmol, 2.50 equiv). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (1:1) as the eluent to give unsymmetrical enediyne **19b** as a yellow oil (41.0 mg, 58 %) and symmetrical by-product **11c** as a yellow oil (13.0 mg, 17 %).

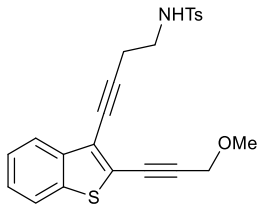
4-(3-(3-Methoxyprop-1-yn-1-yl)benzo[*b*]thiophen-2-yl)but-3-yn-1-ol (19b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.79 (m, 1H, H-Ar), 7.77 – 7.63 (m, 1H, H-Ar), 7.49 – 7.33 (m, 2H, H-Ar), 4.46 (s, 2H, CH_2OCH_3), 3.86 (t, 2H, ^3J = 6.2 Hz, CH_2OH), 3.52 (s, 3H, CH_2OCH_3), 2.81 (t, 2H, ^3J = 6.1 Hz, , $\equiv CCH_2$), 2.20 (br s, 1H, OH). ^{1}H NMR spectrum corresponds to the previously reported data.[15]

4,4'-(benzo[*b*]thiophene-2,3-diyl)bis(but-3-yn-1-ol) (11c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 1H, H-Ar), 7.75 – 7.67 (m, 1H, H-Ar), 7.46 – 7.35 (m, 2H, H-Ar), 3.90 – 3.85 (m, 4H, $CH_2OH\times2$), 2.85 – 2.81 (m, 4H, $\equiv CCH_2\times2$), OH signals overlaps with water signal. ^{1}H NMR spectrum corresponds to the previously reported data.[16]

***N*-(4-(2-(3-methoxyprop-1-yn-1-yl)benzo[*b*]thiophen-3-yl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (19c)**

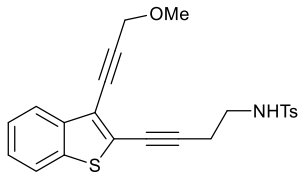


19c

Endiyne **19c** was synthesize according to General procedure *g* from 2,3-diiodobenzo[*b*]thiophene (**4**) (100 mg, 0.259 mmol, 1.00 equiv), first added alkyne was methyl propargyl ether **9a** (21.8 mg, 26.3 μL, 0.311 mmol, 1.20 equiv), second added alkyne was *N*-(but-3-yn-1-yl)-4-methylbenzenesulfonamide (**9d**) (57.7 mg, 0.259 mmol, 1.00 equiv). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) as the eluent to give unsymmetrical enediyne **19c** as a beige solid (39.0

mg, 36 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, 2H, ^3J = 8.3 Hz, H-Ar), 7.78 – 7.73 (m, 2H, H-Ar), 7.46 – 7.41 (m, 2H, H-Ar), 7.29 (d, 2H, ^3J = 8.3 Hz, H-Ar, overlaps with $CHCl_3$ signal), 5.07 (t, 1H, ^3J = 6.3 Hz, NHTs), 4.48 (s, 2H, CH_2OCH_3), 3.51 (s, 3H, CH_2OCH_3), 3.33 – 3.28 (m, 2H, CH_2NHTs), 2.72 (t, 2H, ^3J = 6.3 Hz, $\equiv CCH_2$), 2.40 (s, 3H, CH_3). ^{1}H NMR spectrum corresponds to the previously reported data.[18]

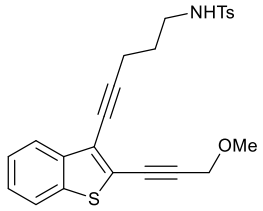
_N_-(4-(3-(3-methoxyprop-1-yn-1-yl)benzo[_b_]thiophen-2-yl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (19d)



19d

Endiyne **19d** was synthesize according to General procedure *g* from 2,3-diiodobenzo[*b*]thiophene (**4**) (100 mg, 0.259 mmol, 1.00 equiv), first added alkyne was *N*-(but-3-yn-1-yl)-4-methylbenzenesulfonamide (**9d**) (57.7 mg, 0.259 mmol, 1.00 equiv), second added alkyne was methyl propargyl ether **9a** (45.4 mg, 54.7 µL, 0.648 mmol, 2.50 equiv). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) as the eluent to give unsymmetrical enediyne **19d** as a beige solid (47.0 mg, 43 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 1H, H-Ar), 7.79 (d, 2H, *J* = 8.2 Hz, H-Ar), 7.75 – 7.67 (m, 1H, H-Ar), 7.48 – 7.37 (m, 2H, H-Ar), 7.28 (d, 2H, *J* = 8.1 Hz, H-Ar), 5.11 (t, 1H, ^3J = 6.2 Hz, N*H*Ts), 4.49 (s, 2H, CH_2OCH_3), 3.51 (s, 3H, CH_2OCH_3), 3.28 – 3.23 (m, 2H, CH_2NHTs), 2.68 (t, 2H, ^3J = 6.4 Hz, $\equiv CCH_2$), 2.39 (s, 3H, CH_3). ^{13}C NMR (101 MHz, acetone-d_6) δ 144.0 (C-Ar), 139.3 (C-Ar), 139.2 (C-Ar), 138.8 (C-Ar), 130.5 (CH-Ar), 127.8 (CH-Ar), 127.7 (C-Ar), 127.4 (CH-Ar), 126.4 (CH-Ar), 123.8 (CH-Ar), 123.3 (CH-Ar), 122.6 (C-Ar), 99.0 (≡C), 93.3 (≡C), 79.7 (≡C), 75.3 (≡C), 60.7 (CH_2O), 57.56 (OCH_3), 42.7 (CH_2NHTs), 22.0 ($\equiv CCH_2$), 21.4 (CH_3). HRMS ESI $[M + Na]^+$ calcd for $C_{23}H_{21}NNaO_3S_2^+$ 446.0855, found 446.0855.

_N_-(5-(2-(3-methoxyprop-1-yn-1-yl)benzo[_b_]thiophen-3-yl)pent-4-yn-1-yl)-4-methylbenzenesulfonamide (19e)

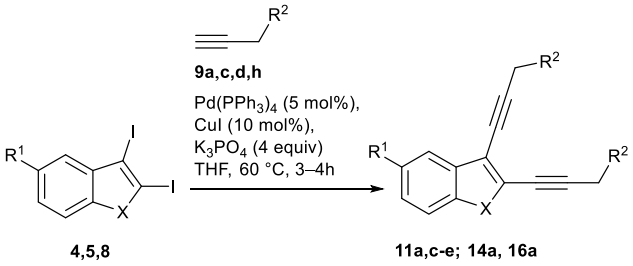


19e

Endiyne **19e** was synthesize according to General procedure *g* from 2,3-diiodobenzo[*b*]thiophene (**4**) (100 mg, 0.259 mmol, 1.00 equiv), first added alkyne was methyl propargyl ether **9a** (21.8 mg, 26.3 µL, 0.311 mmol, 1.20 equiv), second added alkyne was 4-methyl-*N*-(pent-4-yn-1-yl)benzenesulfonamide **9g** (61.1 mg, 0.259 mmol, 1.00 equiv). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) as the eluent to give unsymmetrical enediyne **19e** as a beige solid (53.1 mg, 47 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.65 (m, 4H, H-Ar), 7.52 – 7.36 (m, 2H, H-Ar), 7.27 – 7.16 (m, 2H, H-Ar), 4.85 (br s, 1H, NHTs), 4.40 (s, 2H, CH_2OCH_3), 3.48 (s, 3H, CH_2OCH_3), 3.26 – 3.27 (m, 2H, CH_2NHTs), 2.60 (t, 2H, ^3J = 6.6 Hz, ($\equiv CCH_2$), 2.36 (s, 3H, CH_3), 1.90 – 1.83 (m, 2H, CH_2-CH_2-CH_2). ^{13}C NMR (101 MHz, acetone-d_6) δ 143.8 (C-Ar), 139.5 (C-Ar), 139.06 (C-Ar), 139.03 (C-Ar), 130.4 (CH-Ar), 127.8 (CH-Ar), 127.2 (CH-Ar), 126.3 (CH-Ar), 125.1 (C-Ar), 124.5 (C-Ar), 124.1 (CH-Ar), 123.3 (CH-Ar), 97.7 (≡C), 96.3 (≡C), 79.5 (≡C), 74.7 (≡C), 60.7 (CH_2O), 57.7 (OCH_3), 42.8 (CH_2NHTs),

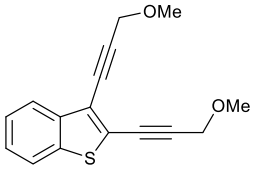
29.6 (≡C*CH*$_2$), 21.3 (CH_3), 17.4 (CH_2-*CH_2*-CH_2, overlaps with the solvent signal, can be observed in DEPT). HRMS ESI $[M + Na]^+$ calcd for $C_{24}H_{23}NNaO_3S_2^+$ 460.1012, found 460.1014.

2.8 Synthesis of Symmetrical Enediynes

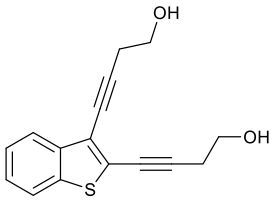


4,5,8 **11a,c-e; 14a, 16a**

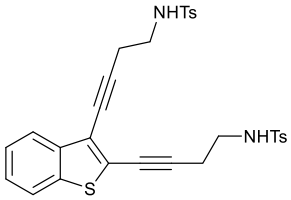
X = S, R^1 = H (**4**); X = NMe, R^1 = COOEt (**5**); X = O, R^1 = H (**8**)
R^2 = OMe (**9a**), CH_2OH (**9c**), CH_2NHTs (**9d**), CH_2OTHP (**h**);



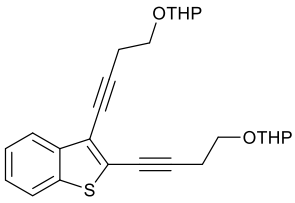
11a (53%)



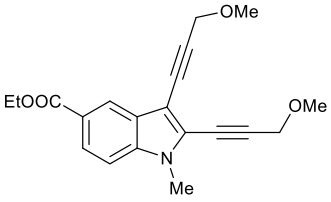
11c (51%)



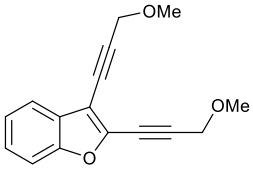
11d (45%)



11e (75%)



14a (34%)

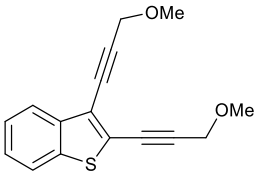


16a (61%)

General Procedure *h* for the Sonogashira coupling in the synthesis of symmetrical enediynes 11

To a solution of diiodoheteroindene (1.00 equiv) in dry THF (c = 0.100 M) in a vial with a stirring bar $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), and K_3PO_4 (4.00 equiv) were added subsequently under argon atmosphere. Then the vial was sealed and the resulting mixture was degassed by bubbling of an Ar stream directly through the mixture. Then an alkyne **9** (2.00 – 3.0 equiv) was added. The vial with the reaction mixture was placed into preheated to 60 °C aluminum vial block and stirred for the corresponding time TLC control). The reaction mixture was cooled to room temperature and passed through a short pad of silica gel eluting with ethyl acetate. The volatiles were removed under reduced pressure. The crude product was purified by column chromatography on silica gel.

2,3-Bis(3-methoxyprop-1-yn-1-yl)benzo[*b*]thiophene (11a)

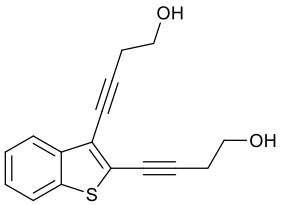


11a

Symmetrical enediyne **11a** was synthesize according to General procedure *h* from 2,3-diiodobenzo[*b*]thiophene **4** (67.0 mg, 0.174 mmol, 1.00 equiv), 3-methoxyprop-1-yne **9a** (25.0 mg, 30.1

μL, 0.348 mmol, 2.00 equiv), $Pd(PPh_3)_4$ (10.0 mg, 0.00868 mmol, 5 mol%), CuI (3.31 mg, 0.0174 mmol, 10 mol%), and K_3PO_4 (147 mg, 0.694 mmol, 4.00 equiv) in THF (1.74 mL). Reaction time – 4 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (5:1) as the eluent to give enediyne **11a** as a brown oil (24.7 mg, 53 %). For the spectral data of enediyne **11a** see Section 2.6.

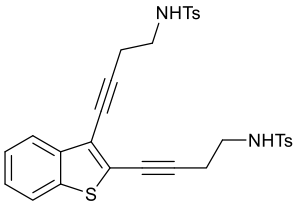
4,4'-(Benzo[*b*]thiophene-2,3-diyl)bis(but-3-yn-1-ol) (11c)



11c

Symmetrical enediyne **11c** was synthesize according to General procedure *h* from 2,3-diiodobenzo[*b*]thiophene (**4**) (70.0 mg, 0.181 mmol, 1.00 equiv), but-3-yn-1-ol (**9c**) (25.0 mg, 27.0 μL, 0.363 mmol, 2.00 equiv), $Pd(PPh_3)_4$ (10.5 mg, 0.00907 mmol, 5 mol%), CuI (3.45 mg, 0.0181 mmol, 10 mol%), and K_3PO_4 (154 mg, 0.725 mmol, 4.00 equiv) in THF (1.81 mL). Reaction time – 4 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (1:1) as the eluent to give enediyne **11b** as a brown oil (25.0 mg, 51 %). For the spectral data of enediyne **11c** see Section 2.7.

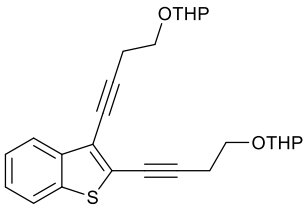
***N,N'*-(benzo[*b*]thiophene-2,3-diylbis(but-3-yne-4,1-diyl))bis(4-methylbenzenesulfonamide) (11d)**



11d

Symmetrical enediyne **11d** was synthesize according to General procedure *h* from 2,3-diiodobenzo[*b*]thiophene (**4**) (30.0 mg, 0.0777 mmol, 1.00 equiv), *N*-(but-3-yn-1-yl)-4-methylbenzenesulfonamide (**9d**) (49.0 mg, 0.217 mmol, 2.80 equiv), $Pd(PPh_3)_4$ (4.50 mg, 3.89 μmol, 5 mol%), CuI (1.48 mg, 7.77 μmol, 10 mol%), and K_3PO_4 (66.0 mg, 0.311 mmol, 4.00 equiv) in THF (0.77 mL). Reaction time – 24 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3:2) as the eluent to give enediyne **11d** as a beige solid (20.0 mg, 45 %). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.93 – 7.70 (m, 6H, H-Ar), 7.51 – 7.44 (m, 2H, H-Ar), 7.39 – 7.35 (m, 4H, H-Ar), 6.71 (two overlapped t, ^3J = 5.8 Hz, 2H, NHTs×2), 3.28 – 3.18 (m, 4H, CH_2NHTs×2), 2.79 – 2.74 (m, 4H, ≡CCH_2×2), 2.38 (s, 6H, CH_3×2). ^{13}C NMR (101 MHz, acetone-d_6) δ 143.98 (C-Ar), 143.96 (C-Ar), 139.6 (C-Ar), 139.19 (C-Ar), 139.13 (C-Ar), 138.7 (C-Ar), 130.52 (CH-Ar), 130.50 (CH-Ar), 127.8 (2×CH-Ar signals from Ts), 127.3 (CH-Ar), 126.6 (C-Ar), 126.2 (CH-Ar), 124.1 (CH-Ar), 123.4 (C-Ar), 123.2 (CH-Ar), 98.5 (≡C), 95.0 (≡C), 75.6 (≡C), 75.5 (≡C), 43.1 (CH_2NHTs), 42.8 (CH_2NHTs), 22.0 (≡CCH_2), 21.8 (≡CCH_2), 21.4 (2×CH_3). HRMS ESI $[M + Na]^+$ calcd for $C_{30}H_{28}N_2NaO_4S_3^+$ 599.1103, found 599.1106.

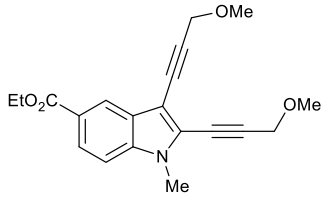
2,2'-((Benzo[*b*]thiophene-2,3-diylbis(but-3-yne-4,1-diyl))bis(oxy))bis(tetrahydro-2*H*-pyran) (11e)



11e

Symmetrical enediyne **11e** was synthesize according to General procedure *h* from 2,3-diiodobenzo[*b*]thiophene (**4**) (70.0 mg, 0.181 mmol, 1.00 equiv), THP-protected but-3-yn-1-ol **9h** (56.0 mg, 0.363 mmol, 2.00 equiv), $Pd(PPh_3)_4$ (10.5 mg, 0.00907 mmol, 5 mol%), CuI (3.45 mg, 0.0181 mmol, 10 mol%), and K_3PO_4 (154 mg, 0.725 mmol, 4.00 equiv) in THF (1.81 mL). Reaction time – 4 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (5:1) as the eluent to give enediyne **11e** as a brown oil (60.0 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.79 (m, 1H, H-Ar), 7.69 – 7.60 (m, 1H, H-Ar), 7.40 – 7.34 (m, 2H, H-Ar), 4.75 – 4.71 (m, 2H, CHO_2×2), 4.07 – 3.87 (m, 4H, CH_2O×2), 3.79 – 3.65 (m, 2H, CH_2O), 3.55 – 3.51 (m, 2H, CH_2O), 2.88 – 2.83 (m, 4H, ≡C*CH*$_2$×2), 1.94 – 1.81 (m, 2H, CH_2-THP), 1.80 – 1.70 (m, 2H, CH_2-THP), 1.70 – 1.48 (m, 8H, CH_2-THP×4). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.2 (C-Ar), 138.2 (C-Ar), 126.03 (C-Ar), 125.98 (CH-Ar), 125.0 (CH-Ar), 123.5 (CH-Ar), 122.4 (C-Ar), 122.1 (CH-Ar), 98.83 (CHO), 98.78 (CHO), 97.6 (≡C), 93.8 (≡C), 74.8 (≡C), 74.7 (≡C), 65.9 (CH_2O) 65.5 (CH_2O), 62.31 (CH_2O), 62.30 (CH_2O), 30.75 (CH_2), 30.71 (CH_2), 25.6 (CH_2×2), 21.8 (≡C*CH*$_2$), 21.6 (≡C*CH*$_2$), 19.50 (CH_2), 19.47 (CH_2). HRMS ESI [M + Na]$^+$ calcd for $C_{26}H_{30}NaO_4S^+$ 461.1757, found 461.1755.

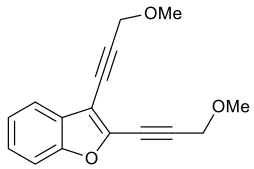
Ethyl 2,3-bis(3-methoxyprop-1-yn-1-yl)-1-methyl-1*H*-indole-5-carboxylate (14a)



14a

Symmetrical indole-fused enediyne **14a** was synthesize according to General procedure *h* from 2,3-diiodoindole **5** (23.0 mg, 0.051 mmol, 1.00 equiv), 3-methoxyprop-1-yne (**9a**) (7.10 mg, 8.54 μL, 0.101 mmol, 2.00 equiv), $Pd(PPh_3)_4$ (2.92 mg, 2.53 μmol, 5 mol%), CuI (0.964 mg, 5.05 μmol, 10 mol%), and K_3PO_4 (42.9 mg, 0.202 mmol, 4.00 equiv) in THF (0.510 mL). Reaction time – 4 h. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) as the eluent to give enediyne **14a** as a brown oil (5.80 mg, 34 %). For the spectral data of enediyne **14a** see Section 2.4.1

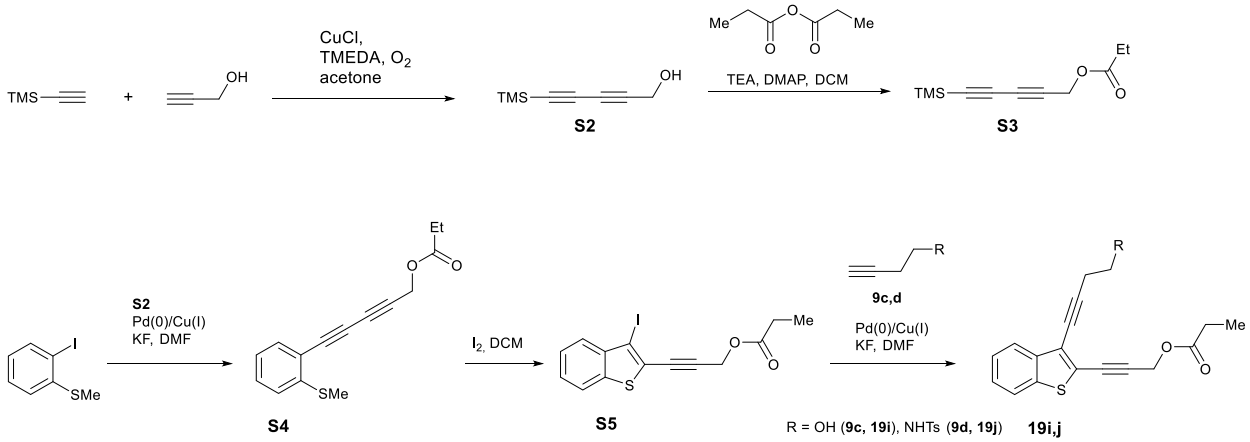
2,3-Bis(3-methoxyprop-1-yn-1-yl)benzofuran (16a)



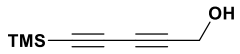
16a

Symmetrical benzofuran-fused enediyne **16a** was synthesize according to General procedure *h* from diiodobenzofuran (34.0 mg, 0.101 mmol, 1.00 equiv), 3-methoxyprop-1-yne (**9a**) (19.3 mg, 23.3 μL, 0.276 mmol, 3.00 equiv), $Pd(PPh_3)_4$ (5.31 mg, 0.000460 mmol, 5 mol%), CuI (1.75 mg, 0.00919 mmol, 10 mol%), and K_3PO_4 (78.0 mg, 0.368 mmol, 4.00 equiv) in THF (2.00 mL) at 60 °C. Reaction time was 3h. Purification of crude product by column chromatography on silica gel using pentane as the eluent gave enediyne 1**6a** as a yellow oil (14.2 mg, 61%). For the spectral data of enediyne **14a** see Section 2.4.2

2.9 Synthesis of Enediynes 19i,j Using «Diacetylenic Approach»



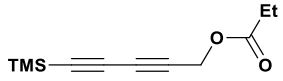
5-(Trimethylsilyl)penta-2,4-diyn-1-ol (S2)



S2

Compound **S2** was obtained by a slightly modified method reported previously.[19] To a stirred solution of ethynyltrimethylsilane (1.96 g, 2.80 mL, 20.0 mmol, 1.00 equiv) and propargyl alcohol (2.20 g, 2.30 mL, 40.0 mmol, 2.00 equiv) and in acetone (60 mL) at room temperature were added copper(I) chloride (0.760 g, 4.00 mmol, 20.0 mol%) and tetramethylethylenediamine (TMEDA) (1.13 mL, 7.60 mmol, 38.0 mol%). A stream of air was bubbled through the stirred reaction mixture for 4 h (the color of the mixture changed from turquoise to peaty). After completion of reaction, the reaction mixture was diluted with saturated aqueous solution of NH_4Cl (100 mL), and the resulting mixture was extracted with ether (3×50.0 mL). Combined organic layers were washed with NH_4Cl (100 mL) and brine (100 mL), and dried over anhydrous Na_2SO_4. After filtration the volatiles were removed under reduced pressure, and the residue was purified by column chromatography using hexane/ethyl acetate (5:1) as the eluent to give a yellow oil **S1** (1.00 g, 33 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (s, 2H, OCH_2), 1.61 (br s, 1H; overlaps with the signal of water), 0.20 (c, 9H, TMS). ^{1}H NMR spectrum corresponds to the previously reported data.[19]

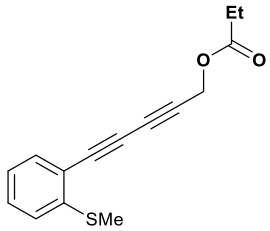
5-((Trimethylsilyl)penta-2,4-diyn-1-yl)propionate (S3)



S3

To a stirred solution of 5-(trimethylsilyl)penta-2,4-diyn-1-ol **S2** (270 mg, 1.77 mmol, 1.00 equiv) in DCM (8.85 mL, c = 0.200 M) at 0 °C, DMAP (21.7 mg, 0.177 mmol, 10.0 mol%) and triethylamine (197 mg, 0.271 ml, 1.95 mmol, 1.10 equiv) followed by propionic anhydride (254.0 mg, 0.249 ml, 1.95 mmol, 1.10 equiv) was added. The reaction mixture was allowed to warm to at room temperature and then was stirred for 2 h. After completion of the reaction, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (15.0 мл), extracted with DCM (3×15.0 мл), washed with saturated solution of $NaHCO_3$ (50.0 mL) and brine (50.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using hexane/ethyl acetate (30:1) to give acylated product **S3** a yellow oil (240 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.72 – 4.71 (m, 2H, CH_2O), 2.38 – 2.32 (m, 2H, CH_2CH_3), 1.16 – 1.12 (m, 3H, CH_2CH_3), 0.18 – 0.17 (m, 9H, TMS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C=O), 88.1 (≡C), 87.1 (≡C), 71.7 (≡C), 71.4 (≡C), 52.3 (CH_2O), 27.4 (CH_2CH_3), 9.0 (CH_2CH_3), –0.4 (TMS).

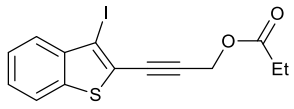
5-(2-(Methylsulfanyl)phenyl)penta-2,4-diyn-1-yl propionate (S4)



S4

To a solution of 2-iodothioanisole (960 mg, 3.62 mmol, 1.00 equiv) and TMS-diacetylene **S3** (1.04 g, 4.99 mmol, 1.30 equiv) in trimethylamine (30.0 mL) $Pd(PPh_3)_4$ (222 mg, 0.192 mmol, 5.00 mol%) was added. The reaction flask was evacuated and purged with argon several times. Then anhydrous KF (1.12 g, 19.2 mmol, 5.00 equiv) and CuI (110 mg, 0.576 mmol, 15.0 mol%) were added. The reaction mixture was again degassed. Then MeOH (1.23 g, 1.55 mL, 38.4 mmol, 10.0 equiv) was added. The resulting reaction mixture was stirred at 40° C overnight (TLC monitoring). After cooling, the reaction mixture was poured into saturated aqueous solution of NH_4Cl (150 ml), and extracted with ethyl acetate (3×70.0 mL). The combained organic layers were washed with saturated solution NH_4Cl (150 mL), brine (150 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a product which was purified by column chromatography using hexane/ethyl acetate (15:1) as the eluent to give diacetylene **S4** (635 mg, 64%) as an orange oil. ^{1}H NMR(400 MHz, $CDCl_3$) δ = 7.47 (dd, 1H, ^3J = 7.7 Hz, ^4J = 1.4, CH-Ar), 7.37 – 7.33 (m, 1H, CH-Ar), 7.19 (d, 1H, ^3J = 7.9 Hz,), 7.13 – 7.09 (m, 1H, CH-Ar), 4.87 (s, 2H, OCH_2), 2.52 (s, 3H, SCH_3), 2.42 (q, 2H, ^3J = 7.6 Hz, CH_2CH_3), 1.20 (t, 3H, ^3J = 7.6 *H*z, CH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C=O), 143.5 (C-Ar), 133.7 (CH-Ar), 129.8 (CH-Ar), 124.5 (CH-Ar), 124.4 (CH-Ar), 119.5 (C-Ar), 79.1 (≡C), 78.1 (≡C), 76.0 (≡C), 70.9 (≡C), 52.5 (OCH_2), 27.3 (CH_2CH_3), 15.2 (SCH_3), 8.9 (CH_2CH_3). HRMS ESI $[M + Na]^+$ calcd for $C_{15}H_{14}O_2NaS^+$ 281.0607, found 281.0608.

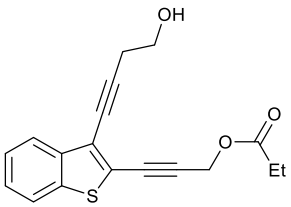
3-(3-Iodobenzo[*b*]thiophen-2-yl)prop-2-yn-1-yl propionate (S5)



S5

To a solution of diacetylene **S4** (570 mg, 2.21 mmol, 1 equiv) in DCM (22.1 mL) a solution I_2 (561 mg, 2.21 mmol, 1 equiv) in DCM (22.1 mL) was added and th reaction mixture was stirred at 40°C for 1.5 h. The reaction mixture was cooled, washed with saturated aqueous solution of $Na_2S_2O_3$ (40.0 mL), the aqueous layer was extracted with DCM (40.0 mL), and the combined organic layers were washed with brine (80.0 mL) anf then dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using hexane / ethyl acetate (40:1) as the eluent to give 3-iodobenzothiophene **S5** (794 mg, 97%) as yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.64 (m, 2H, H-Ar), 7.51 – 7.37 (m, 2H, H-Ar), 5.02 (s, 2H, CH_2O), 2.44 (q, 2H ^3J=7.6 Hz, CH_2CH_3), 1.21 (t, 3H, ^3J=7.6 Hz, CH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C=O), 140.3, 139.1, 126.8, 126.4, 125.8, 123.8, 122.1, 92.6, 88.8 (≡C), 80.7 (≡C), 52.6 (CH_2O), 27.4 (CH_2CH_3), 9.0 (CH_2CH_3). HRMS (ESI), m/z: calculated for $C_{14}H_{11}INaO_2S$, $[M+Na]^+$ 392.9417, found 392.9409.

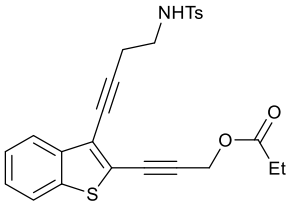
3-(3-(4-Hydroxybut-1-yn-1-yl)benzo[*b*]thiophen-2-yl)prop-2-yn-1-yl propionate (19i)



19i

To a stirred solution of 2-ethynyl-3-iodobenzothiophene **S5** (339 mg, 0.916 mmol, 1.00 equiv) in DMF (15.0 mL) were added $Pd(PPh_3)_4$ (52.9 mg, 0.0458 mmol, 5 mol%) and KF (266 mg, 4.68 mmol, 5.00 equiv). The reaction vial was evacuated and flushed with argon three times. After that, CuI (17.4, 0.0916 mmol, 15 mol%) was added, the vial was sealed and degassed again. But-3-yn-1-ol (**9c**) (193 mg, 0.208 mL, 2.75 mmol, 3.00 equiv) was added using a syringe. The reaction mixture was stirred at 50°C for 24 h. After completion of the reaction, the reaction mixture was cooled, poured into a saturated aqueous solution of NH_4Cl (100 mL), and extracted with ethyl acetate (3×50.0 mL). The combined organic layers were washed with saturated NH_4Cl (100 mL), brine (2×100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude product which was purified column chromatography on silica gel using hexane / ethyl acetate (2:1) as the eluent to enediyne **19i** (250 mg, 88%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 – 7.97 (m, 1H, CH-Ar), 7.86 – 7.82 (m, 1H, CH-Ar), 7.54 – 7.49 (m, 2H, CH-Ar), 5.06 (s, 2H, OCH_2), 4.98 (br s, 1H), 3.68 (t, 2H, ^3J=6.8 Hz, CH_2OH), 2.71 (t, 2H, ^3J =6.8 Hz, ≡CCH_2), 2.41 (q, ^3J=7.5 Hz, 2H, CH_2CH_3), 1.07 (t, ^3J =7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.0 (C=O), 138.0 (C-Ar), 137.7 (C-Ar), 127.0 (CH-Ar), 125.7 (CH-Ar), 123.5 (C-Ar), 123.2 (CH-Ar), 122.94 (C-Ar), 122.83 (CH-Ar), 96.7 (≡C), 94.0 (≡C), 78.3 (≡C), 73.7 (≡C), 59.8 (CH_2O), 52.2 (CH_2O), 26.6(≡CCH_2), 23.6 (CH_2CH_3), 8.9 (CH_2CH_3). HRMS (ESI), m/z: calculated for $C_{18}H_{16}NaO_3S^+$, $[M+Na]^+$ 335.0712, found 335.0709.

3-(3-(4-((4-methylphenyl)sulfonamido)but-1-yn-1-yl)benzo[*b*]thiophen-2-yl)prop-2-yn-1-yl propionate (19j)



19j

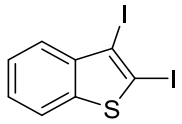
To a stirred solution of 2-ethynyl-3-iodobenzothiophene **S5** (339 mg, 0.916 mmol, 1.00 equiv) in DMF (12.0 mL) were added $Pd(PPh_3)_4$ (52.9 mg, 0.0458 mmol, 5 mol%) and KF (266 mg, 4.68 mmol, 5.00 equiv). The reaction vial was evacuated and flushed with argon three times. After that, CuI (17.4, 0.0916 mmol, 15 mol%) was added, the vial was sealed and degassed again. A solution of alkyne **9d** (215 mg, 0.961 mmol, 3.00 equiv) in DMF (3.00 mL) was added using a syringe. The reaction mixture was stirred at 60°C for 24 h. After completion of the reaction, the reaction mixture was cooled, poured into a saturated aqueous solution of NH_4Cl (100 mL), and extracted with ethyl acetate (3×50.0 mL). The combined organic layers were washed with saturated NH_4Cl (100 mL), brine (2×100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude product which was purified column chromatography on silica gel using hexane / ethyl acetate (2:1) as the eluent to enediyne **19j** (329 mg, 77 %) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 – 7.94 (m, 1H, CH-Ar), 7.90 – 7.82 (m, 2H CH-Ar), 7.72 (d, 2H, ^3J = 8.2 Hz, CH-Ar), 7.55 – 7.47 (m, 2H, CH-Ar), 7.37 (d, 2H, ^3J = 8.2 Hz, CH-Ar), 5.05 (s, 2H, OCH_2), 3.08 – 3.03 (m, 2H, CH_2NHTs), 2.70 (t, 2H, ^3J = 6.9 Hz, ≡CCH_2), 2.39 (q, 2H, ^3J = 7.5 Hz, CH_2CH_3), 2.35 (s, 3H, CH_3), 1.05 (t, 3H, ^3J = 7.5 Hz, CH_2CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.0 (C=O), 142.7 (C-

Ar), 138.0 (C-Ar), 137.68 (C-Ar), 137.65 (C-Ar), 129.6 (CH-Ar), 127.0 (CH-Ar), 126.5 (CH-Ar), 125.7 (CH-Ar), 123.3 (CH-Ar), 123.9 (C-Ar), 123.2 (C-Ar), 123.1 (C-Ar), 122.8 (CH-Ar), 95.5 (≡C), 94.1 (≡C), 78.2 (≡C), 74.1 (≡C), 52.2 (CH_2O), 41.6 (CH_2NHTs), 26.5(≡C*CH_2*), 20.9 (CH_3), 20.6 (*CH_2*CH_3), 8.8 (CH_2*CH_3*). HRMS (ESI), m/z: calculated for $C_{25}H_{23}NNaO_4S_2^+$, $[M+Na]^+$ 488.0961, found 488.0996.

3 Computational details

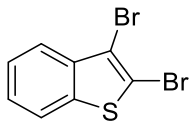
All calculations involved in NBO[20] analysis were done using Gaussian16[21] using B3LYP D3/6-311+G** with LANL08(d) for I or Br. Calculations on the thermodynamics of the organometallic processes were done using MN15-L[22]/def2-TZVP and def2-TZVP(ECP) for iodine[23] and palladium[24] using ORCA[25] with the tightSCF option enabled. This was chosen as MN15-L show superior performance for organometallics to B3LYP. Initial guess geometries for the organometallic complexes was done using R^2-SCAN-3c[26] with def2-TZVP(ECP) for iodine. All calculations used the SMD[27] solvent model with DCM as the solvent. All stationary points were characterized using Frequency calculations, with the ORCA calculations requiring numerical frequencies.

Structures (B3LYP)



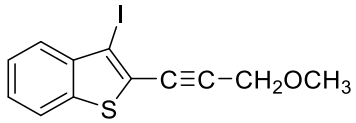
E(RB3LYP) = -728.333249157

C	1.746150000	3.897906000	0.000000000
C	3.072980000	3.435365000	0.000000000
C	3.348664000	2.074021000	0.000000000
C	2.273717000	1.182337000	0.000000000
C	0.931268000	1.626989000	0.000000000
C	0.681027000	3.009561000	0.000000000
C	0.000000000	0.518263000	0.000000000
C	0.611574000	-0.696798000	0.000000000
S	2.367705000	-0.571513000	0.000000000
I	-2.092386000	0.818100000	0.000000000
I	-0.234973000	-2.616918000	0.000000000
H	-0.339726000	3.372467000	0.000000000
H	1.552206000	4.964464000	0.000000000
H	3.891487000	4.146088000	0.000000000
H	4.370545000	1.712644000	0.000000000



E(RB3LYP) = -731.915944772

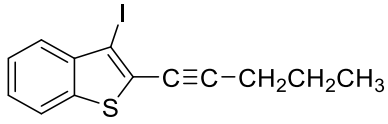
C	3.788581000	0.785650000	0.000001000
C	4.109520000	-0.582409000	0.000000000
C	3.111149000	-1.548273000	0.000000000
C	1.781738000	-1.121477000	0.000000000
C	1.440990000	0.249936000	0.000000000
C	2.467663000	1.207478000	0.000001000
C	0.008881000	0.439662000	0.000000000
C	-0.687792000	-0.729057000	0.000000000
S	0.351866000	-2.146213000	0.000000000
Br	-0.783673000	2.168123000	0.000000000
Br	-2.561172000	-0.972679000	0.000000000
H	2.224671000	2.263240000	0.000001000
H	4.584769000	1.521101000	0.000001000
H	5.148537000	-0.890985000	0.000000000
H	3.357347000	-2.603555000	-0.000001000



E(RB3LYP) = -947.619788951

C	4.701754000	0.867025000	0.314068000
C	3.728019000	1.848112000	0.182894000
C	2.395841000	1.446180000	0.054126000
C	2.028066000	0.078308000	0.054013000
C	0.606576000	-0.082698000	-0.095767000
C	-0.086139000	1.094134000	-0.204197000
S	1.001748000	2.495195000	-0.123427000
H	3.994206000	2.898708000	0.181556000
I	-0.345558000	-1.964954000	-0.138265000
C	-1.468570000	1.296024000	-0.352839000
C	-2.658532000	1.467435000	-0.479334000
C	-4.106729000	1.644731000	-0.599634000
H	-4.484306000	1.003817000	-1.409739000
H	-4.327125000	2.681822000	-0.865108000
O	-4.809996000	1.383051000	0.611653000

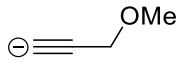
C	-4.801561000	0.005816000	0.986808000
H	-5.403866000	-0.075959000	1.892387000
H	-3.786163000	-0.350499000	1.198289000
H	-5.243358000	-0.619959000	0.199869000
C	4.355533000	-0.496108000	0.316300000
H	5.741033000	1.157859000	0.416137000
C	3.034747000	-0.894277000	0.188045000
H	5.133061000	-1.244228000	0.419914000
H	2.769065000	-1.944633000	0.189450000



E(RB3LYP) = -911.726900569

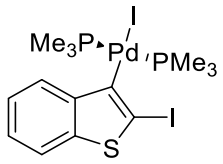
C	4.330962000	-0.774622000	0.056546000
C	4.787788000	0.554977000	0.049194000
C	3.889711000	1.614327000	0.020810000
C	2.523288000	1.324345000	0.000516000
C	2.044086000	-0.008294000	0.008500000
C	2.974957000	-1.061321000	0.036434000
C	0.605669000	-0.049351000	-0.016835000
C	0.003501000	1.180059000	-0.044074000
S	1.208652000	2.485838000	-0.038057000
H	2.625151000	-2.086679000	0.041626000
H	5.049329000	-1.586186000	0.078113000
H	5.852434000	0.758447000	0.065530000
H	4.239929000	2.640151000	0.014769000
I	-0.496916000	-1.849875000	-0.006677000
C	-1.363965000	1.504809000	-0.071082000
C	-2.537594000	1.796557000	-0.097105000
C	-3.962537000	2.103590000	-0.110574000
H	-4.280687000	2.272514000	-1.146919000
H	-4.124501000	3.046604000	0.423195000
C	-4.831807000	0.992127000	0.518366000
C	-4.756457000	-0.335299000	-0.236712000

H	-5.407788000	-1.083177000	0.224926000
H	-3.737912000	-0.734047000	-0.238865000
H	-5.071492000	-0.212370000	-1.278445000
H	-5.864940000	1.353595000	0.534830000
H	-4.527006000	0.849686000	1.560112000



Final Single Point Energy = -230.595996134058

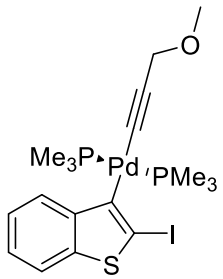
C	-5.770692000	-0.130482000	-0.134641000
C	-4.715559000	-0.188191000	-0.782794000
C	-7.008021000	-0.025544000	0.642036000
O	-7.322962000	1.313531000	1.074441000
H	-6.964884000	-0.684844000	1.527232000
H	-7.873625000	-0.337816000	0.044548000
C	-6.351315000	1.831583000	1.973215000
H	-6.698366000	2.820949000	2.286280000
H	-5.365613000	1.932107000	1.494761000
H	-6.245473000	1.190377000	2.863993000



Final Single Point Energy = -2351.240996979598

P	-5.851655000	0.426318000	-0.201059000
C	-6.374686000	-0.676073000	-1.567722000
C	-7.138552000	0.143600000	1.072175000
C	-6.232719000	2.090744000	-0.867343000
P	-1.460049000	-0.130041000	1.302159000
C	-0.493380000	-1.450111000	0.477925000
C	-0.391331000	1.342537000	1.081864000
C	-1.295169000	-0.547497000	3.078103000
Pd	-3.667112000	0.194585000	0.602812000
C	-4.242448000	-3.231676000	0.953476000
C	-4.479509000	-4.588863000	1.109493000

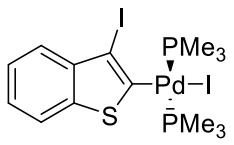
C	-4.238086000	-5.485497000	0.057279000
C	-3.754889000	-2.744164000	-0.270100000
C	-3.518926000	-3.670540000	-1.318293000
C	-3.756011000	-5.035327000	-1.165552000
H	-3.570276000	-5.731244000	-1.979090000
H	-4.429455000	-6.545757000	0.196666000
H	-4.428637000	-2.532978000	1.766243000
H	-4.856702000	-4.964802000	2.056474000
C	-3.449982000	-1.378935000	-0.623429000
C	-2.999994000	-1.308398000	-1.900058000
S	-2.915210000	-2.857315000	-2.752188000
I	-3.985249000	2.291318000	2.293982000
I	-2.427003000	0.421033000	-2.897448000
H	-5.746644000	-0.504343000	-2.447595000
H	-7.419743000	-0.470211000	-1.825772000
H	-6.276653000	-1.724493000	-1.269493000
H	-5.540306000	2.324507000	-1.682853000
H	-6.114151000	2.842483000	-0.081727000
H	-7.260264000	2.117245000	-1.248260000
H	-8.136049000	0.294154000	0.643166000
H	-6.991395000	0.836300000	1.906370000
H	-7.060528000	-0.881389000	1.449750000
H	-0.373112000	1.624536000	0.023875000
H	0.629668000	1.119932000	1.413168000
H	-0.788632000	2.181557000	1.660457000
H	-0.415156000	-1.242125000	-0.593819000
H	-0.984843000	-2.419090000	0.609713000
H	0.512572000	-1.493340000	0.910691000
H	-1.815704000	-1.489239000	3.281996000
H	-1.747441000	0.241356000	3.686743000
H	-0.237670000	-0.655220000	3.345944000



Final Single Point Energy = -2283.884663149759

P	-4.714948000	1.108252000	0.332054000
C	-5.915056000	-0.058493000	-0.415858000
C	-5.773761000	2.141411000	1.411516000
C	-4.319930000	2.236040000	-1.057613000
P	-0.908649000	-0.805757000	2.199474000
C	0.037628000	-2.002673000	1.185811000
C	0.357961000	0.438750000	2.649745000
C	-1.216437000	-1.728662000	3.751228000
Pd	-2.827426000	0.143346000	1.298817000
C	-3.954171000	-2.979811000	0.117679000
C	-4.402929000	-4.224094000	-0.298171000
C	-4.024808000	-4.742418000	-1.546380000
C	-3.111639000	-2.221761000	-0.713195000
C	-2.733999000	-2.775837000	-1.964242000
C	-3.186796000	-4.023743000	-2.390349000
H	-2.890234000	-4.429971000	-3.353629000
H	-4.386330000	-5.718448000	-1.858115000
H	-4.245154000	-2.573631000	1.084215000
H	-5.054567000	-4.806476000	0.347666000
C	-2.550654000	-0.916024000	-0.439502000
C	-1.764071000	-0.540138000	-1.479623000
S	-1.658393000	-1.690351000	-2.826200000
I	-0.593225000	1.181682000	-1.580466000
C	-3.058451000	1.136184000	3.035625000
C	-3.183856000	1.701632000	4.117657000
C	-3.322304000	2.364332000	5.411666000
C	-1.269412000	1.638038000	6.360634000

O	-2.685624000	1.667932000	6.494008000
H	-0.874444000	1.144543000	7.253216000
H	-0.850946000	2.655597000	6.297337000
H	-0.955055000	1.072708000	5.470995000
H	-4.378881000	2.435960000	5.697090000
H	-2.926023000	3.393180000	5.352106000
H	0.727735000	0.923443000	1.739931000
H	1.196783000	-0.037713000	3.170391000
H	-0.087628000	1.203248000	3.292756000
H	0.360721000	-1.526945000	0.254446000
H	-0.589578000	-2.864685000	0.937123000
H	0.918276000	-2.345971000	1.741013000
H	-6.629626000	2.521790000	0.842094000
H	-5.194665000	2.983627000	1.801874000
H	-6.135299000	1.548267000	2.257168000
H	-5.242068000	2.672795000	-1.458904000
H	-3.808516000	1.681578000	-1.850492000
H	-3.662594000	3.039310000	-0.711027000
H	-6.750127000	0.500592000	-0.853673000
H	-6.301897000	-0.739961000	0.348288000
H	-5.425903000	-0.648340000	-1.196384000
H	-1.877424000	-2.577289000	3.544169000
H	-1.708722000	-1.074995000	4.477678000
H	-0.273825000	-2.100052000	4.169755000

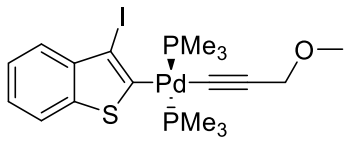


Final Single Point Energy = -2351.246814465544

P	-5.146507000	1.226790000	-1.280525000
C	-5.249090000	1.695881000	-3.046775000
C	-6.397556000	-0.100517000	-1.123714000
C	-5.928392000	2.618523000	-0.382953000
P	-0.821586000	0.186233000	0.201742000

C	0.472792000	0.327018000	-1.085337000
C	-0.226693000	1.238754000	1.576921000
C	-0.578060000	-1.503552000	0.862803000
Pd	-2.964557000	0.746182000	-0.571086000
C	-4.821932000	-4.143435000	1.492851000
C	-4.999200000	-5.457805000	1.085569000
C	-4.664513000	-5.862159000	-0.214842000
C	-4.299661000	-3.205311000	0.590056000
C	-3.966181000	-3.633058000	-0.718236000
C	-4.144938000	-4.951941000	-1.127854000
H	-3.884303000	-5.262671000	-2.135986000
H	-4.811318000	-6.895892000	-0.514611000
H	-5.083324000	-3.834334000	2.501537000
H	-5.403703000	-6.184638000	1.784502000
C	-4.021521000	-1.803773000	0.757420000
C	-3.506314000	-1.155221000	-0.321891000
S	-3.329766000	-2.289157000	-1.661792000
I	-4.379232000	-0.786672000	2.554896000
I	-2.187790000	3.297296000	-1.022777000
H	-6.102984000	-0.973397000	-1.714054000
H	-7.365517000	0.267153000	-1.482568000
H	-6.492334000	-0.401538000	-0.075747000
H	-4.882030000	0.869851000	-3.665174000
H	-4.624799000	2.575305000	-3.231369000
H	-6.286733000	1.918906000	-3.320792000
H	-6.950890000	2.770437000	-0.747764000
H	-5.346428000	3.532321000	-0.531616000
H	-5.957172000	2.390356000	0.687694000
H	0.230907000	-0.337515000	-1.921555000
H	1.449172000	0.047837000	-0.672727000
H	0.512756000	1.355759000	-1.455909000
H	-0.786572000	-2.249666000	0.090222000
H	-1.255760000	-1.672119000	1.705406000
H	0.457271000	-1.616638000	1.203697000

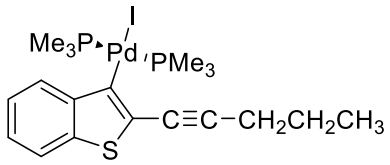
H	-0.210526000	2.287044000	1.266402000
H	0.780861000	0.928112000	1.876725000
H	-0.904448000	1.135702000	2.430880000



Final Single Point Energy = -2283.893669014214

P	-4.850376000	1.369552000	-0.482443000
C	-4.528034000	2.273390000	-2.041280000
C	-6.169678000	0.185369000	-0.938225000
C	-5.727696000	2.581847000	0.572039000
P	-0.961009000	-0.237556000	1.501722000
C	0.523637000	0.102237000	0.486220000
C	-0.608731000	0.546899000	3.117202000
C	-0.828942000	-2.024747000	1.873175000
Pd	-2.916426000	0.526794000	0.495876000
C	-5.345036000	-4.557093000	1.100267000
C	-5.485077000	-5.754150000	0.412455000
C	-4.898143000	-5.935578000	-0.848074000
C	-4.606468000	-3.512025000	0.524974000
C	-4.021931000	-3.713185000	-0.749943000
C	-4.161548000	-4.915363000	-1.439133000
H	-3.706483000	-5.053330000	-2.416300000
H	-5.019328000	-6.880361000	-1.370308000
H	-5.801321000	-4.421324000	2.078010000
H	-6.057714000	-6.563277000	0.857251000
C	-4.312770000	-2.191695000	1.013019000
C	-3.559793000	-1.382365000	0.216833000
S	-3.155221000	-2.267196000	-1.256961000
I	-5.004964000	-1.500390000	2.873516000
C	-2.271289000	2.414049000	0.770255000
C	-1.872757000	3.561583000	0.940192000
C	-1.369214000	4.914283000	1.160425000
C	0.853953000	4.324572000	1.750316000

O	-0.335878000	4.993152000	2.153612000
H	1.587834000	4.468221000	2.548383000
H	1.252545000	4.746502000	0.813466000
H	0.687381000	3.246530000	1.607384000
H	-2.171119000	5.568210000	1.524255000
H	-1.001921000	5.339443000	0.210100000
H	-0.585411000	1.634712000	3.004046000
H	0.352383000	0.196087000	3.510995000
H	-1.403816000	0.288264000	3.825071000
H	0.442829000	-0.432251000	-0.466492000
H	1.430699000	-0.224939000	1.007800000
H	0.588254000	1.174703000	0.277855000
H	-0.908121000	-2.607352000	0.950130000
H	-1.639862000	-2.323828000	2.545336000
H	0.133651000	-2.236110000	2.353030000
H	-6.627792000	2.946046000	0.063465000
H	-5.065105000	3.423751000	0.793126000
H	-6.014186000	2.105095000	1.515422000
H	-5.461873000	2.675199000	-2.451275000
H	-4.076953000	1.593959000	-2.772328000
H	-3.829965000	3.094928000	-1.852179000
H	-7.014381000	0.723688000	-1.383312000
H	-6.513676000	-0.348758000	-0.046529000
H	-5.788620000	-0.546182000	-1.657638000



Final Single Point Energy = -2246.158939021555

P	-6.130066000	0.231881000	-0.149273000
C	-6.633083000	-0.929492000	-1.457512000
C	-7.327687000	-0.100493000	1.176008000
C	-6.637364000	1.829556000	-0.854378000
P	-1.624023000	0.054166000	1.050131000

C	-0.621136000	-1.150853000	0.126793000
C	-0.725738000	1.606003000	0.751144000
C	-1.271934000	-0.363759000	2.784411000
Pd	-3.900413000	0.184857000	0.546315000
C	-4.185425000	-3.264384000	1.051278000
C	-4.309641000	-4.638012000	1.250010000
C	-4.074923000	-5.542362000	0.190677000
C	-3.822353000	-2.771835000	-0.224099000
C	-3.587675000	-3.702957000	-1.279615000
C	-3.712261000	-5.086395000	-1.078599000
H	-3.531637000	-5.791558000	-1.895864000
H	-4.177872000	-6.617750000	0.364732000
H	-4.362336000	-2.550758000	1.867011000
H	-4.591669000	-5.024065000	2.234248000
C	-3.648856000	-1.402814000	-0.636333000
C	-3.292795000	-1.311956000	-1.964197000
S	-3.157361000	-2.887679000	-2.748523000
I	-4.271335000	2.301060000	2.247174000
H	-6.079747000	-0.711473000	-2.386405000
H	-7.714861000	-0.812370000	-1.646485000
H	-6.425111000	-1.971370000	-1.161813000
H	-5.981274000	2.069316000	-1.709770000
H	-6.545642000	2.631009000	-0.104981000
H	-7.682558000	1.771266000	-1.207519000
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H	-7.210557000	0.638510000	1.985003000
H	-7.144150000	-1.107600000	1.588625000
H	-0.871200000	1.906745000	-0.301683000
H	0.353010000	1.461506000	0.940310000
H	-1.111188000	2.405796000	1.402585000
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H	-1.026783000	-2.169700000	0.243766000
H	0.415617000	-1.122791000	0.506223000
H	-1.698285000	-1.354986000	3.015472000

H	-1.731795000	0.380690000	3.454253000
H	-0.181442000	-0.392046000	2.957970000
C	-3.047919000	-0.118304000	-2.685758000
C	-2.846026000	0.931753000	-3.277116000
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C	-2.563080000	2.188906000	-3.967933000
H	-3.258361000	2.971594000	-3.605874000
H	-2.767482000	2.070376000	-5.049739000
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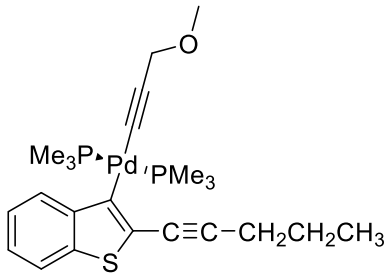

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C	-7.330505000	-0.057340000	1.475979000
C	-6.794823000	1.956296000	-0.488614000
P	-1.712103000	0.284125000	1.084604000
C	-0.627586000	-0.875812000	0.196106000
C	-0.924139000	1.890582000	0.756905000
C	-1.327437000	-0.037630000	2.832330000
Pd	-3.982861000	0.273544000	0.607213000
C	-4.294492000	-3.211103000	0.999087000
C	-4.400804000	-4.587431000	1.191351000
C	-4.083378000	-5.485307000	0.148259000
C	-3.866563000	-2.703233000	-0.251217000

C	-3.550381000	-3.631621000	-1.289422000
C	-3.656704000	-5.018048000	-1.096919000
H	-3.412121000	-5.717482000	-1.902541000
H	-4.171576000	-6.563157000	0.315803000
H	-4.534768000	-2.505107000	1.805328000
H	-4.732461000	-4.980341000	2.157434000
C	-3.702202000	-1.319944000	-0.635129000
C	-3.276977000	-1.232458000	-1.946113000
S	-3.053168000	-2.804267000	-2.727285000
H	-6.319103000	-0.570863000	-2.183900000
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H	-6.658809000	-1.838268000	-0.966544000
H	-6.228976000	2.253985000	-1.387241000
H	-6.618345000	2.704340000	0.300850000
H	-7.871562000	1.925641000	-0.733471000
H	-8.387714000	0.043478000	1.171818000
H	-7.121537000	0.632197000	2.310595000
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H	-1.077077000	2.168518000	-0.300472000
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H	0.404208000	-0.773709000	0.576795000
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H	-0.235962000	0.008058000	2.995701000
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C	-0.848218000	2.564129000	-3.845702000
H	-1.130642000	4.676724000	-4.314135000
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C	-2.337686000	2.185111000	-4.010765000
H	-2.967272000	3.031198000	-3.673203000
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C	-3.297673000	5.309762000	5.019209000
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H	-3.903464000	5.027638000	5.906746000
H	-3.770035000	6.197333000	4.546615000
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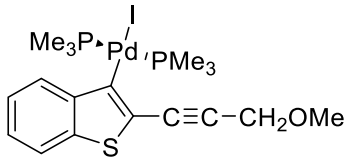

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C	-7.317196000	-0.238469000	1.307773000
C	-6.866510000	1.760899000	-0.695741000
P	-1.650471000	0.172212000	0.953732000
C	-0.620615000	-1.004722000	0.023193000
C	-0.768515000	1.739355000	0.689350000
C	-1.305140000	-0.271587000	2.683225000
Pd	-3.941773000	0.235625000	0.494634000
C	-4.255493000	-3.200759000	0.997894000
C	-4.390884000	-4.571942000	1.201767000
C	-4.130339000	-5.483749000	0.154204000
C	-3.856024000	-2.718268000	-0.270582000
C	-3.594269000	-3.656295000	-1.313138000

C	-3.731127000	-5.038431000	-1.107095000
H	-3.531205000	-5.749473000	-1.914581000
H	-4.242002000	-6.557607000	0.332448000
H	-4.456006000	-2.480437000	1.802139000
H	-4.701608000	-4.951113000	2.179917000
C	-3.670001000	-1.350903000	-0.685072000
C	-3.272514000	-1.273032000	-2.004500000
S	-3.119176000	-2.854757000	-2.774166000
I	-4.321525000	2.353437000	2.188542000
H	-6.233734000	-0.724906000	-2.328140000
H	-7.819949000	-0.917750000	-1.506505000
H	-6.451758000	-2.016487000	-1.107358000
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H	-7.921455000	1.631187000	-0.997312000
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H	-0.889699000	2.051842000	-0.362419000
H	0.306731000	1.602426000	0.902921000
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H	0.413924000	-0.952234000	0.406254000
H	-1.729150000	-1.268264000	2.894979000
H	-1.770848000	0.459990000	3.362983000
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C	-2.963862000	-0.091581000	-2.717203000
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C	-0.721730000	3.774797000	-4.413722000
O	-1.017330000	2.560687000	-3.749500000
H	-1.375885000	4.597960000	-4.057868000
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H	0.327427000	4.024800000	-4.194635000

C	-2.367164000	2.190611000	-3.991721000
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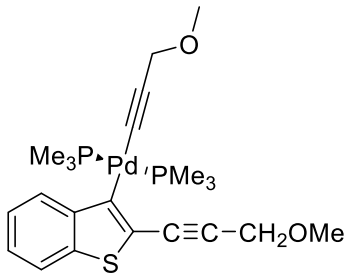

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C	-7.307463000	-0.043527000	1.442688000
C	-6.763342000	1.967456000	-0.523016000
P	-1.687309000	0.282662000	1.070904000
C	-0.607641000	-0.889341000	0.193047000
C	-0.881752000	1.881588000	0.750935000
C	-1.323480000	-0.040704000	2.822760000
Pd	-3.957402000	0.277924000	0.581035000
C	-4.291130000	-3.205569000	0.987310000
C	-4.410047000	-4.579804000	1.182596000
C	-4.098354000	-5.482570000	0.141381000
C	-3.856370000	-2.705374000	-0.263735000
C	-3.545628000	-3.637931000	-1.299633000
C	-3.664923000	-5.023388000	-1.103808000
H	-3.425035000	-5.727285000	-1.906805000
H	-4.196677000	-6.559168000	0.311477000
H	-4.526112000	-2.494934000	1.790853000
H	-4.746906000	-4.968113000	2.148634000
C	-3.681022000	-1.324127000	-0.650066000
C	-3.251376000	-1.246310000	-1.961880000
S	-3.037123000	-2.821088000	-2.738801000
H	-6.286706000	-0.561883000	-2.214520000

H	-7.895676000	-0.621383000	-1.413600000
H	-6.628980000	-1.828024000	-0.996634000
H	-6.193268000	2.263694000	-1.419432000
H	-6.588612000	2.715431000	0.266874000
H	-7.839130000	1.938553000	-0.772115000
H	-8.363921000	0.059112000	1.136636000
H	-7.098392000	0.646339000	2.276995000
H	-7.133205000	-1.076190000	1.789358000
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H	-1.336528000	2.666507000	1.377735000
H	-0.608372000	-0.665812000	-0.886931000
H	-0.957094000	-1.925700000	0.336286000
H	0.422645000	-0.795586000	0.579836000
H	-1.704329000	-1.034570000	3.111306000
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C	-2.937262000	-0.063616000	-2.673061000
C	-2.658039000	0.964841000	-3.269417000
C	-0.679552000	3.755437000	-4.449358000
O	-0.986928000	2.566124000	-3.747546000
H	-1.329419000	4.594956000	-4.124803000
H	-0.805213000	3.620097000	-5.544154000
H	0.370278000	4.005644000	-4.233463000
C	-2.337886000	2.195531000	-3.986956000
H	-3.019348000	3.014332000	-3.663347000
H	-2.504967000	2.052940000	-5.078467000
C	-4.342290000	2.765445000	2.648843000
C	-4.451151000	3.878706000	3.592630000
O	-3.157423000	4.258256000	4.055837000
H	-5.087455000	3.598594000	4.463597000
H	-4.943870000	4.756783000	3.114870000
C	-3.263011000	5.333356000	4.965343000
H	-2.245371000	5.596781000	5.292916000

H	-3.870087000	5.054917000	5.853169000
H	-3.732763000	6.220994000	4.490294000
C	-4.213697000	1.828834000	1.854850000

4 Biological Trials

4.1 Cell Culture

NCI-H460 lung carcinoma cells and WI-26 VA4 lung epithelial-like cells were purchased from the ATCC. NCI-H460 cells were maintained in Advanced RPMI-1640 (Gibco, UK) supplemented with 5% fetal bovine serum (FBS, Gibco, UK), penicillin (100 UI mL^{-1}), streptomycin (100 μg mL^{-1}) and GlutaMax (2 mM, Gibco, UK). WI-26 VA4 cells were maintained in Advanced MEM (Gibco, UK) supplemented with 5% fetal bovine serum (FBS, Gibco, UK), penicillin (100 UI mL^{-1}), streptomycin (100 μg mL^{-1}), and GlutaMax (1.87 mM, Gibco, UK). All cells line cultivation under a humidified atmosphere of 95% air/5% CO_2 at 37 °C. Subconfluent monolayers, in the log growth phase, were harvested by a brief treatment with TrypLE Express solution (Gibco, UK) in phosphate-buffered saline (PBS, Capricorn Scientific, Germany) and washed three times in serum-free PBS. The number of viable cells was determined by trypan blue exclusion.

4.2 Antiproliferative Assay

The effects of the synthesized compounds on cell viability were determined using the MTT colorimetric test. All examined cells were diluted with the growth medium to 3.5×104 cells per mL, and the aliquots (7×103 cells per 200 μL) were placed in individual wells in 96-multiplates (Eppendorf, Germany) and incubated for 24 h. The next day the cells were then treated with synthesized compounds separately at the final concentration of 75 μM and incubated for 72 h at 37 °C in a 5% CO_2 atmosphere. After incubation, the cells were then treated with 40 μL MTT solution (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, 5 mg mL^{-1} in PBS) and incubated for 4 h. After an additional 4 h incubation, the medium with MTT was removed, and DMSO (150 μL) was added to dissolve the crystals formazan. The plates were shaken for 10 min. The optical density of each well was determined at 560 nm using a microplate reader GloMax Multi+ (Promega, USA). Each of the tested compounds was evaluated for cytotoxicity in three separate experiments.

4.3 Plasmid Cleavage Assays for Enediynes 14, 19

pBR322 (4361 bp, Thermo Fisher Scientific) plasmid was dissolved in water to a concentration of 83.3 ng/μL. 6 μL of this solution was added to concentrated solutions (357 μM) of enediynes **14a,b,c,i,j, 19** in DMSO (14 μL). Resulting probes (20 μL) contained 0.5 μg of plasmid and enediynes **14a,b,c,i,j, 17** in final concentrations 250 μM. All samples were incubated at 37 °C for 16 h and analyzed using electrophoresis in 1 % (w/v) agarose gel. Images were taken with ChemiDoc MP system (BioRad). The results were analyzed with ImageJ and GraphPad Prism software.

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6 Copies of NMR spectra

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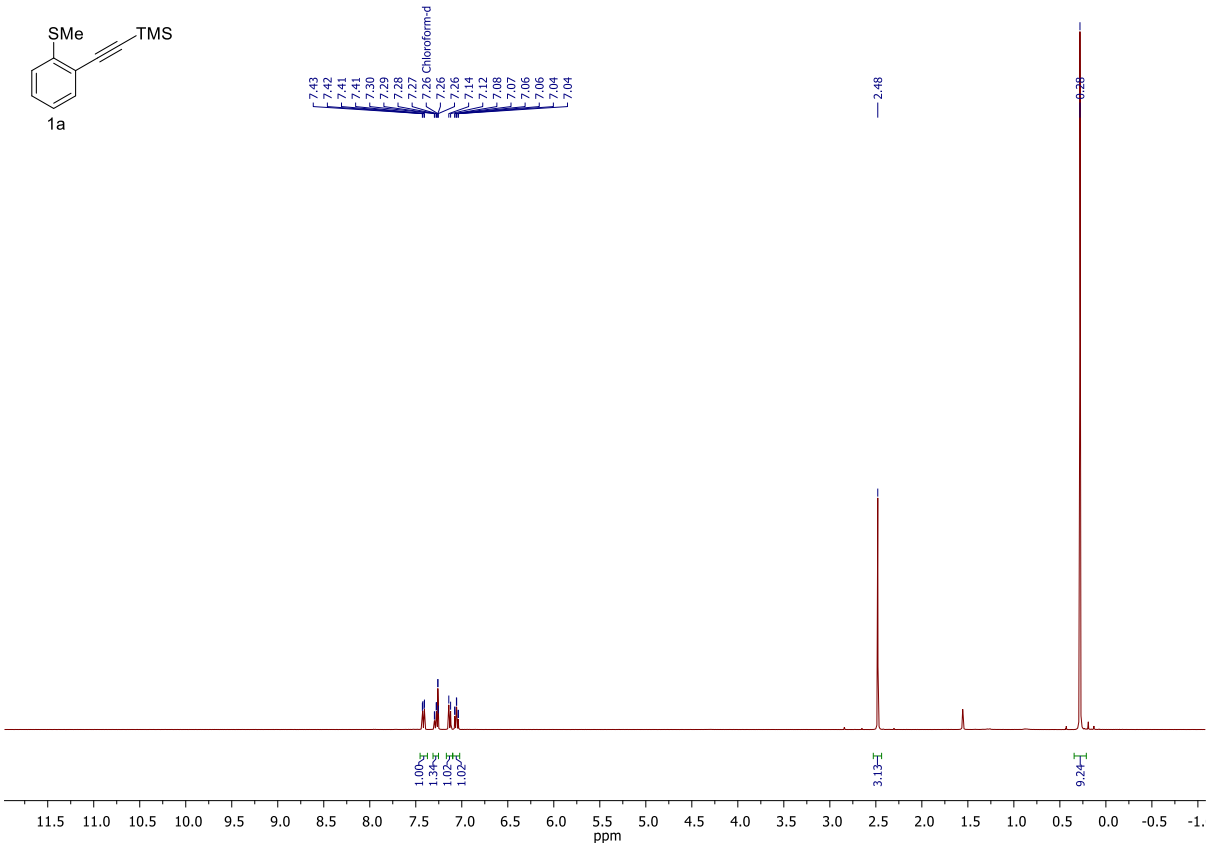

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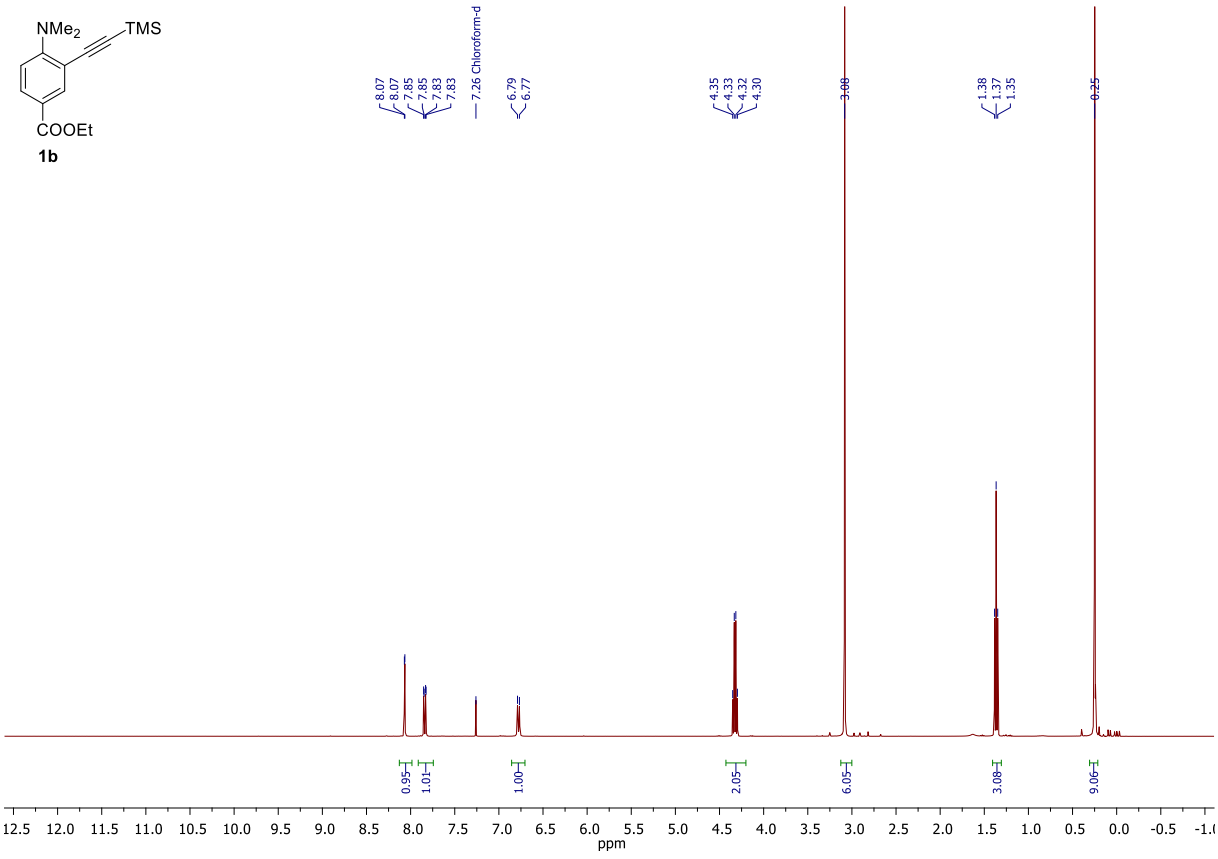
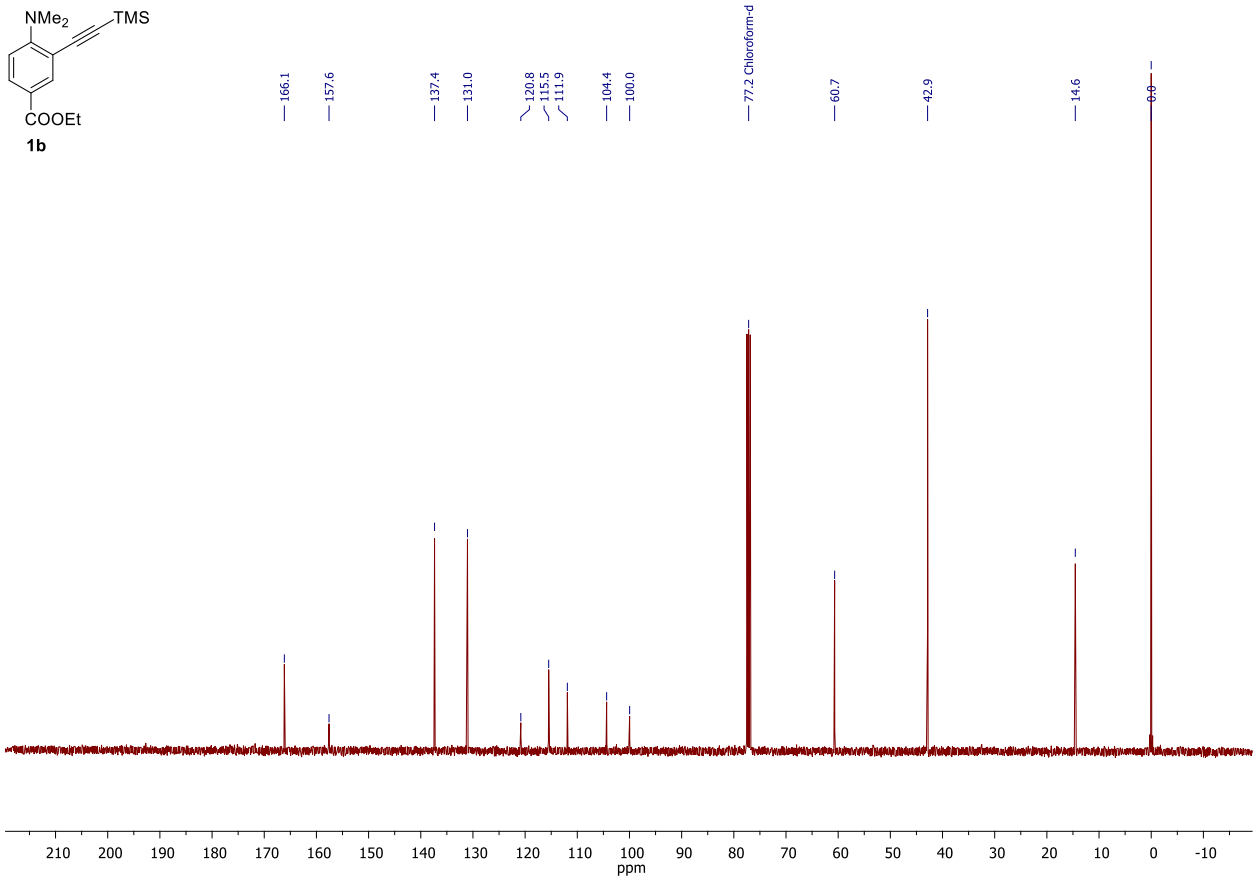
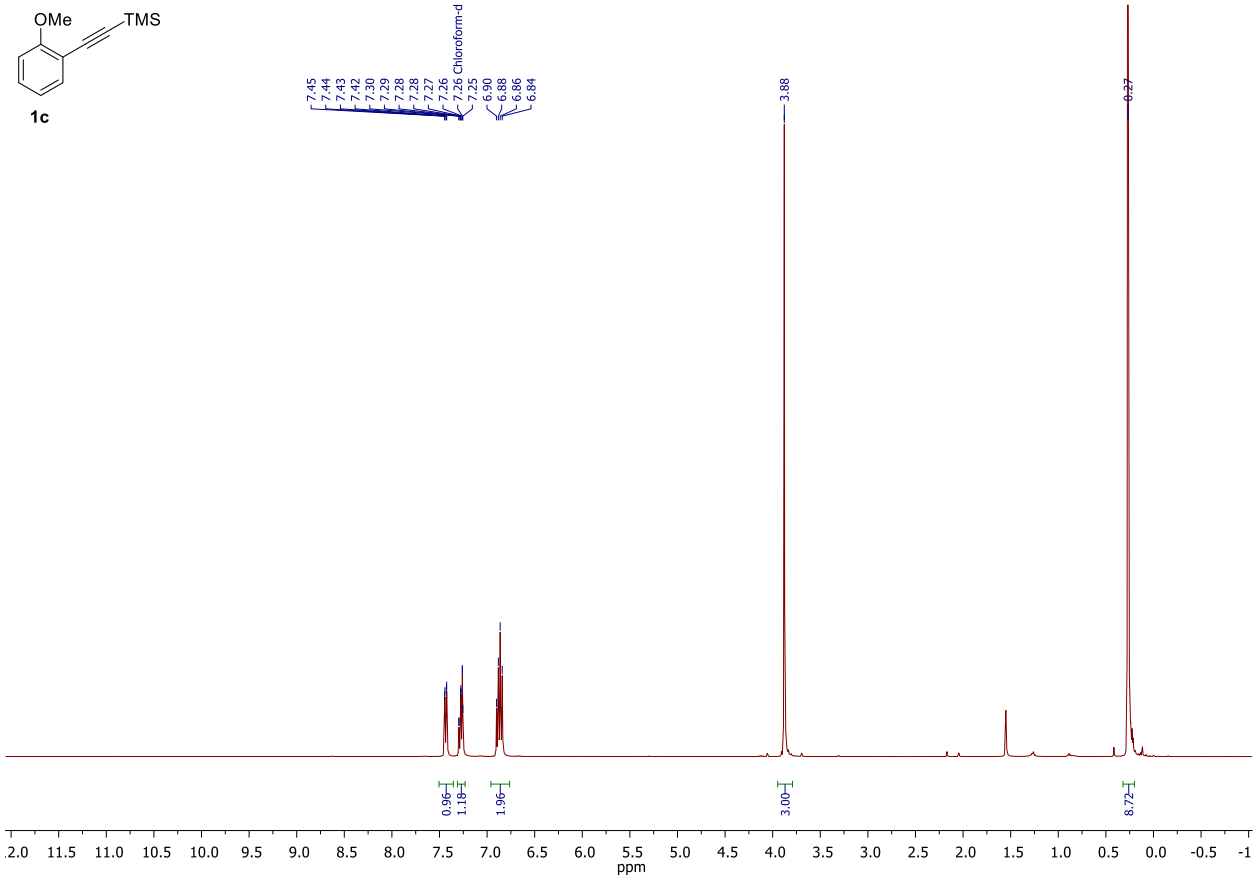


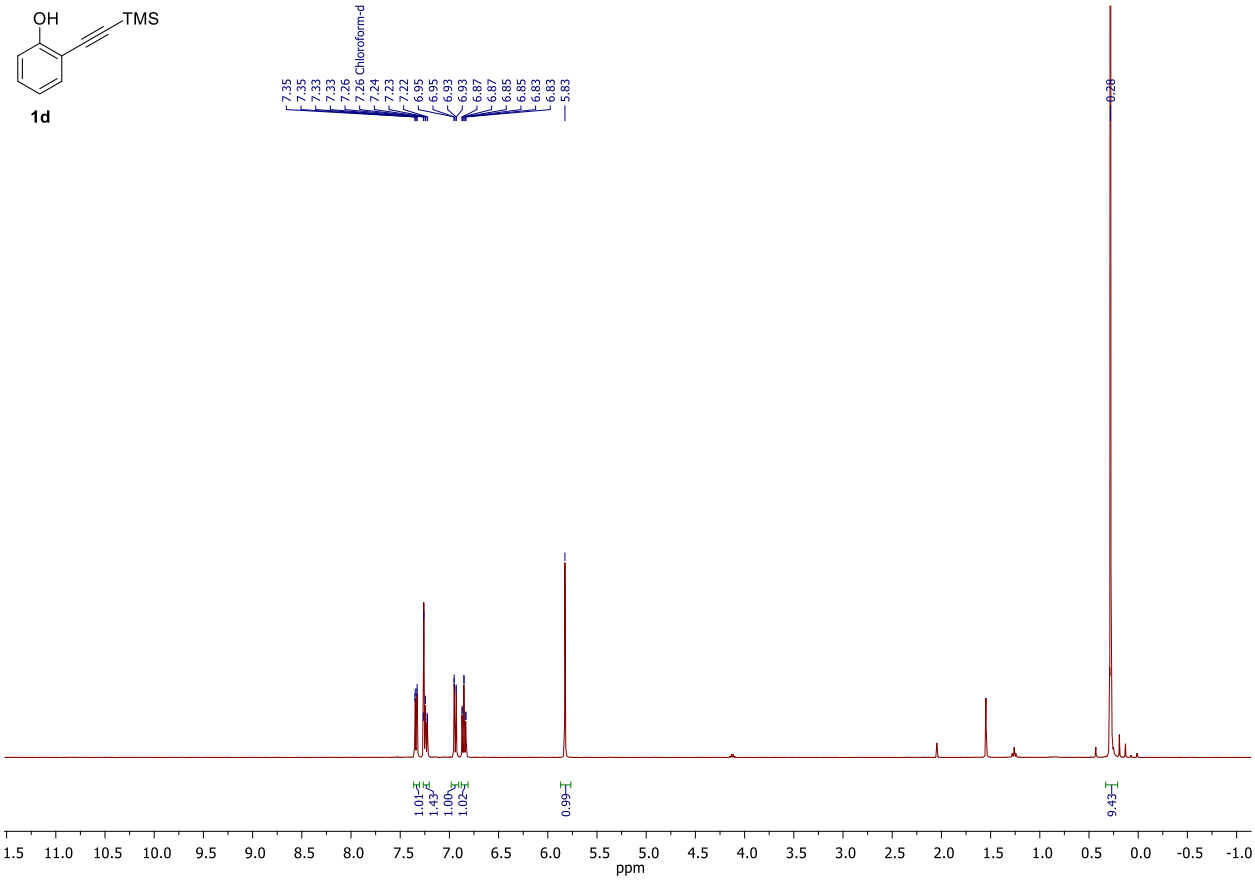
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



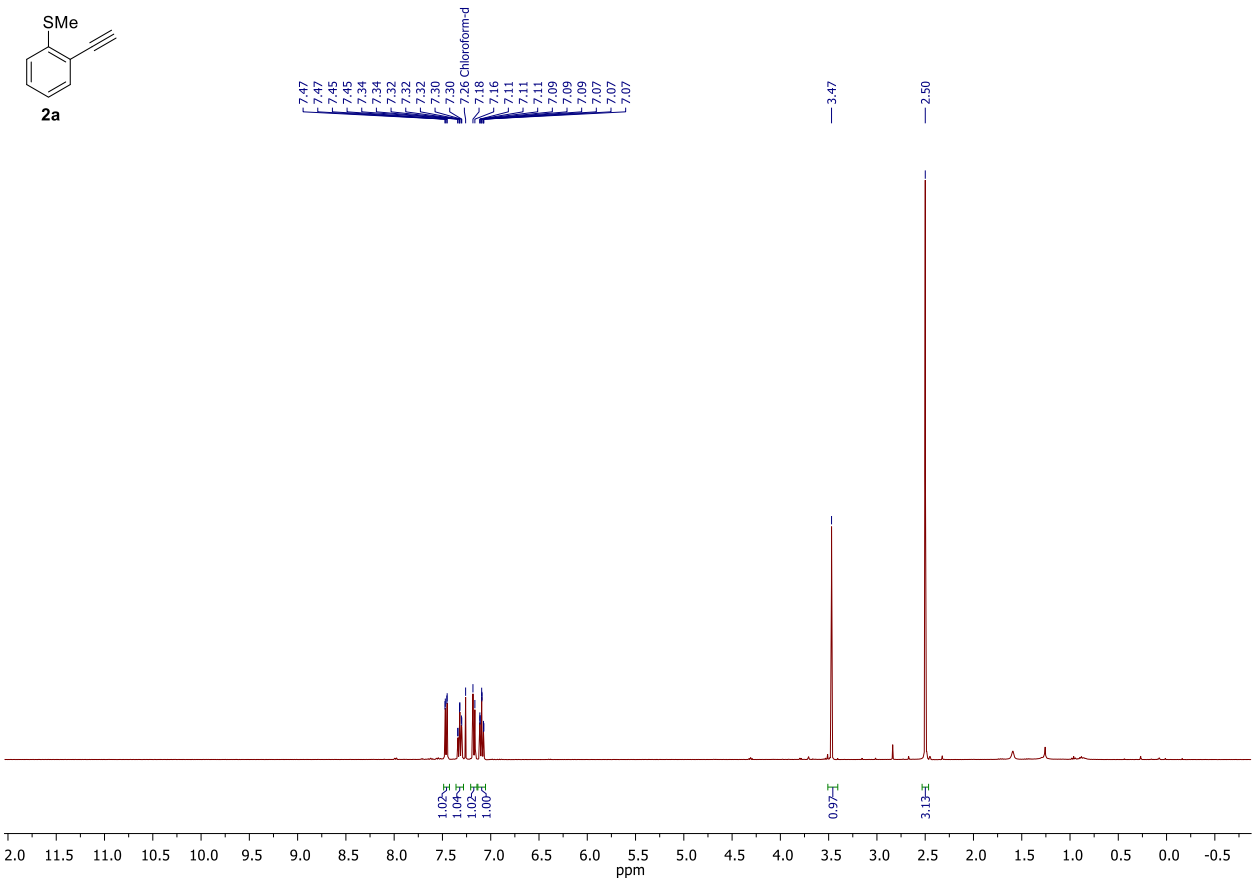
^{1}H NMR, $CDCl_3$, 400 MHz



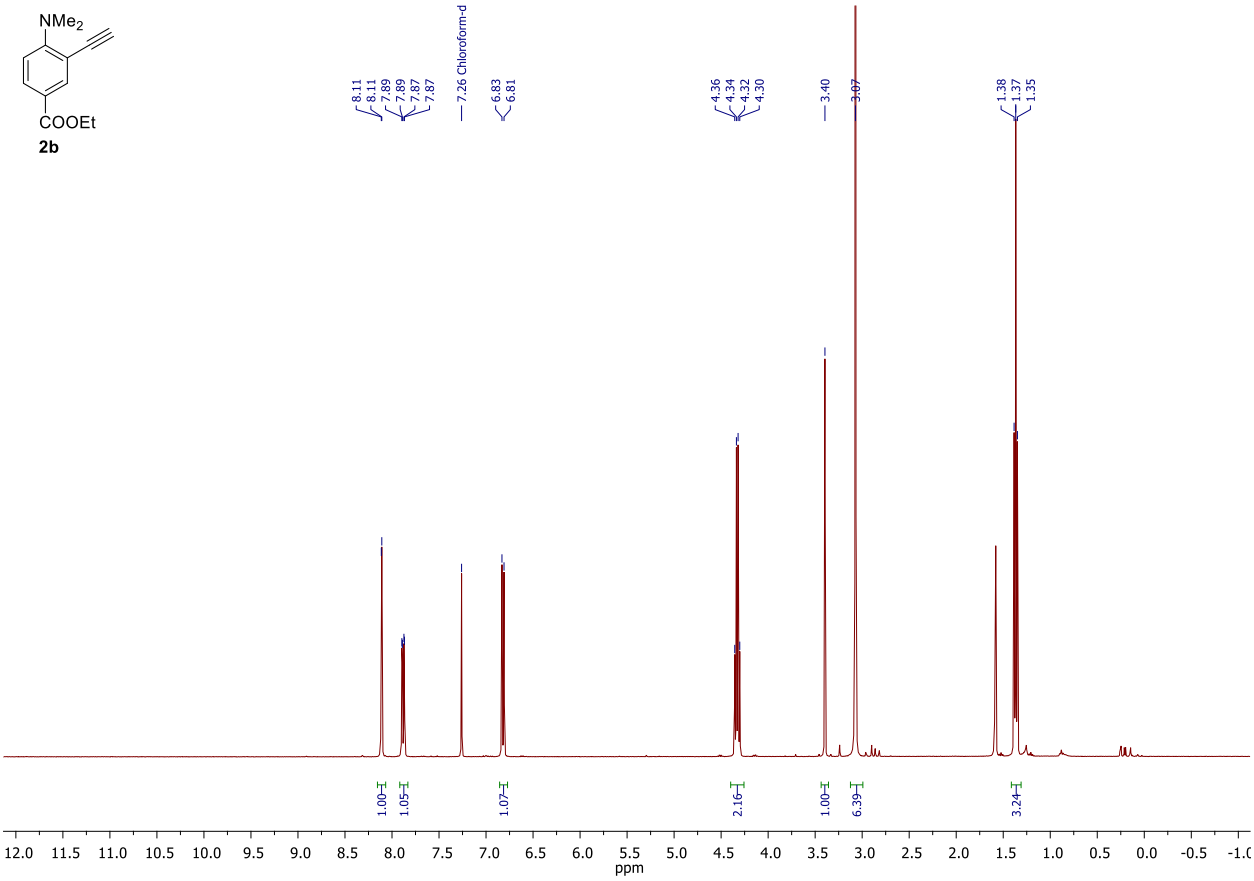
^{1}H NMR, $CDCl_3$, 400 MHz



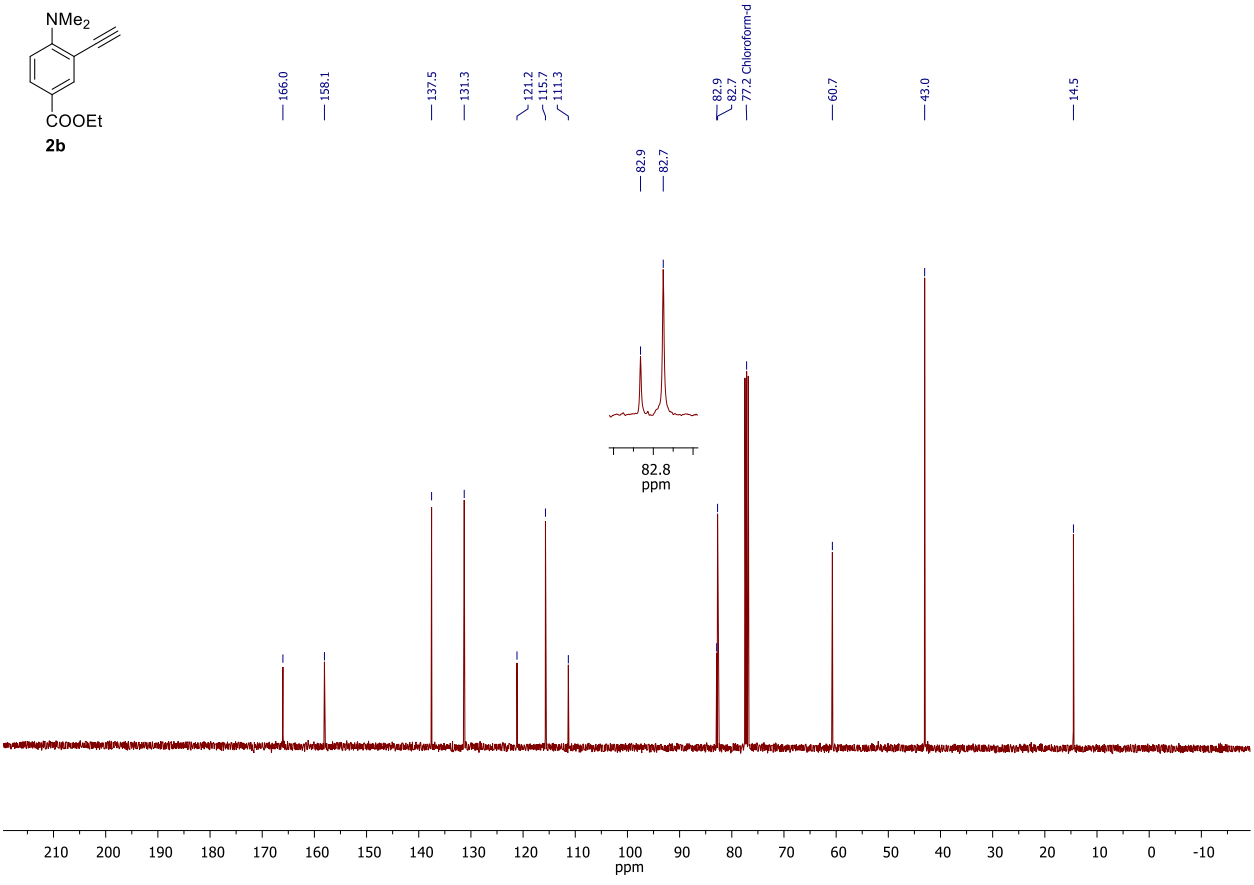
^{1}H NMR, $CDCl_3$, 400 MHz



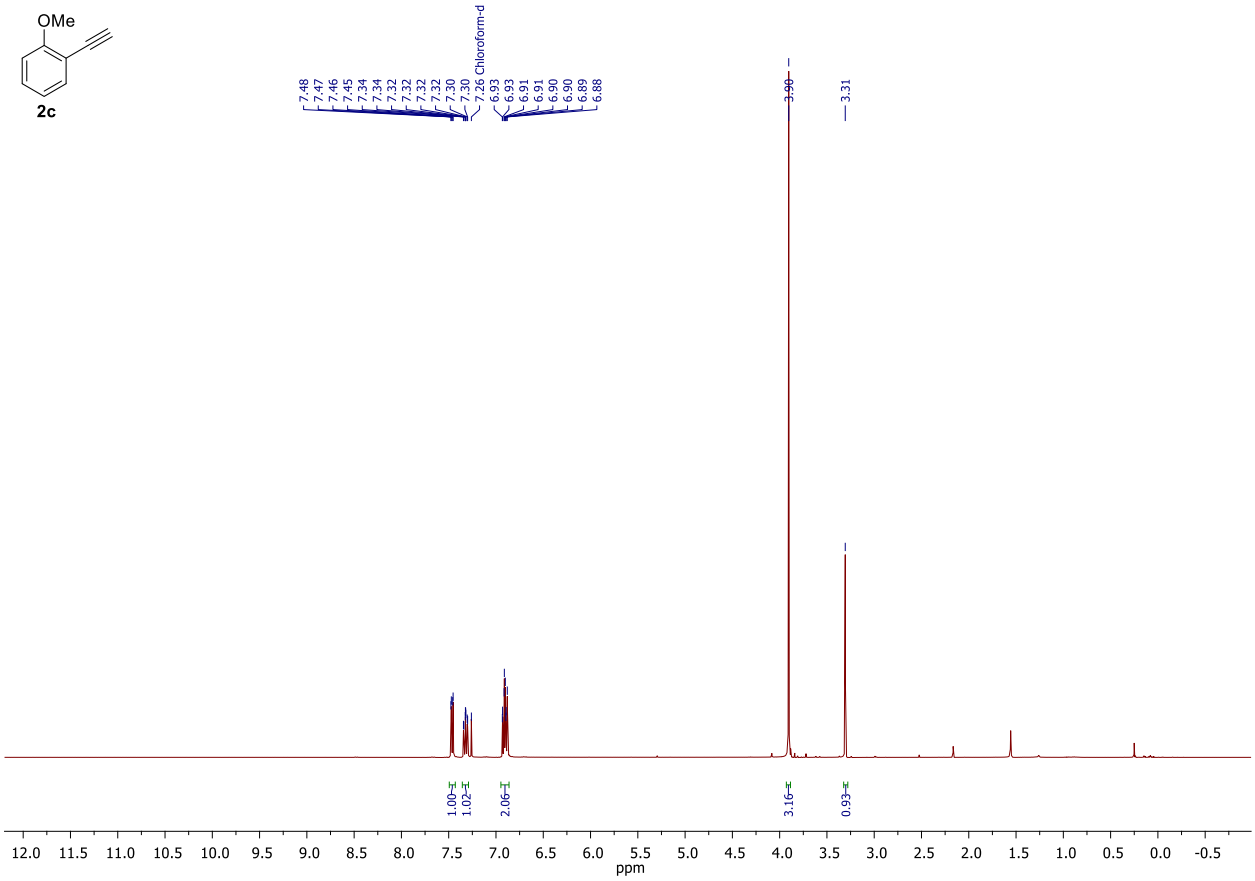
^{1}H NMR, $CDCl_3$, 400 MHz



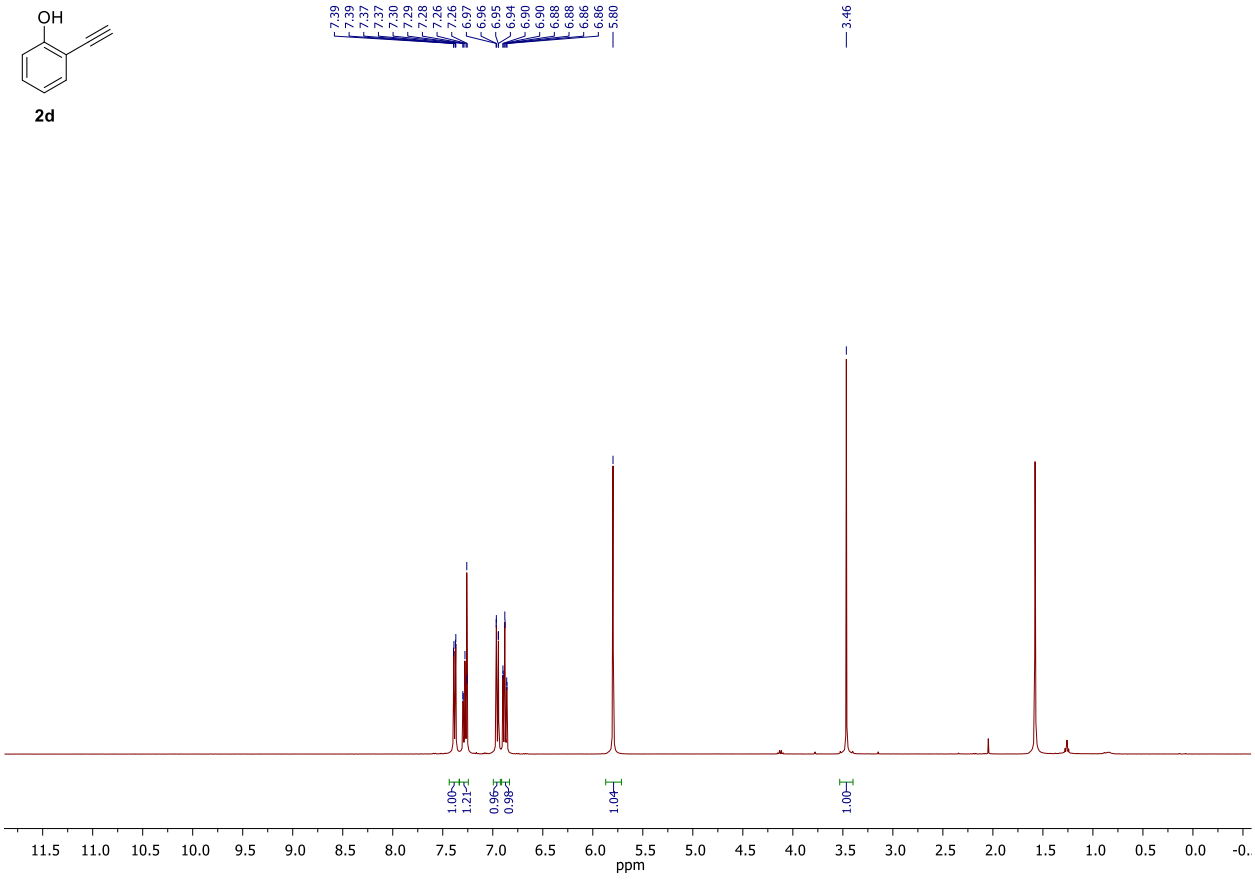
^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



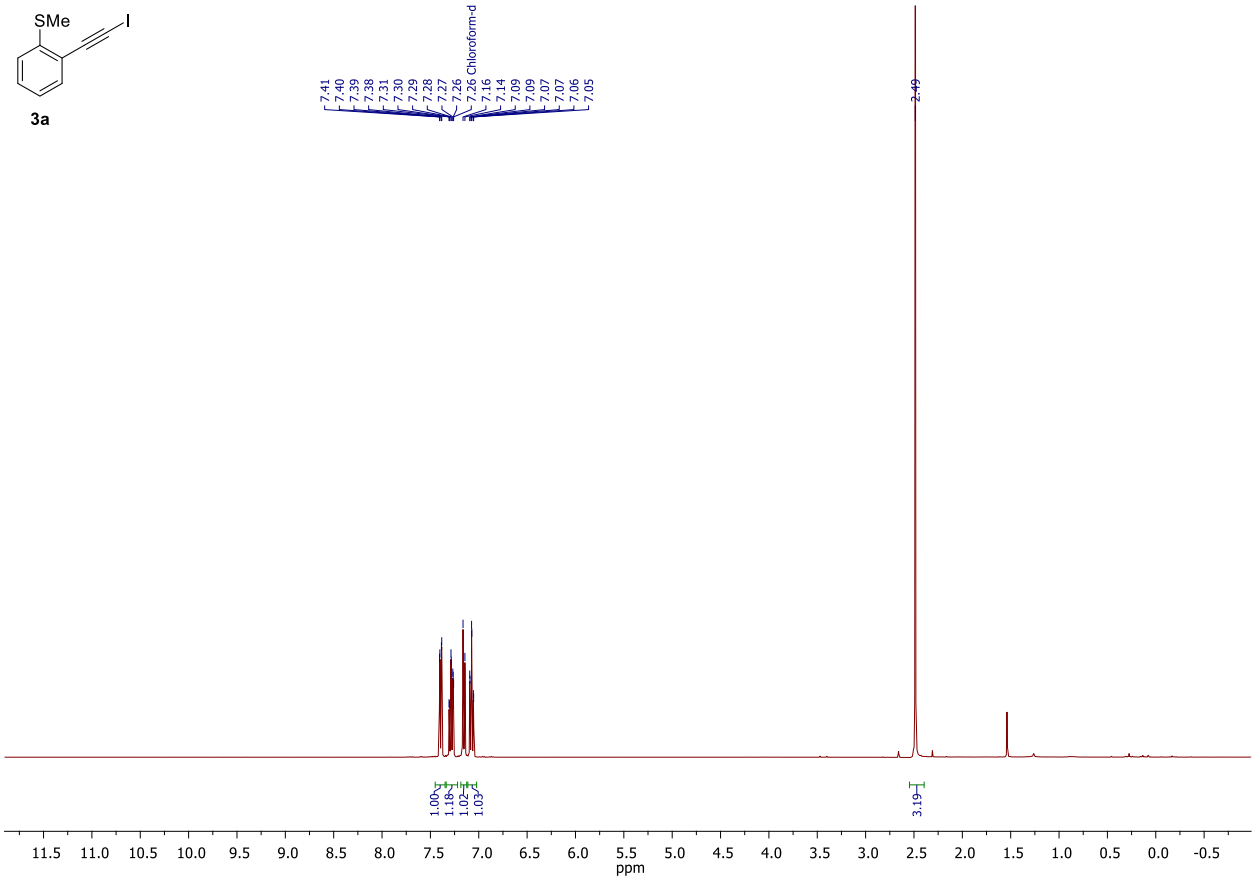
^{1}H NMR, $CDCl_3$, 400 MHz



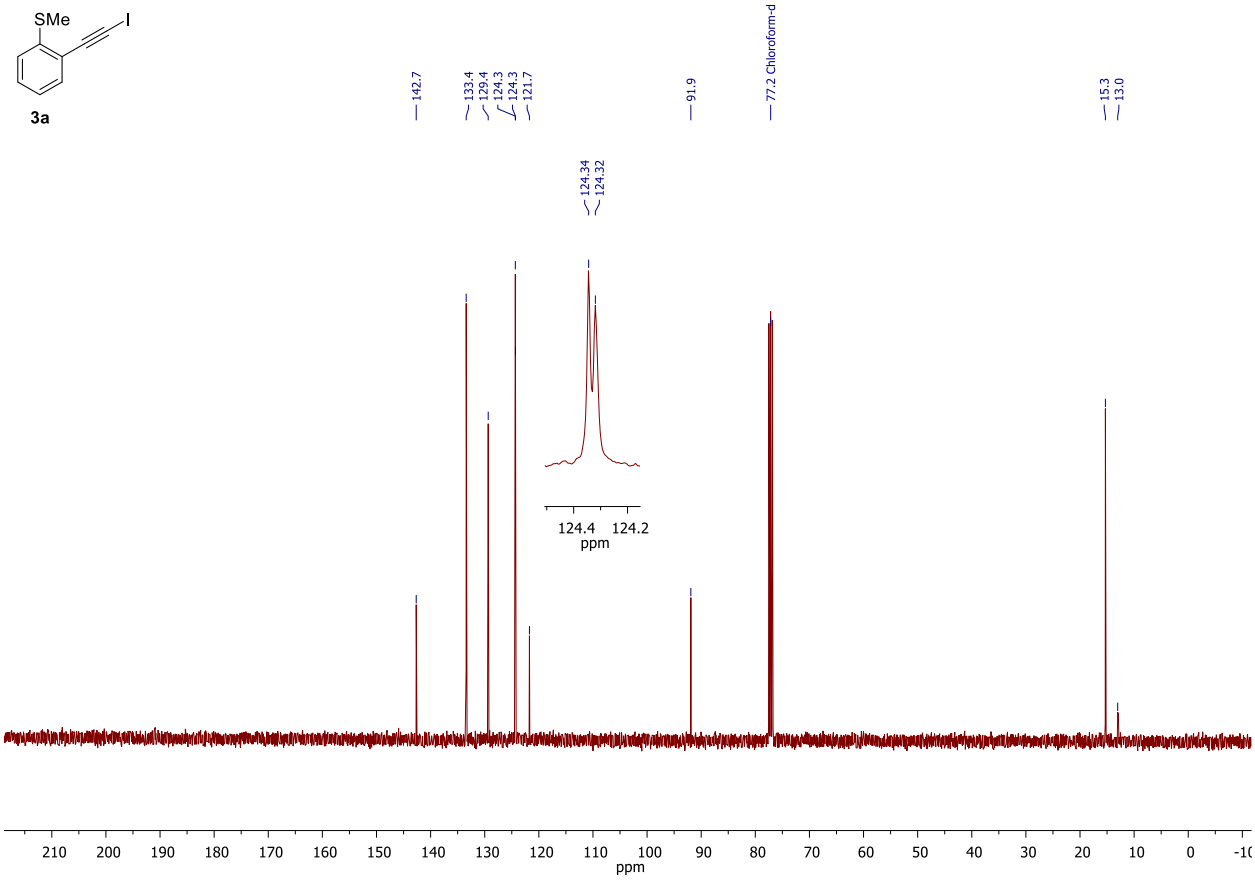
^{1}H NMR, $CDCl_3$, 400 MHz



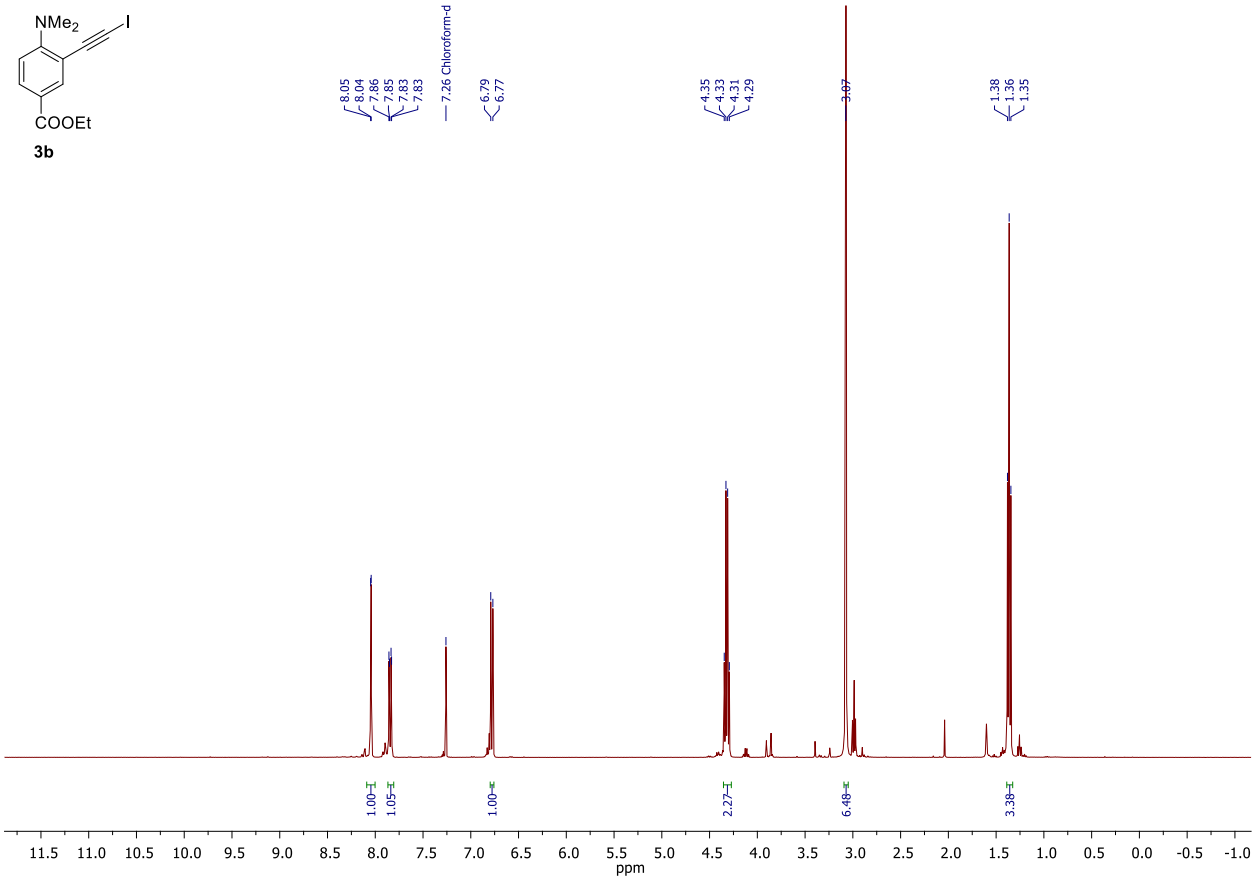
^{1}H NMR, $CDCl_3$, 400 MHz



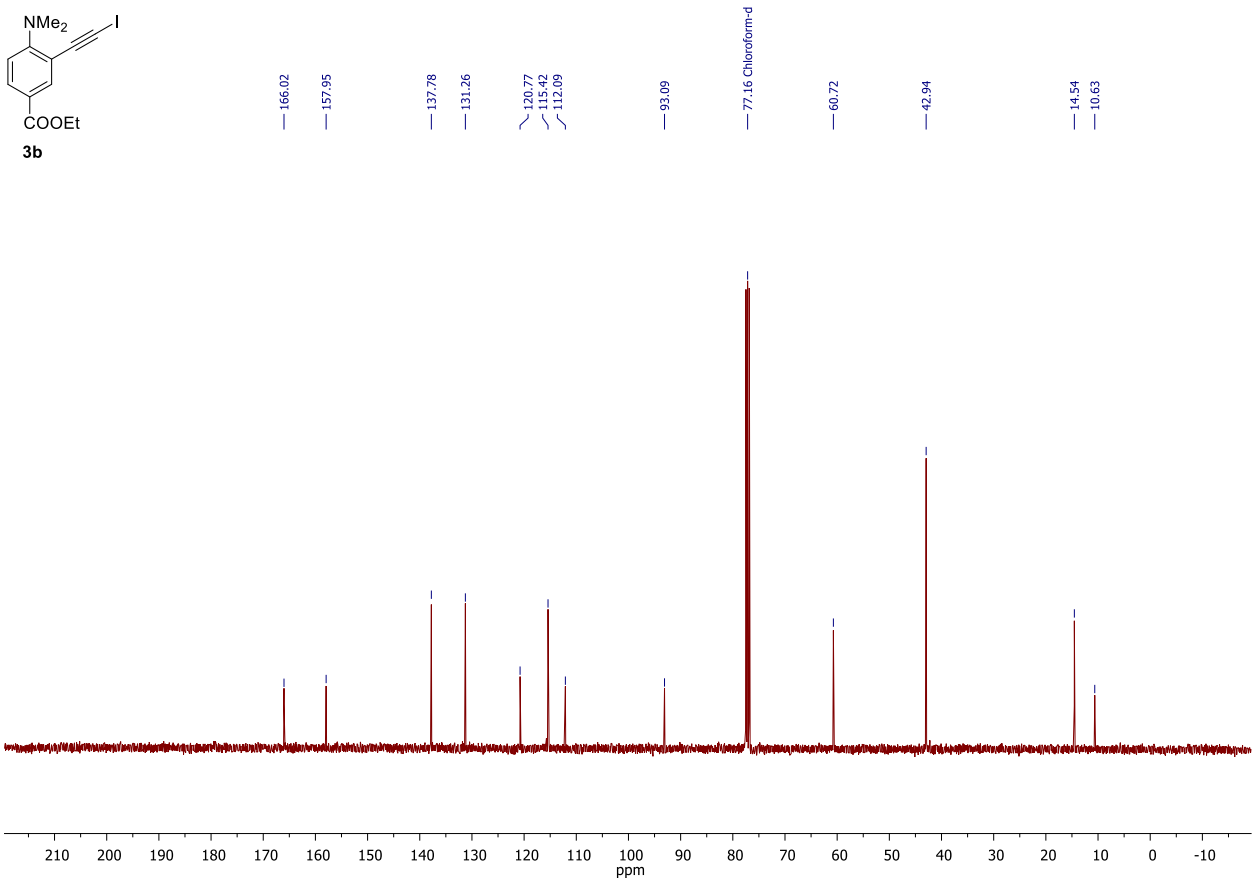
^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



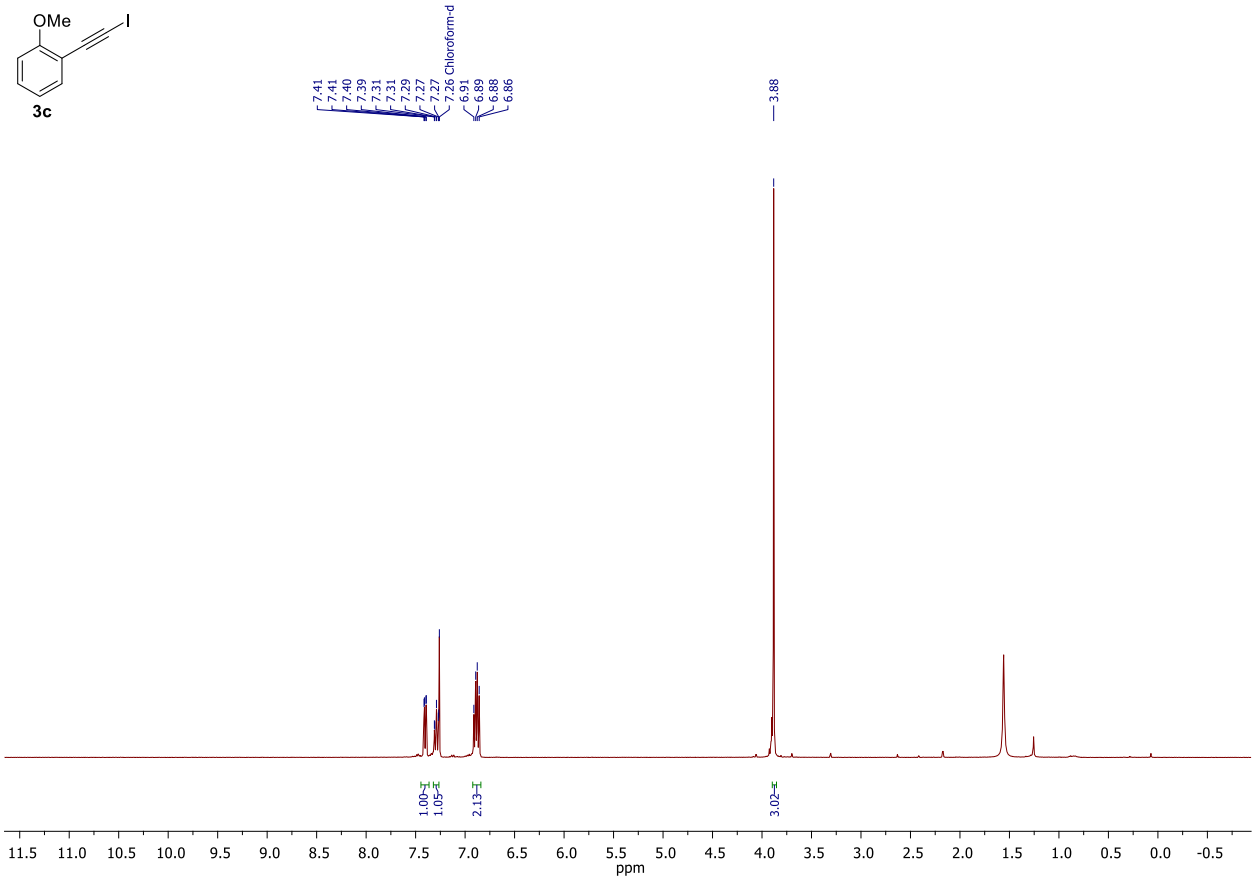
^{1}H NMR, $CDCl_3$, 400 MHz



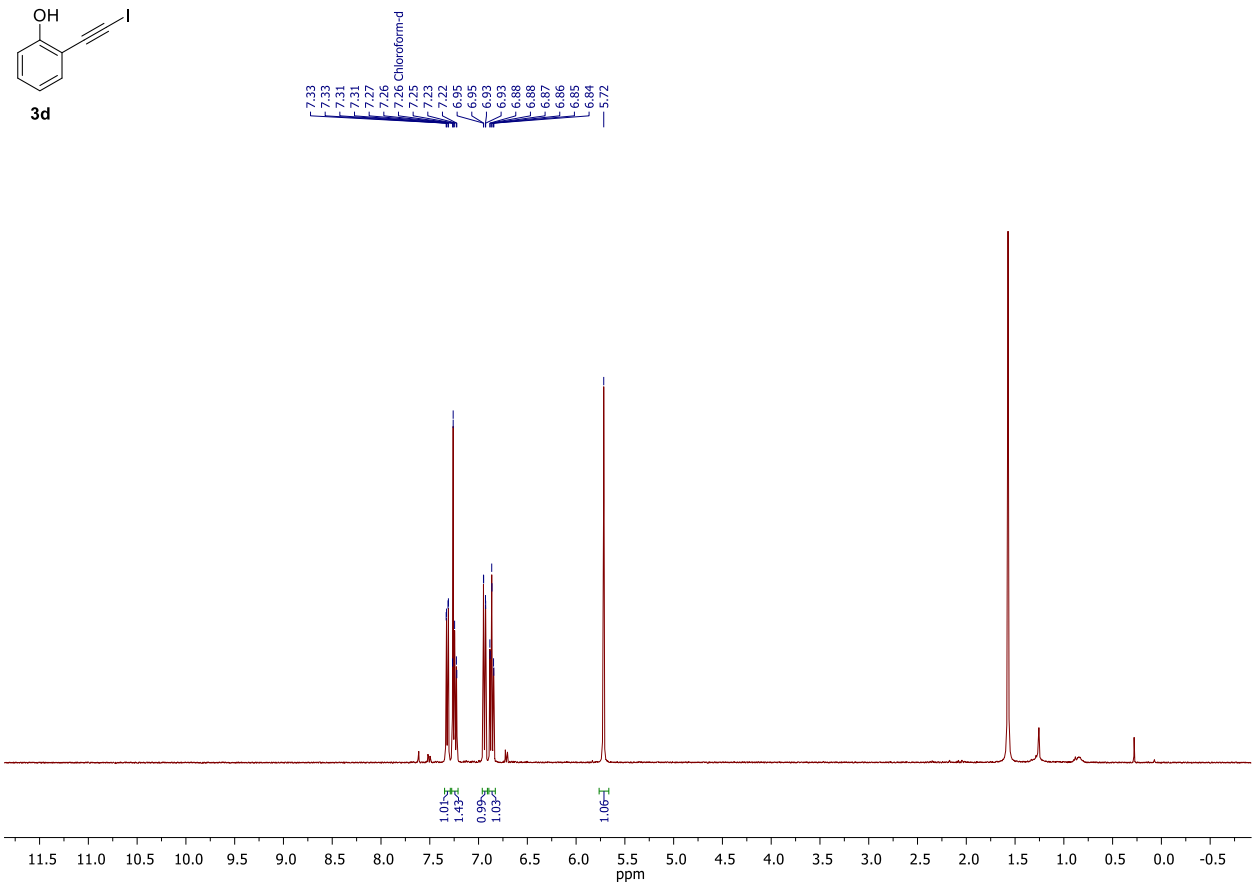
^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



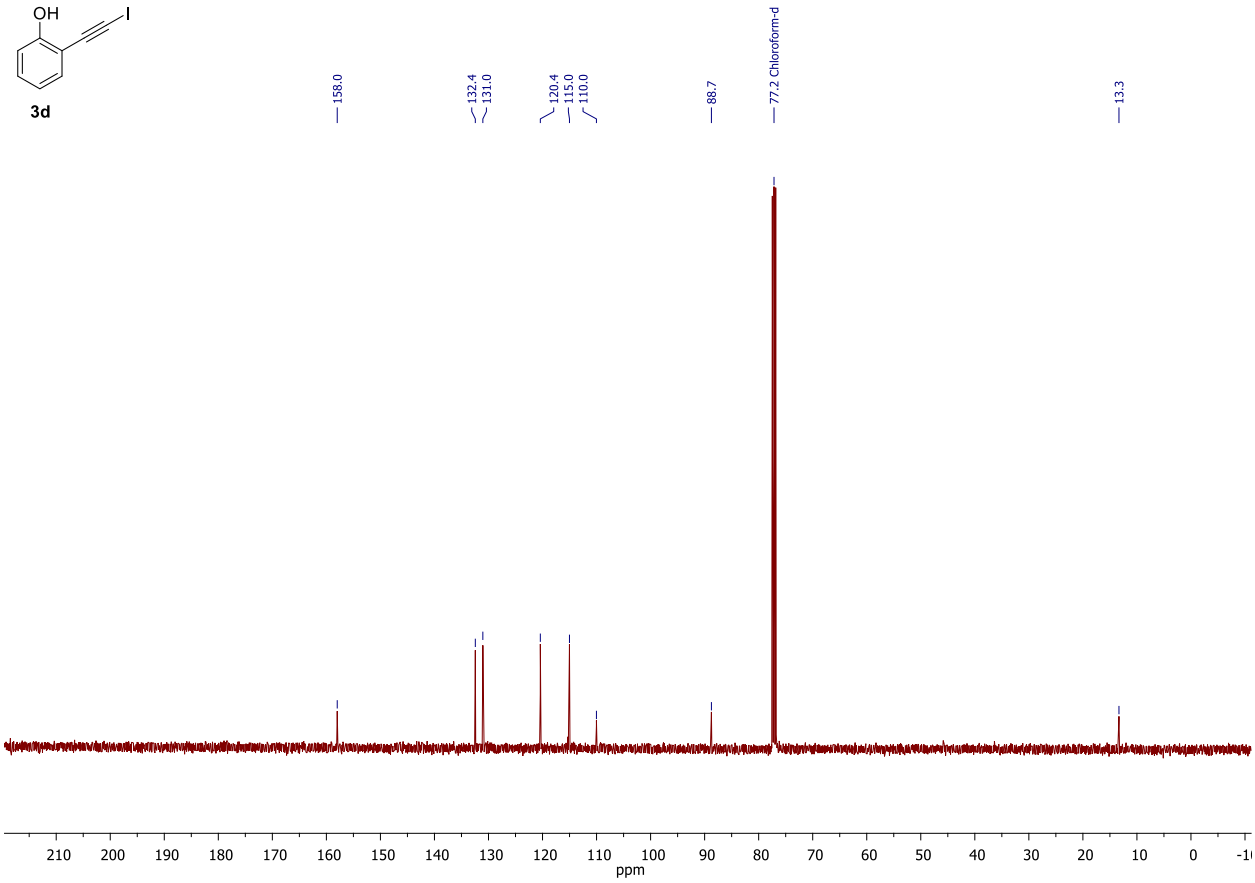
^{1}H NMR, $CDCl_3$, 400 MHz



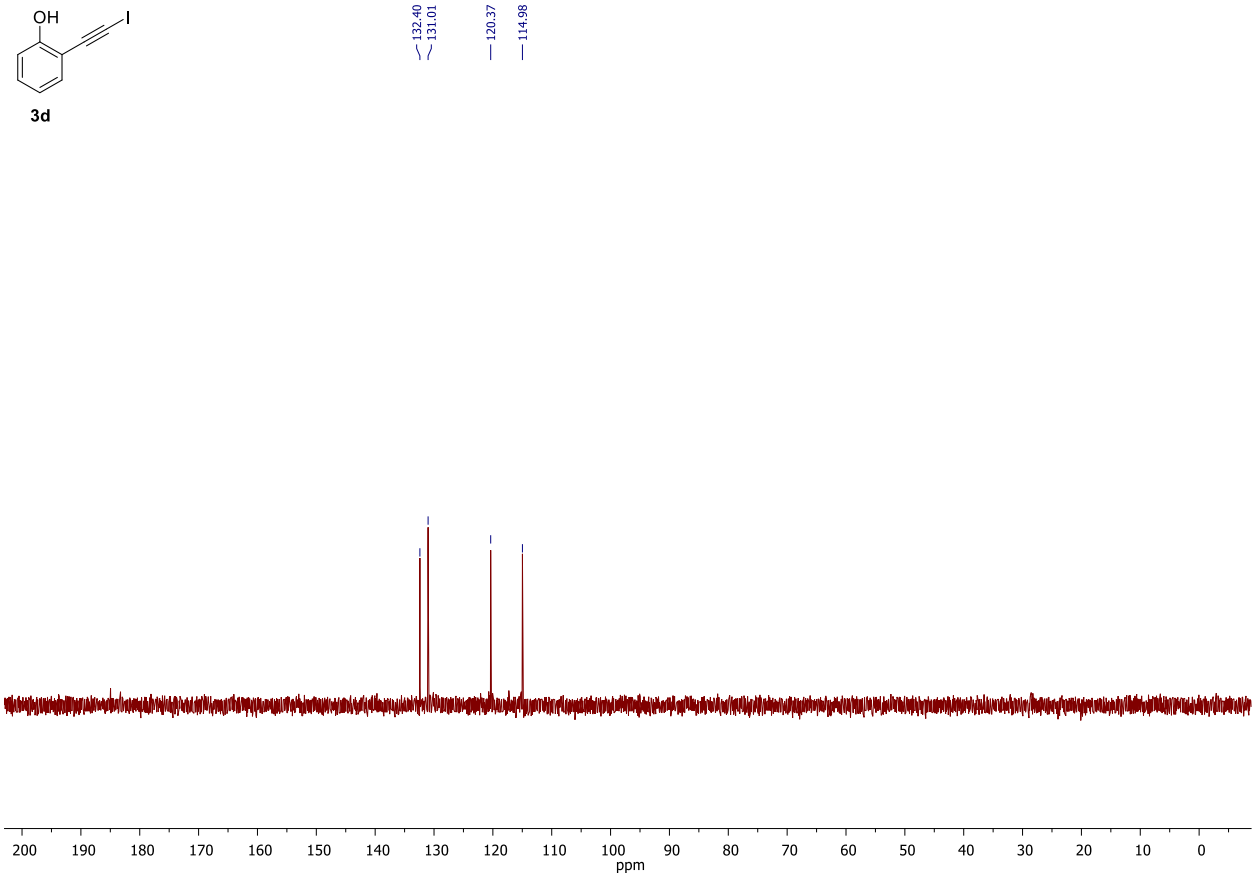
^{1}H NMR, $CDCl_3$, 400 MHz



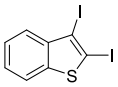
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



DEPT NMR, $CDCl_3$, 101 MHz



^{1}H NMR, $CDCl_3$, 400 MHz



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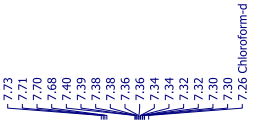
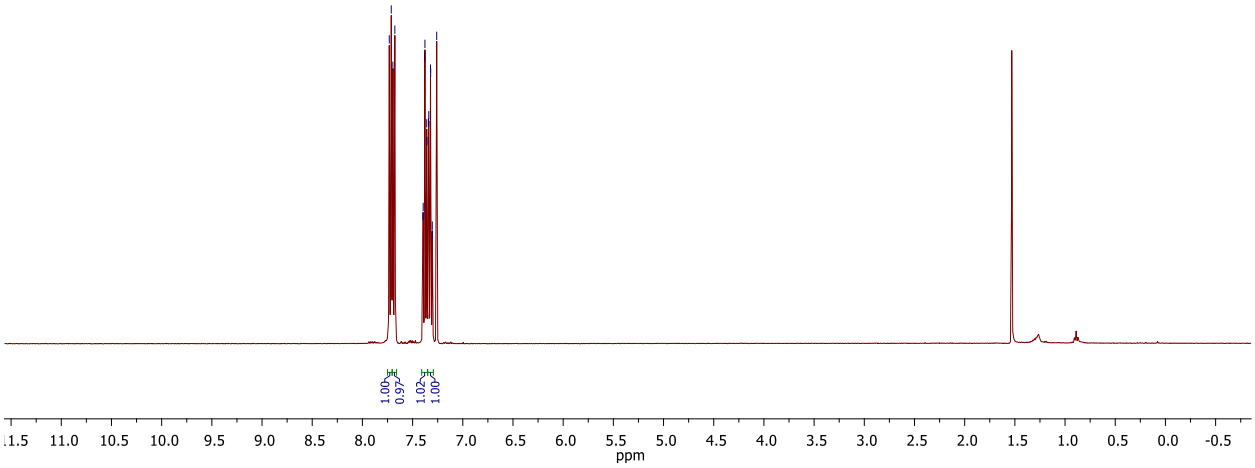
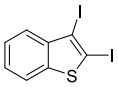




$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



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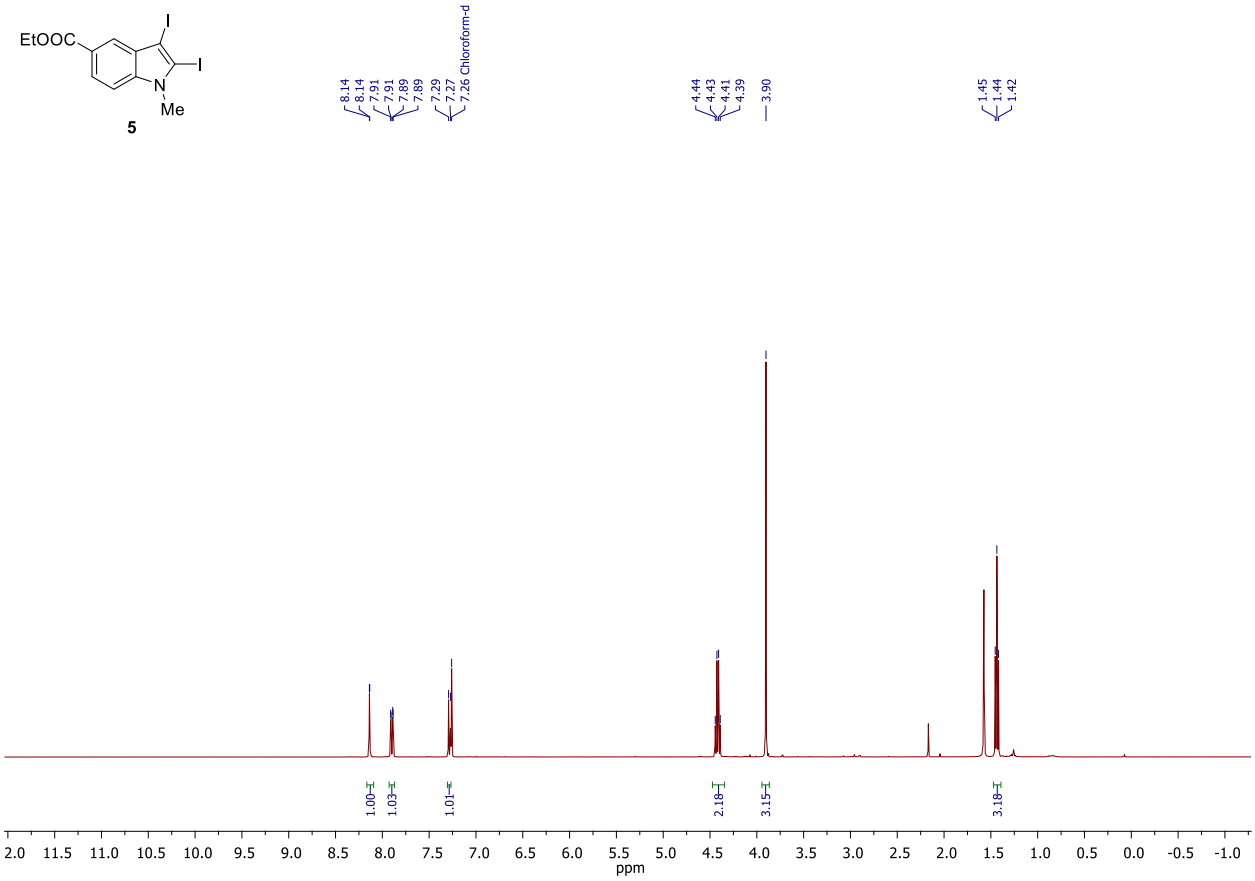
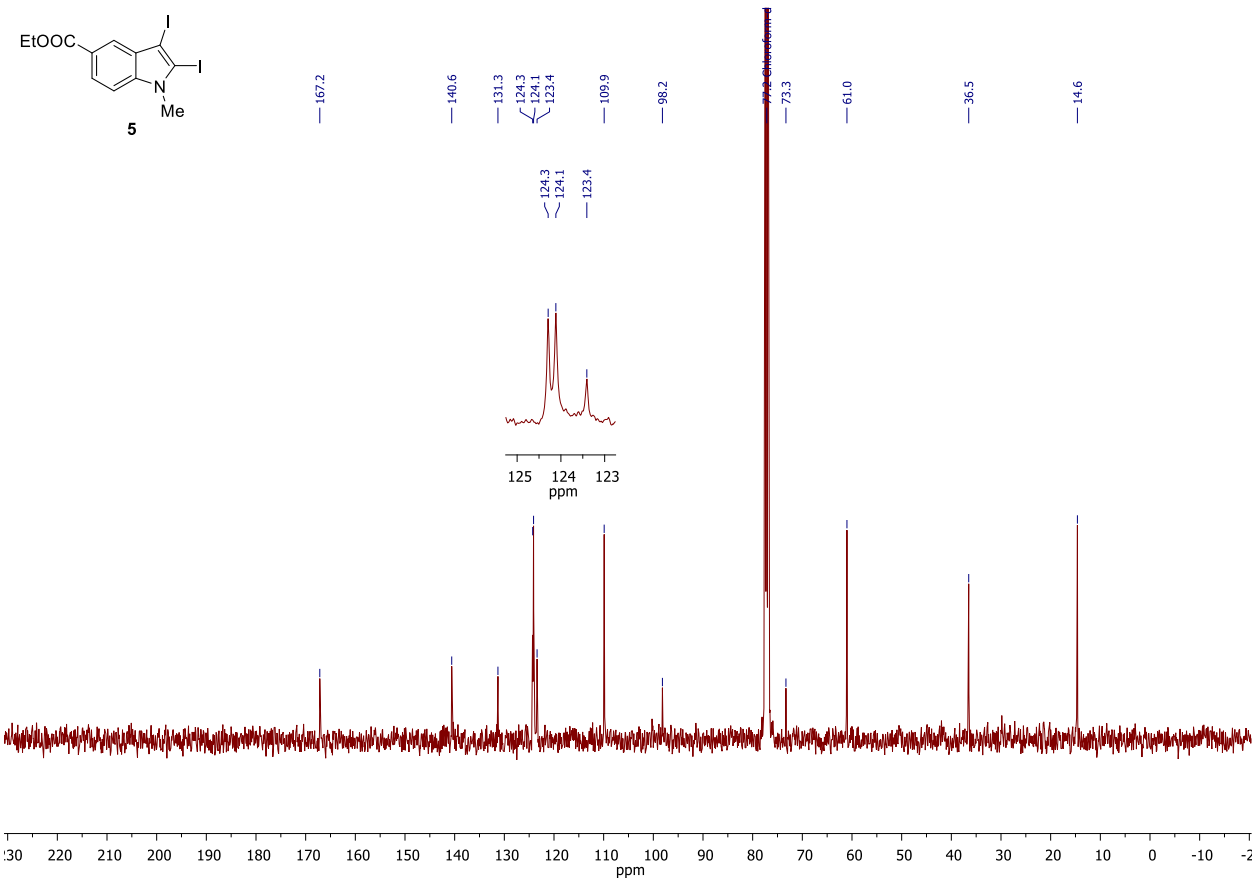
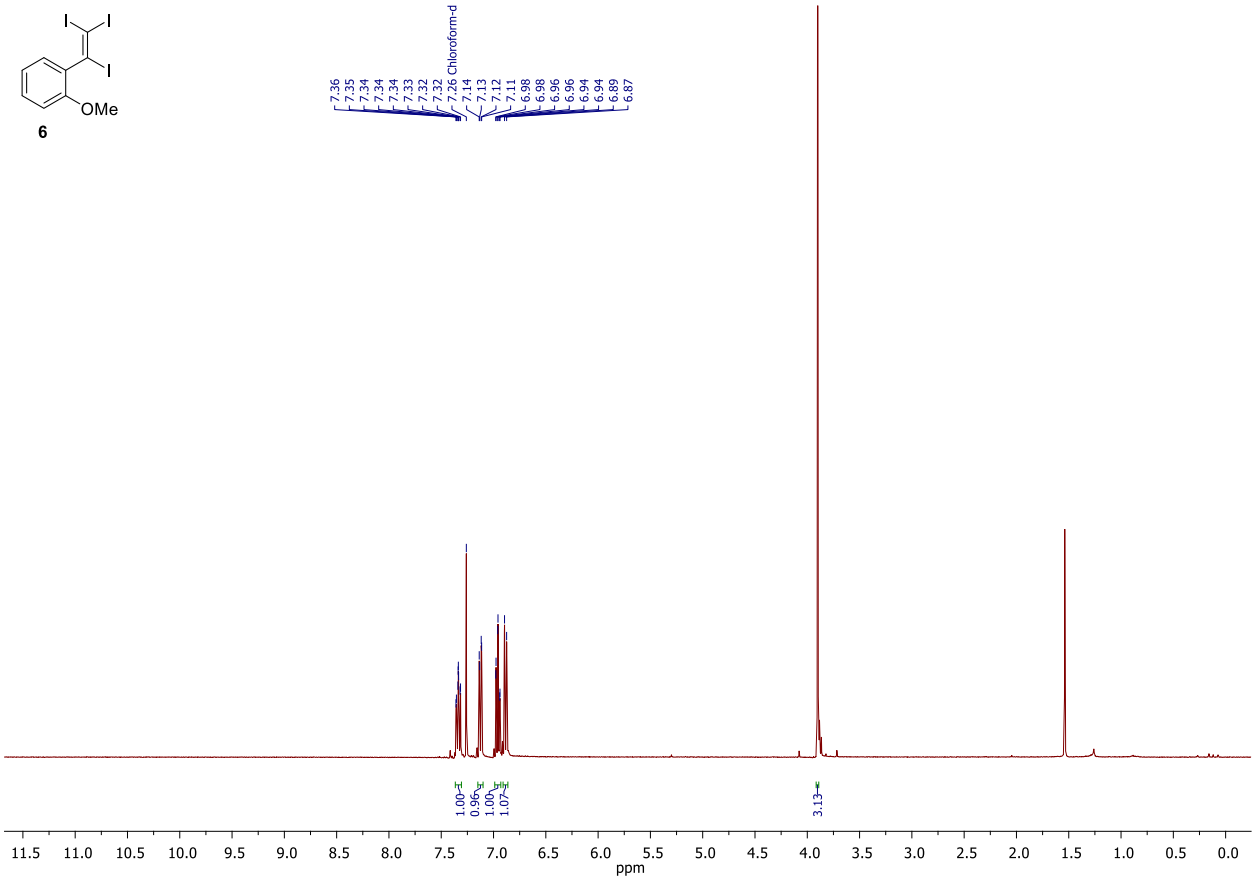
^{1}H NMR, $CDCl_3$, 400 MHz



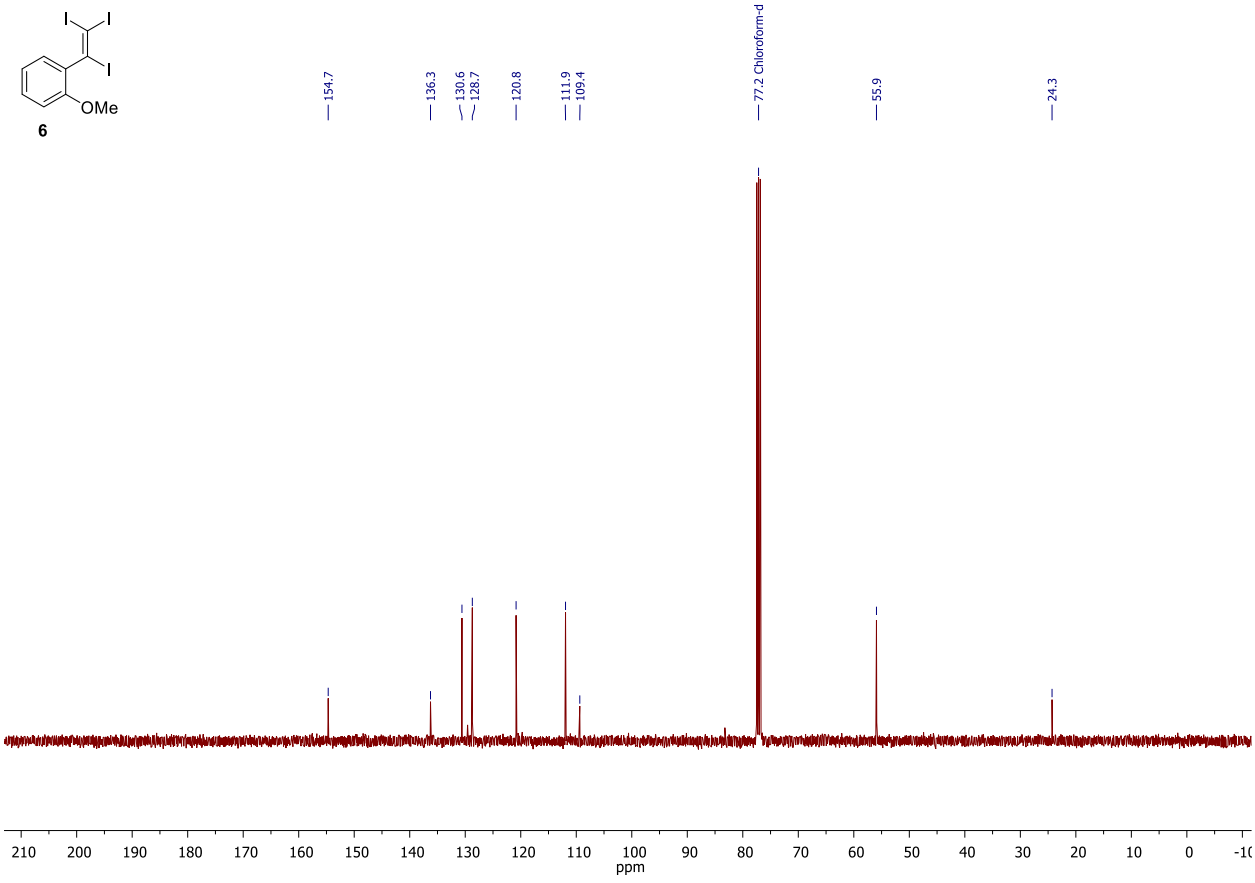
^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



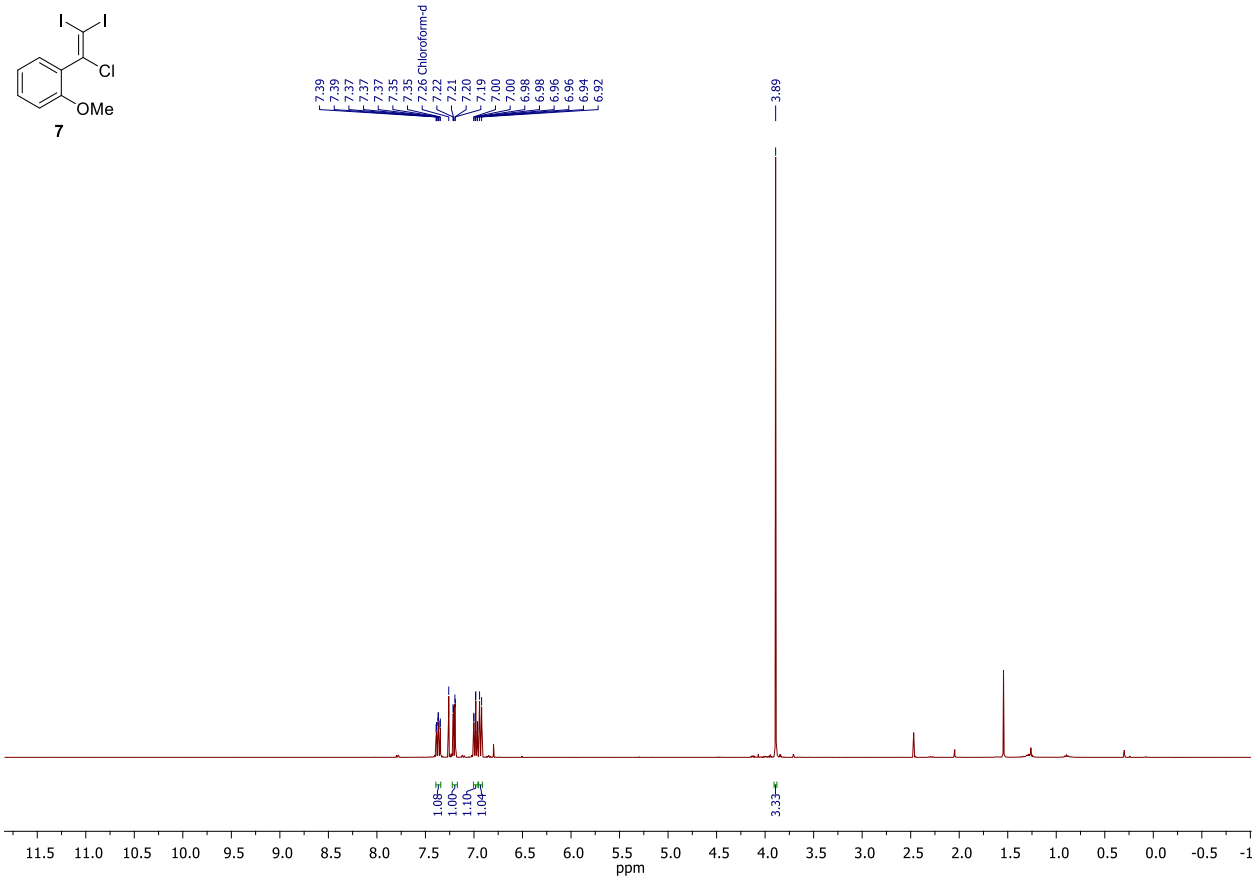
^{1}H NMR, $CDCl_3$, 400 MHz



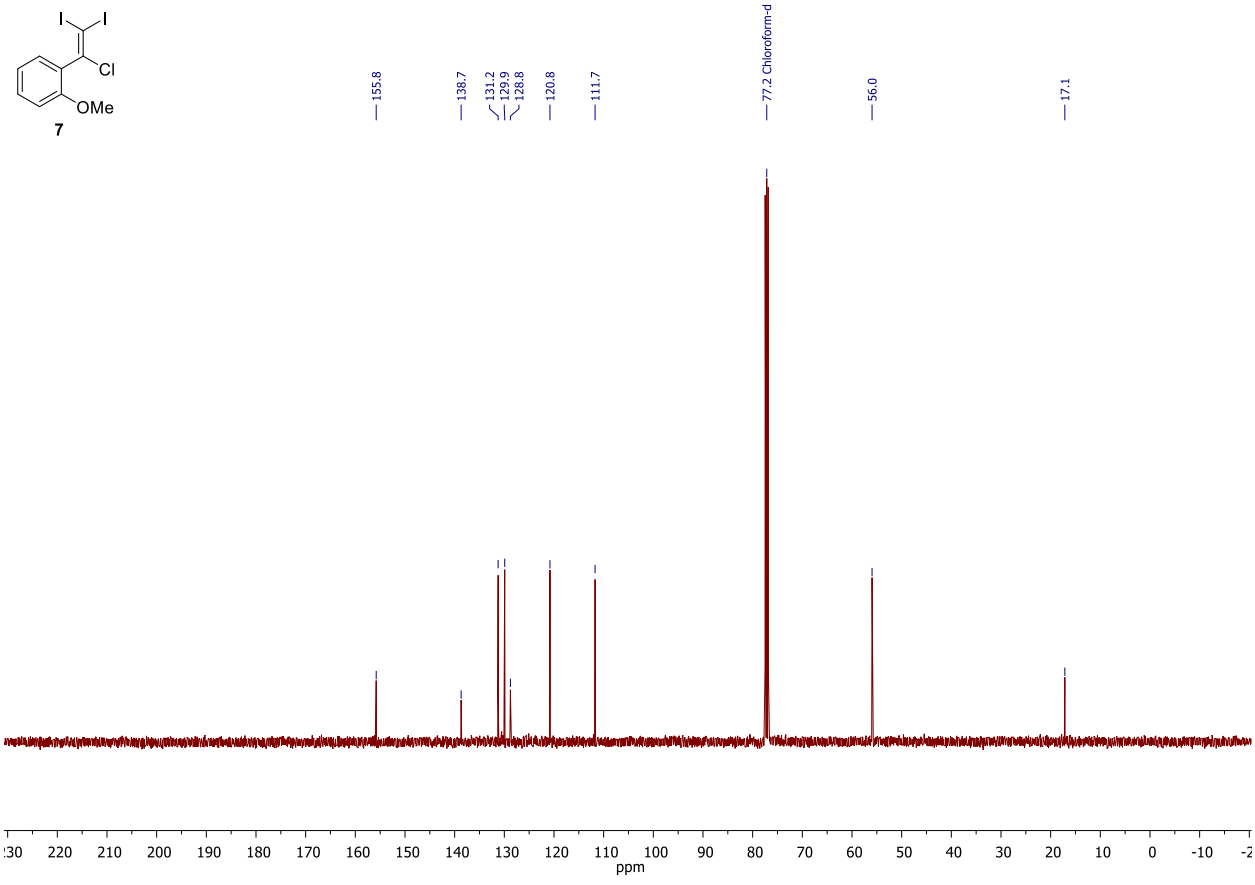
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



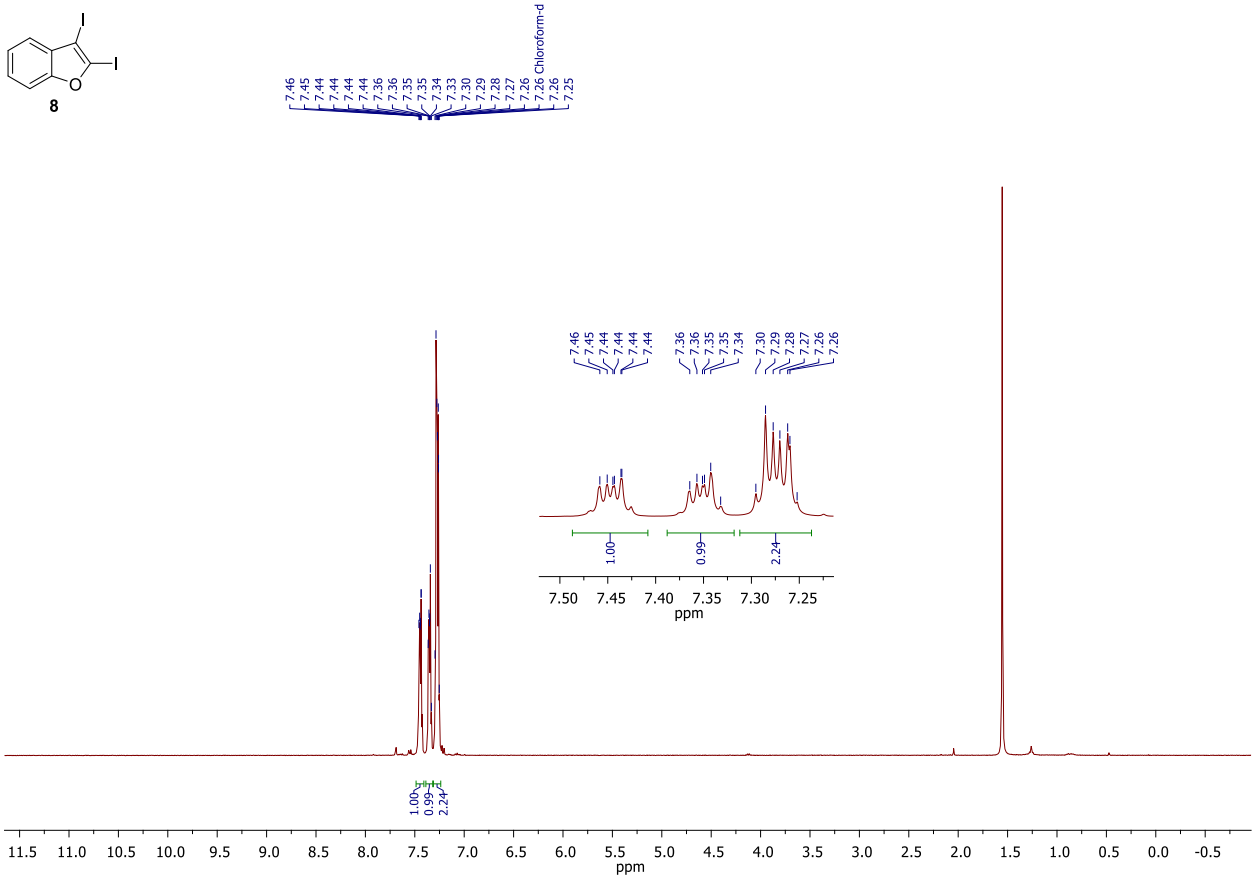
^{1}H NMR, $CDCl_3$, 400 MHz



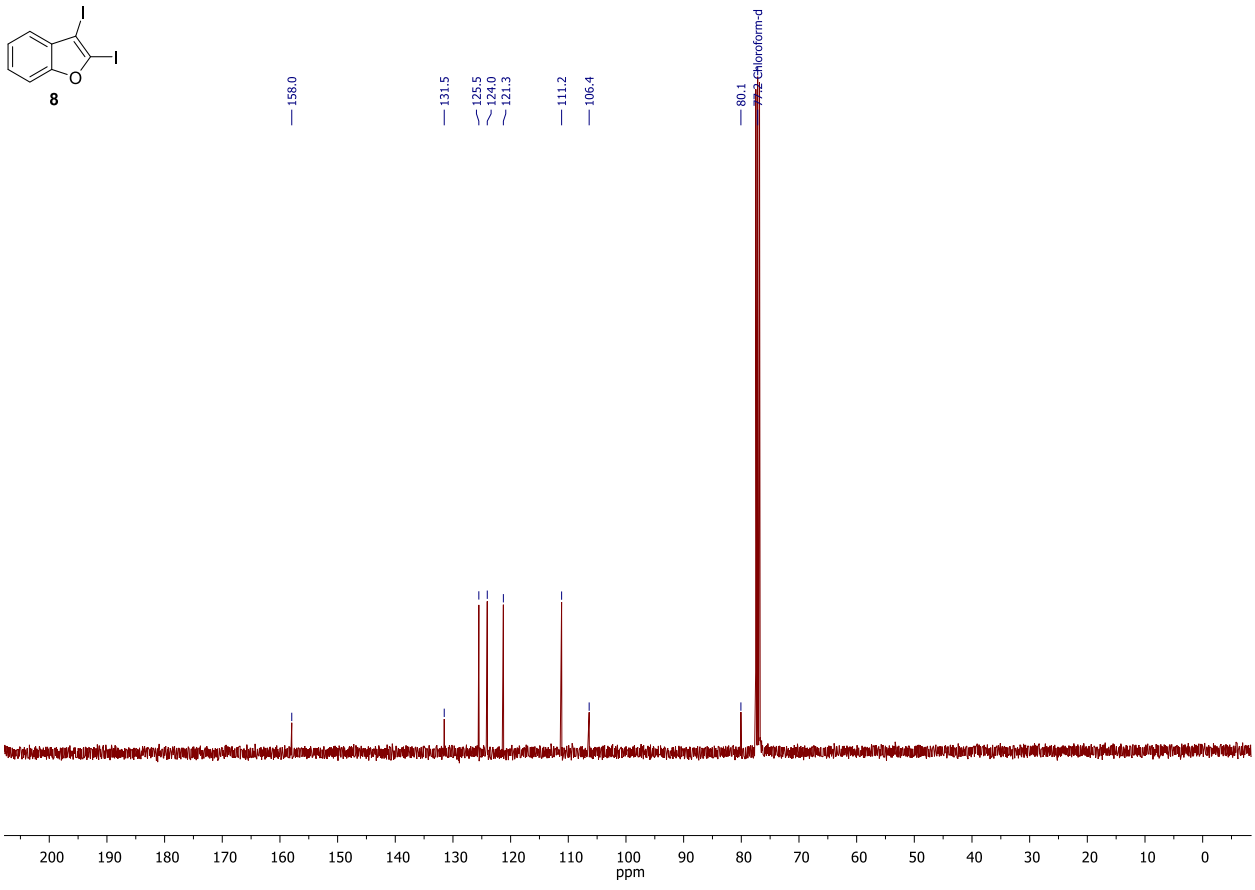
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



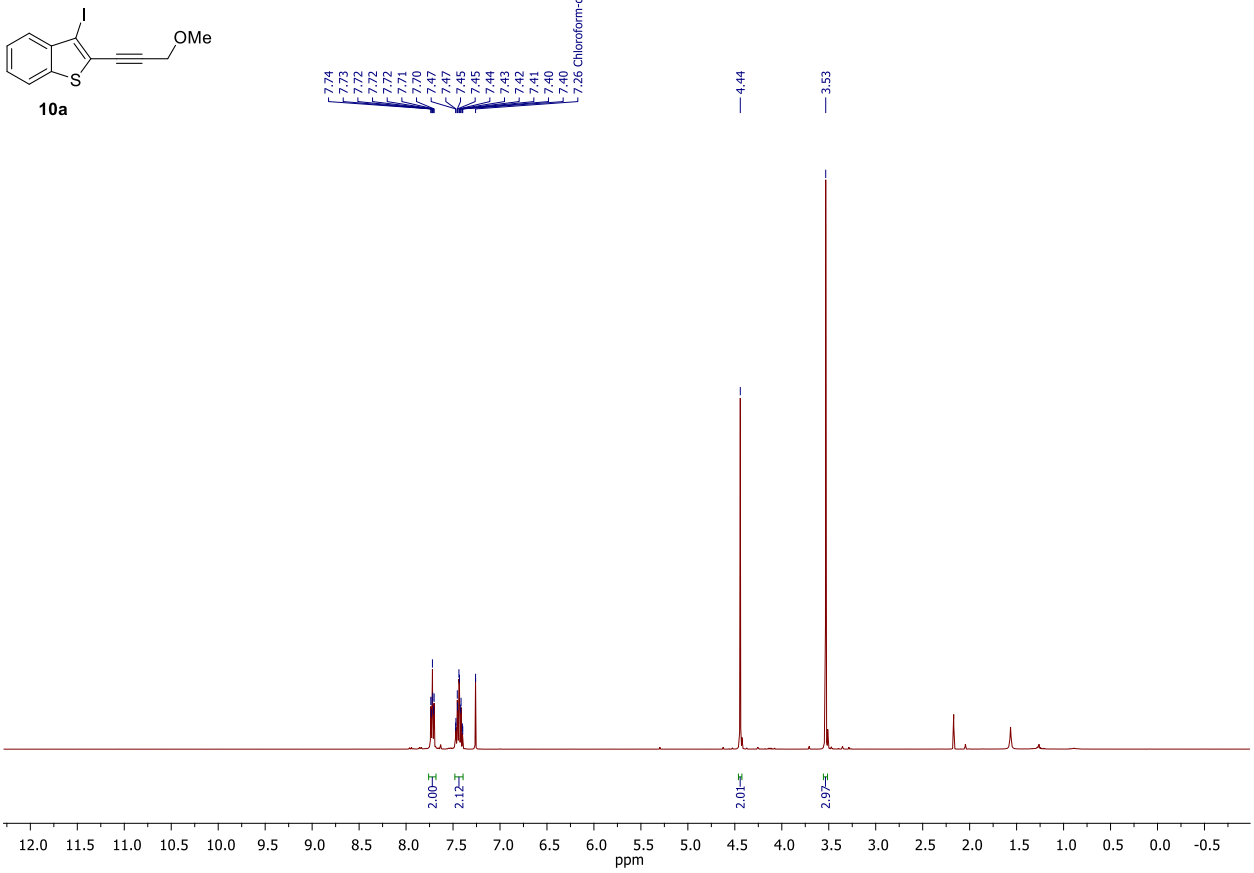
^{1}H NMR, $CDCl_3$, 400 MHz



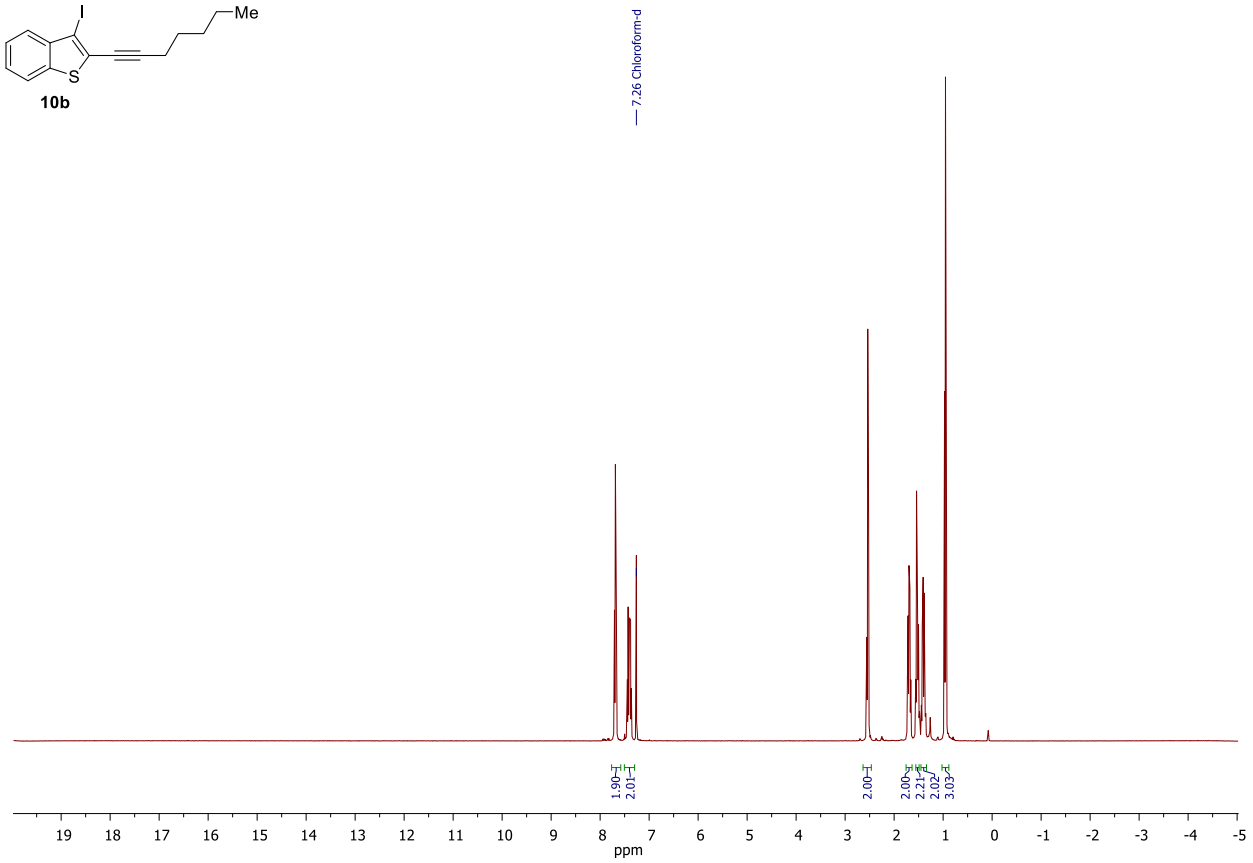
^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



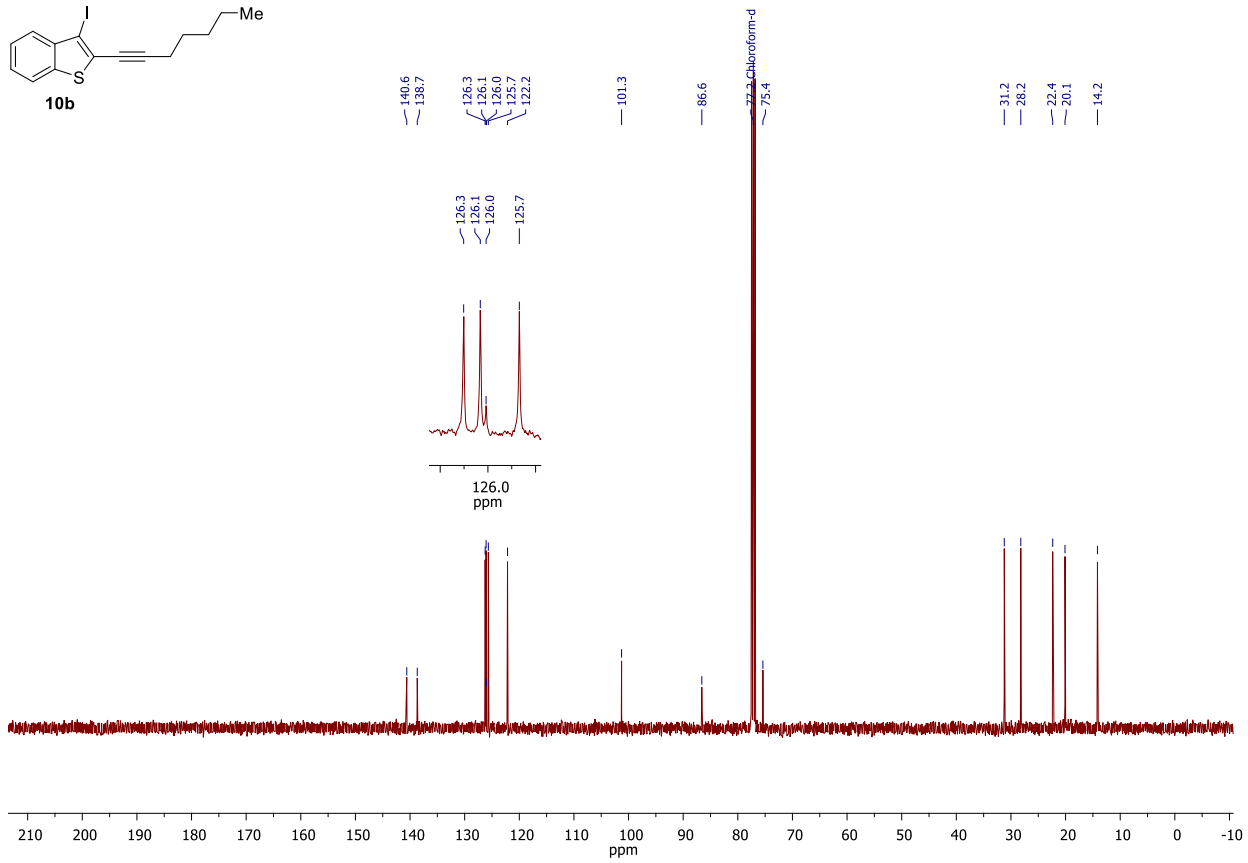
^{1}H NMR, $CDCl_3$, 400 MHz



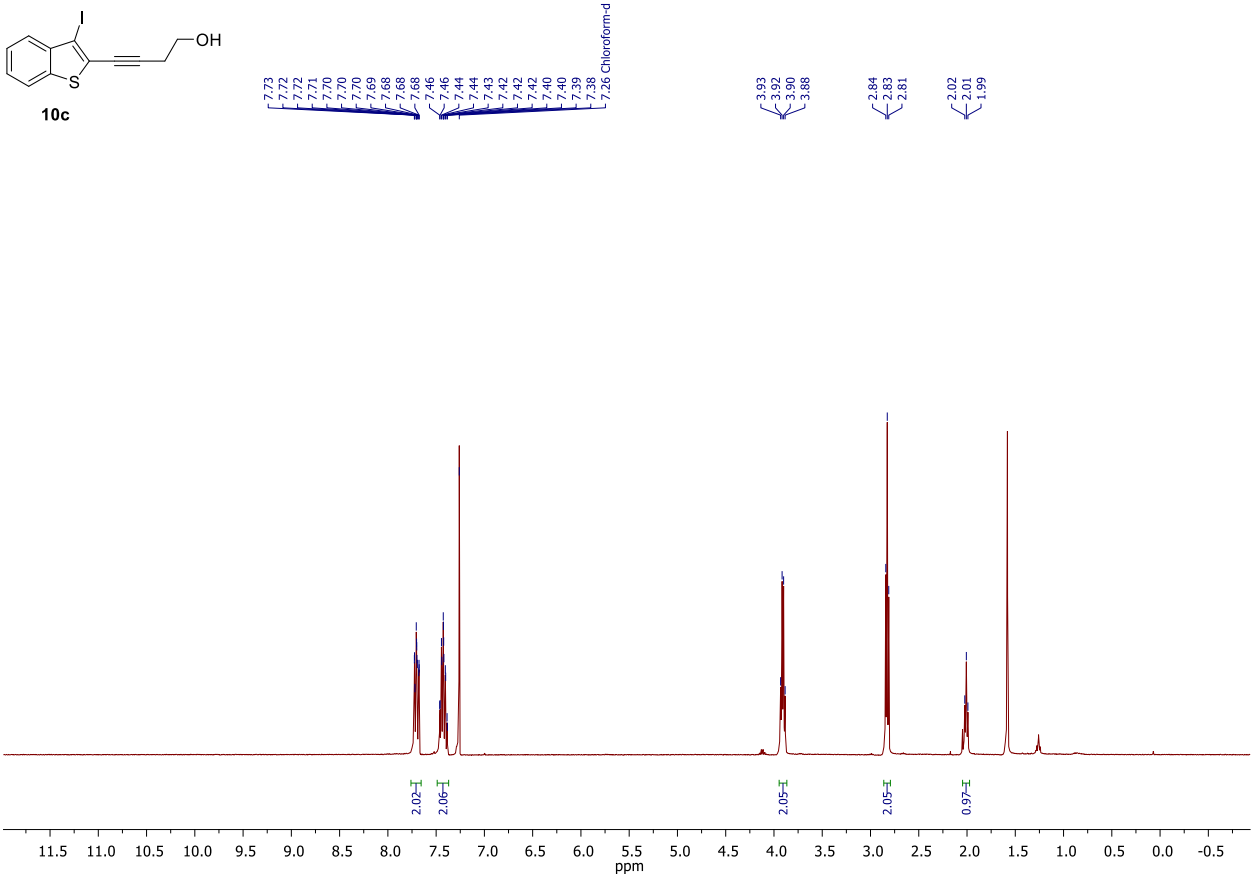
^{1}H NMR, $CDCl_3$, 400 MHz



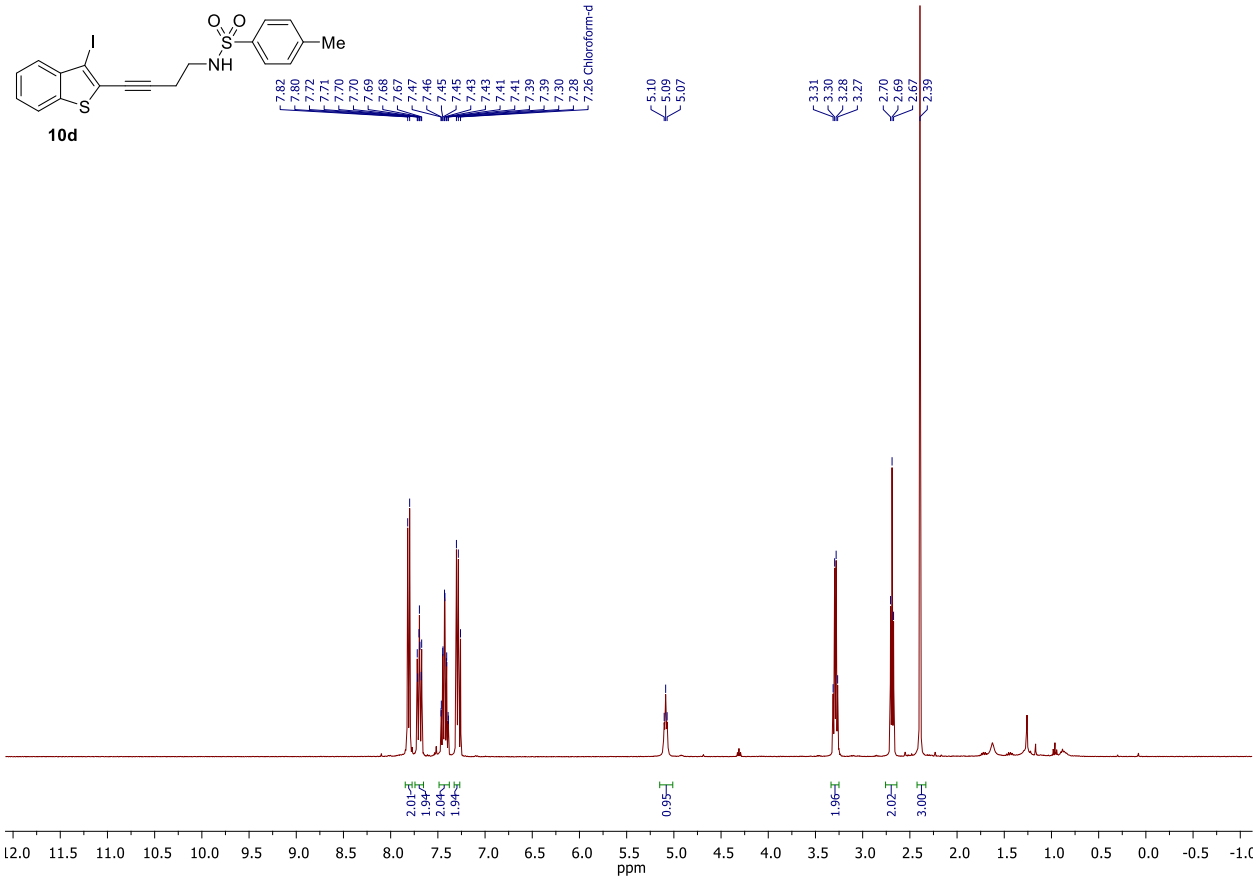
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



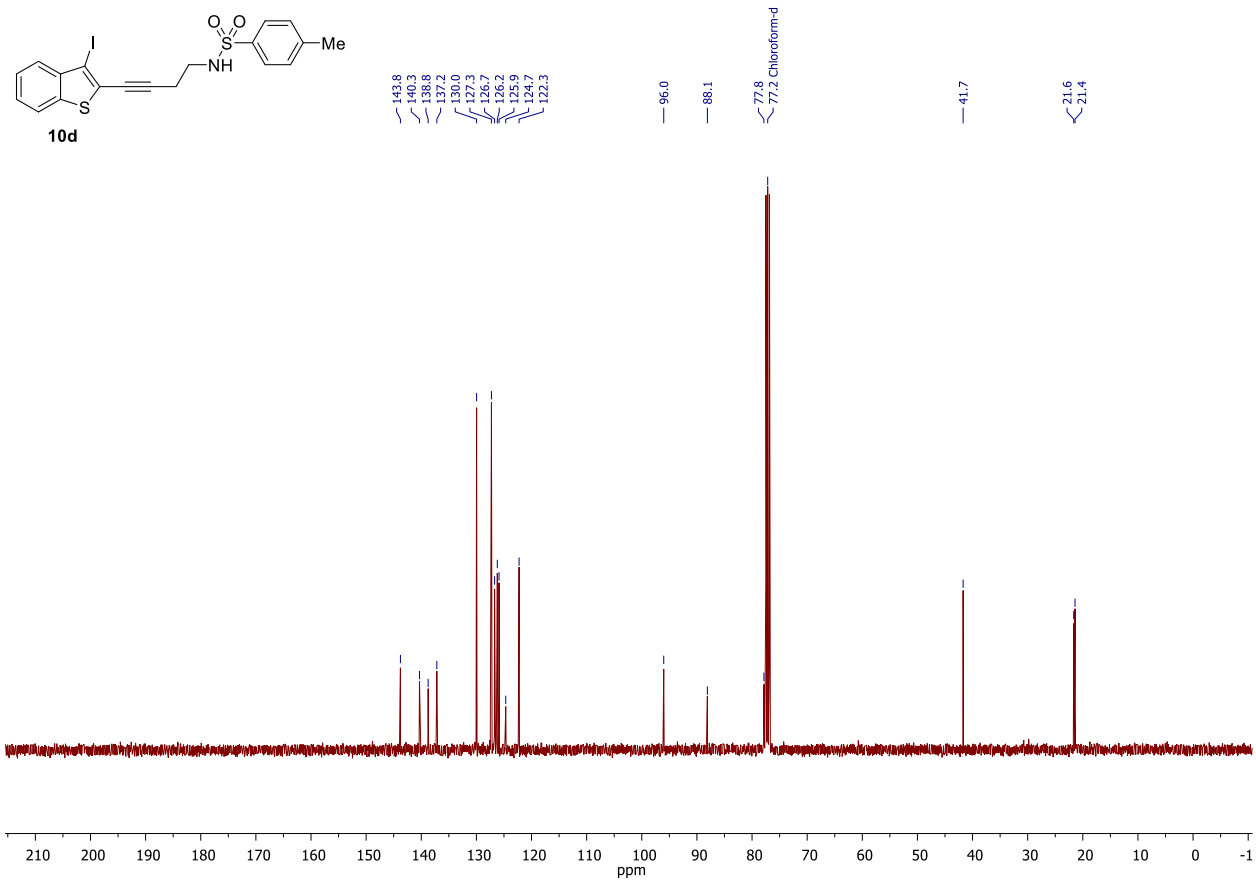
^{1}H NMR, $CDCl_3$, 400 MHz



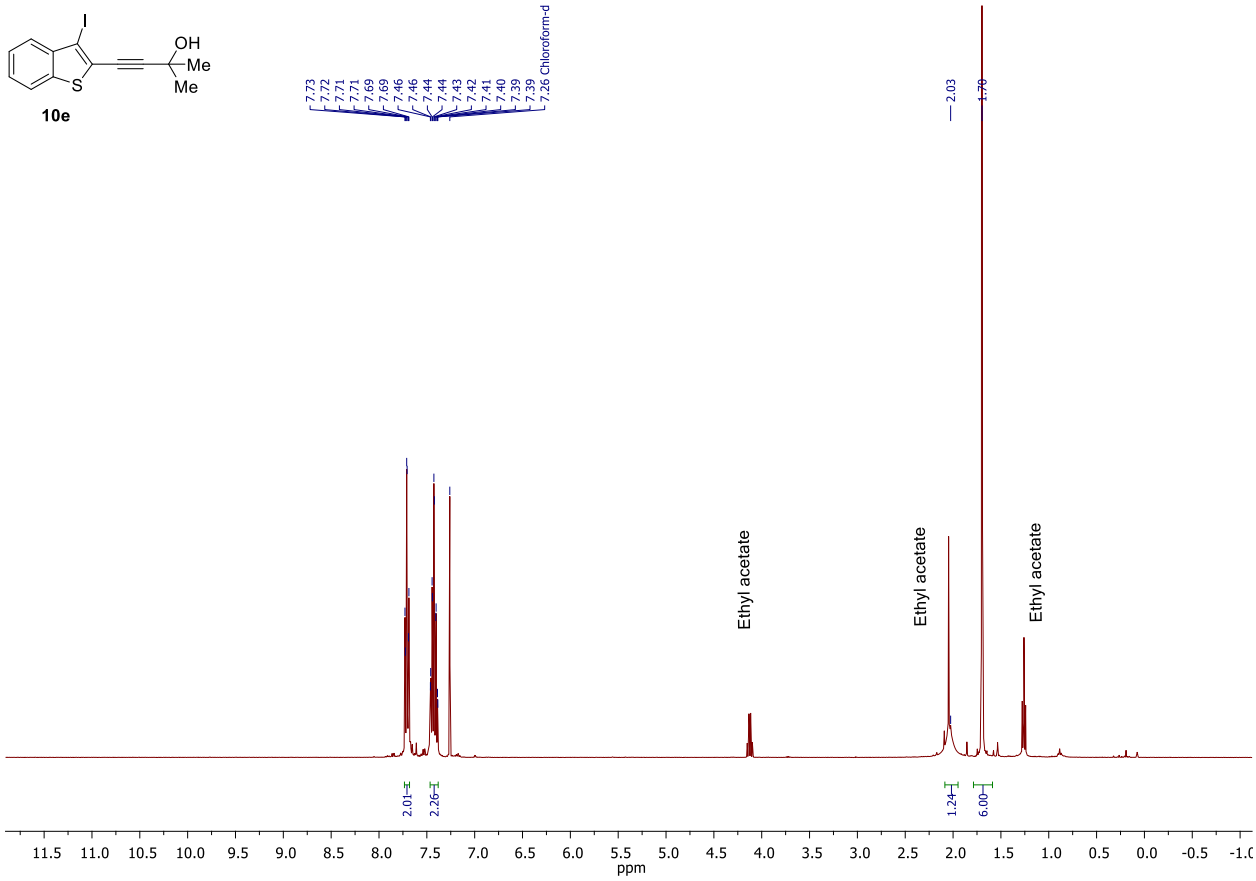
^{1}H NMR, $CDCl_3$, 400 MHz



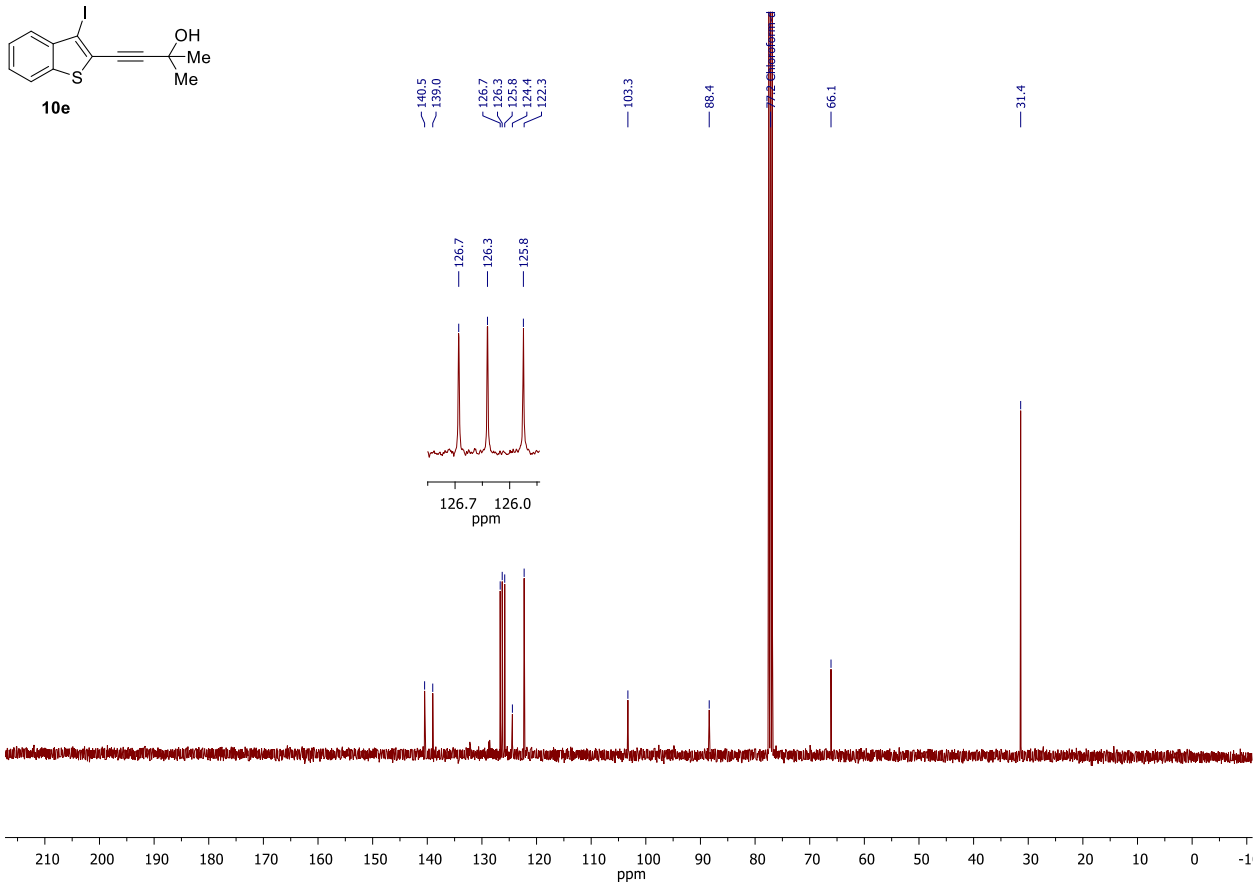
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



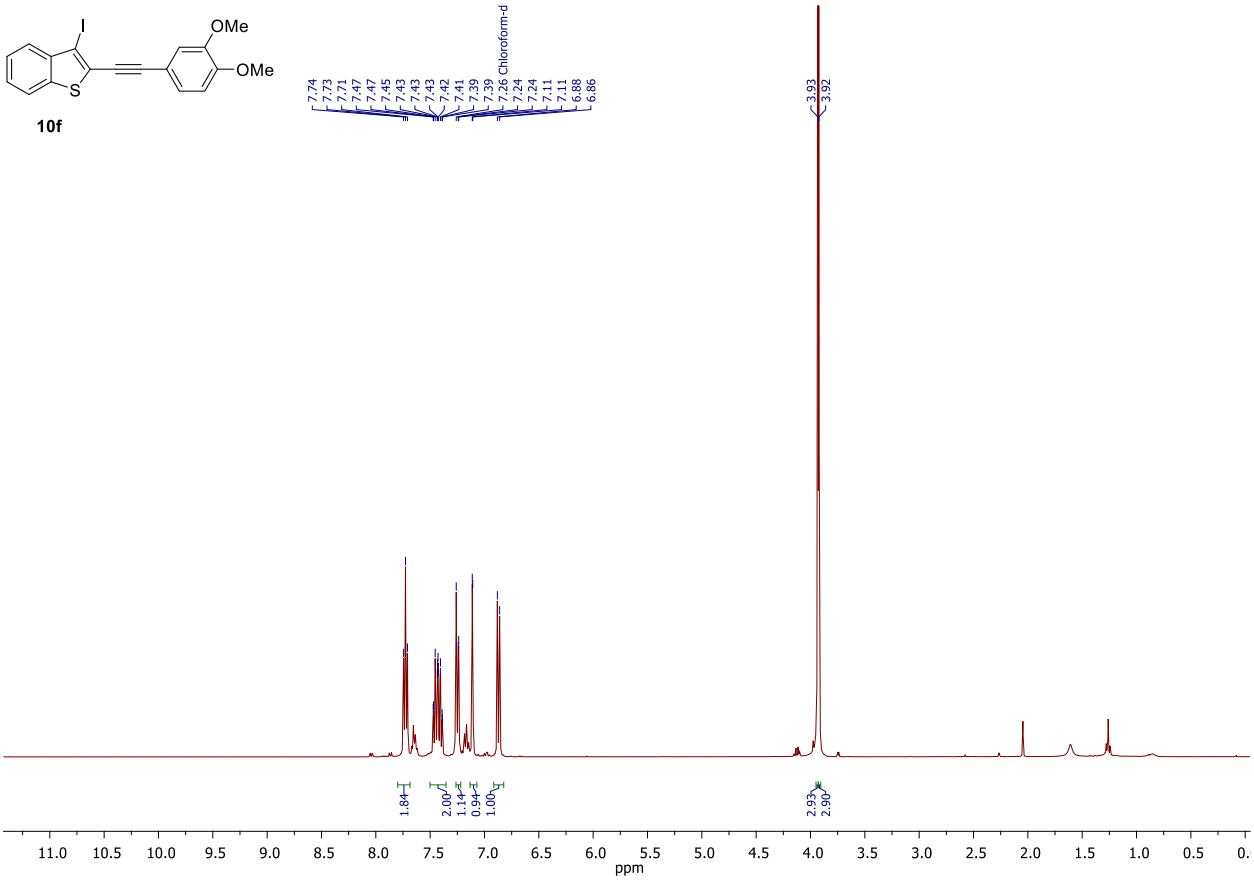
^{1}H NMR, $CDCl_3$, 400 MHz



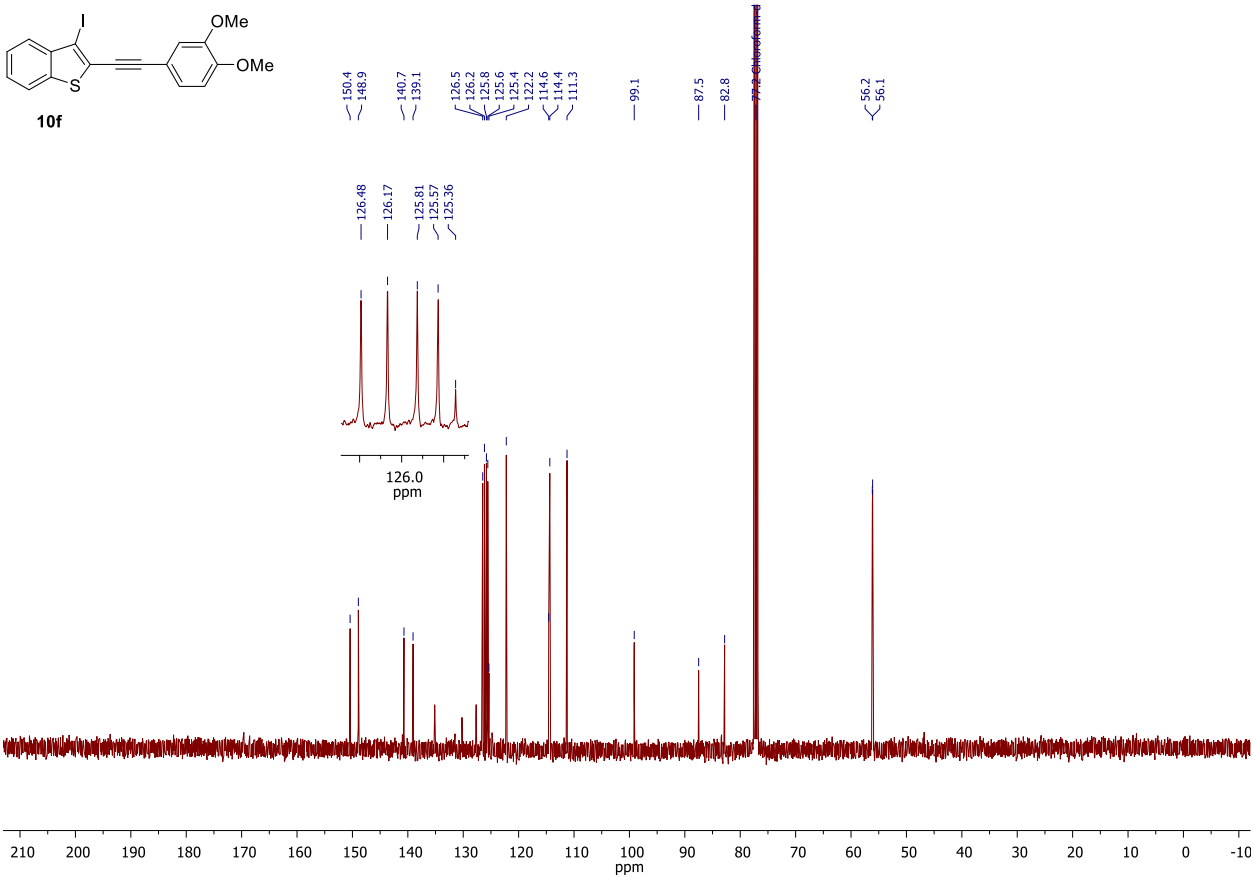
^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



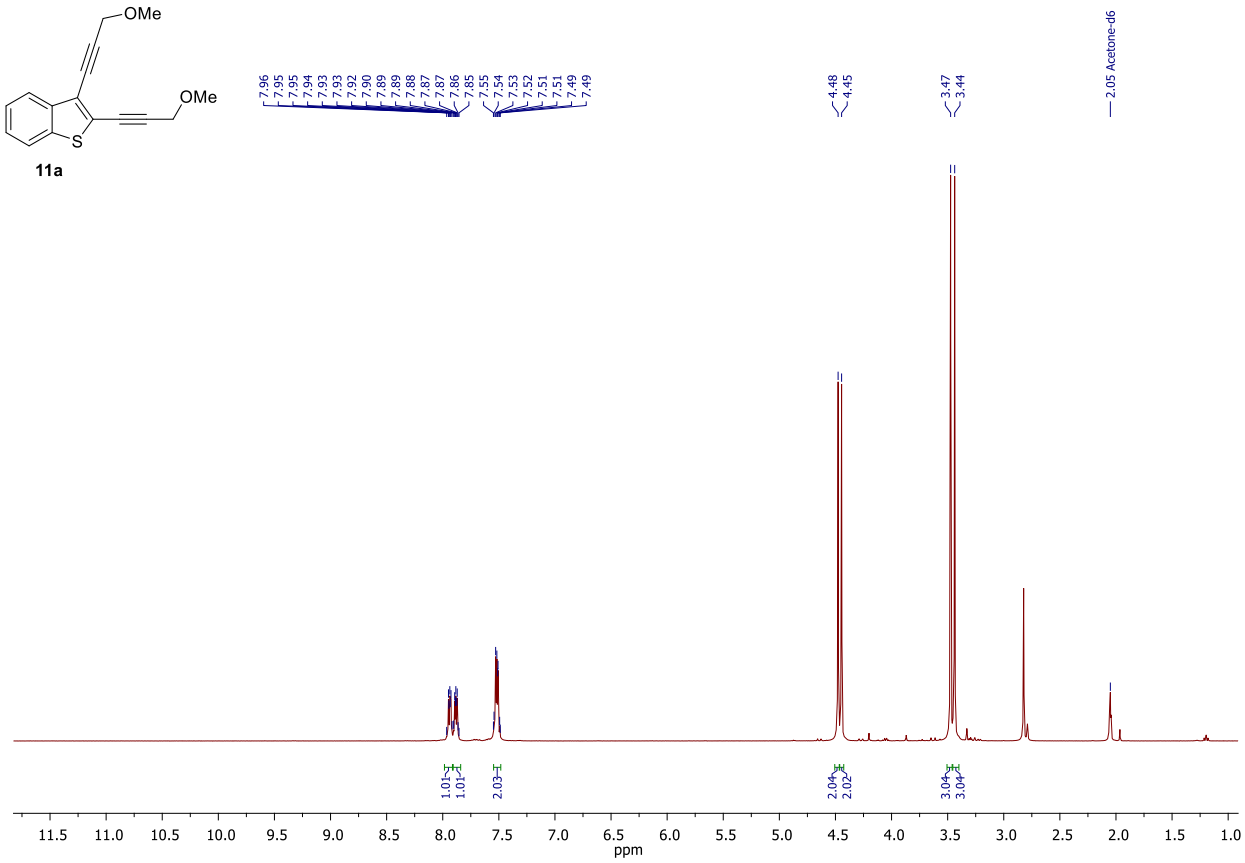
^{1}H NMR, $CDCl_3$, 400 MHz



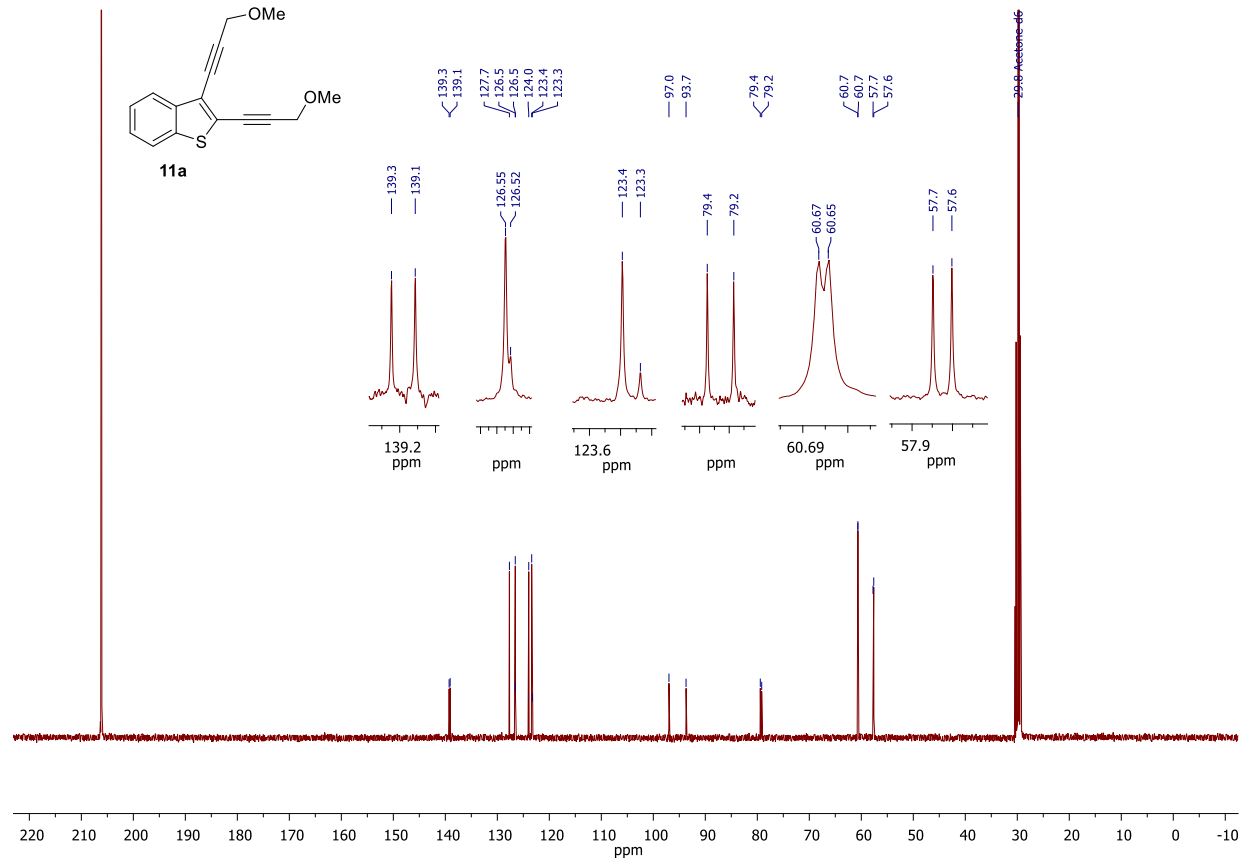
^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



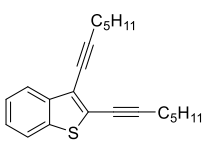
^{1}H NMR, acetone-d_6, 400 MHz



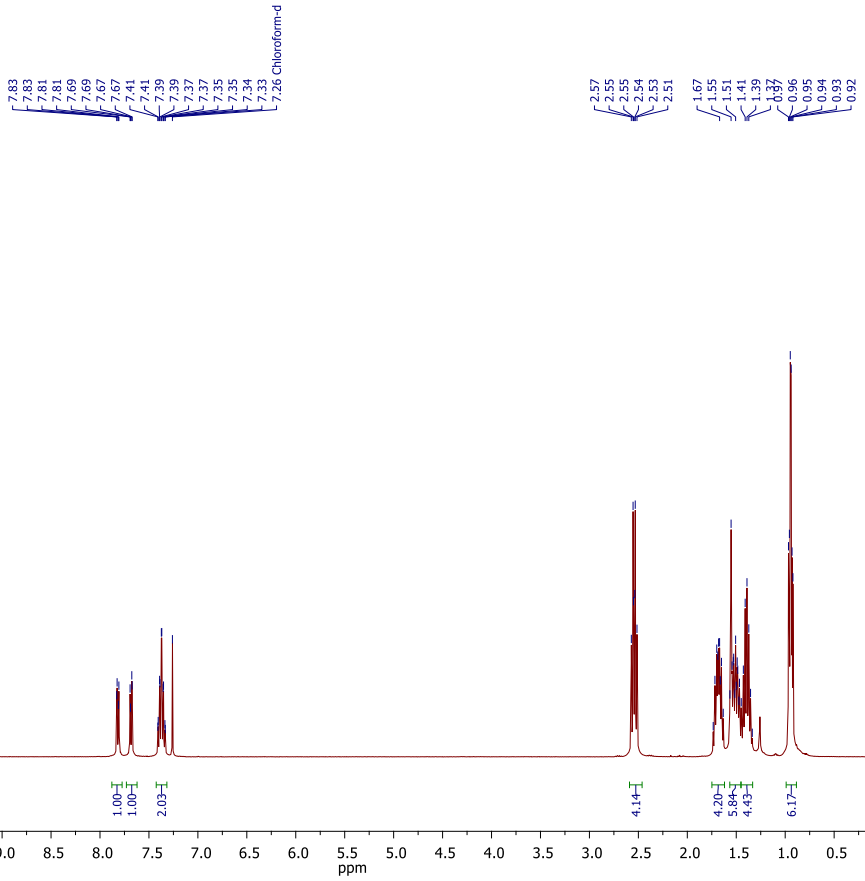
^{13}C{^{1}H} NMR, acetone-d_6, 101 MH



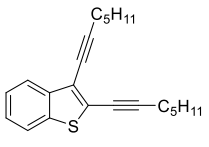
^{1}H NMR, $CDCl_3$, 400 MHz



11b

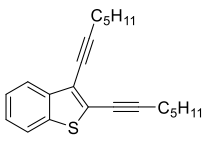


^{1}H NMR, $CDCl_3$, 400 MHz



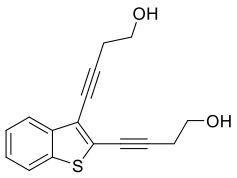
11b

DEPT NMR, $CDCl_3$, 101 MHz



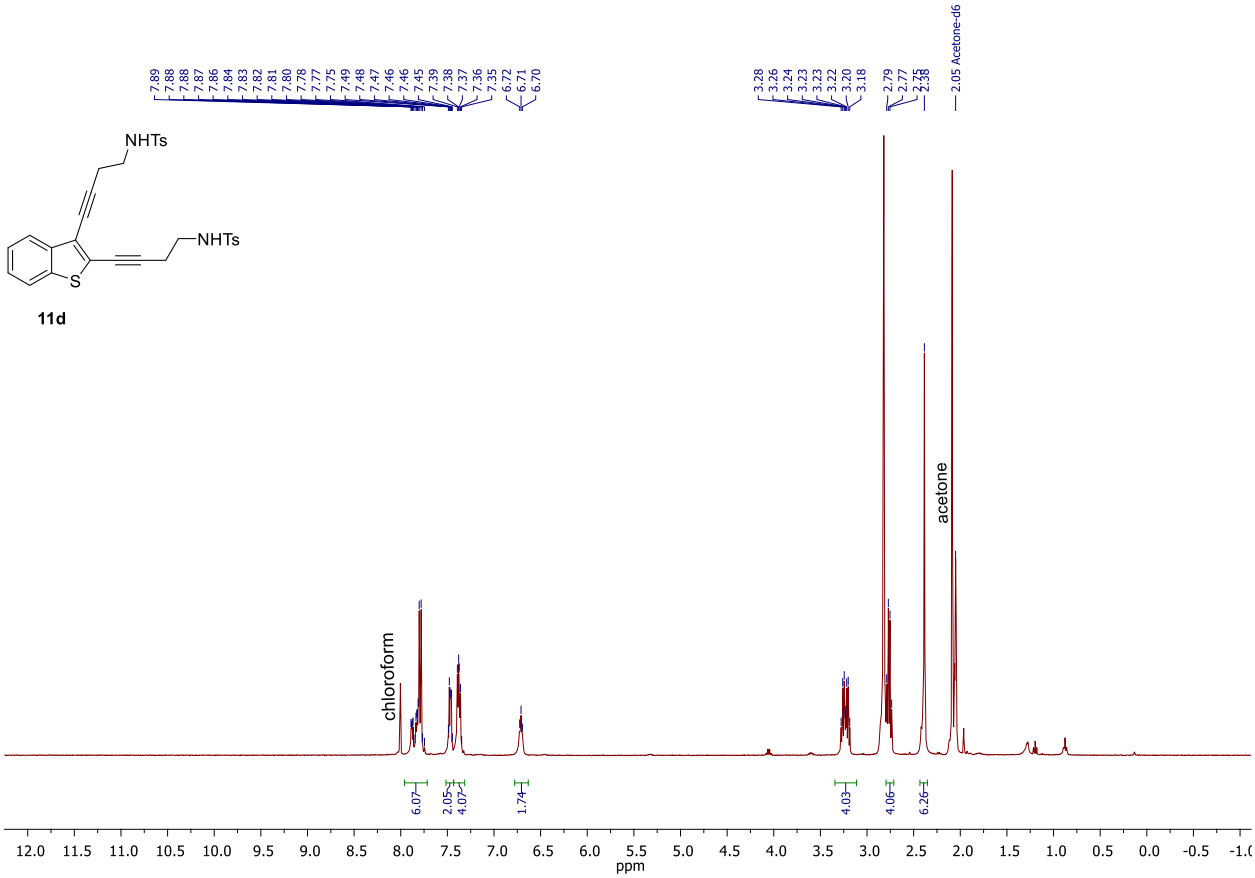
11b

^1H NMR, $CDCl_3$, 400 MHz

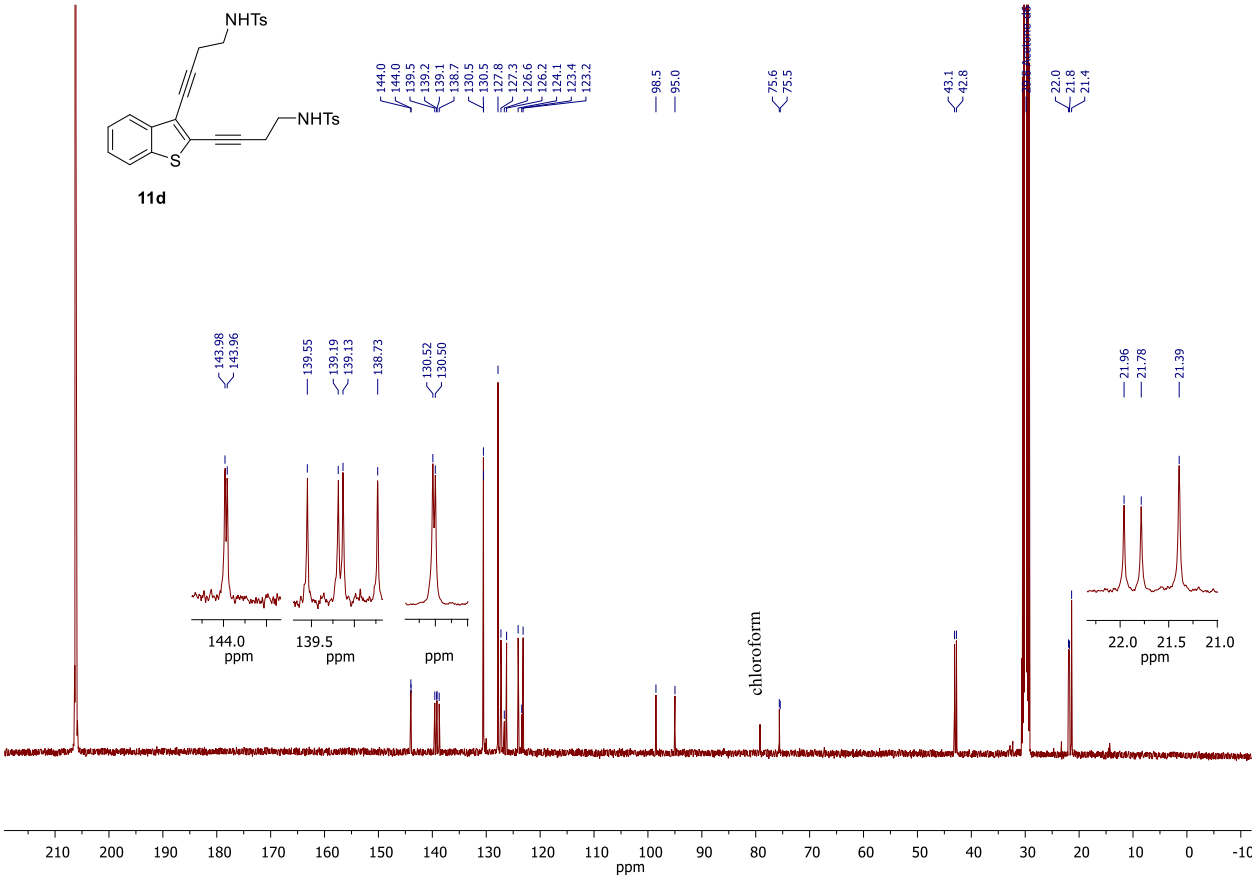


11c

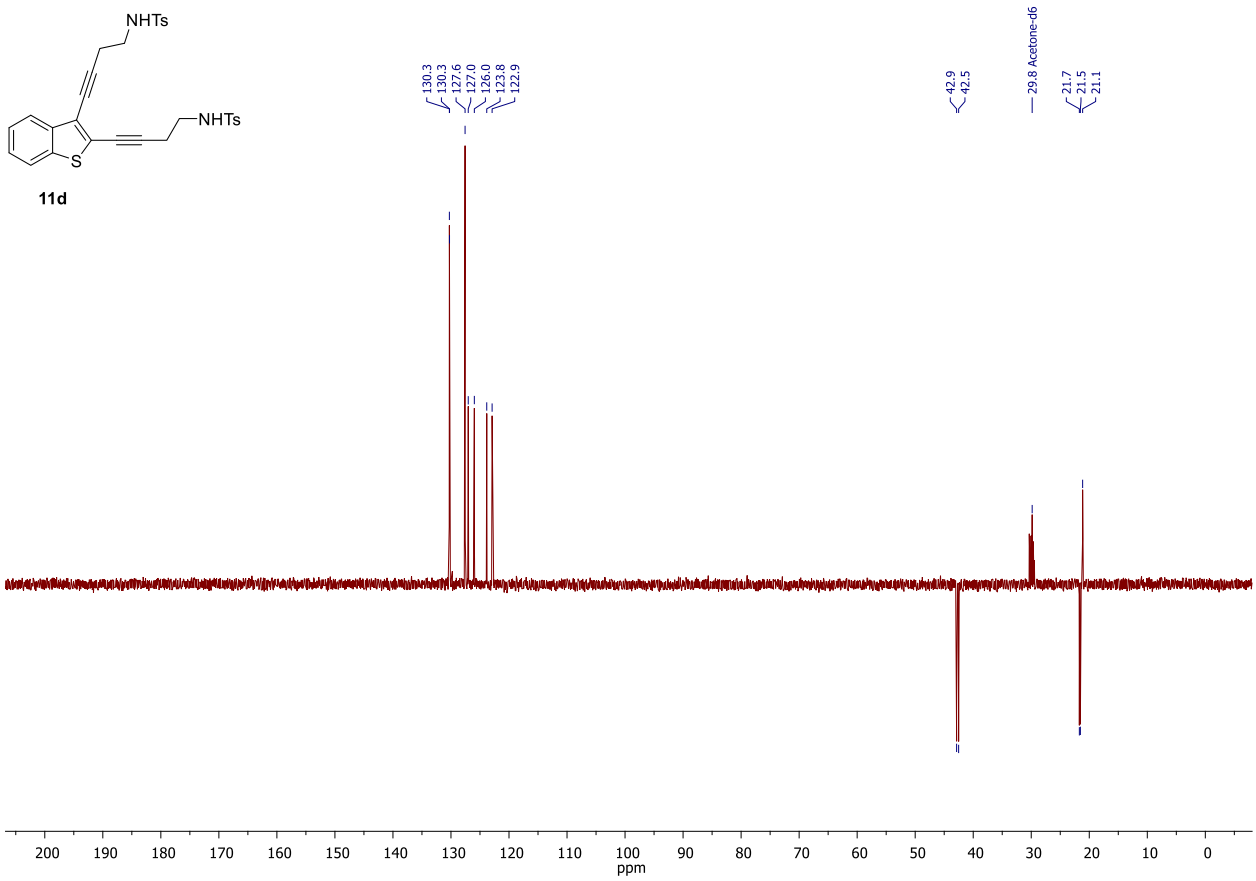
^{1}H NMR, acetone-d_6, 400 MHz



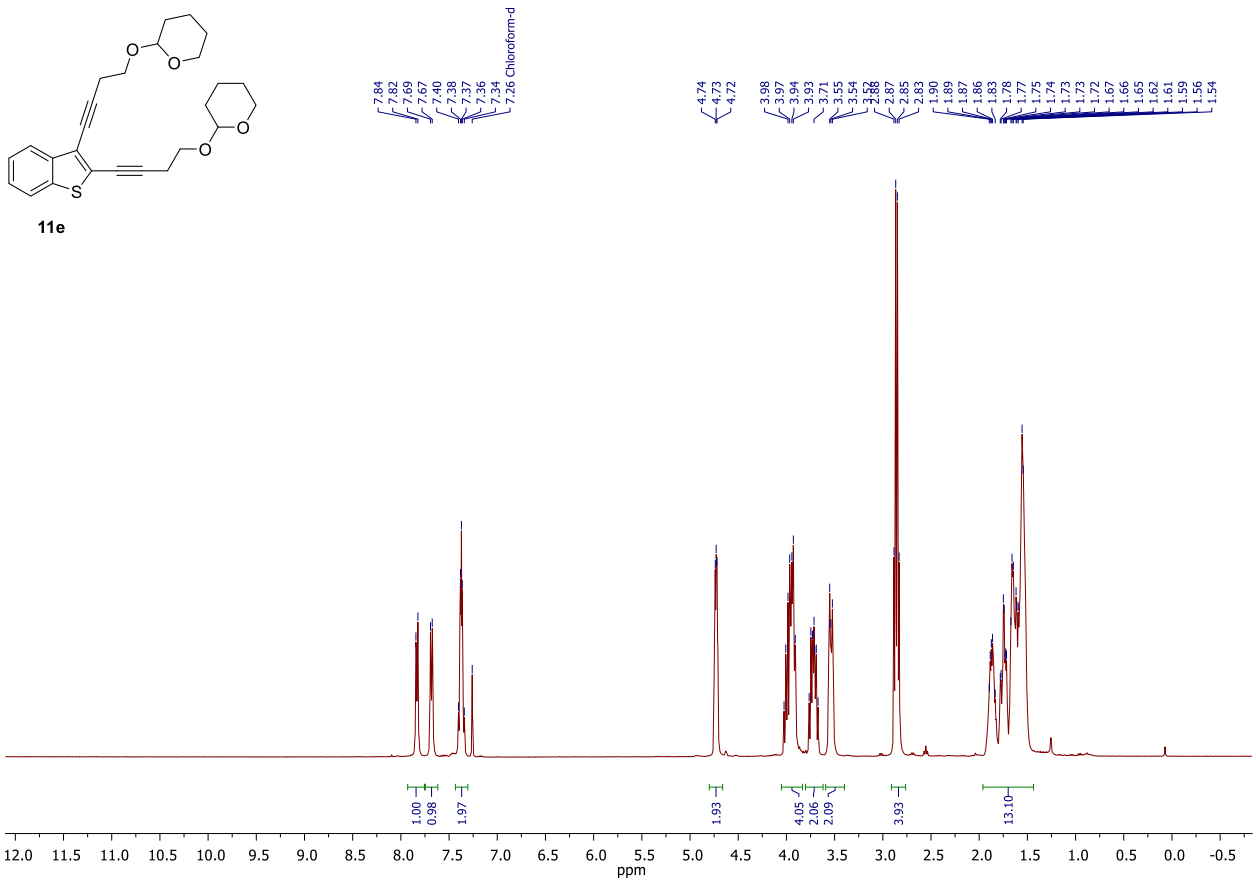
^{13}C{^{1}H} NMR, acetone-d_6, 101 MHz



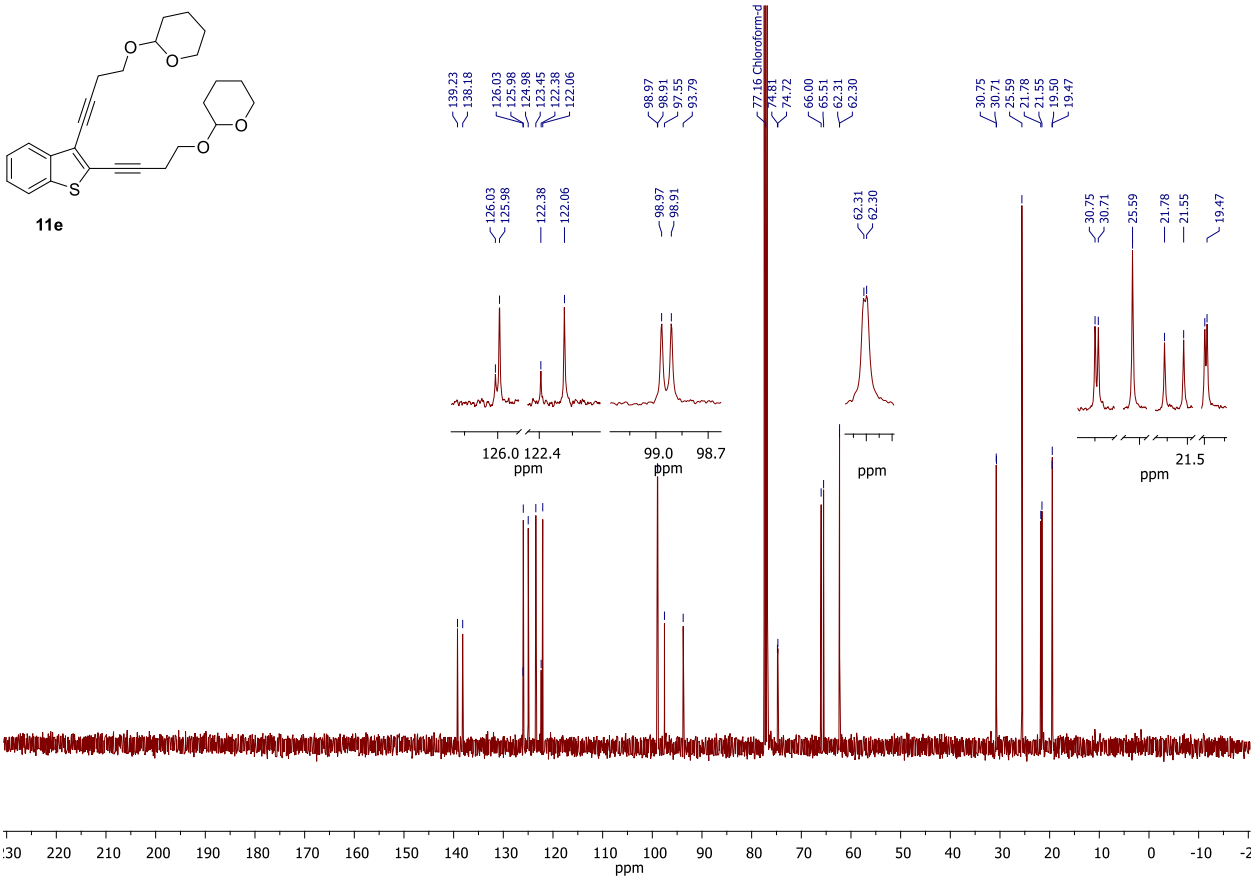
DEPT NMR, acetone-d_6, 101 MHz



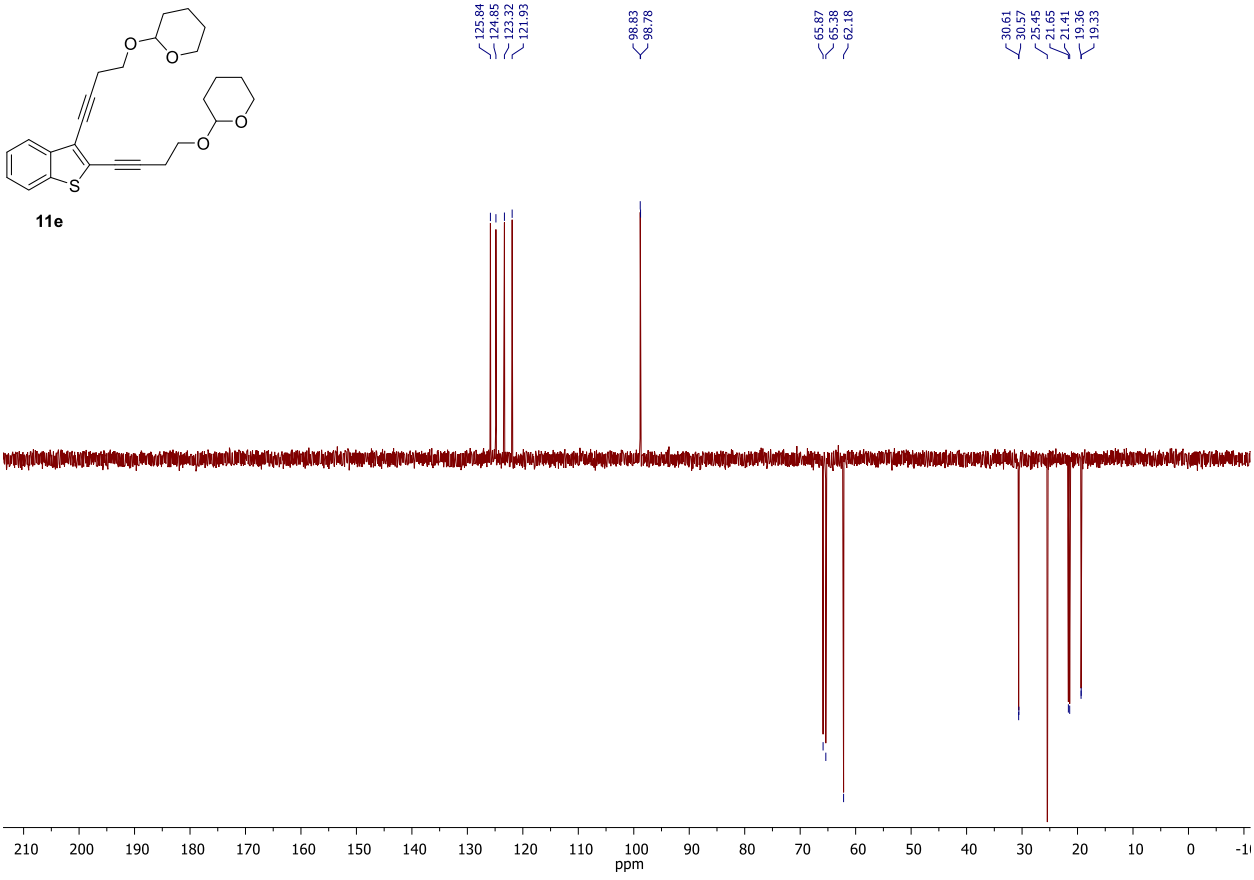
^{1}H NMR, $CDCl_3$, 400 MHz



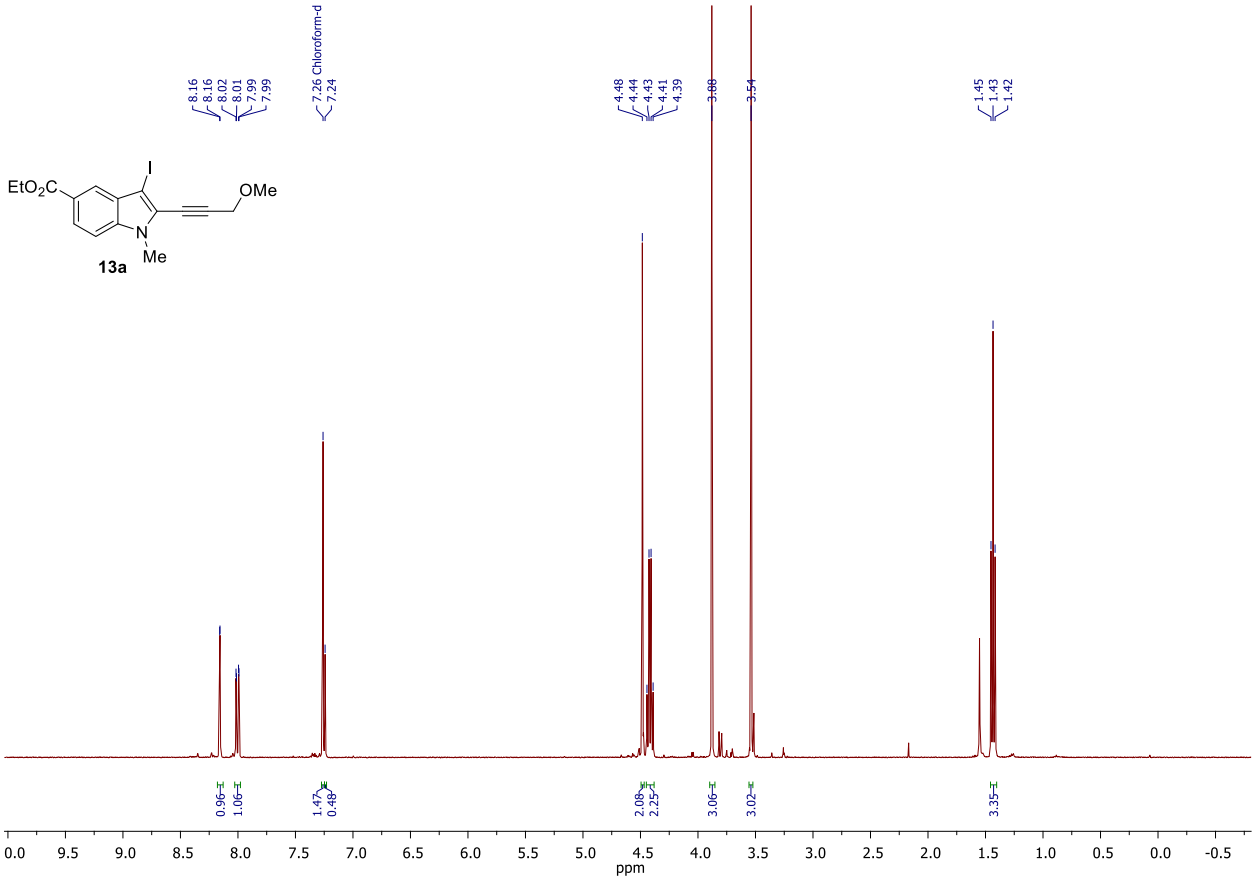
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



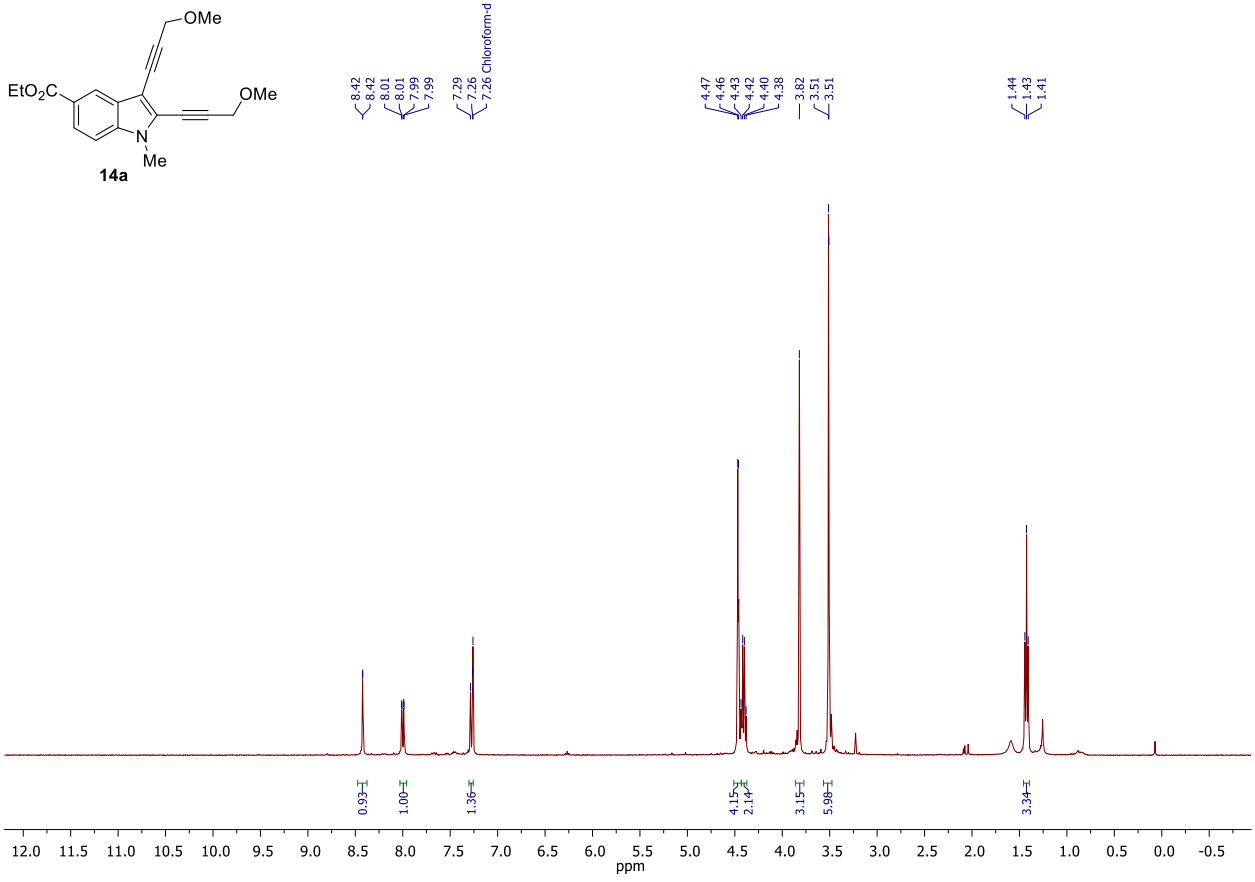
DEPT NMR, $CDCl_3$, 101 MHz



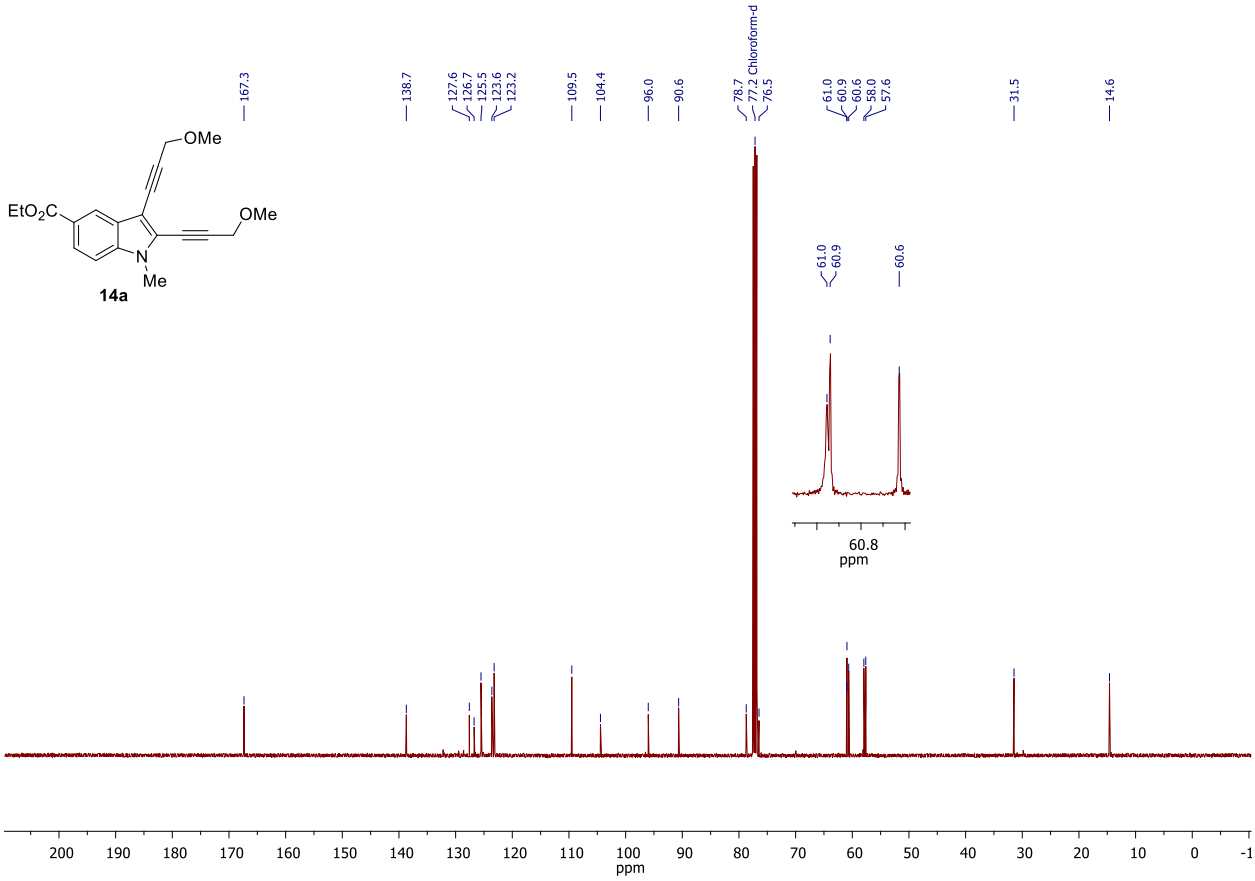
^{1}H NMR, $CDCl_3$, 400 MHz



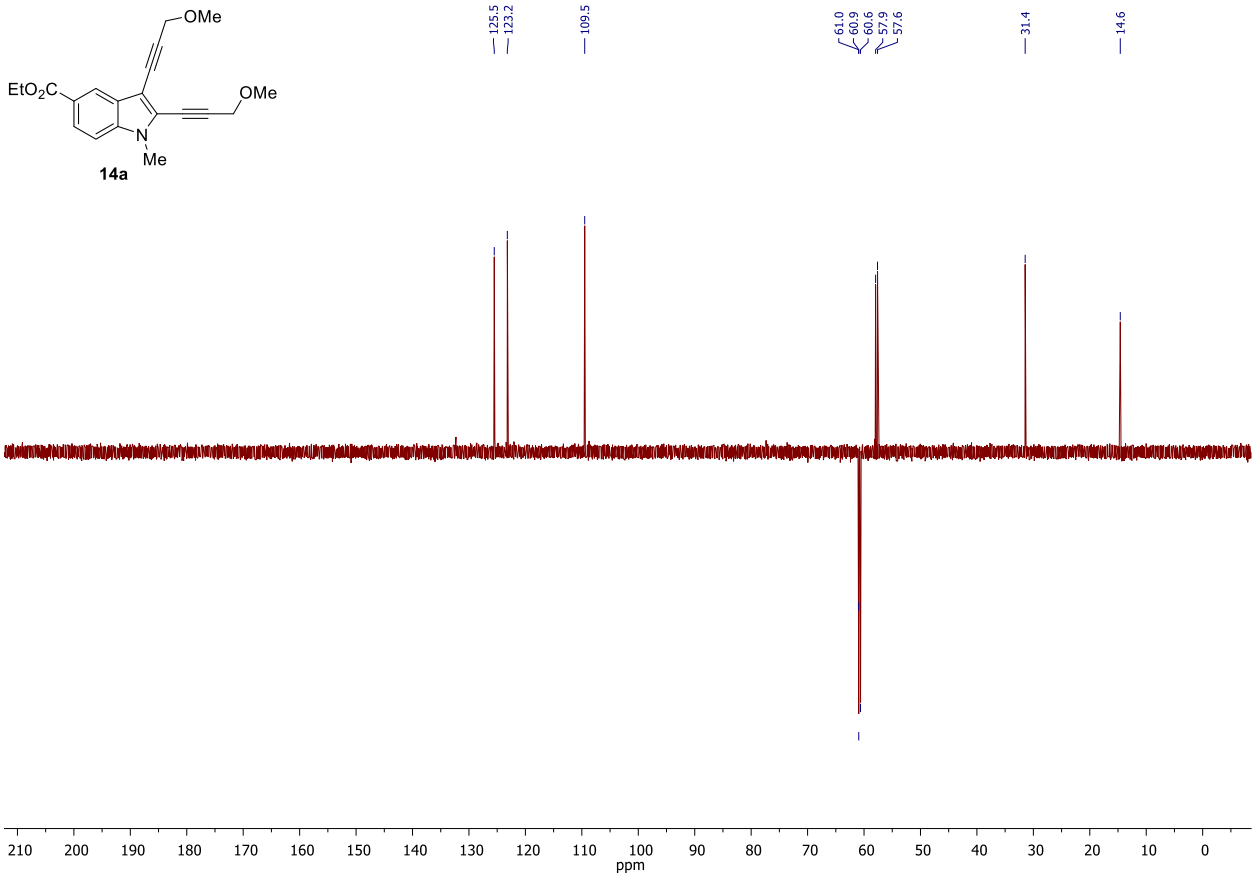
^{1}H NMR, $CDCl_3$, 400 MHz



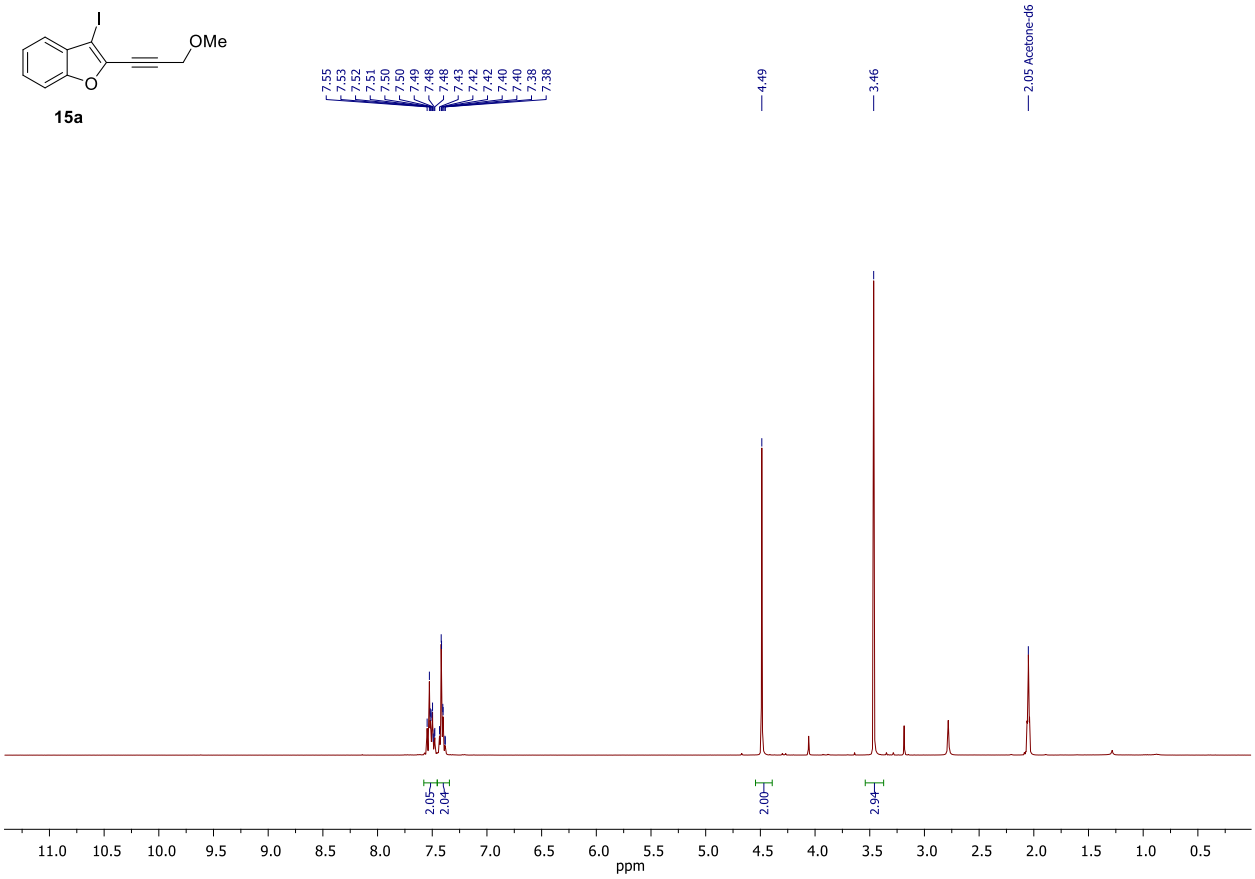
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



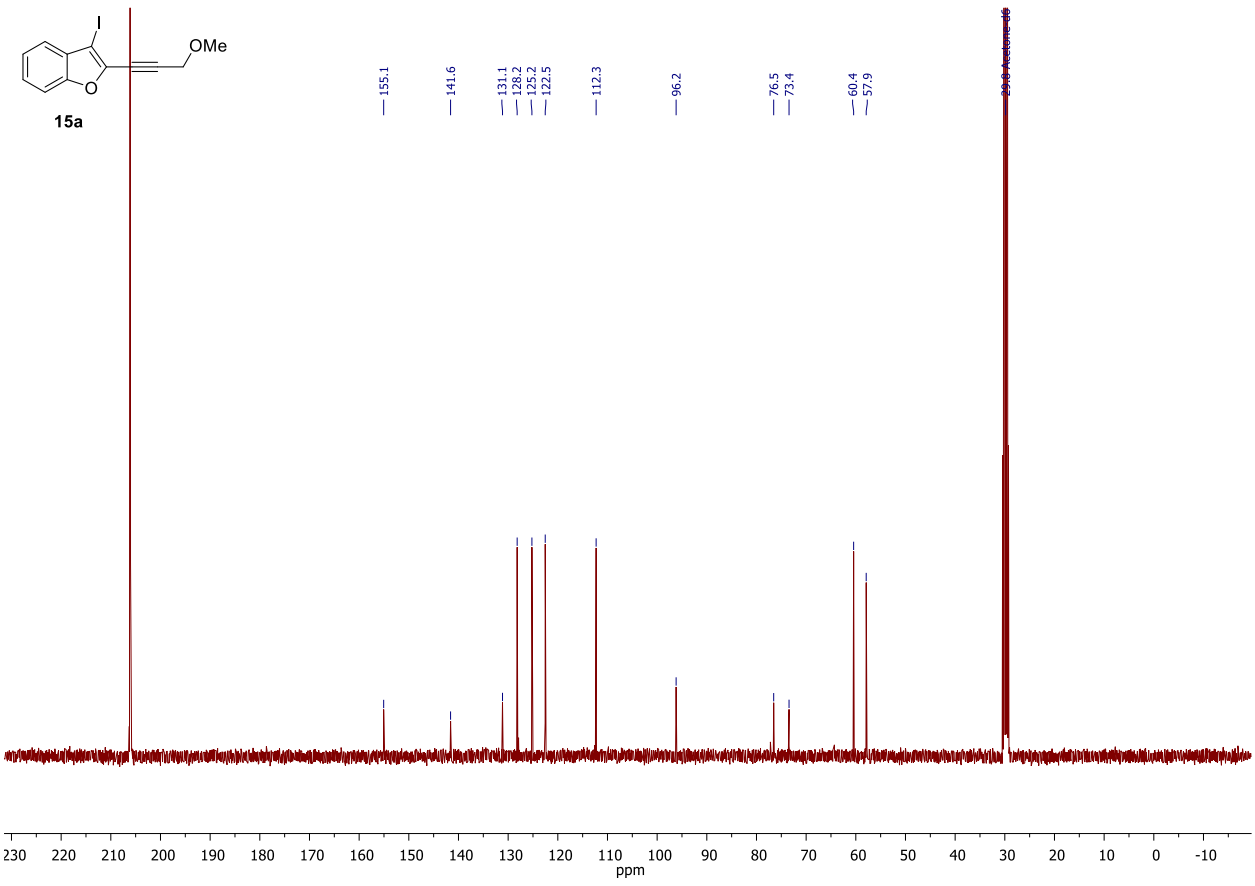
DEPT NMR, $CDCl_3$, 101 MHz



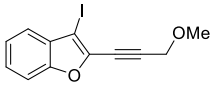
^{1}H NMR, acetone-d_6, 400 MHz



^{13}C{^{1}H} NMR, acetone-d_6, 101 MHz

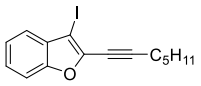


DEPT NMR, acetone-d_6, 101 MHz



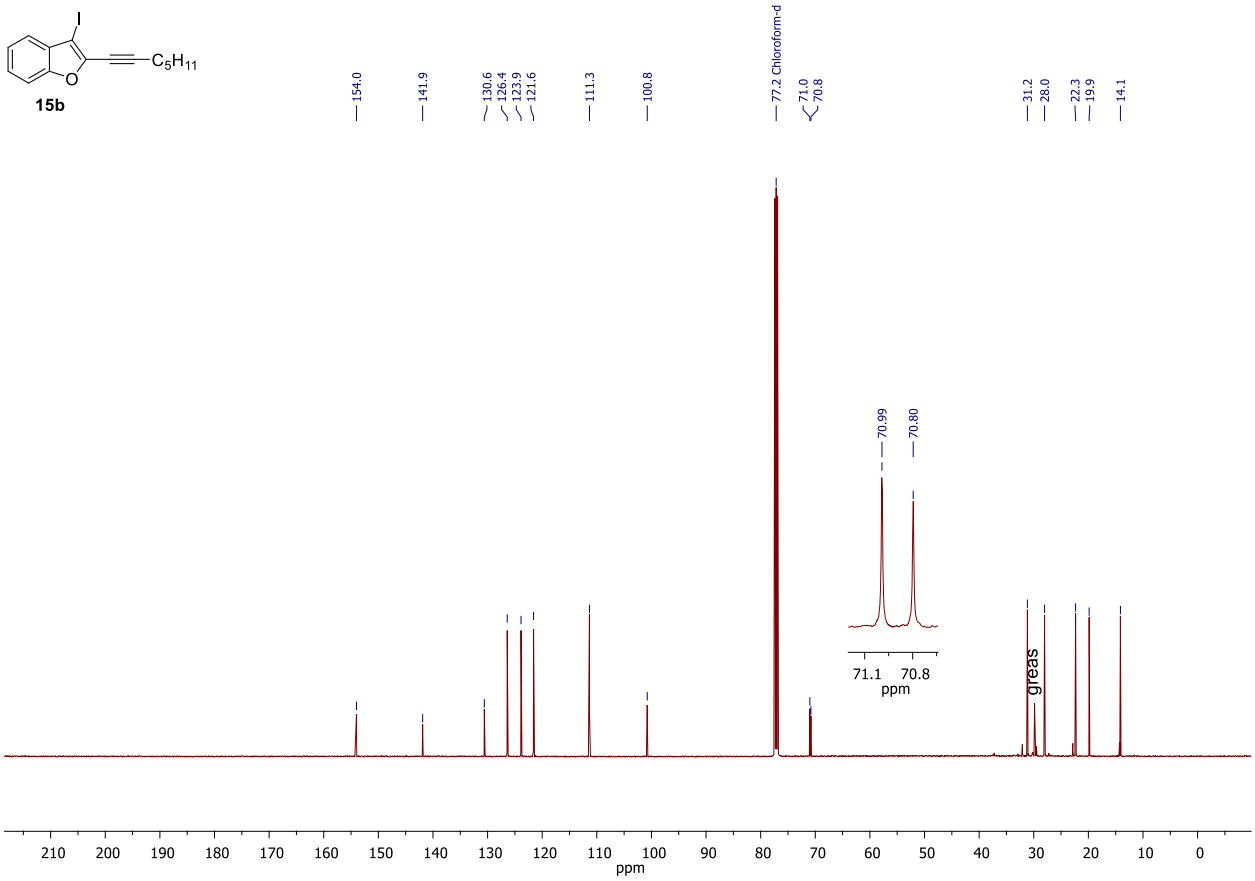
15a

^{1}H NMR, $CDCl_3$, 400 MHz

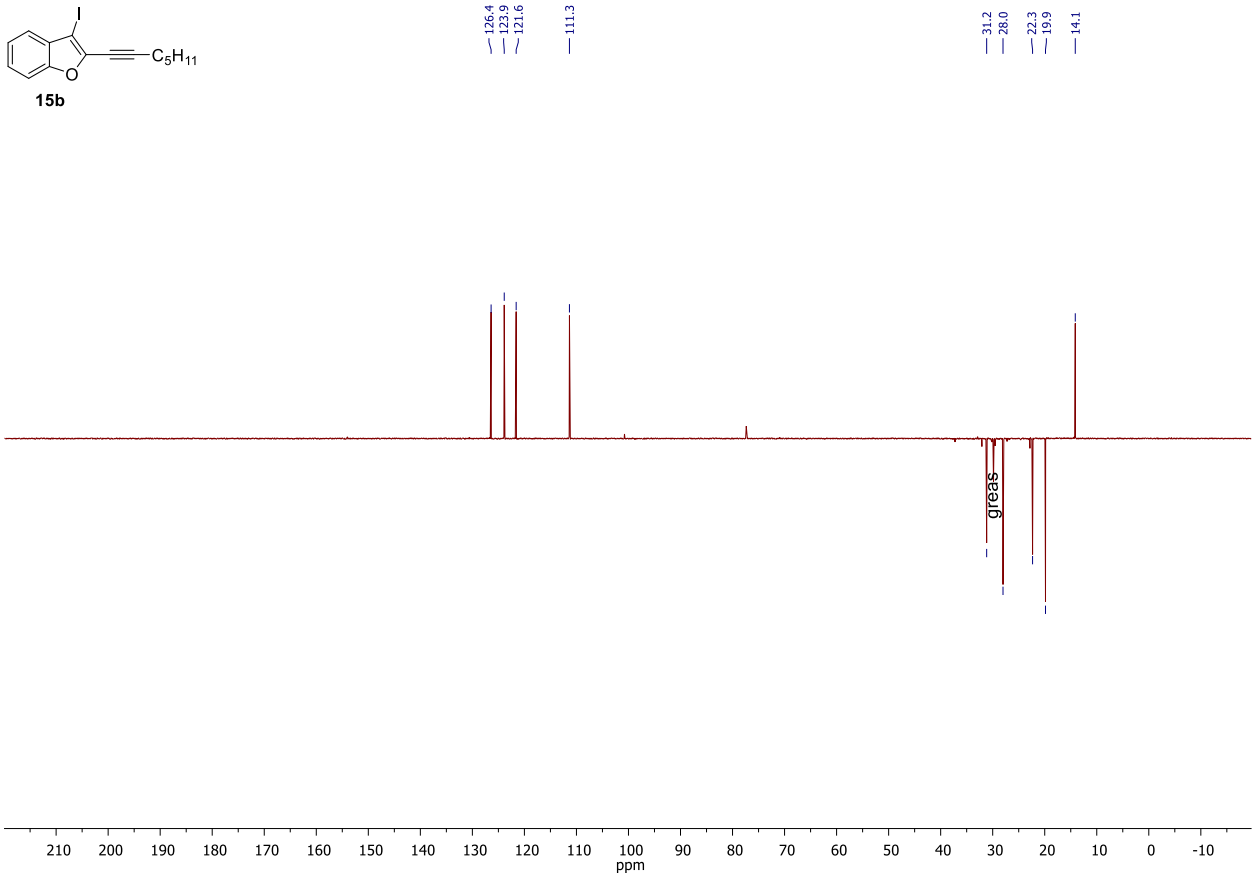


15b

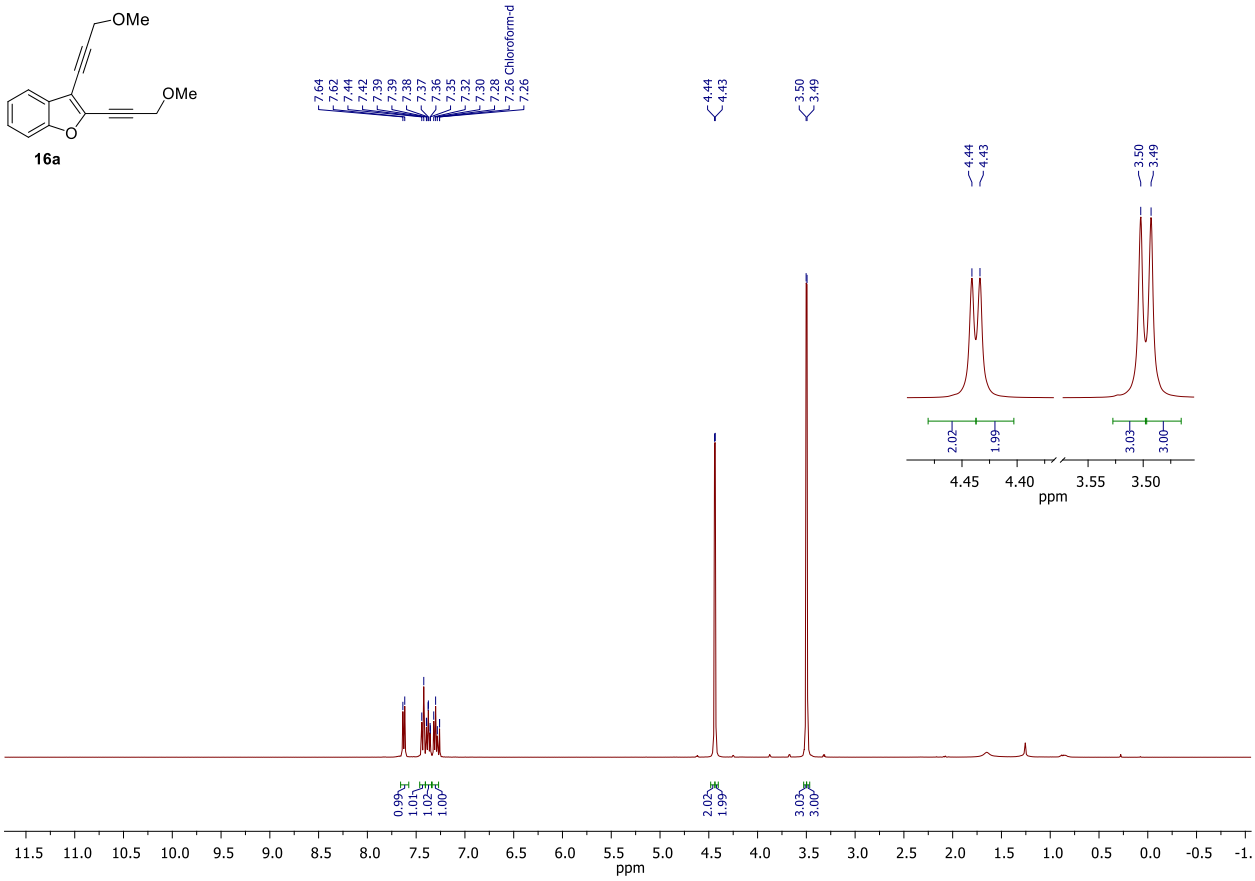
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



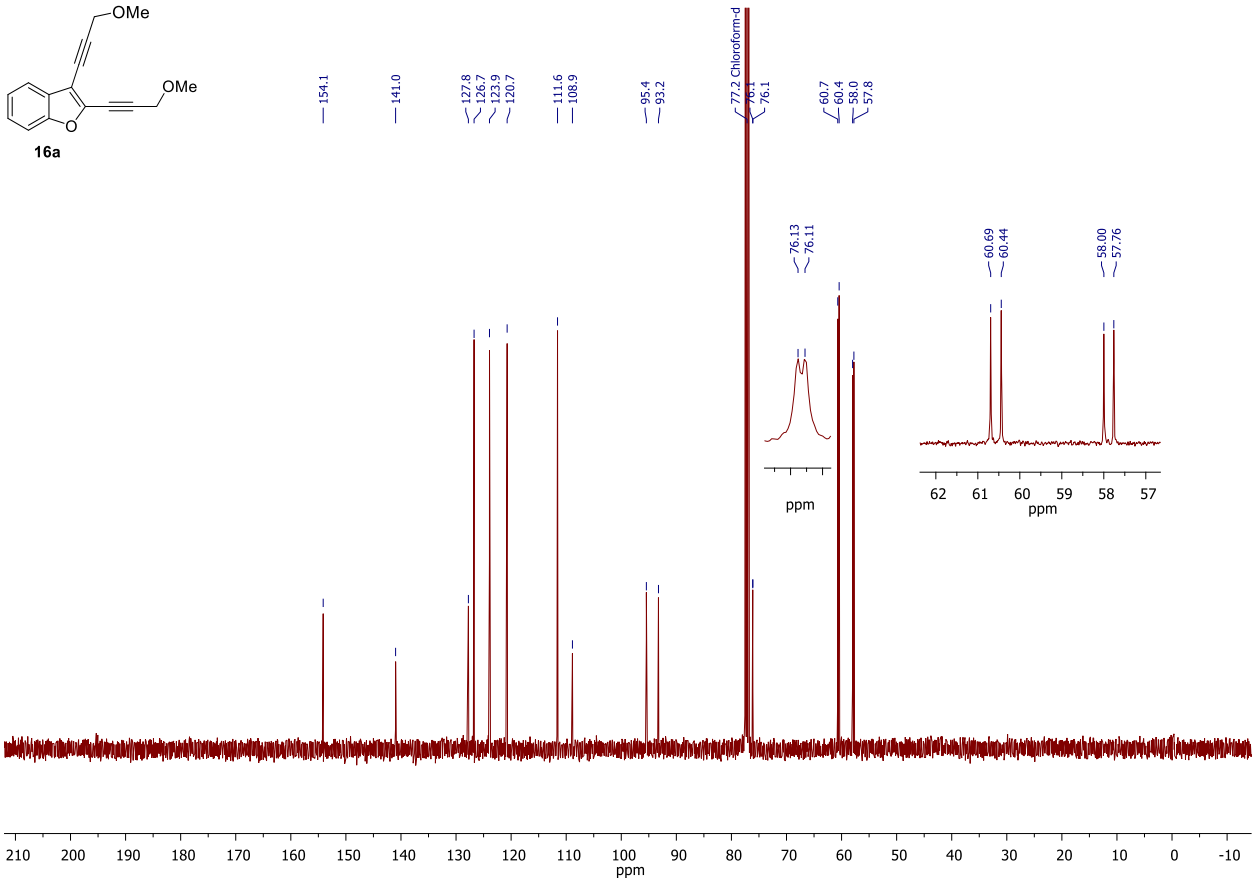
DEPT NMR, $CDCl_3$, 101 MHz



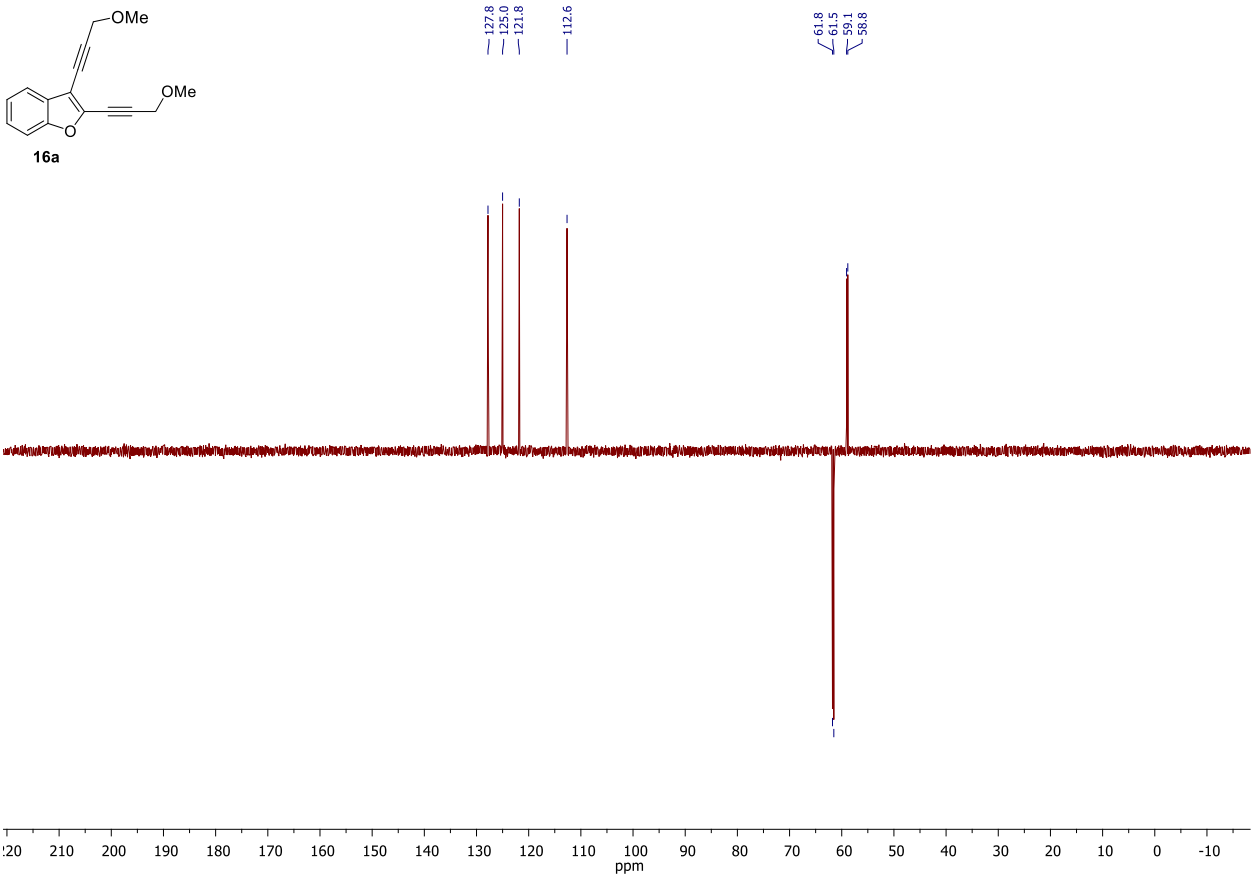
^{1}H NMR, $CDCl_3$, 400 MHz



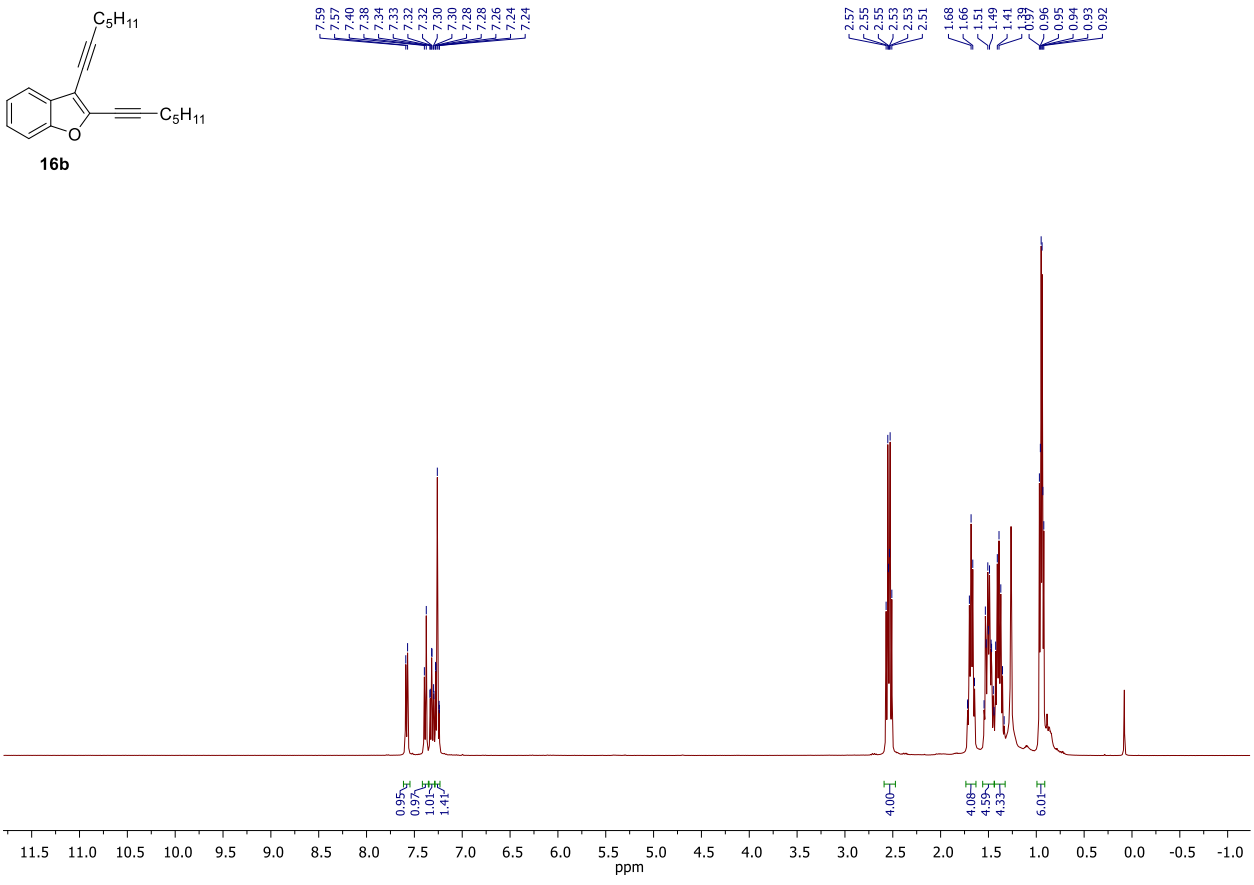
^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



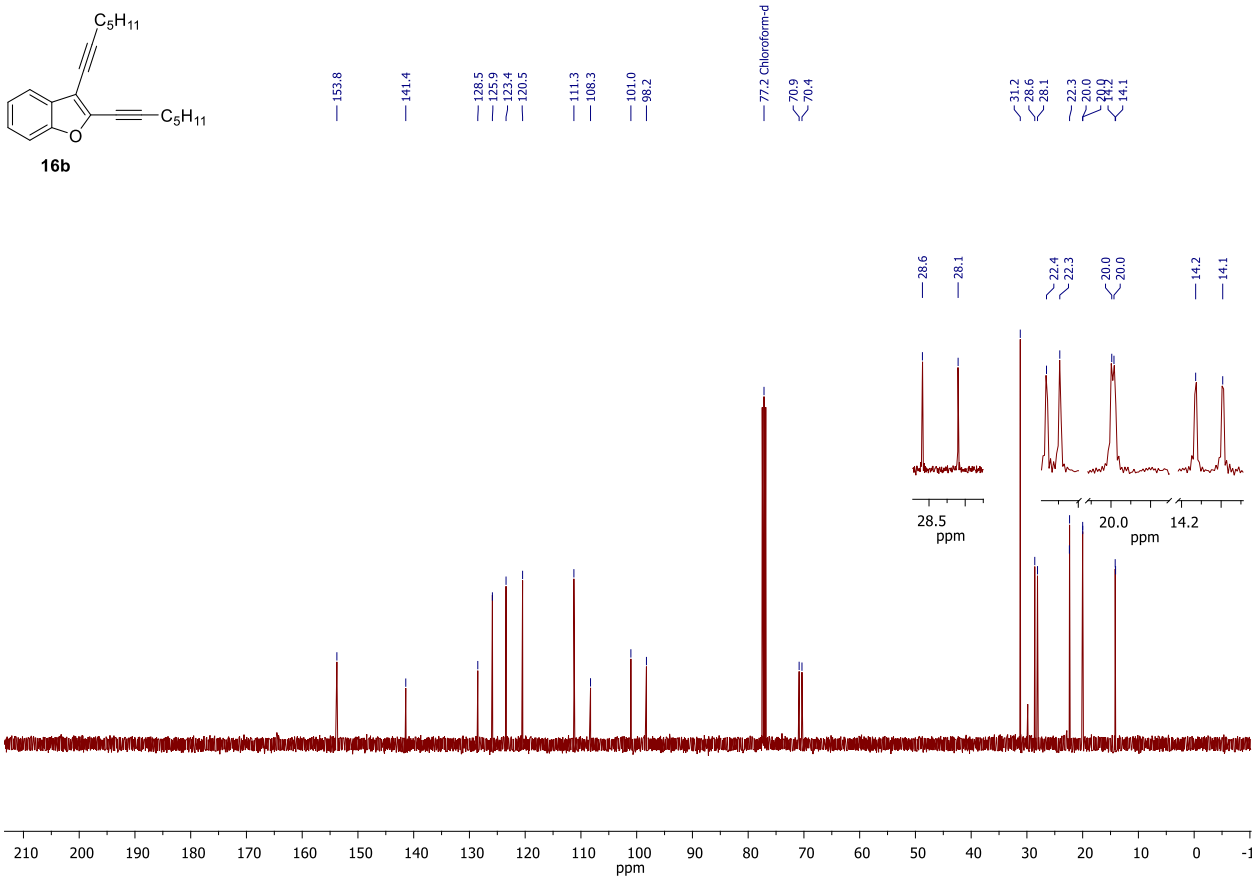
DEPT NMR, $CDCl_3$, 101 MHz



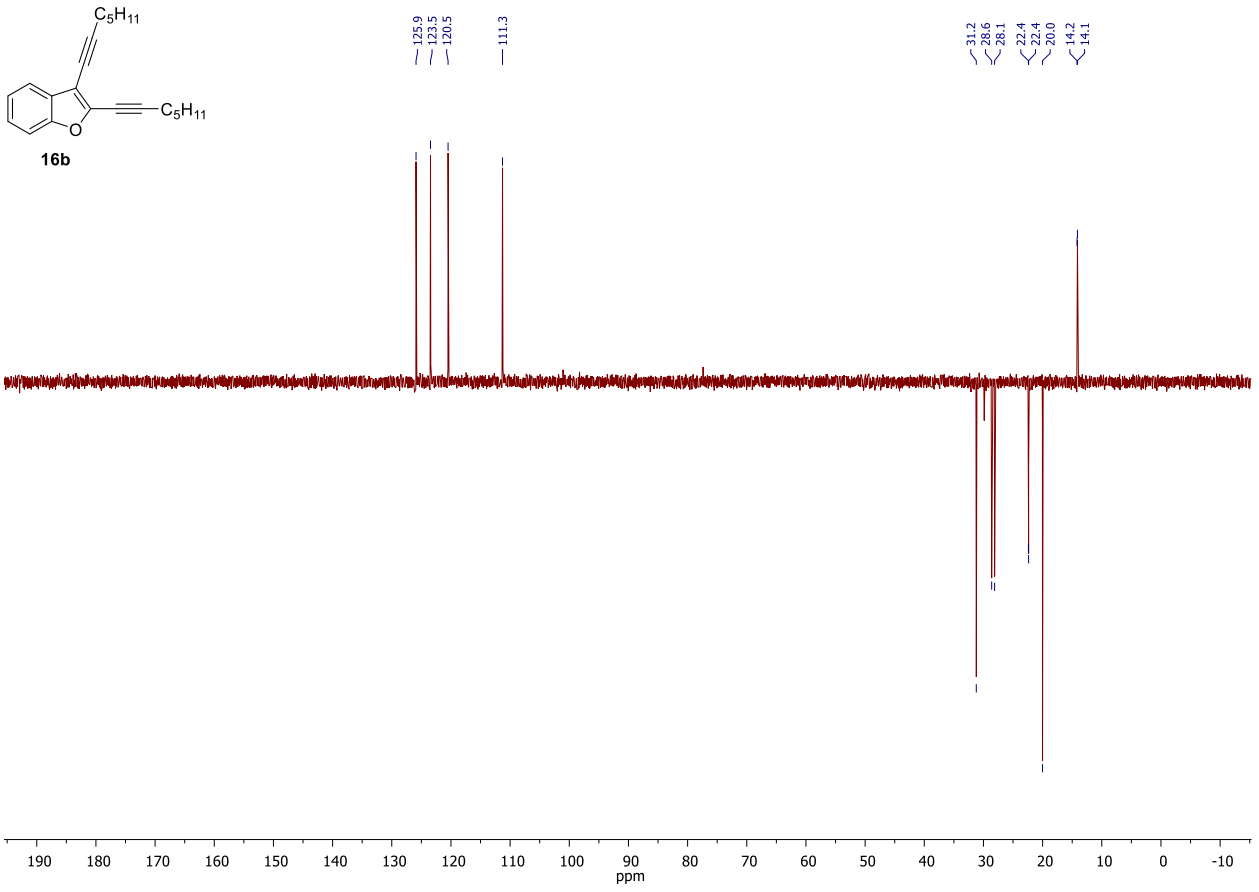
^1H NMR, $CDCl_3$, 400 MHz



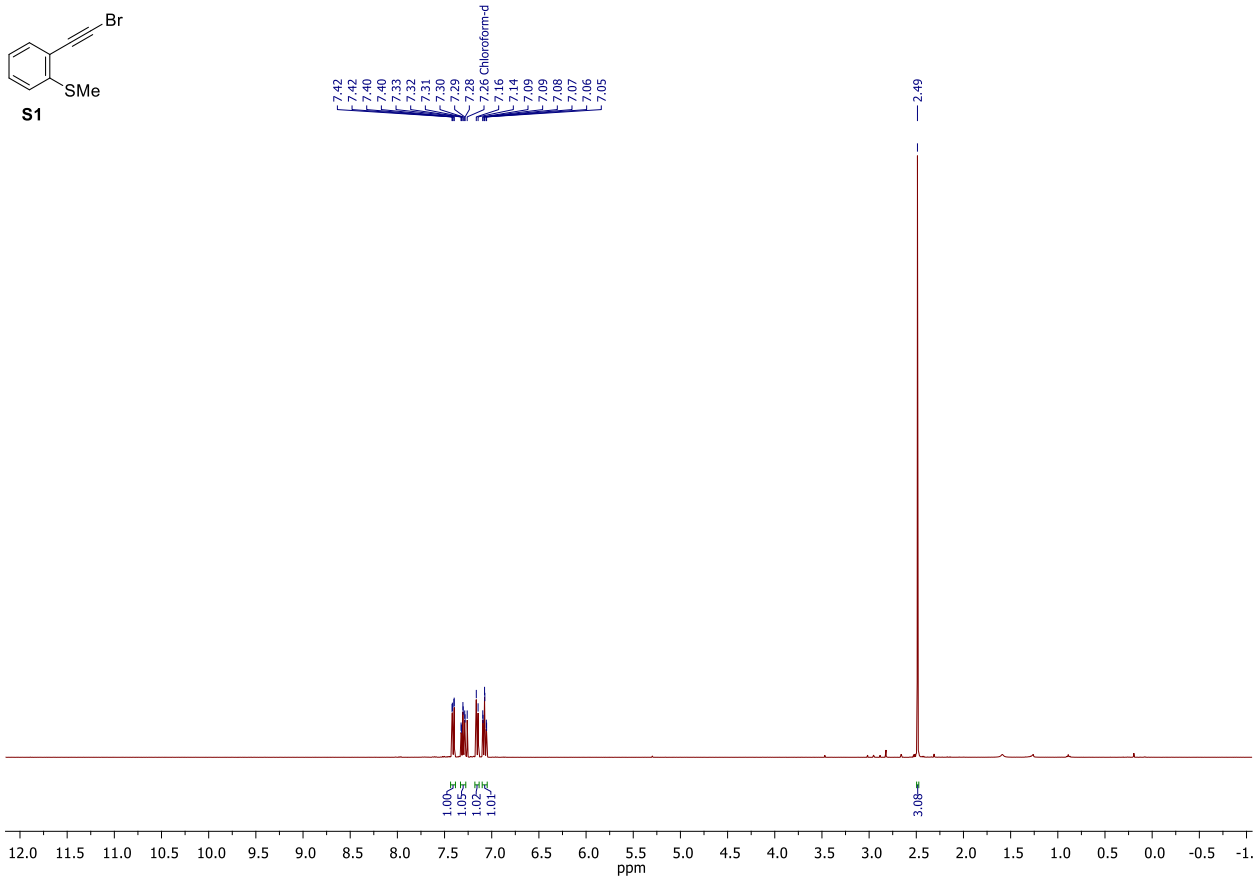
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



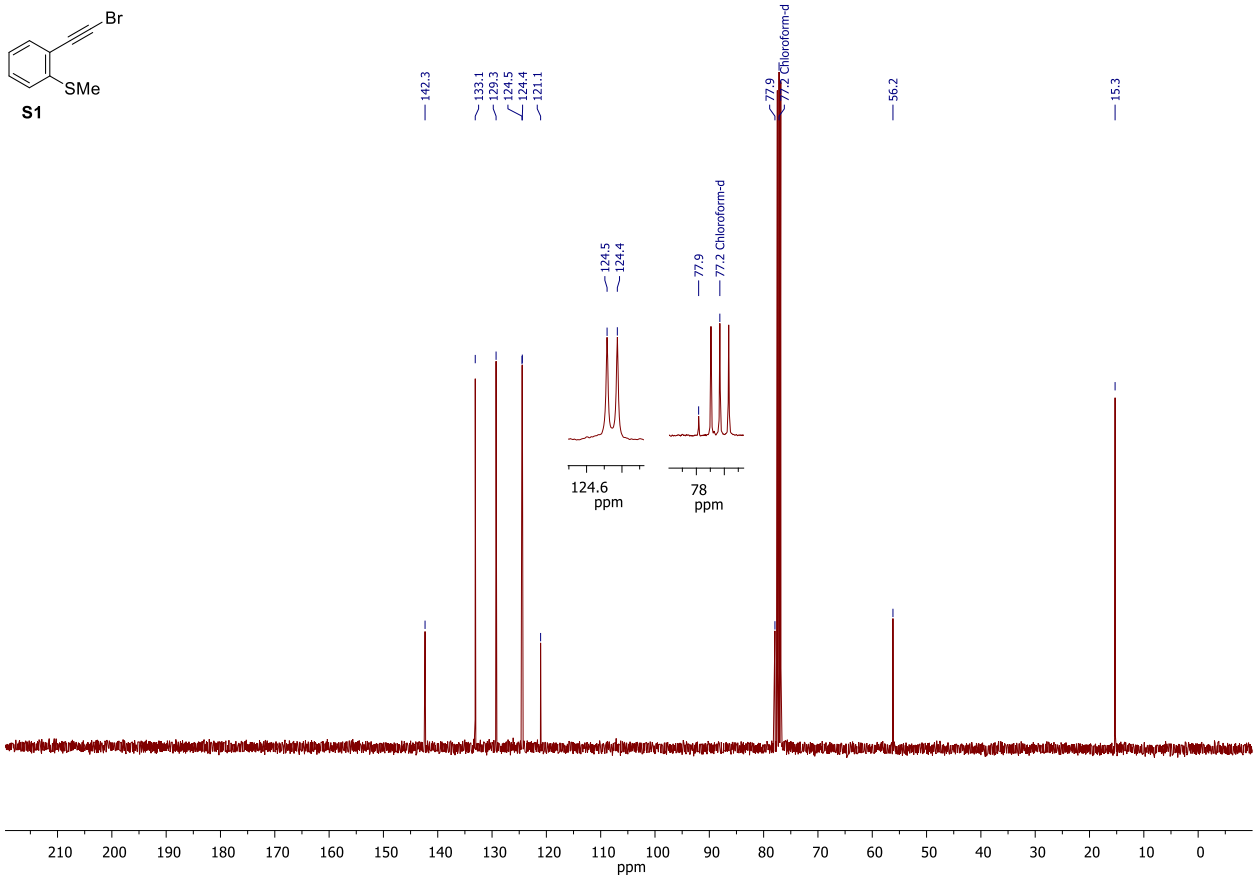
DEPT NMR, $CDCl_3$, 101 MHz



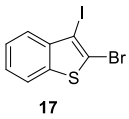
^{1}H NMR, $CDCl_3$, 400 MHz



^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



^{1}H NMR, $CDCl_3$, 400 MHz



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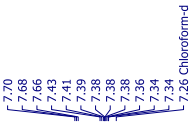
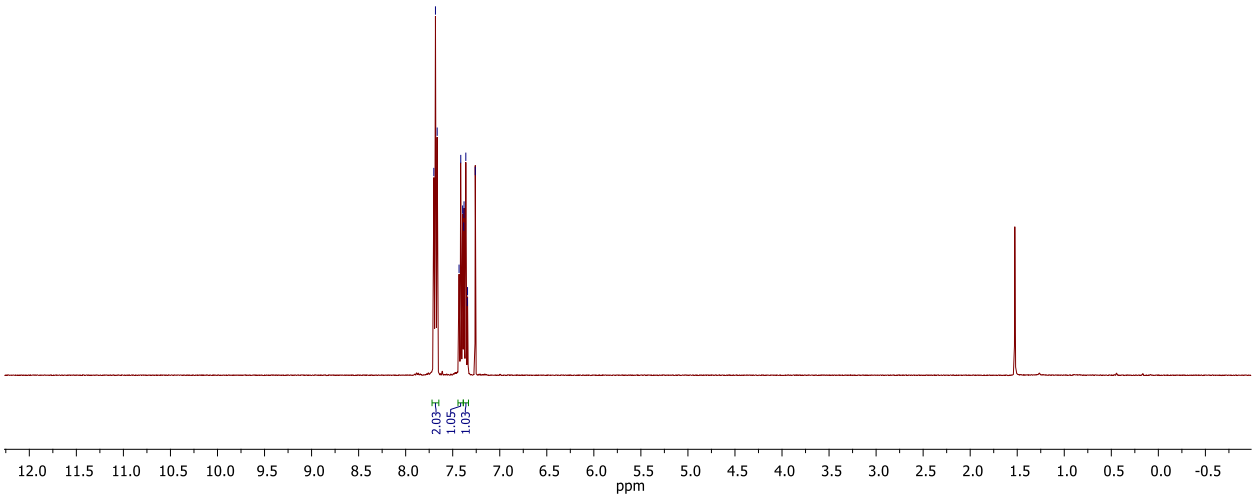
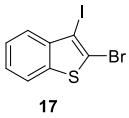




^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



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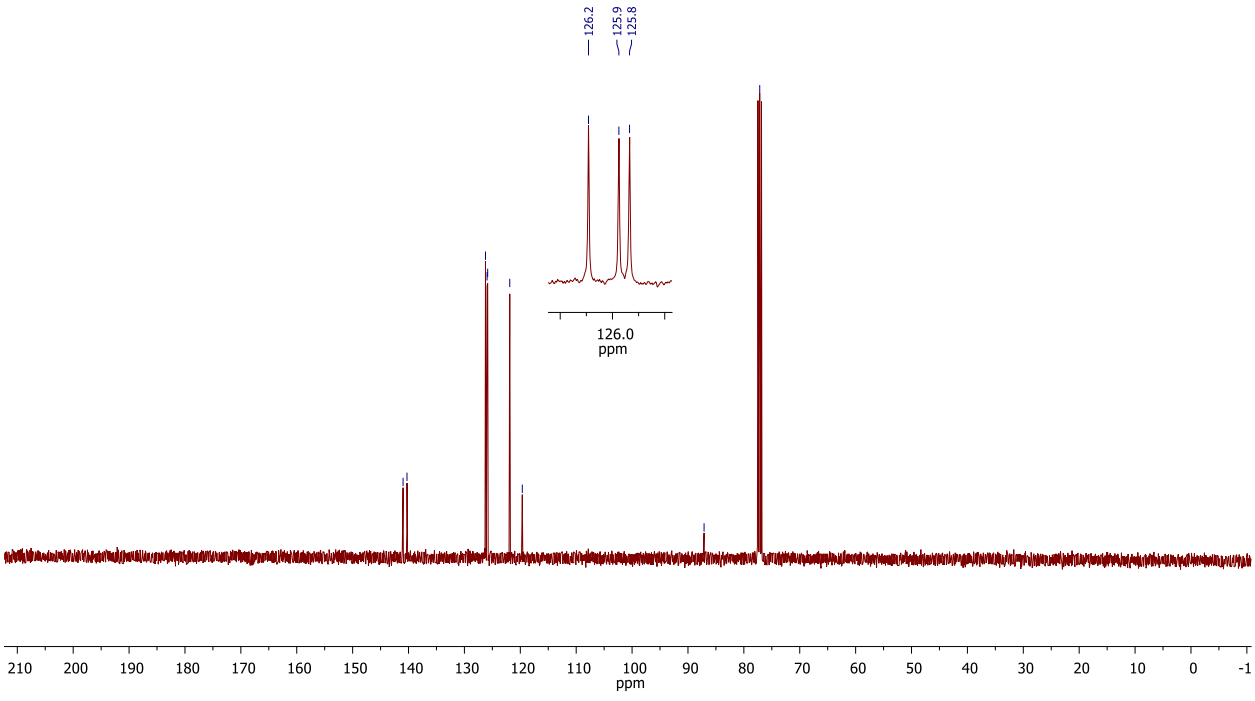
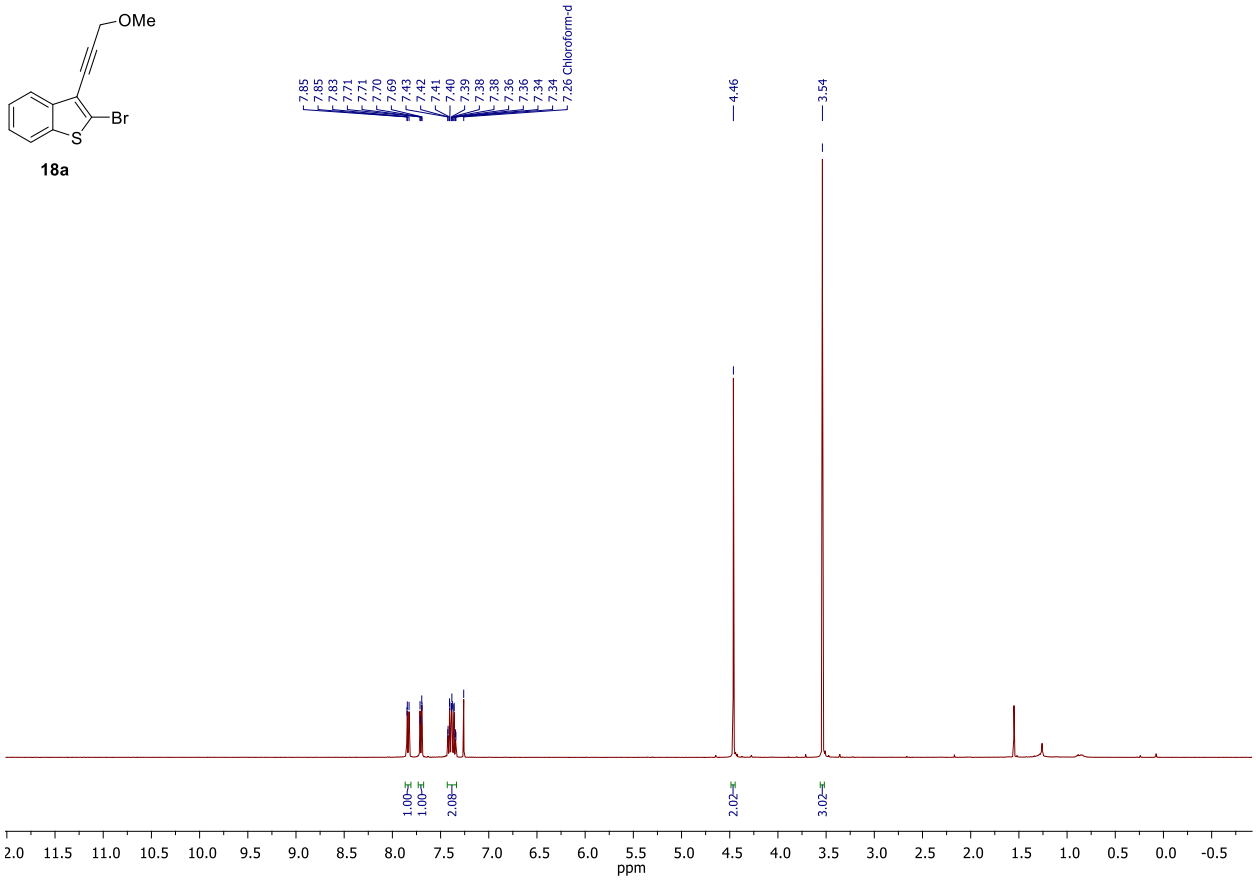
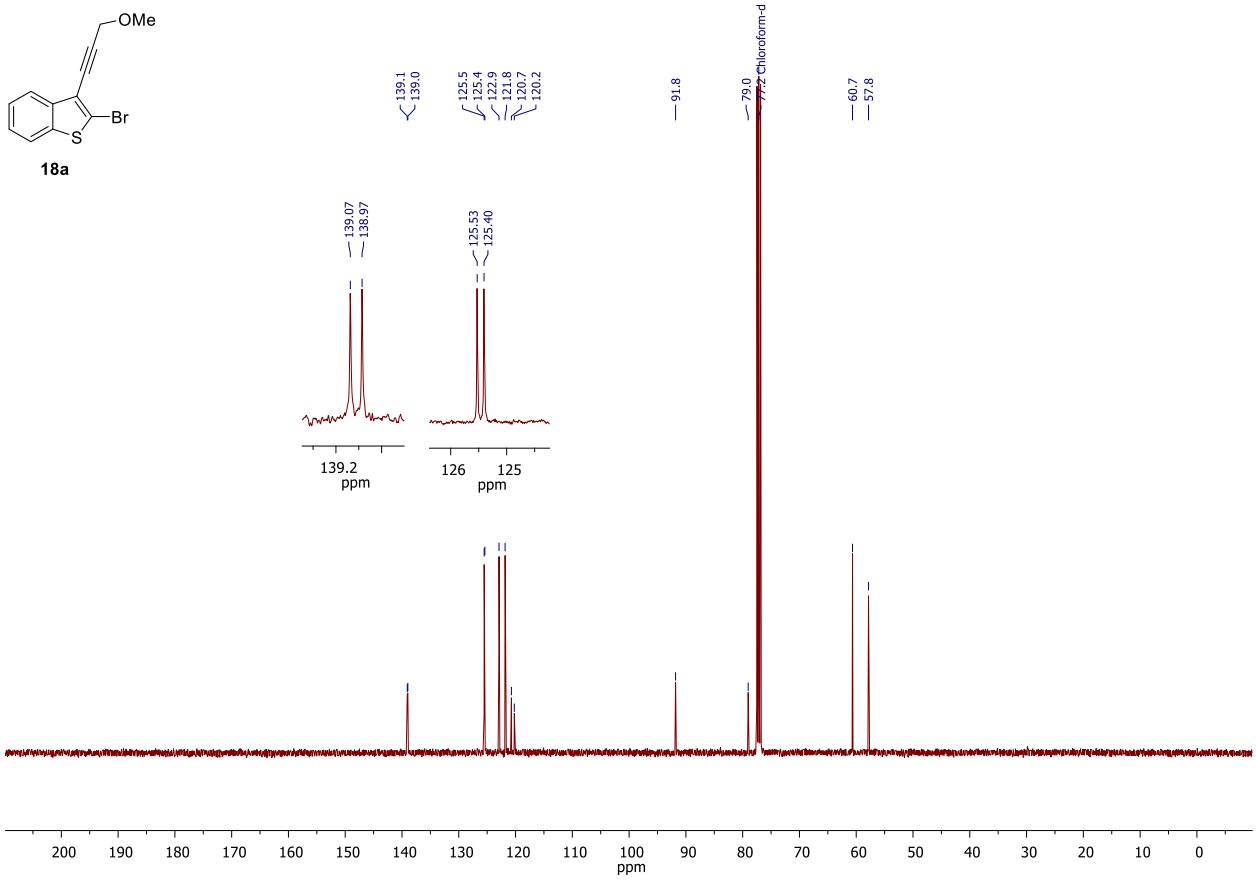


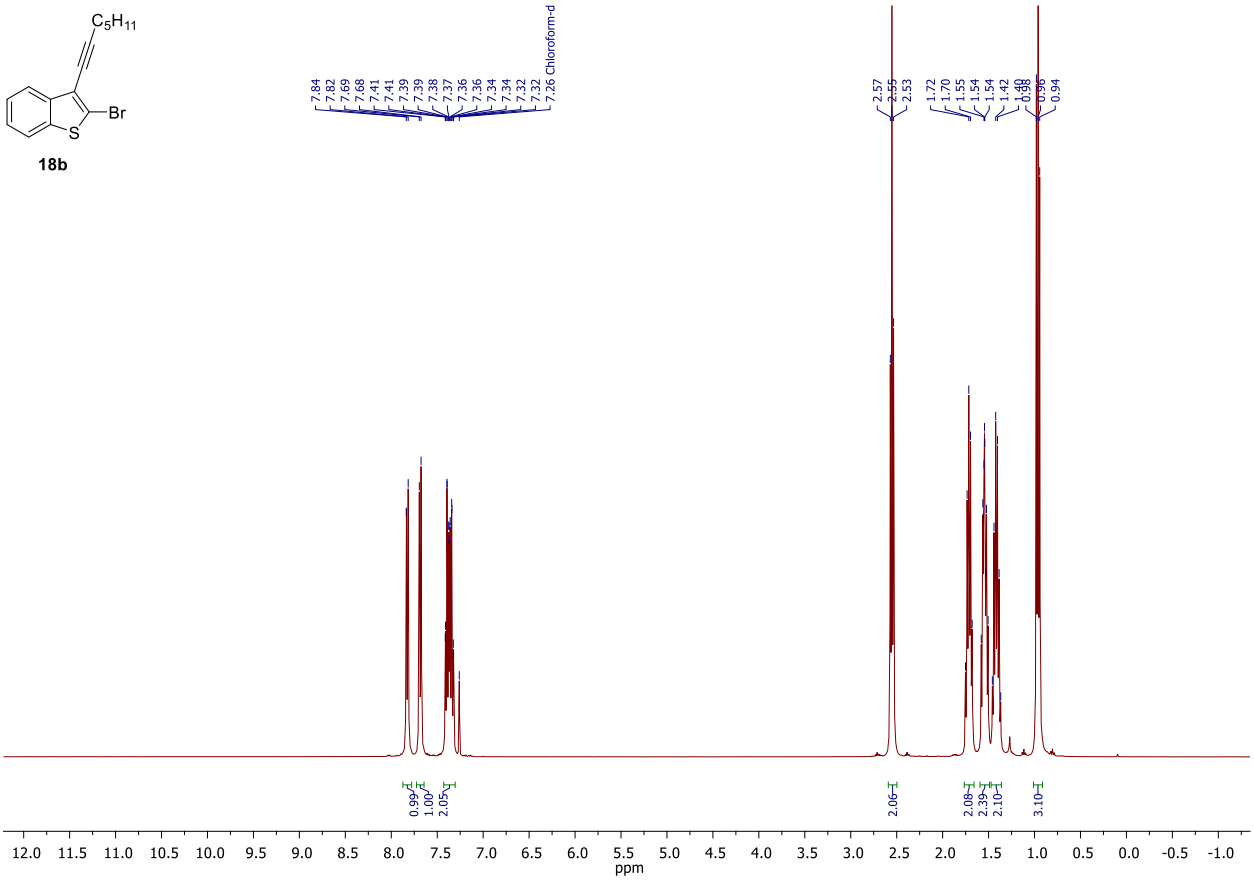
^{1}H NMR, $CDCl_3$, 400 MHz



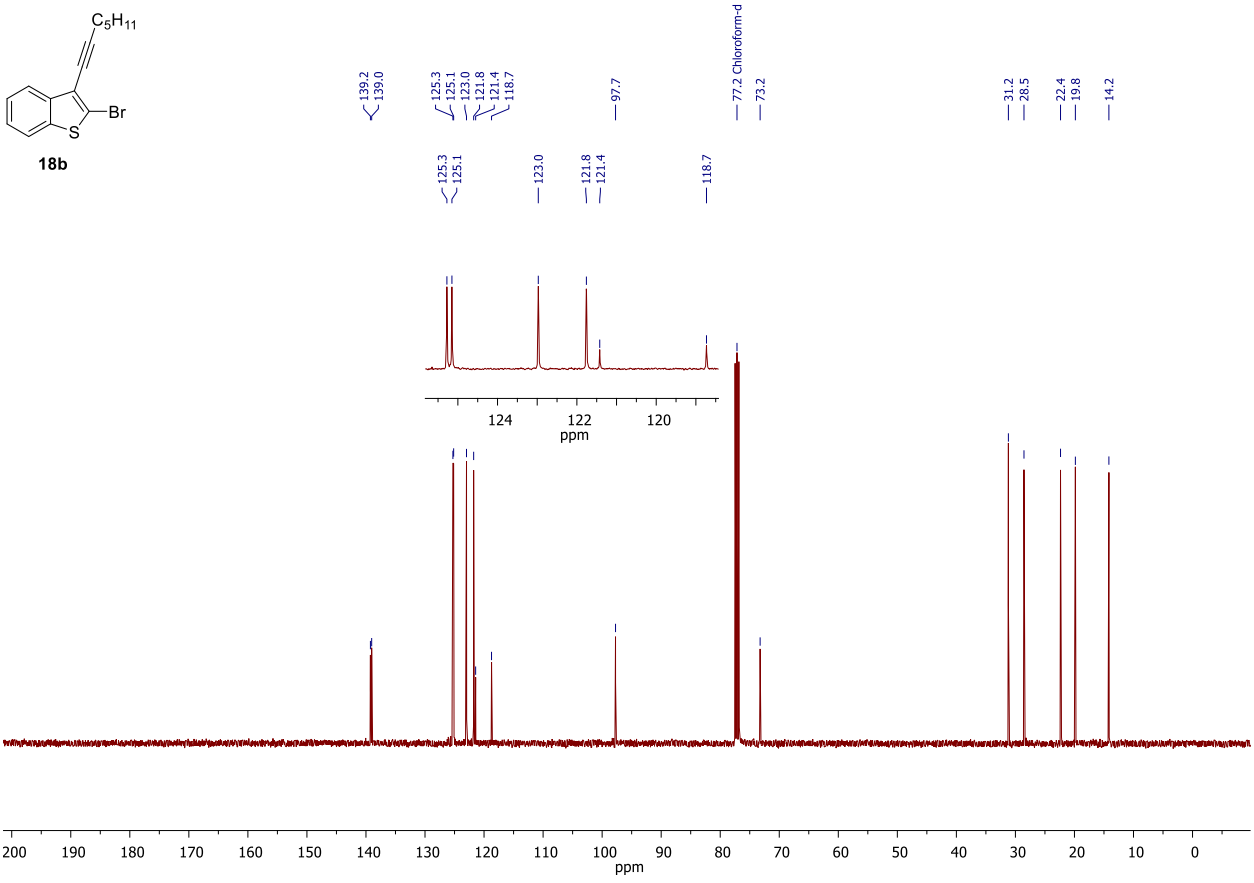
^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



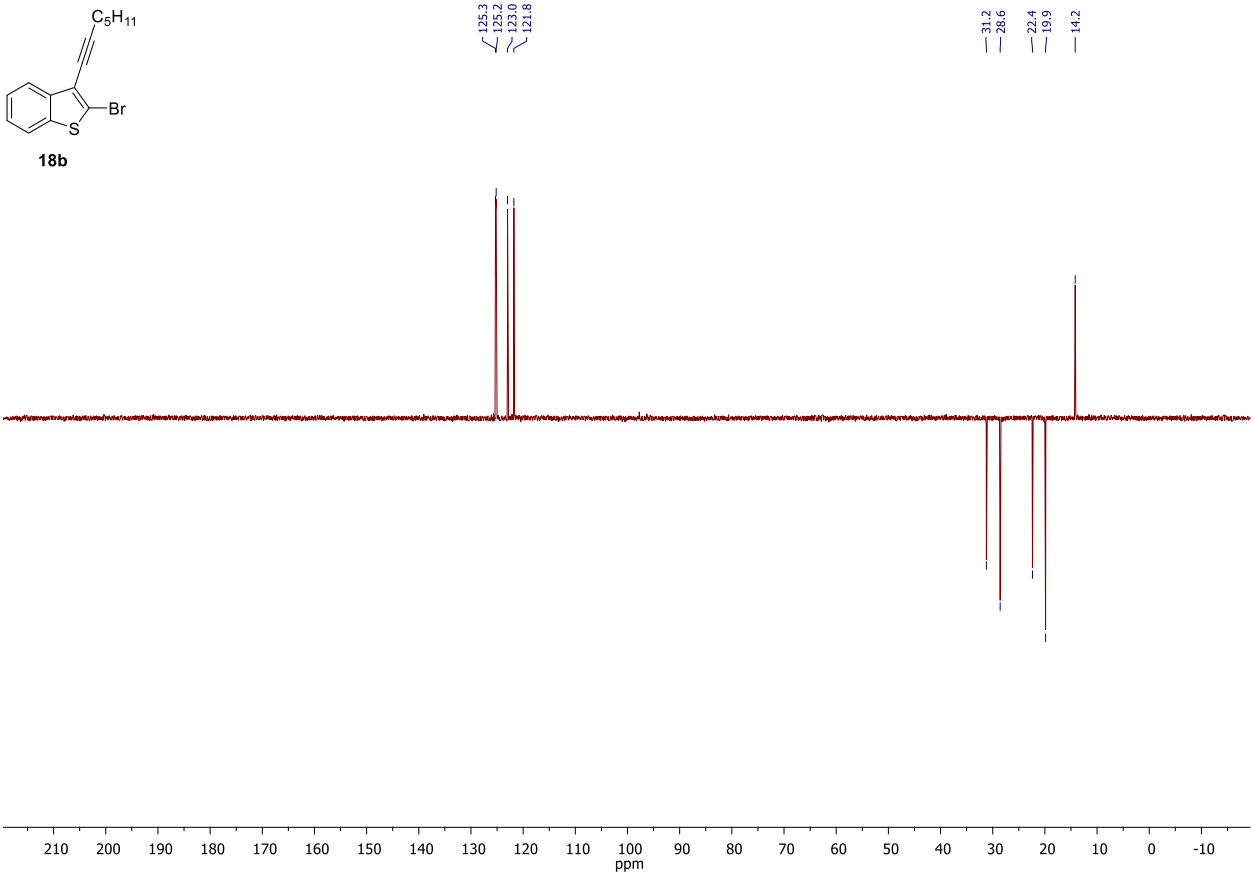
^{1}H NMR, $CDCl_3$, 400 MHz



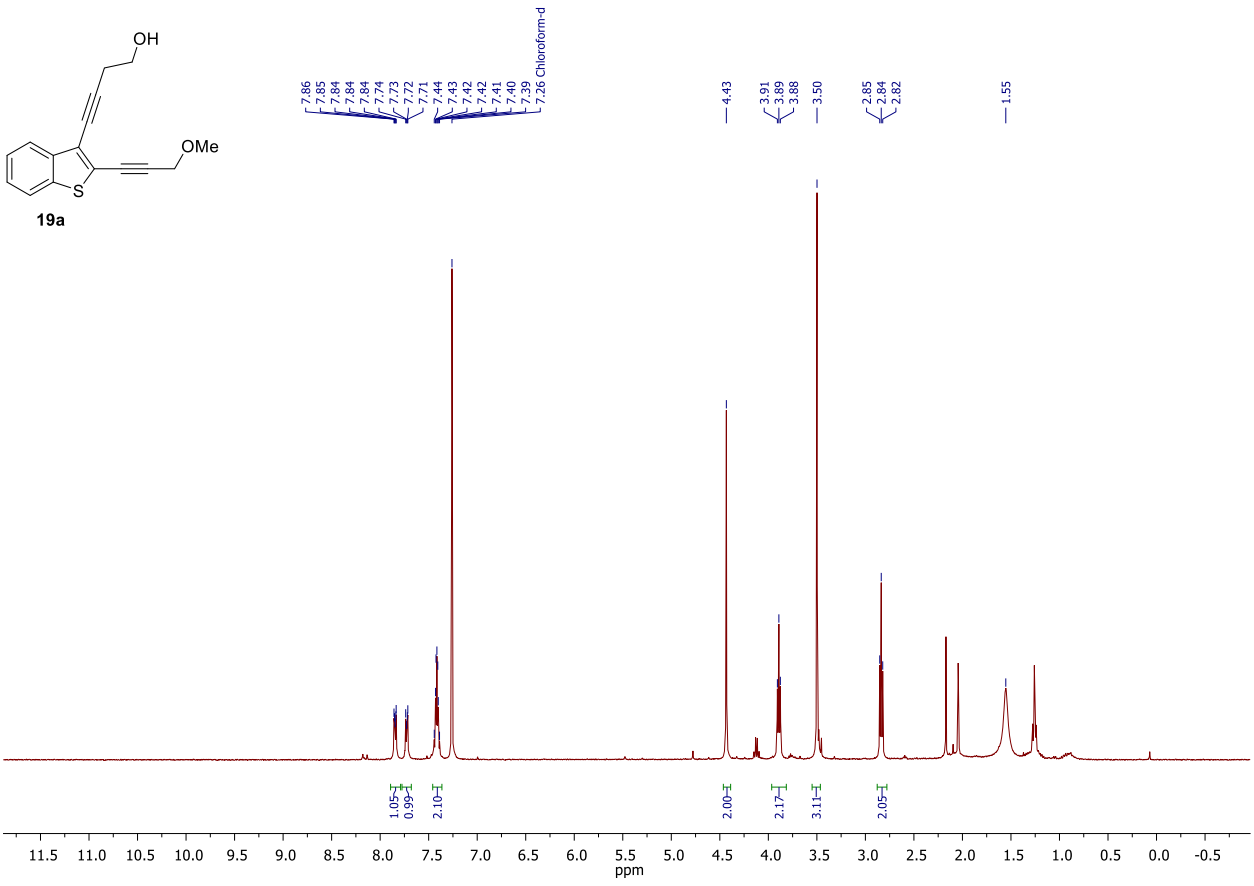
^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



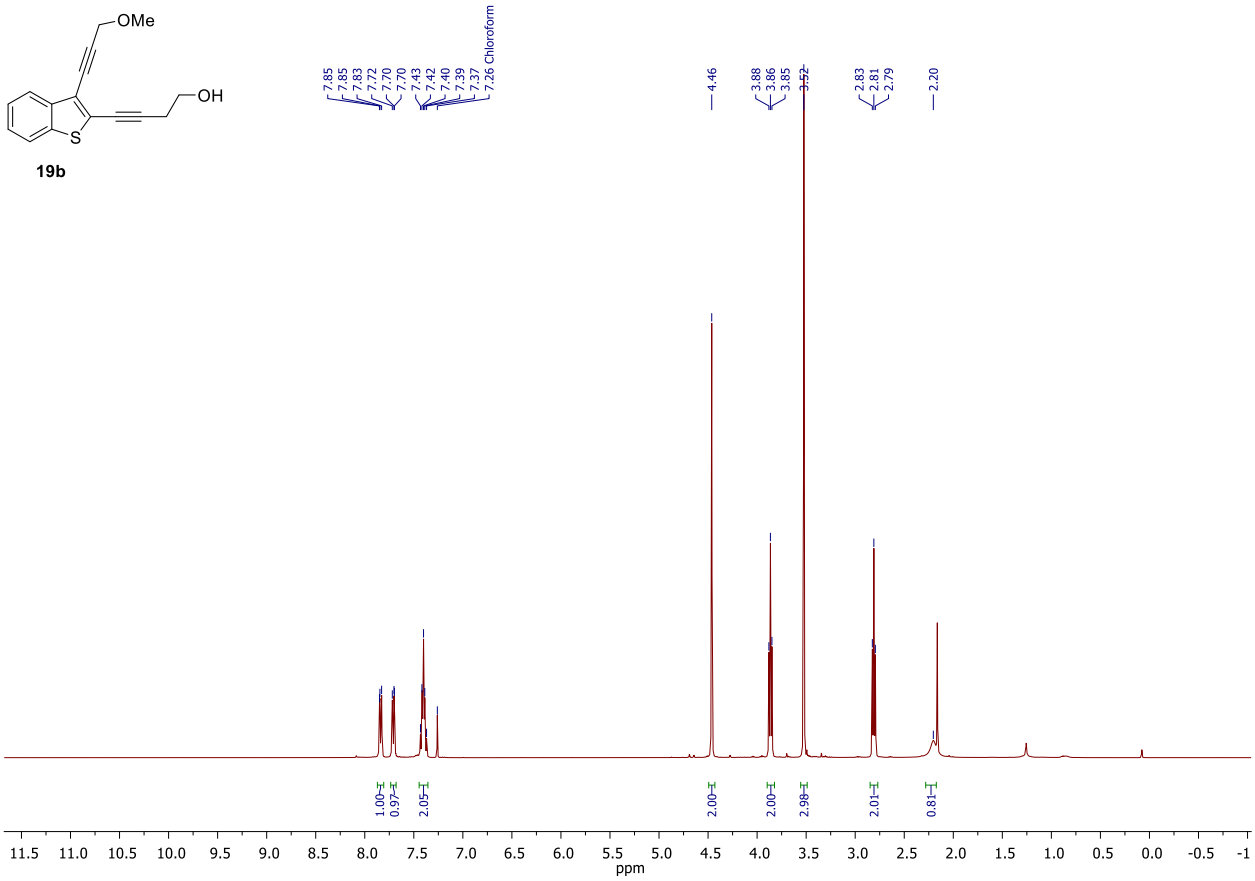
DEPT NMR, $CDCl_3$, 101 MHz



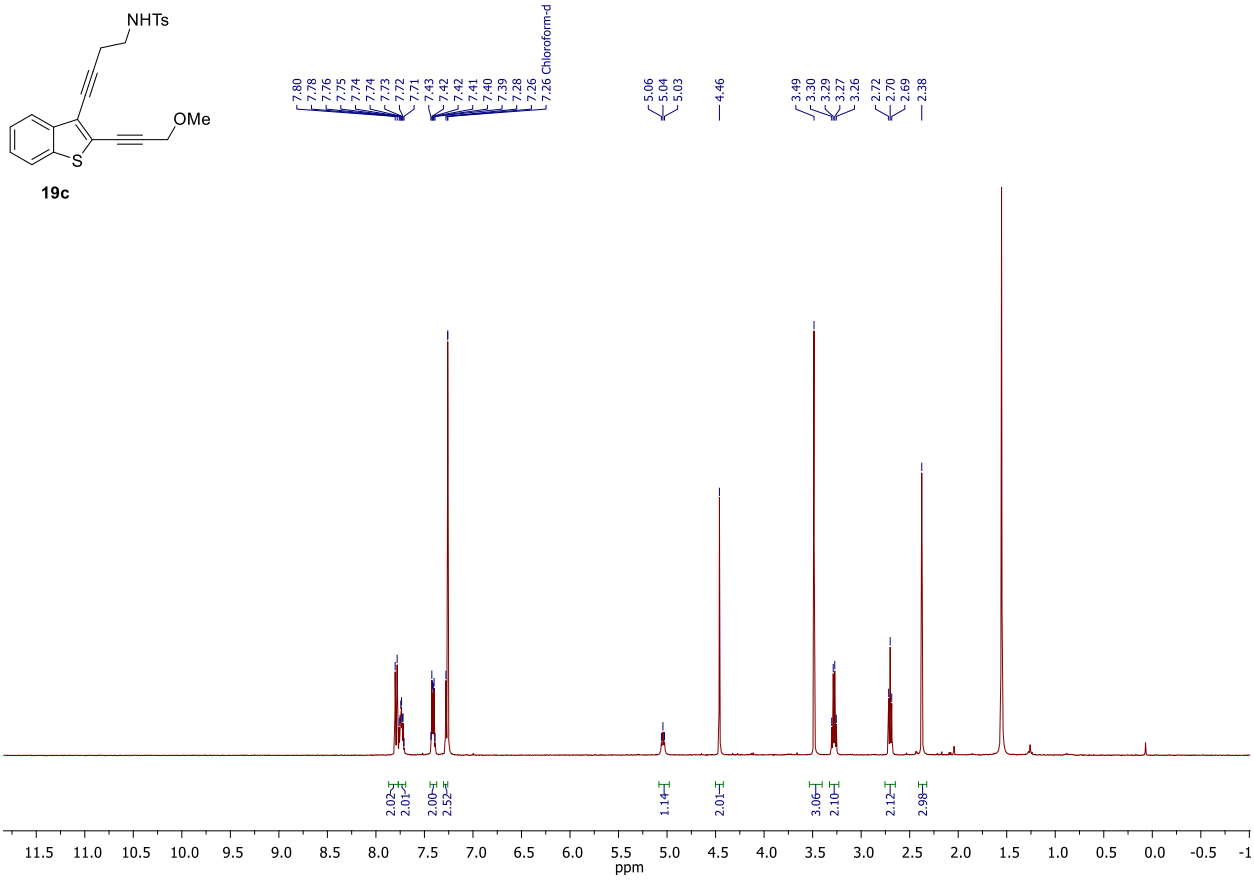
^1H NMR, $CDCl_3$, 400 MHz



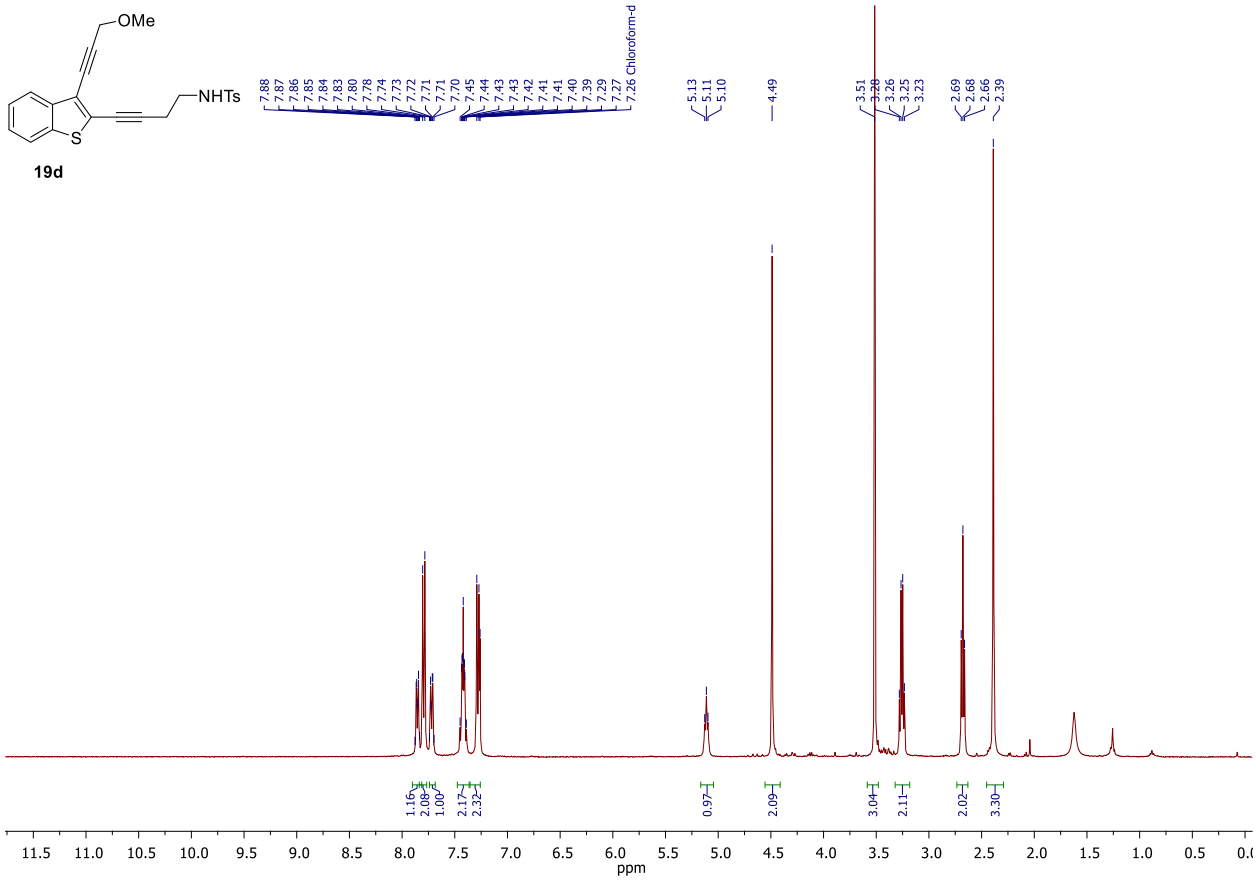
^{1}H NMR, $CDCl_3$, 400 MHz



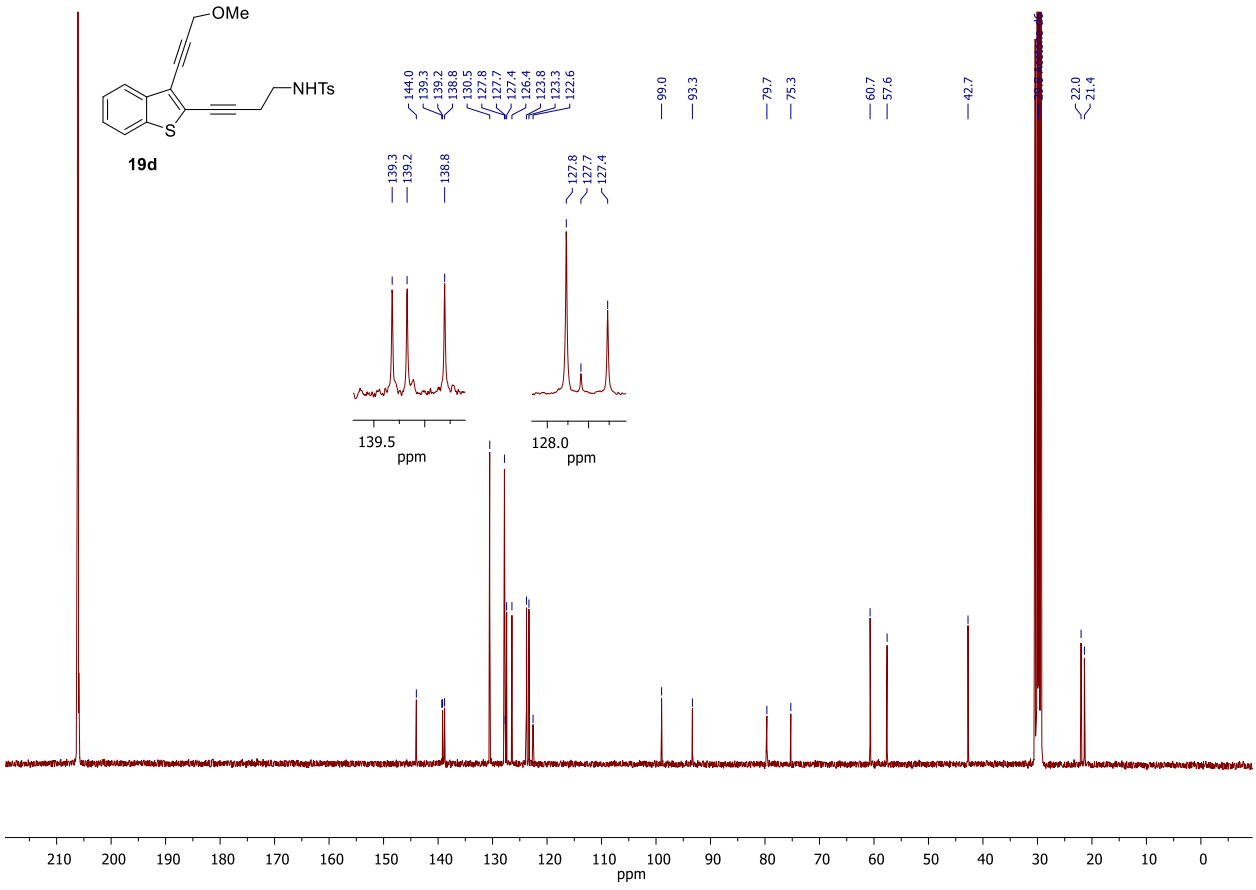
^{1}H NMR, $CDCl_3$, 400 MHz



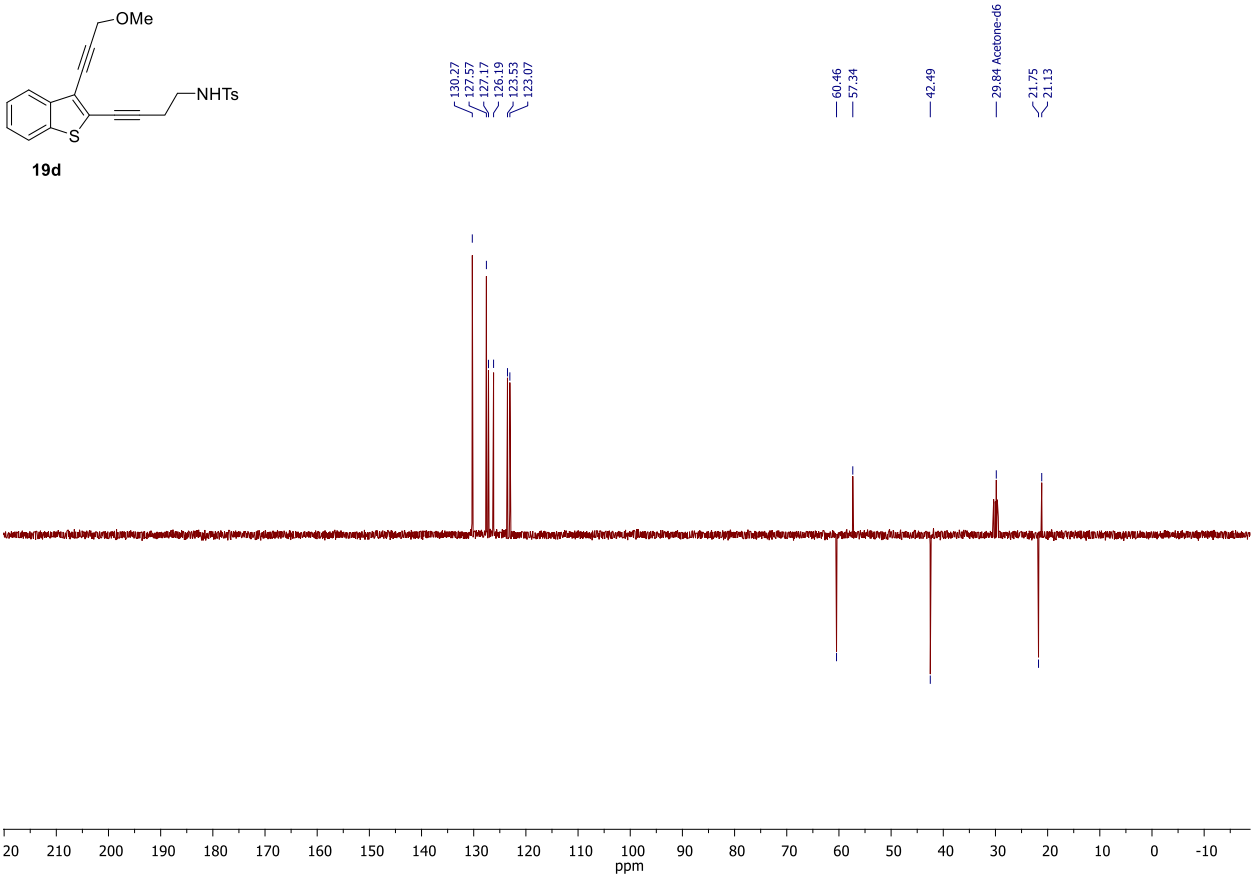
^{1}H NMR, $CDCl_3$, 400 MHz



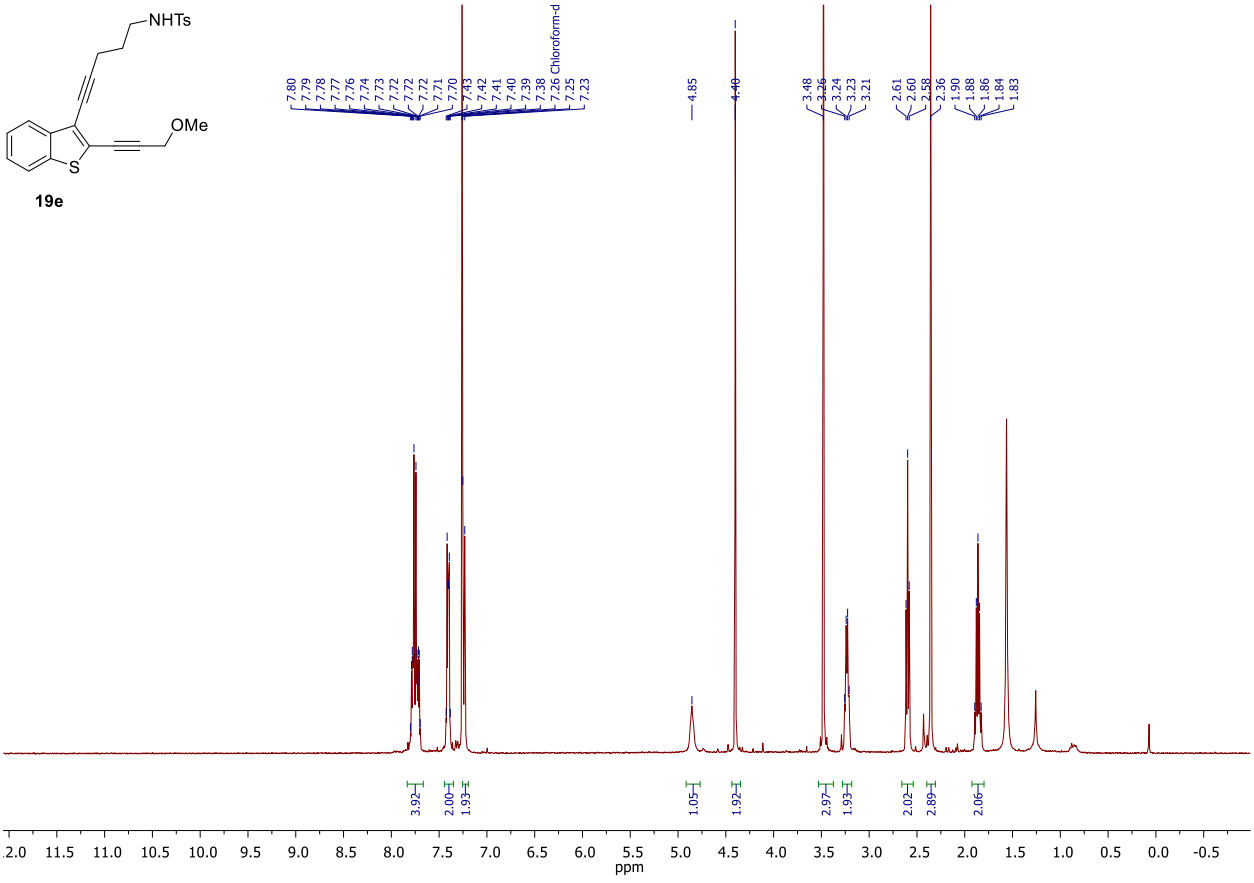
^{13}C{^{1}H} NMR, acetone-d_6, 101 MHz



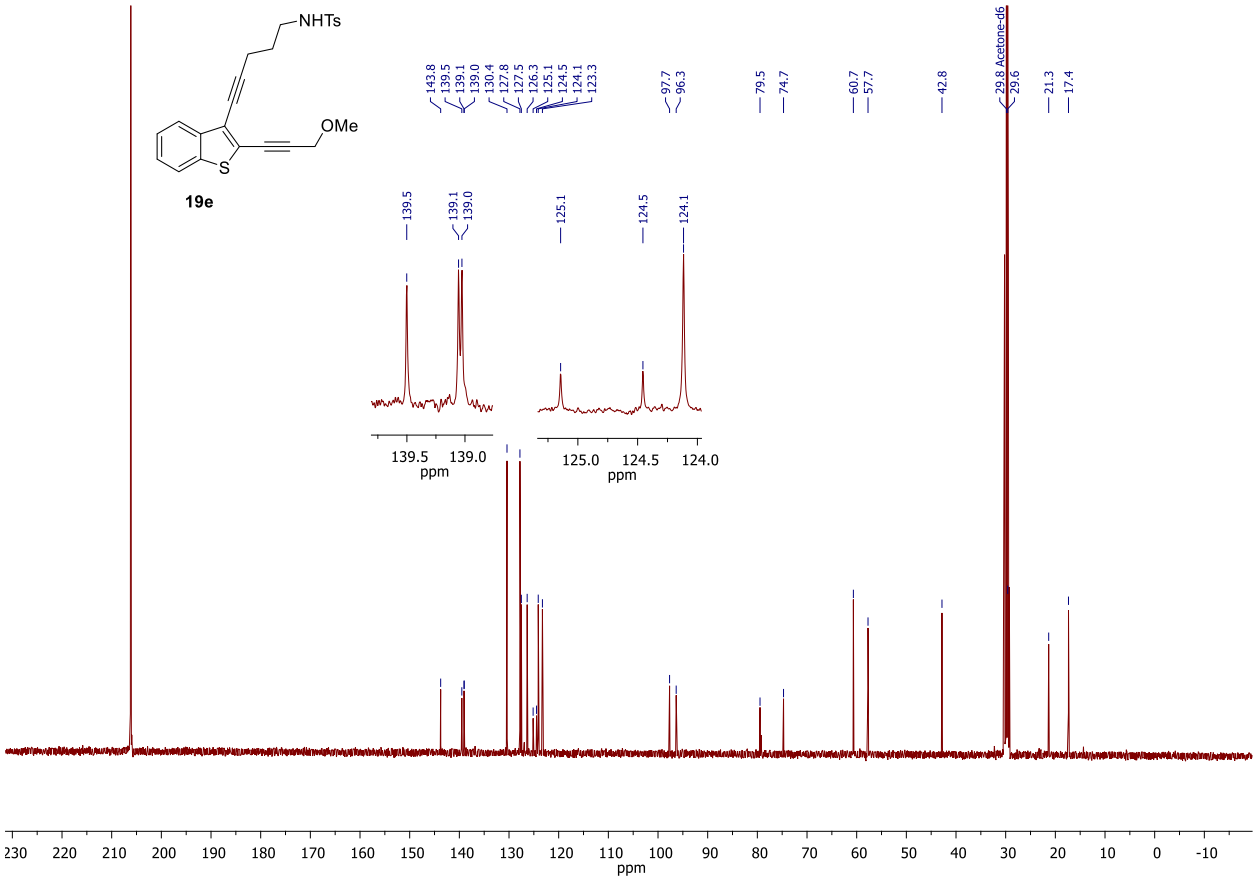
DEPT NMR, acetone-d_6, 101 MHz



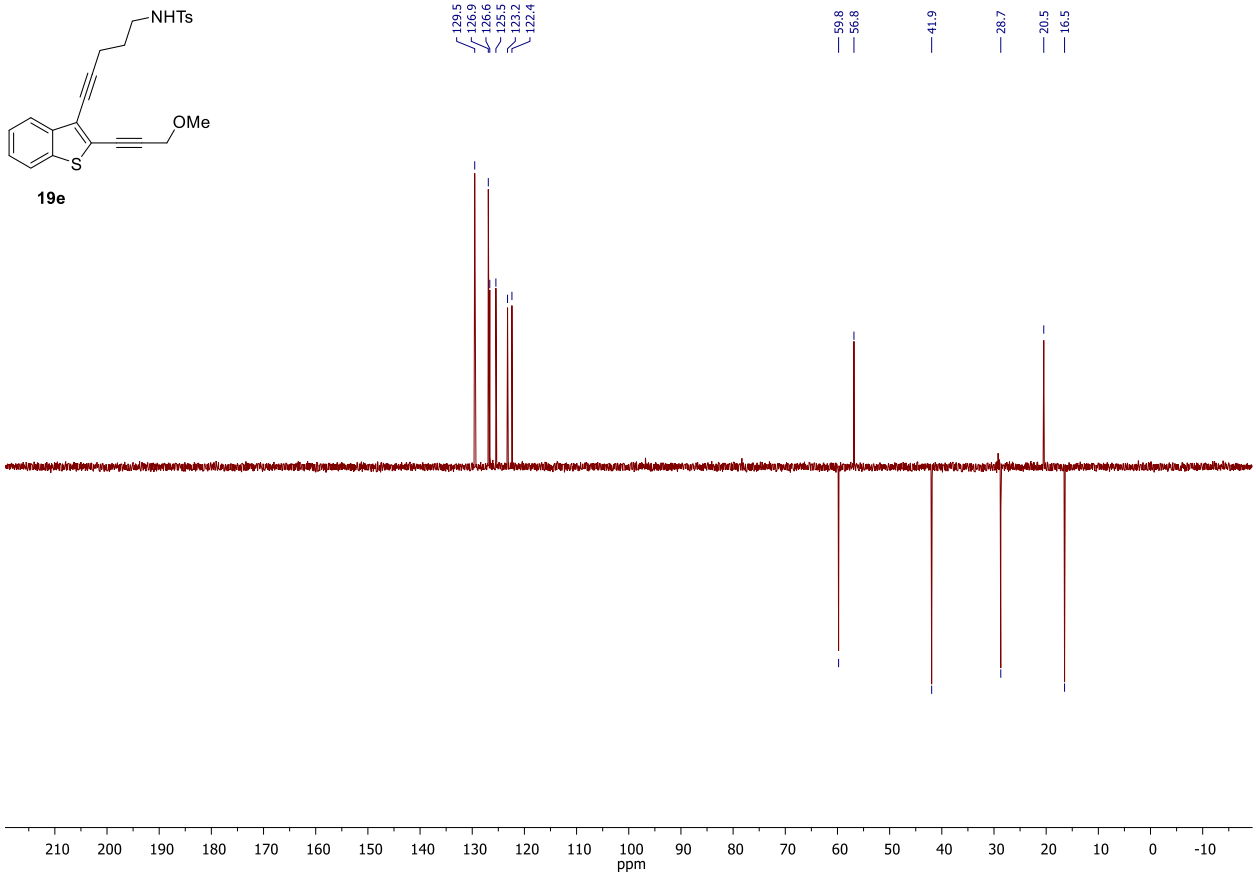
^{1}H NMR, $CDCl_3$, 400 MHz



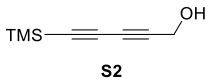
$^{13}C\{^{1}H\}$ NMR, acetone-d_6, 101 MHz



DEPT NMR, acetone-d_6, 101 MHz



^{1}H NMR, $CDCl_3$, 400 MHz

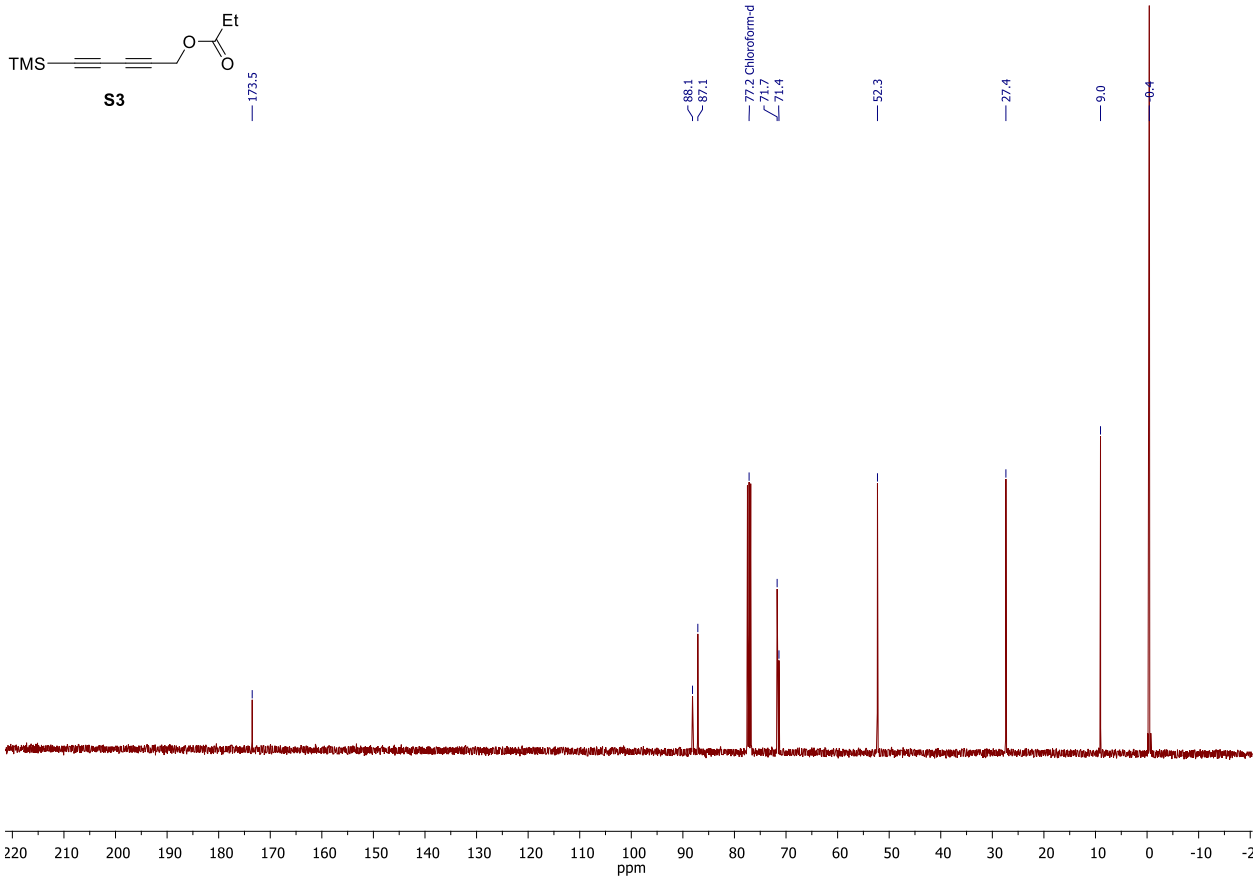


S2

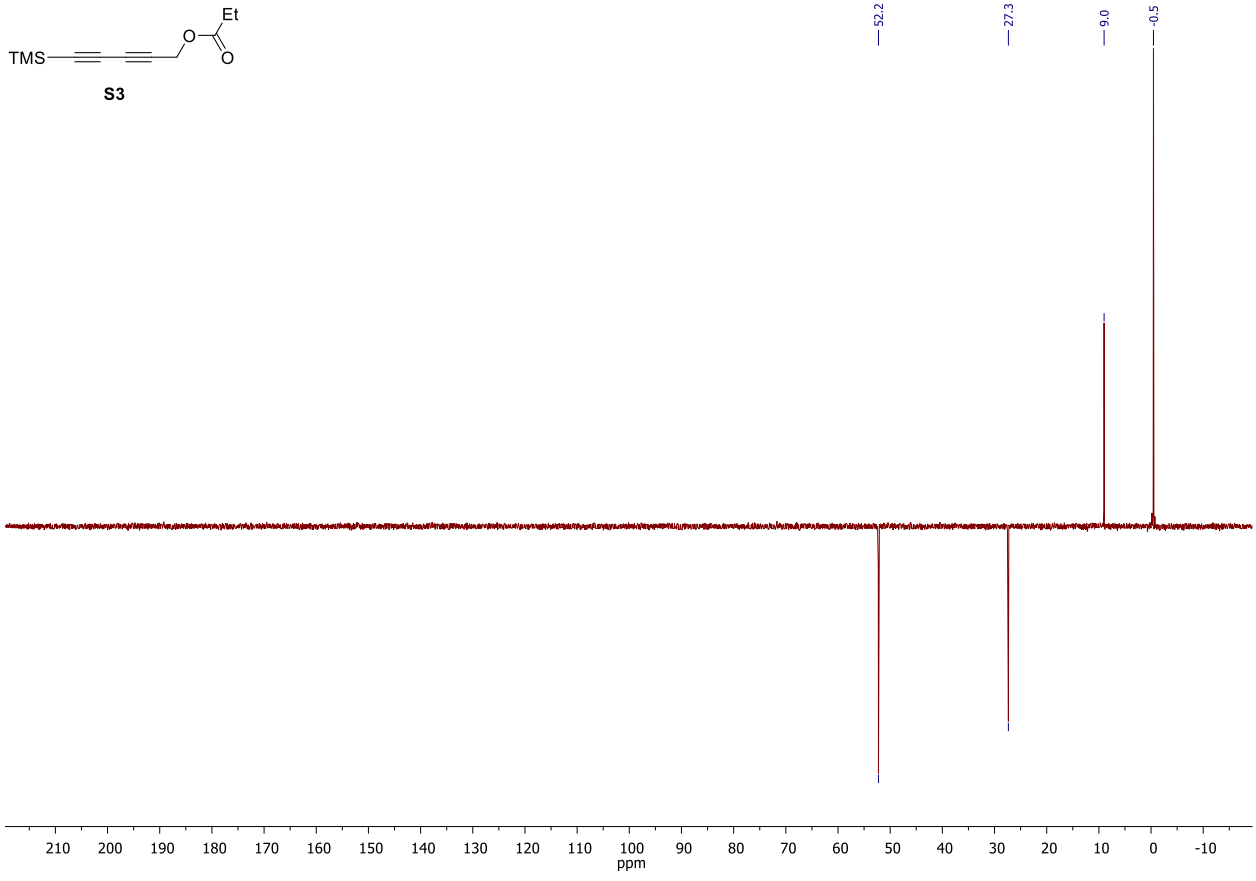
^{1}H NMR, $CDCl_3$, 400 MHz

S3

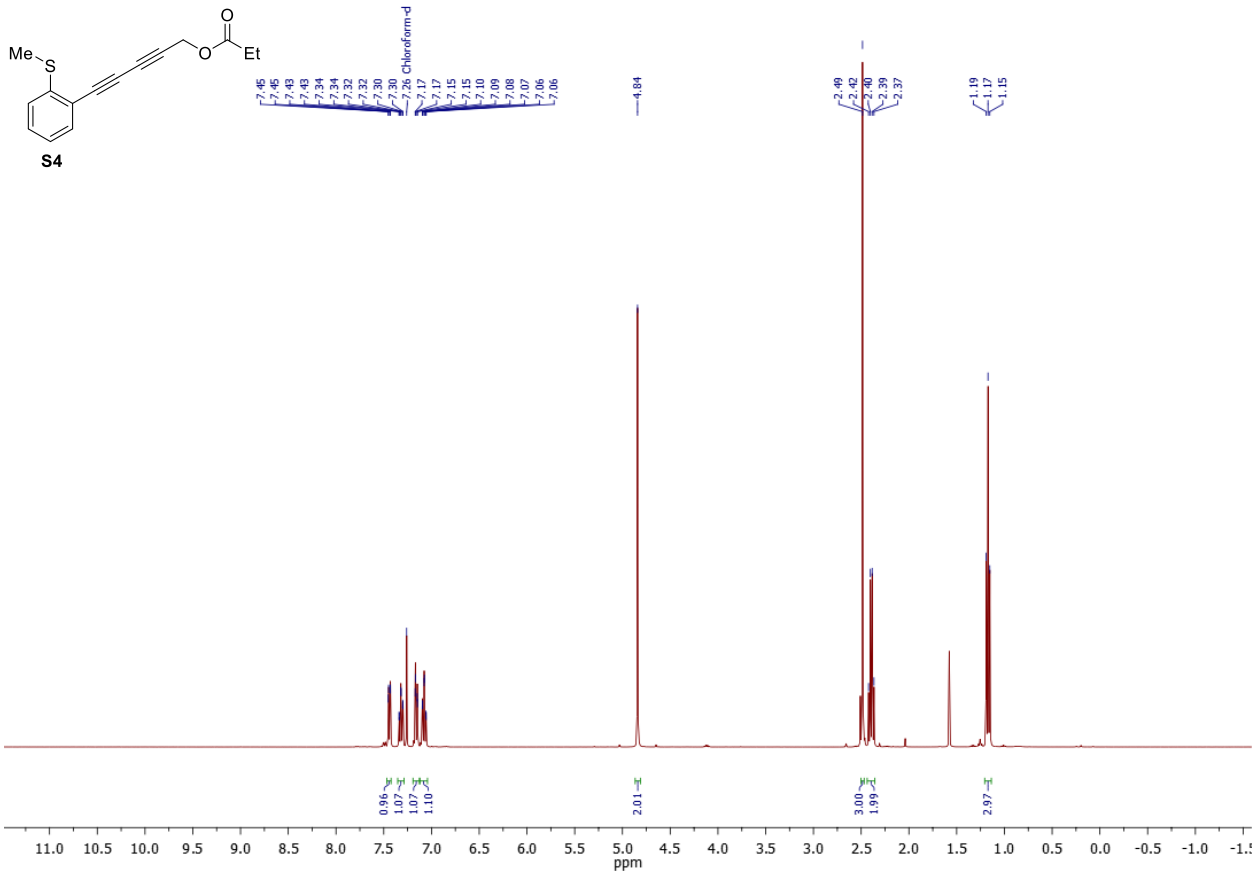
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



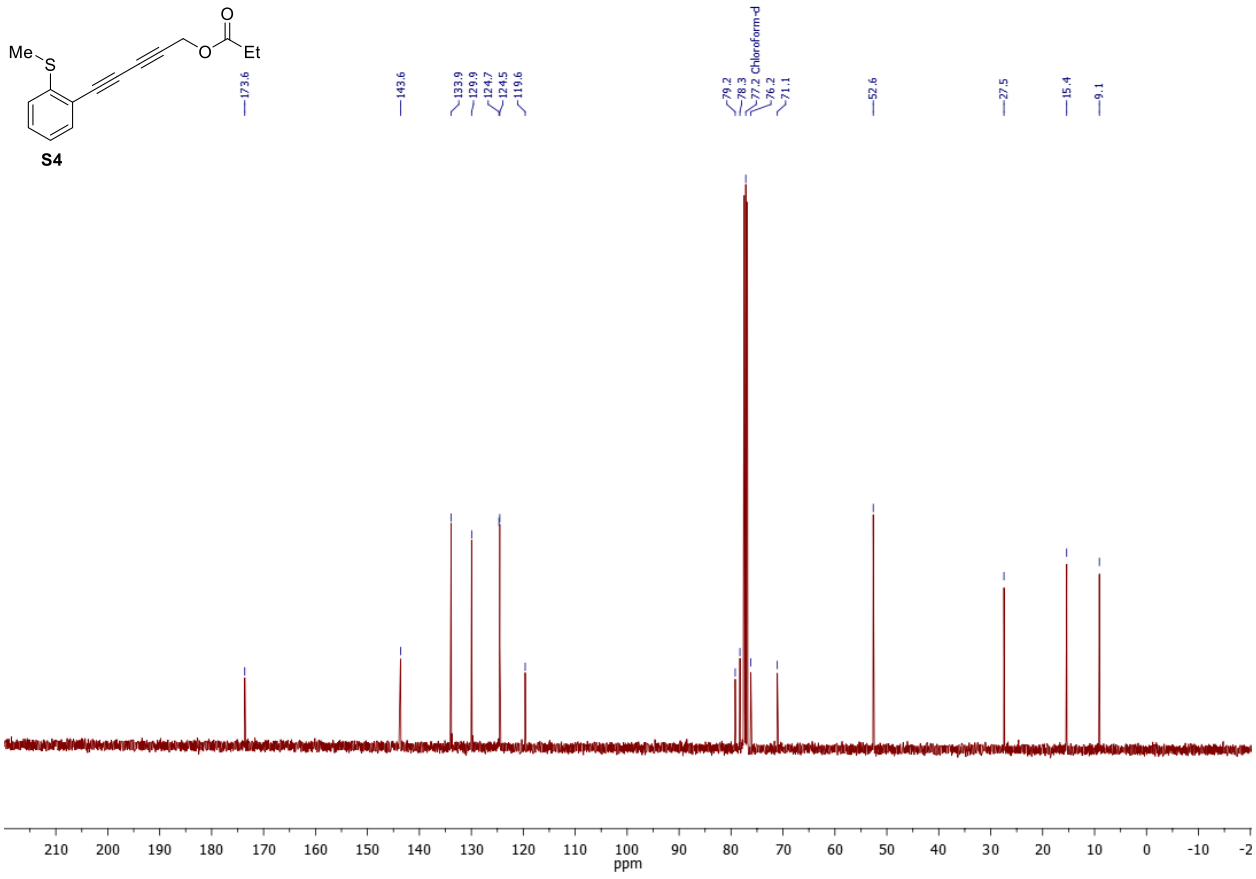
DEPT NMR, $CDCl_3$, 101 MHz



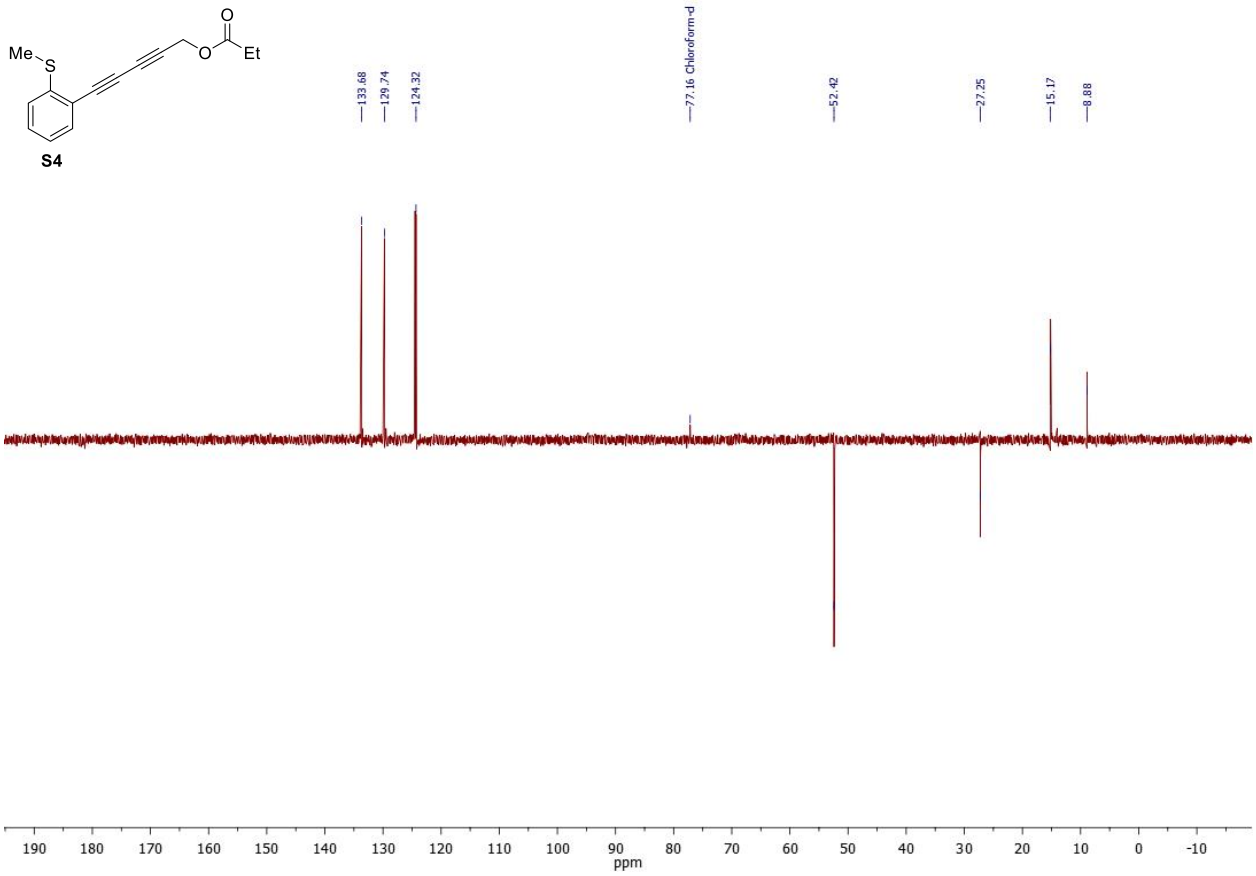
^{1}H NMR, $CDCl_3$, 400 MHz



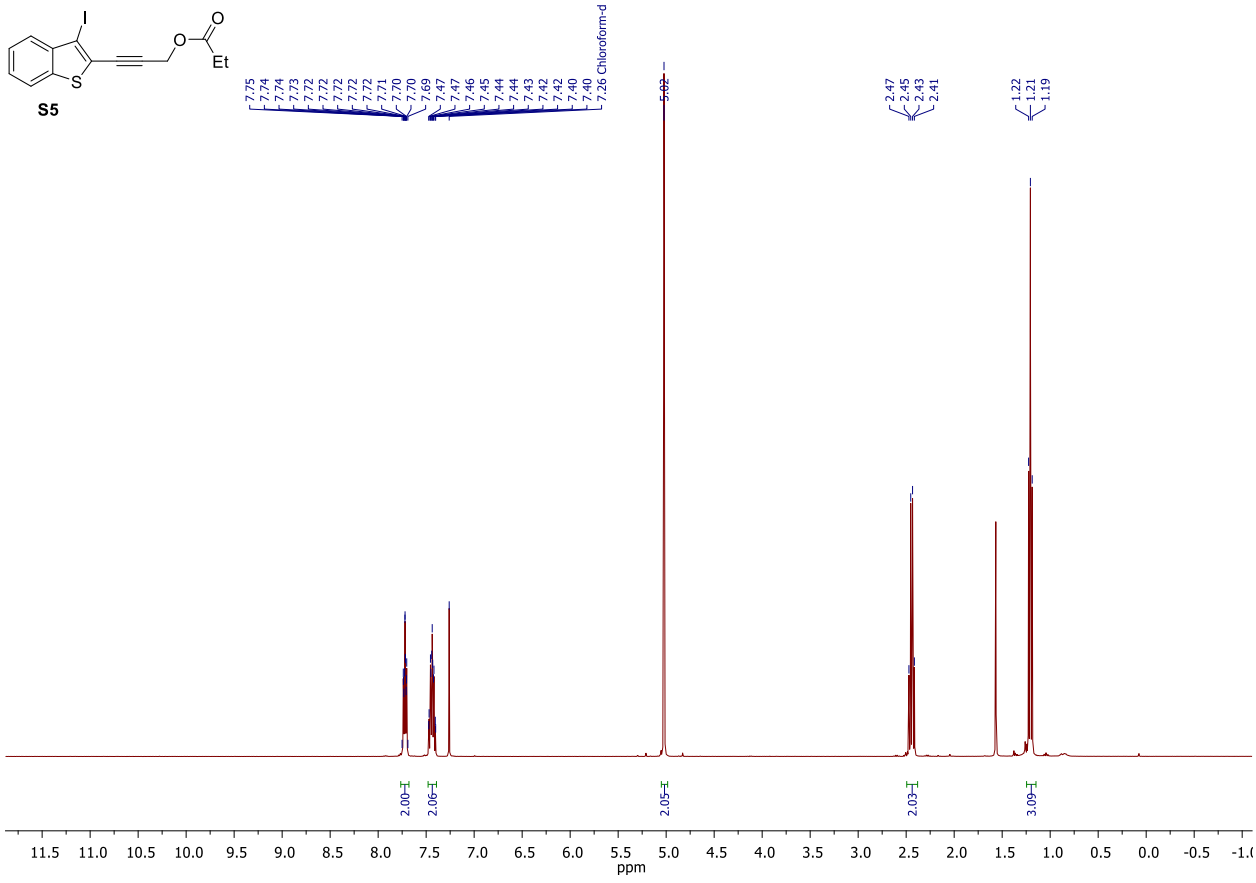
^{13}C{^{1}H} NMR, $CDCl_3$, 101 MHz



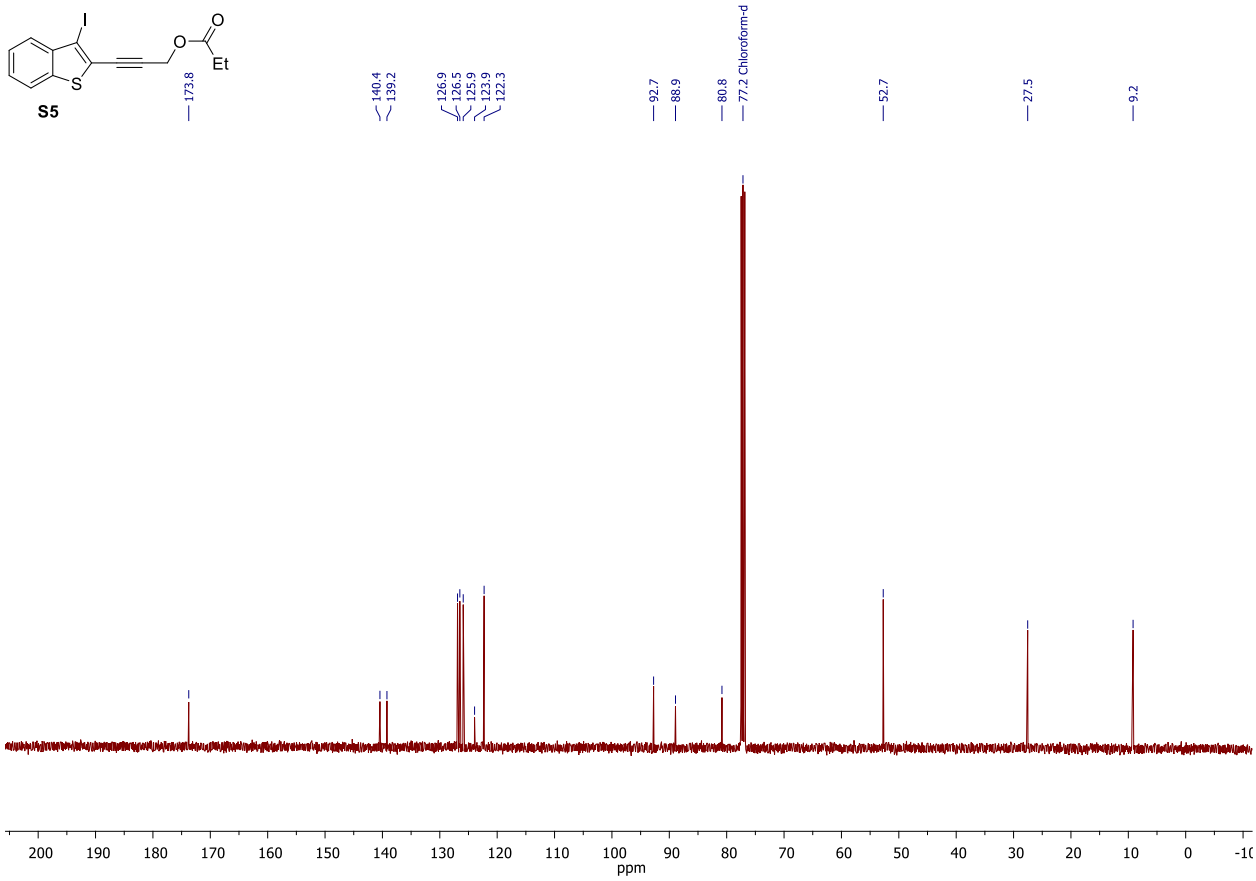
DEPT NMR, $CDCl_3$, 101 MHz



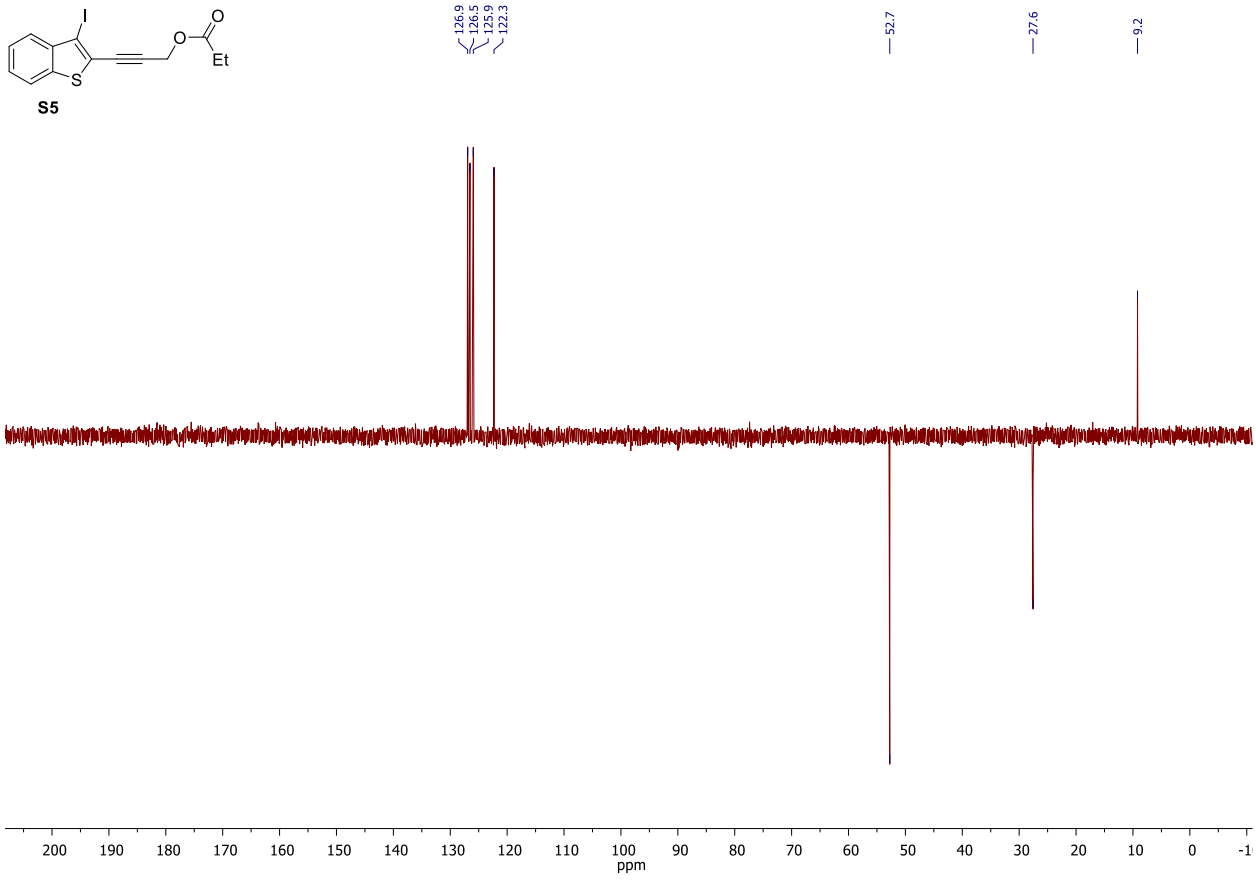
^1H NMR, $CDCl_3$, 400 MHz



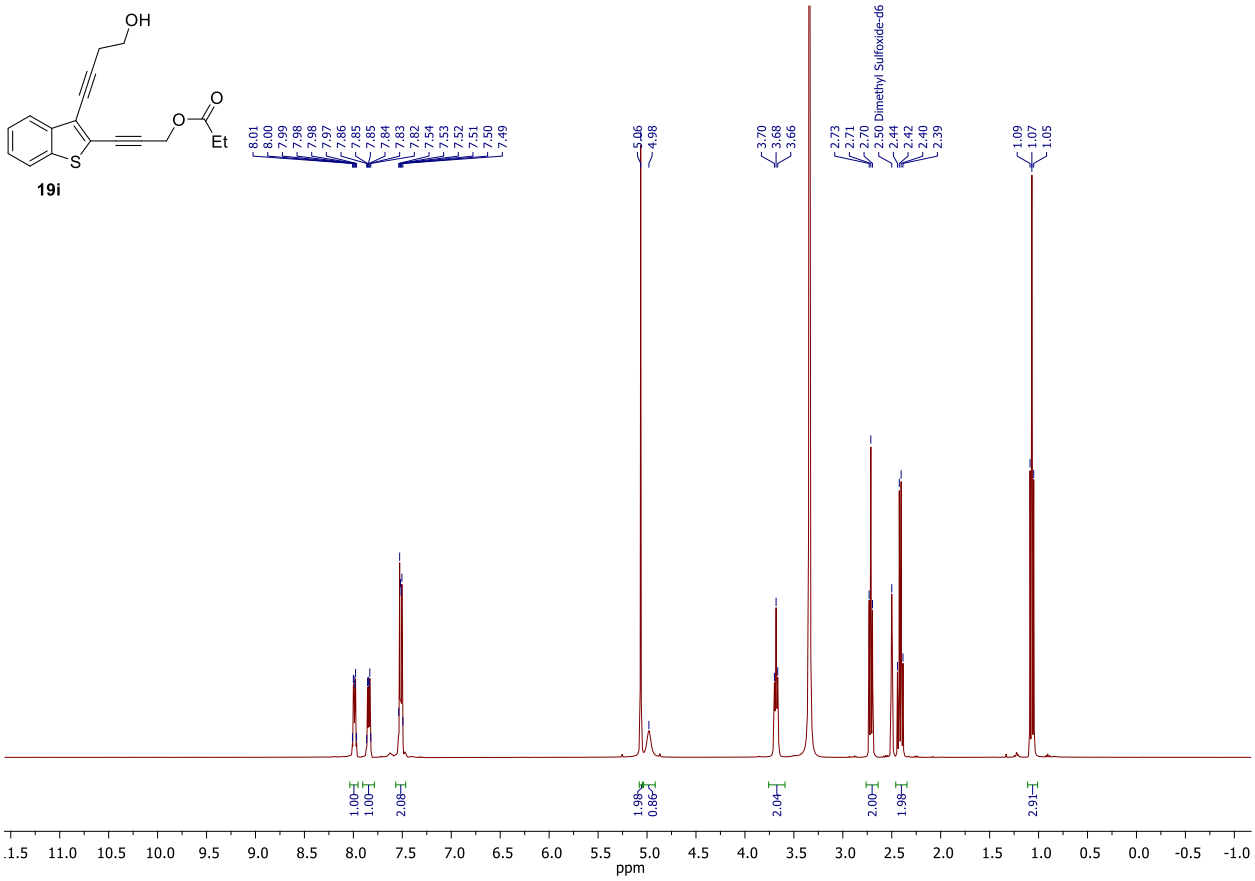
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 101 MHz



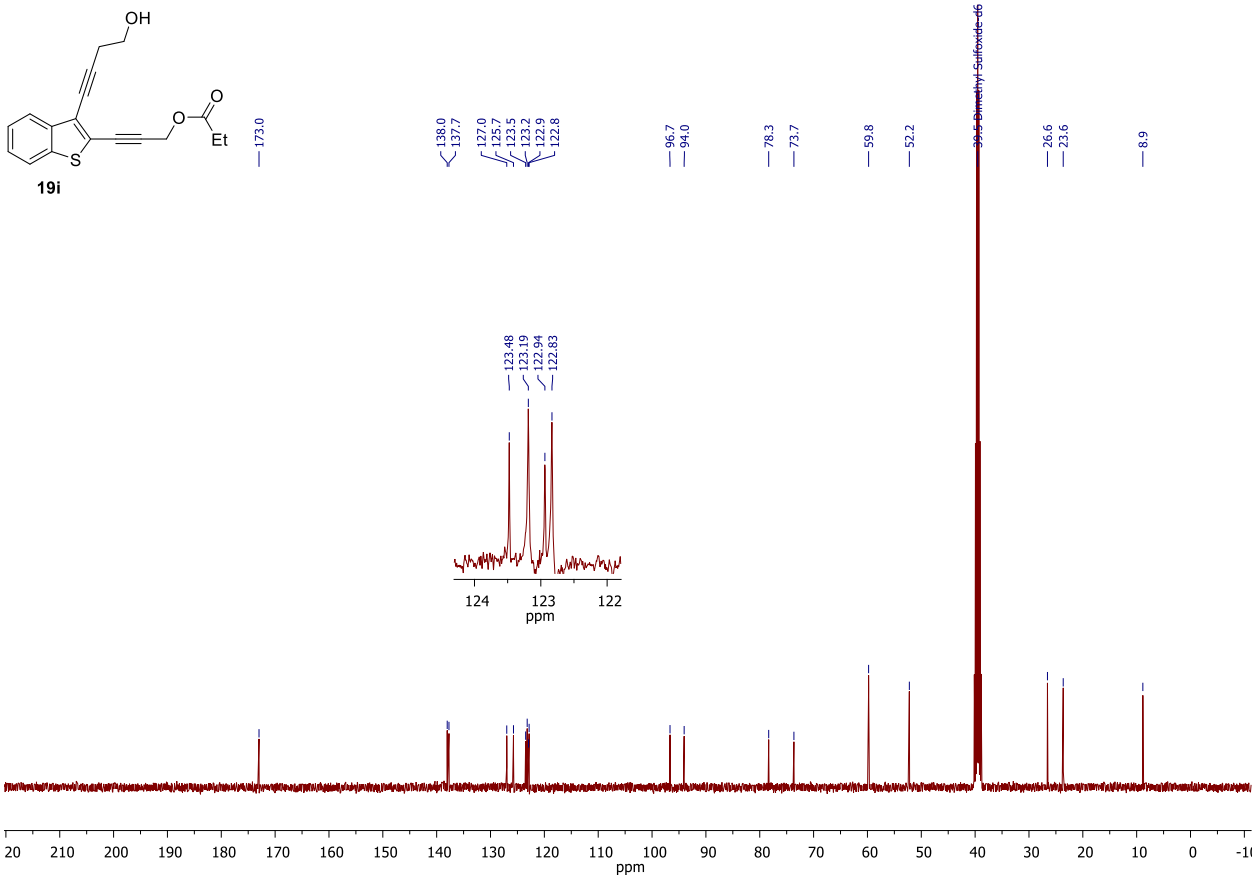
DEPT NMR, $CDCl_3$, 101 MHz



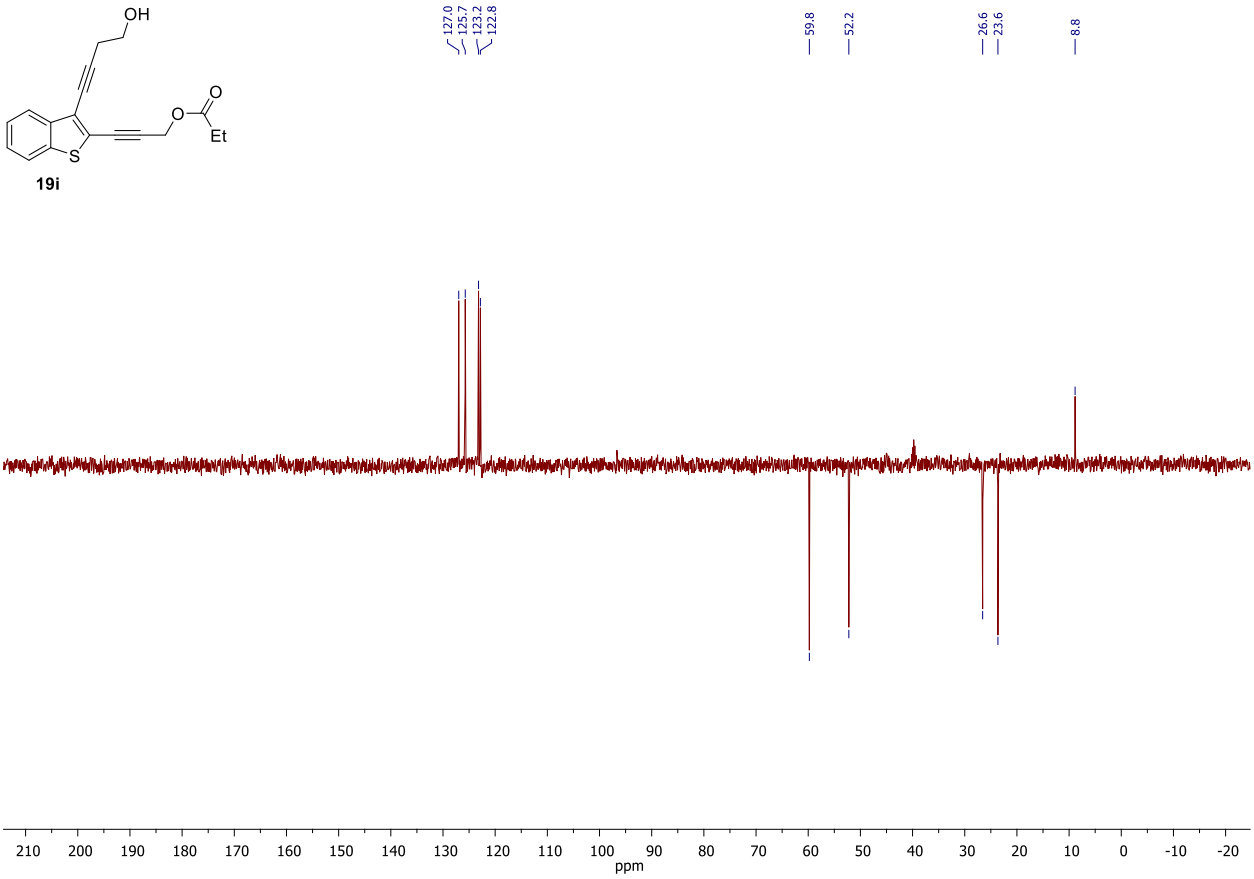
^{1}H NMR, DMSO-d_6, 400 MHz



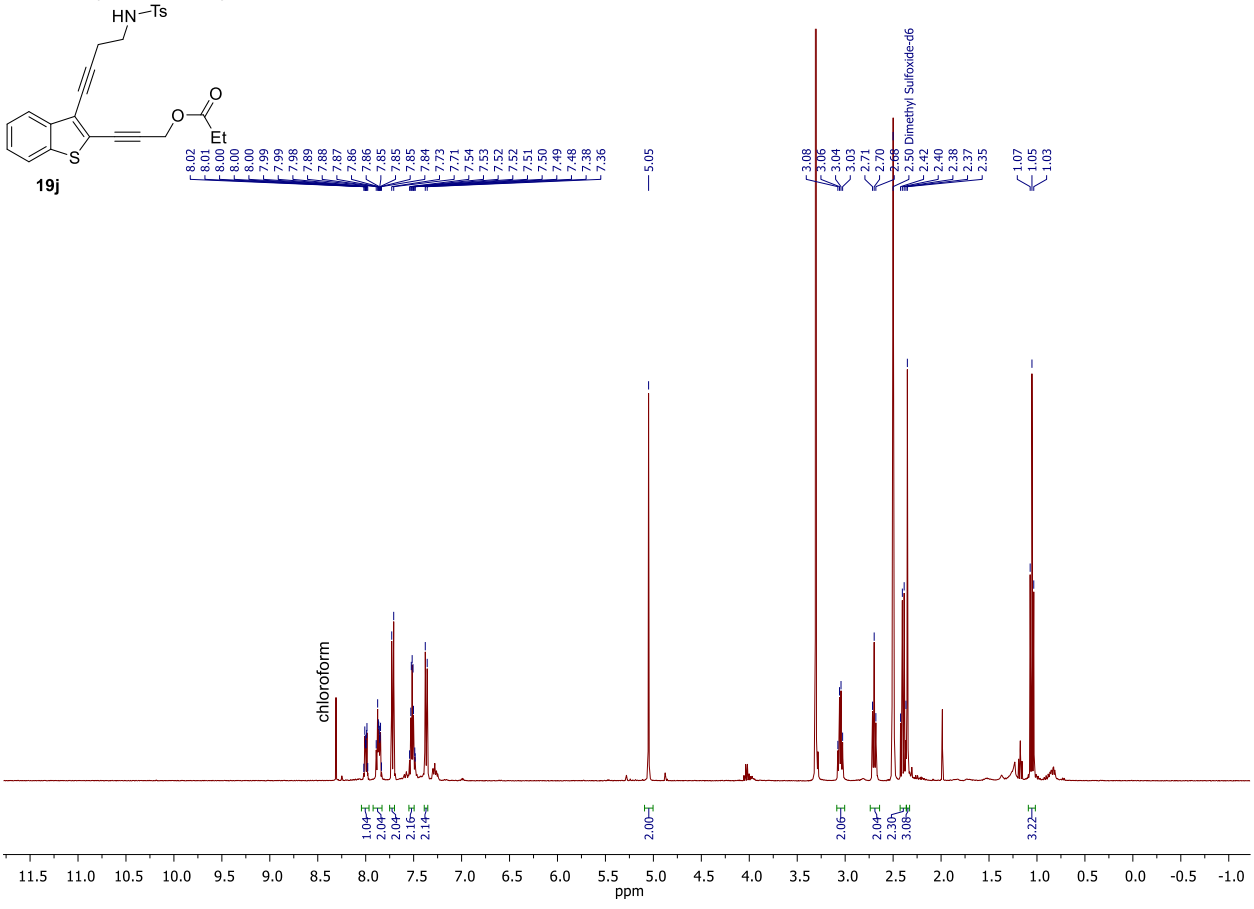
^{13}C{^{1}H} NMR, DMSO-d_6, 101 MHz



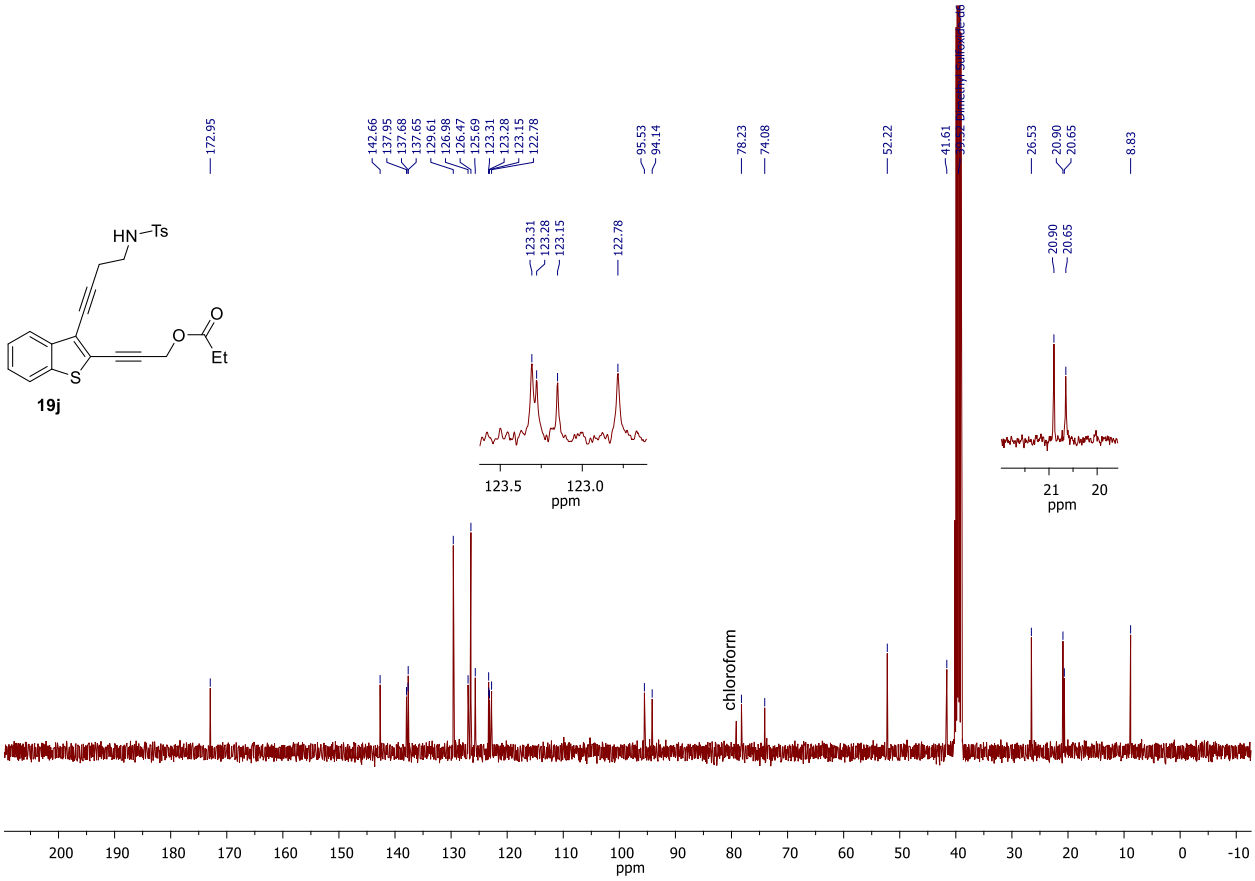
DEPT NMR, DMSO-d_6, 101 MHz



^{1}H NMR, DMSO-d_6, 400 MHz



$^{13}C\{^{1}H\}$ NMR, DMSO-d_6, 101 MHz



DEPT NMR, DMSO-d_6, 101 MHz