

Electronic Supplementary Information

Re-Orienting Coupling of Organocuprates with Propargyl Electrophiles from S_N2' to S_N2 with Stereocontrol.

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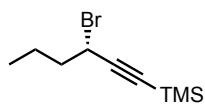
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General Experimental Methods

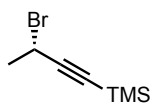
Air and/or moisture sensitive reactions were carried out under an argon atmosphere in oven-dried glassware and with anhydrous solvents. All compounds were purchased from commercial sources unless otherwise noted and used without further purification. Solvents were freshly distilled or dried by passing through an alumina column. 1,4-dioxane was distilled over sodium benzophenone under a nitrogen atmosphere. Thin layer chromatography was carried out on glass plates coated with silica gel SiO₂ 60 F254 from Merck; visualization with a UV lamp (254 nm) or by staining with a p-anisaldehyde or a vanilin solution. Flash chromatography was performed with silica gel SiO₂ 60 (0.040–0.063 μm, 230–400 mesh), technical solvents, and a head pressure of 0.2–0.4 bar. Melting points (m.p.) were measured on a Thomas Hoover capillary melting point apparatus in open capillaries and are uncorrected. Proton (¹H) and carbon (¹³C) nuclear magnetic resonance (NMR) spectroscopy was performed on a Mercury NMR instrument at 400 MHz (¹H) or 100 MHz (¹³C) and on a Unity NMR spectrometer at 500 MHz (¹H) or 125 MHz (¹³C). Chemical shifts are reported in ppm relative to the residual protiated solvent (CDCl₃: δ_H = 7.26 ppm, δ_C = 77.0 ppm). All ¹³C NMR spectra are proton decoupled. The resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Infrared spectroscopic (IR) data were recorded on sodium chloride plates neat or as thin films on a Perkin-Elmer Paragon 500 FT-IR spectrometer. Absorption bands are reported in wavenumbers (cm⁻¹) in the range of 4000–1000 cm⁻¹. High-resolution mass spectrometry (HRMS) was measured on a Bruker micrOTOF-Q II electrospray ionization (ESI) mass spectrometer by the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford University. Mass peaks are reported in m/z units.

List of starting propargyl bromides 4 : characterization and spectra pages



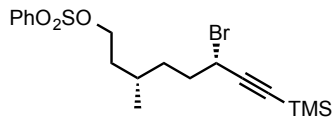
4a

Characterization: S6
Spectra: S20



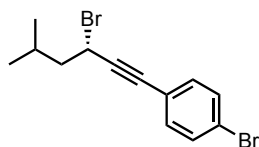
4b

Characterization: S6
Spectra: S21



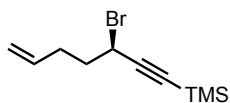
4c

Characterization: S6
Spectra: S22-23



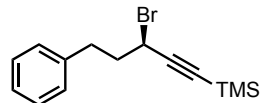
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Characterization: S7
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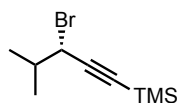
4e

Characterization: S8
Spectra: S25



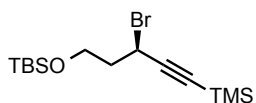
4f

Characterization: S8
Spectra: S26



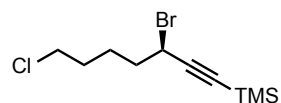
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Characterization: S8
Spectra: S27



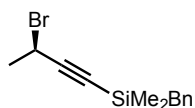
4h

Characterization: S9
Spectra: S228



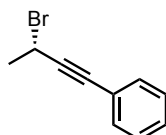
4i

Characterization: S9
Spectra: S29



4j

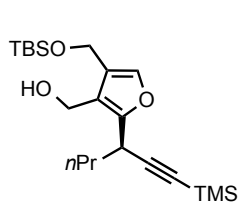
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Spectra: S30



4k

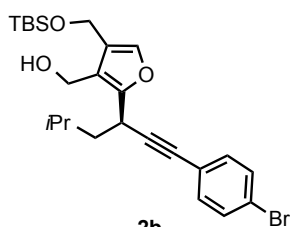
Characterization: S10
Spectra: S31

List of final products 2 and 5 : characterization and spectra pages



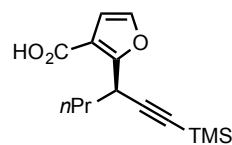
2a

Characteriation: S11
Spectra: S32



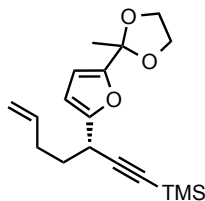
2b

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Spectra: S33



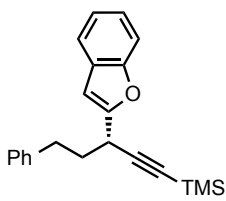
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Spectra: S34



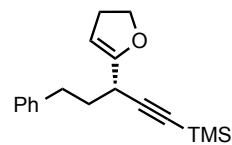
2d

Characteriation: S12
Spectra: S35



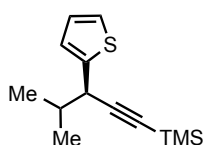
2e

Characteriation: S13
Spectra: S36



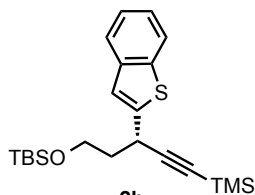
2f

Characteriation: S13
Spectra: S37



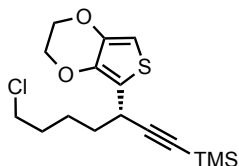
2g

Characteriation: S13
Spectra: S38



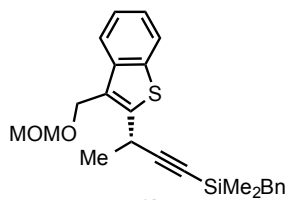
2h

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Spectra: S39



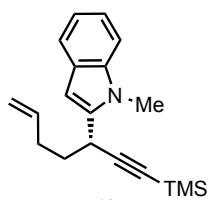
2i

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Spectra: S40



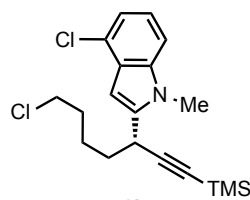
2j

Characteriation: S15
Spectra: S41



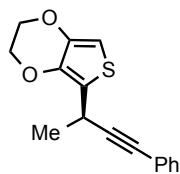
2k

Characteriation: S15
Spectra: S42



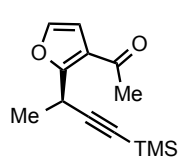
2l

Characteriation: S16
Spectra: S43



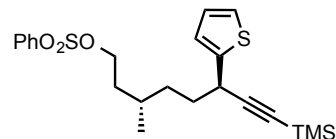
2m

Characteriation: S16
Spectra: S44



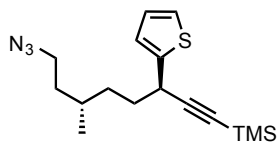
5a

Characteriation: S17
Spectra: S45



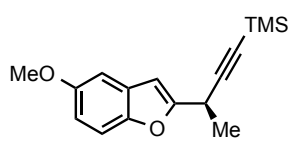
2o

Characteriation: S17
Spectra: S46-47



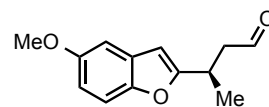
5b

Characteriation: S17
Spectra: S48-49



2p

Characteriation: S18
Spectra: S50



5c

Characteriation: S19
Spectra: S52

General procedure A for the preparation of the enantioenriched propargyl alcohol

A mixture of freshly distilled *iso*-propanol¹ (3n mL) and ynone **3** (n mL) was degassed by bubbling of Ar_(g) during 15 minutes. At this point RuCl(p-cymene)[(R,R)-Ts-DPEN] or RuCl(p-cymene)[(R,R)-Ts-DPEN] (1 mol%) was added and the resulting mixture was stirred for 6 hours. Additional portions of catalyst were added every 6 hours until full conversion of the starting ynone as determined by TLC analysis. The crude mixture was evaporated to dryness and the residual oil was purified by chromatography over silica gel to afford the enantioenriched propargyl alcohol.

General procedure B for the preparation of the propargyl bromides **4**²

A round bottom flask was charged with triphenylphosphine (1.2n mmol) and DCM (2n mL). The mixture was cooled to 0°C under argon and bromine (1.2n mmol) was added dropwise. A yellow pale precipitate formed and the reaction mixture was stirred for an additional 30 minutes. A separate round bottom flask was charged with the propargyl alcohol (n mmol), imidazole (1.2n mmol) and DCM (2n mL) and the mixture was cooled to 0°C under argon. The bromotriphenylphosphonium bromide suspension was added dropwise to the alcohol solution and the mixture was warmed to room temperature over 3 hours. Silica (1.5n mL) was added to the and the mixture was evaporated to dryness and purified by column chromatography over silica gel (pentane:ether) to afford the desired propargyl bromide **4**.

General procedure C for the S_N2 displacement reaction and formation of **2**³

A flamed dried flask was charged with the heterocycle **1** of choice (2n mmol) and freshly distilled DME (6n mmol) and the solution was cooled to -78°C under argon. *n*BuLi (2.5 M in hexanes, 2.2n mmol) was then added dropwise and the resulting solution was stirred for 1.5 hours. CuCN_(s) (n mmol) was the added and the resulting suspension was then allowed to warm up to -40°C over 1.5 hours. The mixture was then cooled back to -78°C and the propargyl bromide electrophile **4** was added via syringe. The reaction mixture was stirred between -78°C and -40°C over 3 hours and then quenched with a saturated ammonium chloride solution. The mixture was diluted with diethyl ether and after standard work up (NH₄Cl_(sat.), NaCl_(sat.)), the combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness. The residual oil was then purified by column chromatography over silica gel to afford the desired alkyne **2**.

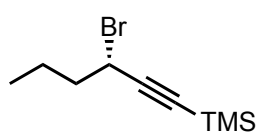
¹ *Iso*-propanol was distilled over CaH_{2(s)} under Ar_(g).

² The enantiomeric excess of the propargyl bromides **4** could not always be determined either by chiral GC or HPLC analyses. In these cases, the enantiomeric excess of the propargyl bromide **4** was considered to be identical to the one of the starting propargyl alcohol.

³ All the reaction temperature given are cold bath temperature. All reactions were run twice: once with the racemic and once with the enantioenriched bromide **4**.

(S)-(3-bromohex-1-yn-1-yl)trimethylsilane 4a

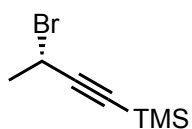
(R)-1-(trimethylsilyl)hex-1-yn-3-ol (8.52 g, 50 mmol, 98% ee) was prepared according to general procedure A. It was engaged in the next step following general procedure B using triphenyl phosphine (1.57 g), bromine (3.07 mL) and imidazole (4.08 g). Purification by chromatography over silica gel (pentane) afforded the desired bromide 4a (10.15 g, 87%, 98% ee).



¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 4.51 (t, *J* = 7.0 Hz, 1H), 2.03-1.92 (m, 2H), 1.61-1.46 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.17 (s, 9H). ¹³C NMR (CDCl₃, 125 MHz, δ (ppm)) 103.9, 91.7, 41.6, 37.1, 20.6, 13.2, 0.3. IR (thin film) ν = 2920, 2861, 2834, 2143, 1444, 1233. [α]₂₅^D = -10.6 (*c* = 1.0 in CHCl₃). Chiral GC: Cyclodex-B 90 C, 1C.min⁻¹ t_R = 15.1 (minor), 15.6 (major). HRMS Calcd for C₉H₁₇BrSi+NH₄⁺: 250.0621, found 250.0627.

(S)-(3-bromobut-1-yn-1-yl)trimethylsilane 4b⁴

(R)-4-(trimethylsilyl)but-3-yn-2-ol (3.55 g, 25 mmol, 98% ee) was prepared according to general procedure A. It was engaged in the next step following general procedure B using triphenyl phosphine (7.87 g), bromine (1.54 mL) and imidazole (2.04 g). Purification by chromatography over silica gel (pentane) afforded the desired bromide 4b (3.95 g, 77%).



¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 4.60 (q, *J* = 6.8 Hz, 1H), 1.89 (d, *J* = 6.8 Hz, 1H), 0.17 (s, 9H). ¹³C NMR (CDCl₃, 125 MHz, δ (ppm)) 104.9, 91.0, 31.3, 27.3, -0.3. IR (thin film) ν = 2919, 2138, 1423, 1355, 1233, 1166, 1089. [α]₂₅^D = -18.1 (*c* = 1.0 in CHCl₃). MS Calcd for C₉H₁₇BrSi-Br+NH₄⁺: 143.1, found: 143.1.

(3S,6S)-6-bromo-3-methyl-8-(trimethylsilyl)oct-7-yn-1-ylbenzenesulfonate 4c

(S)-6-hydroxy-4-methylhexanal⁵ (2.60 g, 20 mmol) in DCM (50 mL) was added triethylamine (4.05 mL, 30 mmol) and benzene sulfonylchloride (3.53 g, 20 mmol). After full conversion, the reaction mixture was worked-up and the residue was purified by chromatography over silica gel to afford (S)-3-methyl-6-oxohexyl benzenesulfonate (5.30 g, 98 %).

To a -78°C solution of lithium trimethylsilylacetylene in THF (50 mL) formed from trimethylsilyl acetylene (3.96 mL, 28 mmol) and *n*BuLi (2.5M in hexanes, 10 mL, 25 mmol) was added the freshly prepared aldehyde (5.14 g, 19 mmol) in THF (2x6 mL).

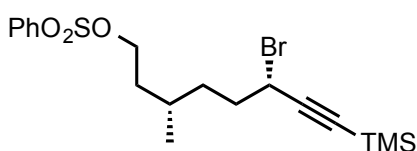
⁴ The ee of the bromide could not be measured and was assumed to be identical to the ee reported for the starting alcohol ee = 98%, see: Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

⁵ (S)-6-hydroxy-4-methylhexanal was prepared according to the literature protocol, see: Sheng, G.; Jie, L.; Dawei, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 1298.

The reaction medium was warmed to -20°C over 1 hour and quenched with $\text{NH}_4\text{Cl}_{(\text{sat.})}$. After usual work up the residue was purified by chromatography over silica gel to afford (3*S*)-6-hydroxy-3-methyl-8-(trimethylsilyl)oct-7-yn-1-yl benzenesulfonate (6.44 g, 92%) as a one to one mixture of diastereoisomers.

The previously obtained mixture of diastereoisomers (4.42 g, 12 mmol) was dissolved in DCM (30 mL). Celite (10.3 g) and PCC (10.3 g, 48 mmol) and the resulting mixture was stirred until full conversion. It was then purified by chromatography over silica gel to afford (*S*)-3-methyl-6-oxo-8-(trimethylsilyl)oct-7-yn-1-yl benzenesulfonate (3.61g, 82%).

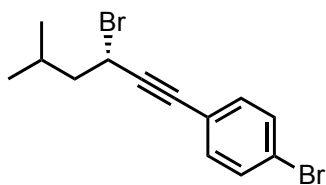
(3*S*,6*R*)-6-hydroxy-3-methyl-8-(trimethylsilyl)oct-7-yn-1-yl benzenesulfonate (3.26 g, 8.84 mmol, 93%) was prepared as a unique diastereoisomer from (*S*)-3-methyl-6-oxo-8-(trimethylsilyl)oct-7-yn-1-yl benzenesulfonate (3.50 g, 9.5 mmol) according to general procedure **A**. It was engaged in the next step following general procedure **B** using triphenyl phosphine (2.78 g), bromine (543 μL) and imidazole (722 mg). Purification by chromatography over silica gel afforded the desired bromide **4c** as a unique diastereoisomer (3.36 g, 88%).



$^1\text{H NMR}$ (CDCl_3 , 500 MHz, δ (ppm)) 7.93-7.89 (m, 2H), 7.67-7.62 (m, 1H), 7.58-7.53 (m, 2H), 4.42 (t, $J = 6.8$ Hz, 1H), 4.14-4.05 (m, 2H), 1.99-1.81 (m, 2H), 1.73-1.65 (m, 1H), 1.63-1.53 (m, 1H), 1.49-1.40 (m, 2H), 1.37-1.25 (m, 1H), 0.84 (d, $J = 6.5$ Hz, 3H), 0.17 (s, 9H). **$^{13}\text{C NMR}$** (CDCl_3 , 125 MHz, δ (ppm)) 136.1, 133.7, 129.2, 127.8, 103.5, 92.1, 68.8, 37.3, 36.8, 35.5, 33.9, 28.5, 19.0, -0.3. $[\alpha]_{25}^{\text{D}} = -5.3$ ($c = 1.0$ in CHCl_3).

(*S*)-1-bromo-4-(3-bromo-5-methylhex-1-yn-1-yl)benzene **4d**⁶

(*R*)-1-(4-bromophenyl)-5-methylhex-1-yn-3-ol (1.50 g, 5.6 mmol, 97% ee) was prepared according to general procedure **A**. It was engaged in the next step following general procedure **B** using triphenyl phosphine (1.76 g), bromine (344 μL) and imidazole (457 mg). Purification by chromatography over silica gel (pentane/diethyl ether, 95:5) afforded the desired bromide **4d** (1.75 g, 95%).

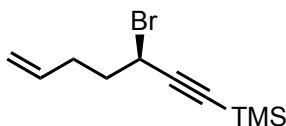


$^1\text{H NMR}$ (CDCl_3 , 400 MHz, δ (ppm)) 7.47-7.42 (m, 2H), 7.32-7.27 (m, 2H), 4.75 (t, $J = 7.6$ Hz, 1H), 2.04-1.90 (m, 3H), 0.98 (d, $J = 6.4$ Hz, 3H), 0.97 (d, $J = 6.4$ Hz, 3H). **$^{13}\text{C NMR}$** (CDCl_3 , 100 MHz, δ (ppm)) 133.2, 131.6, 123.0, 121.2, 89.4, 85.6, 48.6, 36.0, 26.9, 21.9, 21.9. **IR (thin film)** $\nu = 3046, 2910, 2858, 2827, 2199, 1464, 1447, 1373, 1364, 1346, 1323, 1302, 1268, 1241, 1150, 1111$. $[\alpha]_{25}^{\text{D}} = -6.8$ ($c = 1.0$ in CHCl_3). **MS** Calcd for $\text{C}_{13}\text{H}_{14}\text{Br}_2\text{-HBr}$: 248.0, found: 248.2.

⁶ The ee of the bromide could not be measured and was assumed to be identical to the ee of the starting alcohol (ee = 97%, **Chiral HPLC**: Chiralpak® IC, 2% isopropanol in heptane, 0.8 mL.min⁻¹, $\lambda = 254$ nm, $t_{\text{R}} = 11.5$ (minor), 12.2 (major)).

(R)-(3-bromohept-6-en-1-yn-1-yl)trimethylsilane 4e

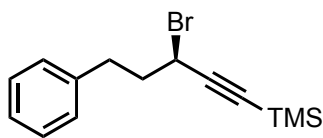
(S)-1-(benzyltrimethylsilyl)hept-6-en-1-yn-3-ol (1.64 g, 9 mmol, 99% ee) was prepared according to general procedure A. It was engaged in the next step following general procedure B using triphenyl phosphine (2.83 g), bromine (553 μ L) and imidazole (753 mg). Purification by chromatography over silica gel (pentane) afforded the desired bromide **4e** (1.90 g, 86%, 99% ee).



¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 5.84-5.70 (m, 1H), 5.12-5.05 (m, 1H), 5.05-5.0 (m, 1H), 4.50 (t, J = 6.8 Hz, 1H), 2.35-2.23 (m, 2H), 2.13-2.02 (m, 2H), 0.18 (s, 9H). ¹³C NMR (CDCl₃, 100 MHz, δ (ppm)) 136.3, 116.1, 103.6, 94.4, 92.2, 38.6, 36.5, 31.4, -0.3. IR (thin film) ν = 3036, 2919, 2861, 2142, 1619, 1424, 1395, 1233, 1147. [α]₂₅^D = -0.5 (c = 1.0 in CHCl₃). Chiral GC: Cyclodex-B 90 C, 1C.min⁻¹ t_R = 18.3 (major), 18.6 (minor). MS Calcd for C₁₀H₁₇BrSi-Br⁻+NH₄⁺: 183.1, found: 183.1.

(R)-(3-bromo-5-phenylpent-1-yn-1-yl)trimethylsilane 4f⁷

(S)-5-phenyl-1-(trimethylsilyl)pent-1-yn-3-ol (2.05g, 8.8 mmol, 99% ee) was prepared according to general procedure A. It was engaged in the next step following general procedure B using triphenyl phosphine (2.77 g), bromine (541 μ L) and imidazole (719 mg). Purification by chromatography over silica gel (pentane/diethyl ether, 95:5) afforded the desired bromide **4f** (2.29 g, 88%).



¹H NMR (CDCl₃, 500 MHz, δ (ppm)) 7.33-7.27 (m, 2H), 7.24-7.29 (m, 3H), 4.44 (t, J = 7.0 Hz, 1H), 2.90-2.79 (m, 2H), 2.35-2.25 (m, 2H), 0.19 (s, 9H). ¹³C NMR (CDCl₃, 125 MHz, δ (ppm)) 140.0, 128.5, 126.3, 103.5, 92.3, 41.1, 36.4, 33.4, -0.2. IR (thin film) ν = 2934, 1707, 1461, 1379, 1266, 1143. [α]₂₅^D = -13.5 (c = 1.0 in CHCl₃). HRMS Calcd for C₁₄H₁₉BrSi+NH₄⁺: 312.0783, found: 312.0790.

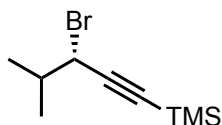
(S)-(3-bromo-4-methylpent-1-yn-1-yl)trimethylsilane 4g⁸

(R)-1-(benzyltrimethylsilyl)-4-methylpent-1-yn-3-ol (2.11 g, 12.4 mmol, 99% ee) was prepared according to general procedure A. It was engaged in the next step

⁷ The ee of the bromide could not be measured and was assumed to be identical to the ee reported for the starting alcohol ee = 99%, see: Mizuta, S.; Engle, K. M.; Verhoog, S.; Galicia-López, O.; O'Duill, M.; Médebielle, M.; Wheelhouse, K.; Rassias, G.; Thompson, A. L.; Gouverneur, V. *Org. Lett.* **2013**, *15*, 1250.

⁸ **4g** was obtained as an inseparable mixture with trimethyl(4-methylpent-3-en-1-yn-1-yl)silane (95:5 to 90:10) as determined by ¹H NMR; however, this impurity did not affect the subsequent S_N2 reaction. The ee of the bromide could not be measured and was assumed to be identical to the ee = 99% of the starting alcohol: Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

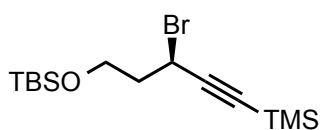
following general procedure **B** using triphenyl phosphine (3.90 g), bromine (762 μL) and imidazole (1.01 g). Purification by chromatography over silica gel (pentane) afforded the desired bromide **4g** (2.46 g, 85%).



$^1\text{H NMR}$ (CDCl_3 , 400 MHz, δ (ppm)) 4.46 (d, $J = 4.4$ Hz, 1H), 2.09-1.97 (m, 1H), 1.10 (d, $J = 6.5$ Hz, 3H), 1.08 (d, $J = 6.5$ Hz, 3H), 0.17 (s, 9H). $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz, δ (ppm)) 102.6, 92.7, 45.6, 35.7, 19.6, 19.2, -0.3. **Chiral GC**: Cyclodex-B 70 C, $0.5\text{C}\cdot\text{min}^{-1}$ $t_{\text{R}} = 26.6$ (minor), 26.9 (major). **IR (thin film)** $\nu = 2923, 2892, 2860, 2834, 2144, 2123, 1446, 1366, 1292, 1233, 1152$. $[\alpha]_{25}^{\text{D}} = -6.8$ ($c = 1.0$ in CHCl_3). **HRMS** Calcd for $\text{C}_9\text{H}_{17}\text{BrSi} + \text{NH}_4^+$: 250.0627, found: 250.0632.

(*R*)-(3-bromo-5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)trimethylsilane **4h**⁹

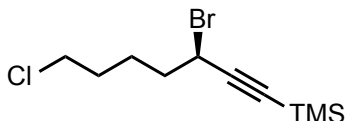
(*S*)-5-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-yn-3-ol (720 mg, 2.5 mmol, 98% ee) was prepared according to general procedure **A**. It was engaged in the next step following general procedure **B** using triphenyl phosphine (787 mg), bromine (154 μL) and imidazole (204 mg). Purification by chromatography over silica gel (pentane/diethyl ether, 95:5) afforded the desired bromide **4h** (778 mg, 89%).



$^1\text{H NMR}$ (CDCl_3 , 500 MHz, δ (ppm)) 4.69 (t, $J = 7.0$ Hz, 1H), 3.80-3.71 (m, 2H), 2.24-2.13 (m, 2H), 0.89 (s, 9H), 0.18 (s, 9H), 0.07 (s, 6H). $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz, δ (ppm)) 103.8, 91.9, 60.1, 42.4, 34.1, 25.9, 18.3, -0.3, -5.4, -5.5. **IR (thin film)** $\nu = 2915, 2889, 2859, 2818, 2141, 1450, 1367, 1234, 1093$. $[\alpha]_{25}^{\text{D}} = -3.0$ ($c = 1.0$ in CHCl_3). **HRMS** Calcd for $\text{C}_{14}\text{H}_{29}\text{BrOSi} + \text{H}^+$: 349.1018, found: 349.1031.

(*R*)-(3-bromo-7-chlorohept-1-yn-1-yl)trimethylsilane **4i**

(*S*)-7-chloro-1-(trimethylsilyl)hept-1-yn-3-ol (1.75 g, 8 mmol, 99% ee) was prepared according to general procedure **A**. It was engaged in the next step following general procedure **B** using triphenyl phosphine (2.52 g), bromine (492 μL) and imidazole (654 mg). Purification by chromatography over silica gel (pentane/ether, 98:2) afforded the desired bromide **4i** (1.85 g, 82%, 98%).



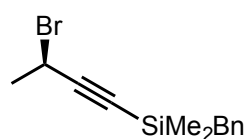
$^1\text{H NMR}$ (CDCl_3 , 400 MHz, δ (ppm)) 4.51 (t, $J = 6.8$ Hz, 1H), 3.55 (t, $J = 6.4$ Hz, 2H), 2.06-1.96 (m, 2H), 1.88-1.78 (m, 2H), 1.75-1.54 (m, 2H), 0.18 (s, 9H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz, δ (ppm)) 103.4, 92.4, 44.5, 38.7, 36.7, 31.6,

⁹ The ee of the bromide could not be measured and was assumed to be identical to the ee reported for the starting alcohol ee = 98%, see: Hartman, O.; Kalesse, M. *Org. Lett.* **2012**, *14*, 3064.

24.7, -0.3. **IR (thin film)** $\nu = 2917, 2860, 2828, 2140, 1436, 1293, 1233, 1158$. $[\alpha]_{25}^D = 1.9$ ($c = 1.0$ in CHCl_3). **Chiral GC:** Cyclodex-B 110 C, $1\text{C}\cdot\text{min}^{-1}$ $t_R = 32.3$ (major), 32.7 (minor). **HRMS** Calcd for $\text{C}_{20}\text{H}_{36}\text{Cl}_2\text{Si}_2+\text{NH}_4^+$:¹⁰ 420.2076, found: 420.2082.

(R)-benzyl(3-bromobut-1-yn-1-yl)dimethylsilane 4j

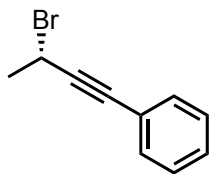
(S)-4-(benzyltrimethylsilyl)but-3-yn-2-ol (2.42 g, 11.1 mmol, 98% ee) was prepared according to general procedure A. It was engaged in the next step following general procedure B using triphenyl phosphine (3.49 g), bromine (682 μL) and imidazole (907 mg). Purification by chromatography over silica gel (pentane/diethyl ether, 98:2) afforded the desired bromide **4j** (2.75 g, 88%).



¹H NMR (CDCl_3 , 400 MHz, δ (ppm)) 7.30-7.21 (m, 2H), 7.16-7.06 (m, 3H), 4.61 (q, $J = 6.8$ Hz, 1H), 2.23 (s, 2H), 1.91 (d, $J = 6.8$ Hz, 3H), 0.16 (s, 6H). **¹³C NMR** (CDCl_3 , 125 MHz, δ (ppm)) 138.6, 128.4, 128.2, 124.4, 106.2, 89.5, 31.0, 27.2, 25.9, -2.4. **IR (thin film)** $\nu = 3038, 3017, 2982, 2918, 2884, 2852, 2137, 1577, 1472, 1431, 1389, 1354, 1288, 1233, 1190, 1165$. $[\alpha]_{25}^D = -20.6$ ($c = 1.0$ in CHCl_3). **HRMS** Calcd for $\text{C}_{13}\text{H}_{17}\text{BrSi}+\text{NH}_4^+$: 298.0627, found: 298.0624.

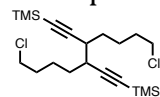
(S)-(3-bromobut-1-yn-1-yl)benzene 4k¹¹

(R)-4-phenylbut-3-yn-2-ol (3.20 g, 21.9 mmol, 97% ee) was prepared according to general procedure A. It was engaged in the next step following general procedure B using triphenyl phosphine (6.89 g), bromine (1.35 mL) and imidazole (1.79 g). Purification by chromatography over silica gel (pentane/diethyl ether, 98:2) afforded the desired bromide **4k** (3.62 g, 79%).



¹H NMR (CDCl_3 , 500 MHz, δ (ppm)) 7.46-7.41 (m, 2H), 7.36-7.28 (m, 3H), 4.87 (q, $J = 7.0$ Hz, 1H), 2.0 (d, $J = 7.0$ Hz, 3H). **¹³C NMR** (CDCl_3 , 125 MHz, δ (ppm)) 131.8, 128.8, 128.3, 122.1, 89.1, 86.0, 32.0, 27.5. **IR (thin film)** $\nu = 3037, 3014, 2991, 2952, 2935, 2884, 2821, 2204, 2178, 1574, 1469, 1421, 1355, 1300, 1164, 1051$. $[\alpha]_{25}^D = -14.8$ ($c = 1.0$ in CHCl_3). **HRMS** Calcd for $\text{C}_{10}\text{H}_9\text{Br}^+$: 207.9888, found: 207.9895.

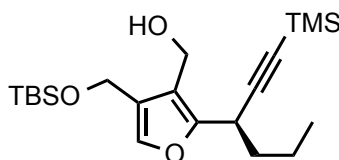
¹⁰ The observed mass corresponds to the dimer resulting from recombination of the corresponding radical:



¹¹ The ee of the bromide could not be measured and was assumed to be identical to the ee reported for the starting alcohol ee = 97%, see: Newcomb, E. T.; Ferreira, M. *Org. Lett.* **2013**, *15*, 1772.

(R)-(4-(((tert-butyl dimethylsilyl)oxy)methyl)furan-3-yl)methanol 2a

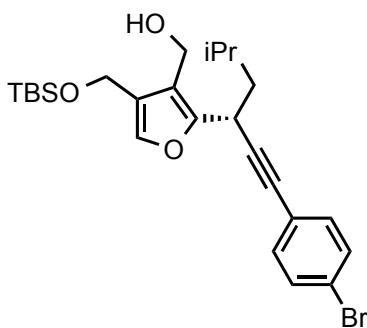
Product **2a** was prepared according to general procedure **C**¹² using (4-(((tert-butyl dimethylsilyl)oxy)methyl)furan-3-yl)methanol **1a**¹³ (485 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (S)-(3-bromohex-1-yn-1-yl)trimethylsilane **4a** (233 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/ethyl acetate, 95:5 to 90:10), **2a** was obtained (304 mg, 77%, 96% ee).



¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 7.20 (s, 1H), 4.59 (s, 2H), 4.55 (d, J = 2.8 Hz), 3.78 (t, J = 7.2 Hz, 1H), 3.13 (brs, 1H), 1.85-1.71 (m, 1H), 1.46-1.30 (m, 1H), 0.89 (s, 9H), 0.14 (s, 9H), 0.10 (s, 6H). ¹³C NMR (CDCl₃, 100 MHz, δ (ppm)) 150.7, 137.8, 125.0, 119.6, 105.3, 86.4, 56.6, 54.6, 37.4, 30.8, 25.8, 20.3, 18.2, 13.5, 0.0, -5.4. IR (thin film) ν = 3419, 2916, 2890, 2819, 2143, 1544, 1445, 1390, 1233, 1033. $[\alpha]_{25}^D$ = -19.2 (c = 1.0 in CHCl₃). Chiral HPLC: Chiralpak® IA, 0.1% isopropanol in heptane, 0.8 mL.min⁻¹, λ = 220 nm, t_R = 14.40 (minor), 19.45 (major). HRMS Calcd for C₂₁H₃₈O₃Si₂+Na⁺: 417.2257, found: 417.2254.

(R)-(2-(1-(4-bromophenyl)-5-methylhex-1-yn-3-yl)-4-(((tert-butyl dimethylsilyl)oxy)methyl)furan-3-yl)methanol 2b

Product **2b** was prepared according to general procedure **C**¹² using (4-(((tert-butyl dimethylsilyl)oxy)methyl)furan-3-yl)methanol **1a** (485 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (S)-1-bromo-4-(3-bromo-5-methylhex-1-yn-1-yl)benzene **4d** (330 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/ethyl acetate, 95:5 to 90:10), **2b** was obtained (310 mg, 63%, 97% ee).



¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 7.43-7.38 (m, 2H), 7.30-7.26 (m, 2H), 4.62 (s, 2H), 4.60 (s, 2H), 4.05 (t, J = 7.6 Hz, 1H), 3.20 (brs, 1H), 1.93-1.82 (m, 1H), 1.78-1.66 (m, 2H), 0.97 (d, J = 7.7 Hz, 3H), 0.95 (d, J = 7.7 Hz, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, δ (ppm)) 150.8, 138.0, 33.1, 131.6, 125.1, 122.8, 122.0, 119.6, 104.9, 90.0, 81.0, 56.7, 54.7, 44.0, 28.6, 25.8, 22.5, 21.9, 18.3, -5.4. IR (thin film) ν = 3400, 3011, 2913, 2889, 2872, 1544, 1465, 1449, 1371, 1238, 1055. $[\alpha]_{25}^D$ = 35.5 (c = 1.0 in CHCl₃). Chiral

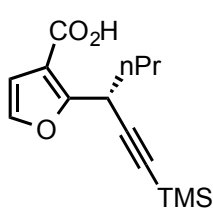
¹² Except that 4.4 mmol of *n*BuLi was used instead of 2.2 mmol.

¹³ **1a** was prepared from 4-(hydroxymethyl)furan-3-carbaldehyde by TBS protection followed NaBH₄(s) reduction, see: Clark, J. S.; Marlin, F.; Nay, B.; Wilson, C. *Org. Lett.* **2003**, *5*, 89.

HPLC: Chiralpak® IC, 0.5% isopropanol in heptane, 0.8 mL.min⁻¹, λ = 254 nm, t_R = 10.5 (major), 11.8 (minor). **HRMS** Calcd for C₂₅H₃₅BrO₃Si+Na⁺: 513.1437, found: 513.1425.

(*R*)-2-(1-(trimethylsilyl)hex-1-yn-3-yl)furan-3-carboxylic acid **2c**

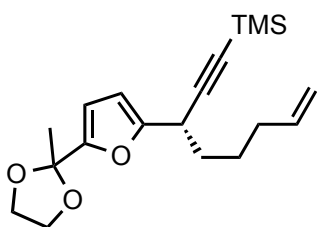
Product **2c** was prepared according to general procedure **C**¹² using 3-furoic acid (224 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (*S*)-(3-bromohex-1-yn-1-yl)trimethylsilane **4a** (233 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/ethyl acetate/acetic acid, 78:20:2), **2c** was obtained (188 mg, 71%, 95% ee).



¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 7.35 (d, *J* = 2.0 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 4.67 (dd, *J* = 7.2 Hz, *J* = 7.2 Hz, 1H), 1.95-1.73 (m, H), 1.52-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H), 0.16 (s, 9H). **¹³C NMR** (CDCl₃, 100 MHz, δ (ppm)) 169.3, 161.2, 141.5, 12.6, 110.8, 103.9, 86.5, 37.0, 30.9, 20.3, 13.6, 0.0. **IR (thin film)** ν = 3300, 2919, 2834, 2146, 1663, 1575, 1498, 1435, 1301, 1233, 1187. [α]₂₅^D = 118.3 (c = 1.0 in CHCl₃). **Chiral HPLC:** Chiralpak® IB, 10% isopropanol in heptane, 0.8 mL.min⁻¹, λ = 254 nm, t_R = 8.81 (major), 10.65 (minor). **HRMS** Calcd for C₁₄H₂₀O₃Si+Na⁺: 287.1080, found: 287.1073.

(*S*)-trimethyl(3-(5-(2-methyl-1,3-dioxolan-2-yl)furan-2-yl)oct-7-en-1-yn-1-yl)silane **2d**

Product **2d** was prepared according to general procedure **C** using 2-(furan-2-yl)-2-methyl-1,3-dioxolane¹⁴ (308 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (*R*)-(3-bromohept-6-en-1-yn-1-yl)trimethylsilane **4e** (245 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/diethyl ether 95:5), **2d** was obtained (276 mg, 83%, 98% ee).

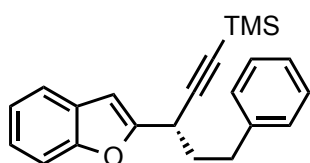


¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 6.22 (d, *J* = 3.2 Hz, 1H), 6.14 (dd, *J* = 3.2 Hz, *J* = 1.2 Hz, 1H), 5.86-5.76 (m, 1H), 5.05 (dd, *J* = 17.2 Hz, *J* = 2.0 Hz, 1H), 4.98 (dd, *J* = 10.4 Hz, *J* = 1.2 Hz, 1H), 4.06-3.95 (m, 4H), 3.76 (dd, *J* = 8.4 Hz, *J* = 5.6 Hz, 1H), 2.25-2.15 (m, 2H), 1.98-1.77 (m, 2H), 1.71 (s, 3H), 0.17 (s, 9H). **¹³C NMR** (CDCl₃, 100 MHz, δ (ppm)) 154.1, 153.3, 137.6, 115.2, 107.1, 106.1, 104.9, 104.6, 87.1, 65.1, 65.0, 33.7, 31.9, 30.9, 24.2, 0.0. **IR (thin film)** ν = 3035, 2916, 2854, 2145, 1617, 1576, 1530, 1421, 1356, 1233, 1177, 1094. [α]₂₅^D = 19.5 (c = 1.0 in CHCl₃). **Chiral HPLC:** Chiralpak® IC, heptane, 0.8 mL.min⁻¹, λ = 220 nm, t_R = 4.42 (major), t_R = 5.03 (minor). **HRMS** Calcd for C₁₉H₂₈O₃Si+Na⁺: 341.1549, found: 341.1536.

¹⁴ Dang, Q. et al. *J. Med. Chem.* **2011**, *54*, 153.

(S)-(3-(benzofuran-2-yl)-5-phenylpent-1-yn-1-yl)trimethylsilane 2e

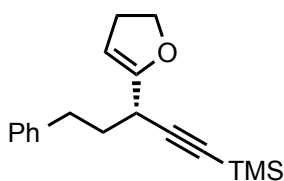
Product **2e** was prepared according to general procedure **C** using benzofuran (236 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (*R*)-(3-bromo-5-phenylpent-1-yn-1-yl)trimethylsilane **4f** (295 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/diethyl ether 98:2), **2e** was obtained (229 mg, 69%, 94% ee).



¹H NMR (CDCl₃, 500 MHz, δ (ppm)) 7.54 (dd, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.34-7.28 (m, 2H), 7.27-7.18 (m, 5H), 6.66 (s, 1H), 3.92 (dd, *J* = 8.0 Hz, *J* = 5.3 Hz, 1H), 2.94-2.77 (m, 2H), 2.34-2.26 (m, 1H), 2.24-2.14 (m, 1H), 0.25 (s, 9H). **¹³C NMR** (CDCl₃, 125 MHz, δ (ppm)) 157.1, 154.9, 141.2, 128.5, 128.4, 126.0, 123.6, 122.6, 120.6, 111.0, 104.3, 103.1, 88.0, 35.8, 32.9, 32.3, 0.1. **IR (thin film)** ν = 3024, 3020, 2985, 2915, 2859, 2146, 1578, 1563, 1433, 1234. **[α]₂₅^D** = 18.7 (*c* = 1.0 in CHCl₃). **Chiral HPLC¹⁵**: Chiralpak® IA, heptane, 1.0 mL.min⁻¹, λ = 254 nm, *t_R* = 7.70 (major), *t_R* = 9.77 (minor). **HRMS** Calcd for C₂₂H₂₄OSi+Na⁺: 355.1494, found: 355.1489.

(S)-(3-(4,5-dihydrofuran-2-yl)-5-phenylpent-1-yn-1-yl)trimethylsilane 2f

Product **2f** was prepared according to general procedure **C** using dihydrofuran (140 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (*R*)-(3-bromo-5-phenylpent-1-yn-1-yl)trimethylsilane **4f** (295 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/diethyl ether/tirethylamine 97:2:1), **2f** was obtained (182 mg, 64%, 91% ee).



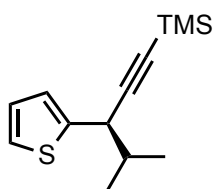
¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 7.32-7.26 (m, 2H), 7.24-7.14 (m, 3H), 4.91 (brs, 1H), 4.36 (t, *J* = 9.2 Hz, 1H), 3.15-3.17 (m, 1H), 2.86-2.69 (m, 2H), 2.67-2.59 (m, 2H), 2.09-1.98 (m, 1H), 1.96-1.84 (m, 1H), 0.21 (s, 9H). **¹³C NMR** (CDCl₃, 125 MHz, δ (ppm)) 157.0, 141.7, 128.5, 128.3, 125.8, 105.5, 95.7, 87.0, 70.6, 4.5, 32.9, 31.8, 29.8, -0.1. **IR (thin film)** ν = 3019, 2916, 2855, 2821, 2146, 1641, 1475, 1434, 1231, 1135.). **[α]₂₅^D** = 20.9 (*c* = 1.0 in CHCl₃). **Chiral HPLC**: Chiralpak® IA, 1% isopropanol in heptane, 0.8 mL.min⁻¹, λ = 220 nm, *t_R* = 4.6 (major), 4.8 (minor). **HRMS** Calcd for C₁₈H₂₄OSi+Na⁺: 307.1494, found: 307.1489.

(R)-trimethyl(4-methyl-3-(thiophen-2-yl)pent-1-yn-1-yl)silane 2g

Product **2g** was prepared according to general procedure **C** using thiophene **1c** (168 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (*S*)-(3-bromo-4-methylpent-1-yn-1-yl)trimethylsilane **4g** (233 mg, 1 mmol). After purification by flash chromatography

¹⁵ Chiral HPLC analysis was ran on the corresponding terminal alkyne which was obtained by deprotection of the TMS protecting group (TBAF 3 equiv., AcOH 30 mol%, THF, rt)

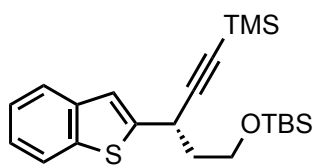
over silica gel (petroleum ether/diethyl ether 99:1), **2g** was obtained (165 mg, 70%, 94% ee).



¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 7.19-7.15 (m, 1H), 6.99-6.92 (m, 2H), 3.84 (d, *J* = 5.2 Hz, 1H), 2.09-1.97 (m, 1H), 1.05 (dd, *J* = 6.8 Hz, *J* = 1.6 Hz, 3H), 0.96 (dd, *J* = 6.8 Hz, *J* = 1.6 Hz, 3H), 0.21 (s, 9H). **¹³C NMR** (CDCl₃, 125 MHz, δ (ppm)) 144.3, 126.4, 125.0, 123.7, 105.7, 88.2, 41.2, 35.3, 20.8, 18.2, 0.1. **IR (thin film)** ν = 2919, 2889, 2857, 2831, 2142, 1443, 1232. [α]₂₅^D = -8.1 (c = 1.0 in CHCl₃). **Chiral HPLC:** Chiralpak® IA, heptane, 0.8 mL.min⁻¹, λ = 220 nm, t_R = 4.88 (major), 5.29 (minor). **HRMS** Calcd for C₁₃H₂₀SSi+NH₄⁺: 254.1399, found: 254.1407.

(*S*)-(3-(benzo[*b*]thiophen-2-yl)-5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)trimethylsilane **2h**

Product **2h** was prepared according to general procedure **C** using benzothiophene (268 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (*R*)-(3-bromo-5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)trimethylsilane **4h** (349 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/diethyl ether 98:2), **2h** was obtained (248 mg, 71%, 98% ee).



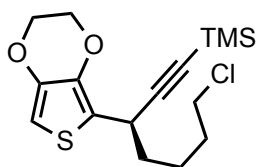
¹H NMR (CDCl₃, 500 MHz, δ (ppm)) 7.80-7.76 (m, 1H), 7.71-7.67 (m, 1H), 7.34-7.30 (m, 1H), 7.29-7.25 (m, 1H), 7.20 (s, 1H), 4.22 (dd, *J* = 9.0 Hz, *J* = 5.5 Hz, 1H), 3.89-3.83 (m, 1H), 3.77-3.71 (m, 1H), 2.16-2.08 (m, 1H), 2.06-1.99 (m, 1H), 0.92 (s, 9H), 0.20 (s, 9H), 0.1 (s, 3H), 0.1 (s, 3H). **¹³C NMR** (CDCl₃, 125 MHz, δ (ppm)) 146.0, 139.7, 139.4, 124.1, 123.8, 123.1, 122.2, 121.0, 106.2, 87.8, 60.2, 40.8, 30.9, 26.0, 18.4, 0.0, -5.3, -5.4. **IR (thin film)** ν = 3017, 2987, 2914, 2857, 2142, 1899, 1440, 1233, 1087. [α]₂₅^D = 16.6 (c = 1.0 in CHCl₃). **Chiral HPLC:**¹⁶ Chiralpak® IC, 2% isopropanol in heptane, 0.6 mL.min⁻¹, λ = 254 nm, t_R = 16.27 (major), 16.99 (minor). **HRMS** Calcd for C₂₂H₃₄OSSi₂+H⁺: 403.1947, found: 403.1943.

(*S*)-(7-chloro-3-(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-yl)hept-1-yn-1-yl)trimethylsilane **2i**

Product **2i** was prepared according to general procedure **C** using 2,3-dihydrothieno[3,4-*b*][1,4]dioxine (284 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (*R*)-(3-bromo-7-chlorohept-1-yn-1-yl)trimethylsilane **4i** (282 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/diethyl ether 95:5 to 90:10), **2i** was obtained (322 mg, 94%, 97% ee).

¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 6.18 (s, 1H), 4.17 (s, 4H), 3.96 (dd, *J* = 7.2 Hz, *J* = 7.2 Hz, 1H), 3.53 (t, *J* = 6.8 Hz, 2H), 1.85-1.72 (m, 4H), 1.68-1.45 (m, 2H), 0.17 (s, 9H).

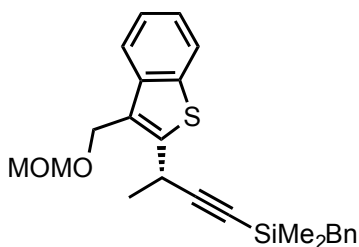
¹⁶ Chiral HPLC analysis was ran on the corresponding alcohol which was obtained by deprotection of the TBS protecting group (2N HCl_(aq.) in MeOH, 5 min.)



¹³C NMR (CDCl₃, 125 MHz, δ (ppm)) 141.2, 137.3, 117.9, 106.5, 106.5, 96.5, 86.9, 64.7, 64.6, 44.9, 36.0, 32.1, 30.1, 24.3, 0.0. IR (thin film) ν = 3071, 2915, 2830, 2141, 1480, 1419, 1347, 1231, 1149. [α]₂₅^D = 1.2 (c = 1.0 in CHCl₃). Chiral HPLC: Chiralpak® IC, heptane, 0.8 mL·min⁻¹, λ = 254 nm, t_R = 37.9 (minor), 38.9 (major). HRMS Calcd for C₁₆H₂₃ClO₂SSi+H⁺: 343.0955, found: 343.0943.

(S)-benzyl(3-(3-((methoxymethoxy)methyl)benzo[b]thiophen-2-yl)but-1-yn-1-yl)dimethylsilane **2j**

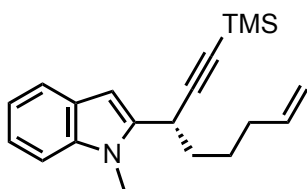
Product **2j** was prepared according to general procedure C using 3-((methoxymethoxy)methyl)benzo[b]thiophene¹⁷ (416 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (R)-benzyl(3-bromobut-1-yn-1-yl)dimethylsilane **4j** (281 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/diethyl ether 98:2 to 90:10), **2j** was obtained (339 mg, 87%, 93% ee).



¹H NMR (CDCl₃, 500 MHz, δ (ppm)) 7.83-7.80 (m, 2H), 7.41-7.36 (m, 1H), 7.35-7.30 (m, 1H), 7.20-7.15 (m, 2H), 7.09-7.05 (m, 3H), 4.83 (d, J = 12.0 Hz, 1H), 4.78 (d, J = 12.0 Hz, 1H), 4.69 (d, J = 7.0 Hz, 1H), 4.68 (d, J = 7.0 Hz, 1H), 4.37 (q, J = 7.5 Hz, 1H), 3.44 (s, 3H), 2.21 (s, 2H), 1.62 (d, J = 7.5 Hz, 3H), 0.13 (s, 3H), 0.13 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz, δ (ppm)) 146.8, 139.8, 139.0, 138.2, 128.4, 128.1, 126.6, 124.3, 124.2, 122.3, 121.8, 109.2, 95.2, 84.9, 59.7, 55.5, 26.9, 26.2, 24.5, -2.1. IR (thin film) ν = 3036, 3017, 2982, 2918, 2782, 2736, 2138, 1912, 1577, 1472, 1431, 1416, 1384, 1353, 1273. [α]₂₅^D = -23.4 (c = 1.0 in CHCl₃). Chiral HPLC: Chiralpak® IB, 0.1% isopropanol in heptane, 0.8 mL·min⁻¹, λ = 254 nm, t_R = 20.1 min (major), 22.3 (minor). HRMS Calcd for C₂₄H₂₈O₂SSi+NH₄⁺: 426.1923, found: 426.1918.

(S)-1-methyl-2-(1-(trimethylsilyl)oct-7-en-1-yn-3-yl)-1H-indole **2k**

Product **2k** was prepared according to general procedure C using N-methylindole (262 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (R)-(3-bromohept-6-en-1-yn-1-yl)trimethylsilane **4e** (245 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/DCM 95:5 to 80:20), **2k** was obtained (251 mg, 81%, 95% ee).



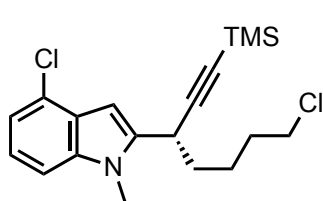
¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 7.62 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.26-7.22 (m, 1H), 7.16-7.11 (m, 1H), 6.44 (s, 1H), 5.96-5.85 (m, 1H), 5.19 (d, J = 18.8 Hz, 1H), 5.13 (d, J = 10.0 Hz, 1H), 3.96 (t, J = 7.4 Hz, 2H), 3.85 (s,

¹⁷ 3-((methoxymethoxy)methyl)benzo[b]thiophene was obtained by reacting benzo[b]thiophen-3-ylmethanol with MOMCl and Hünig's base in DCM.

3H), 2.47-2.32 (m, 2H), 2.16-2.02 (m, 2H), 0.26 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz, δ (ppm)) 139.2, 137.7, 137.5, 127.5, 121.1, 120.2, 119.4, 115.6, 108.8, 105.7, 99.3, 87.3, 33.7, 31.3, 30.3, 30.0, 0.0. IR (thin film) ν = 3013, 2915, 2140, 1617, 1519, 1448, 1414, 1379, 1320, 1298, 1232. $[\alpha]_{25}^{\text{D}}$ = 1.5 (c = 1.0 in CHCl_3). Chiral HPLC: Chiralpak® HRMS Calcd for $\text{C}_{19}\text{H}_{25}\text{NSi}+\text{H}^+$: 296.1829, found: 296.1835.

(S)-4-chloro-2-(7-chloro-1-(trimethylsilyl)hept-1-yn-3-yl)-1-methyl-1H-indole 2l

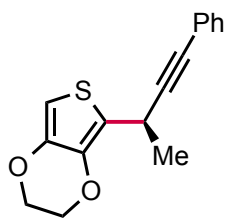
Product **2l** was prepared according to general procedure C using 4-chloro-1-methyl-1H-indole (331 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (R)-(3-bromo-7-chlorohept-1-yn-1-yl)trimethylsilane **4i** (282 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/DCM 95:5 to 80:20), **2l** was obtained (202 mg, 55%, 97% ee).



^1H NMR (CDCl_3 , 500 MHz, δ (ppm)) 7.24-7.15 (m, 1H), 7.13-7.05 (m, 2H), 6.47 (s, 1H), 3.85 (t, J = 7.2 Hz, 1H), 3.79 (s, 3H), 3.58 (t, J = 6.8 Hz, 2H), 2.04-1.82 (m, 4H), 1.82-1.60 (m, 2H), 0.16 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz, δ (ppm)) 139.9, 138.5, 126.2, 125.6, 121.7, 119.2, 107.6, 105.0, 97.9, 44.7, 33.6, 32.1, 31.0, 30.5, 24.7, 0.0. $[\alpha]_{25}^{\text{D}}$ = 27.0 (c = 1.0 in CHCl_3). Chiral HPLC: Chiralpak® IA, 0.1% isopropanol in heptane, 0.8 mL.min $^{-1}$, λ = 254 nm, t_{R} = 8.9 (major), 9.6 (minor). HRMS Calcd for $\text{C}_{19}\text{H}_{25}\text{Cl}_2\text{NSi}+\text{H}^+$: 366.1212, found: 366.1203.

(R)-5-(4-phenylbut-3-yn-2-yl)-2,3-dihydrothieno[3,4-b][1,4]dioxine 2m

Product **2m** was prepared according to general procedure C using 2,3-dihydrothieno[3,4-*b*][1,4]dioxine (284 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (S)-(3-bromobut-1-yn-1-yl)benzene **4k** (209 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/diethyl ether 95:5 to 90:10), **2m** was obtained (197 mg, 73%, 80% ee).

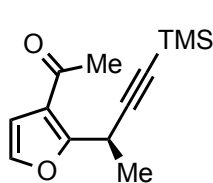


^1H NMR (CDCl_3 , 400 MHz, δ (ppm)) 7.48-7.41 (m, 2H), 7.32-7.27 (m, 3H), 6.19 (s, 1H), 4.26 (q, J = 6.8 Hz, 1H), 4.24-4.17 (m, 4H), 1.59 (d, J = 6.8 Hz, 3H). ^{13}C NMR (CDCl_3 , 75 MHz, δ (ppm)) 141.4, 137.0, 131.6, 128.1, 127.8, 123.4, 119.6, 96.1, 91.4, 81.5, 64.7, 64.6, 24.5, 22.9. IR (thin film) ν = 3112, 2978, 2928, 2871, 2362, 2340, 1597, 1499, 1439, 1365, 1166, 1133, 1082, 1065. $[\alpha]_{25}^{\text{D}}$ = -50.7 (1M in CHCl_3). Chiral HPLC: Chiralpak® IC, 0.1% isopropanol in heptane, 0.8 mL.min $^{-1}$, λ = 254 nm, t_{R} = 35.6 min (minor), 44.4 min (major). HRMS Calcd for $\text{C}_{16}\text{H}_{14}\text{SO}_2+\text{H}^+$: 271.0788, found: 271.0793.

(*R*)-1-(2-(4-(trimethylsilyl)but-3-yn-2-yl)furan-3-yl)ethan-1-one **5a**

Product **2n** was prepared according to general procedure **C** using 3-furan carboxaldehyde **1b** (192 mg, 2 mmol), CuCN (89 mg, 1 mmol) and (*S*)-(3-bromobut-1-yn-1-yl)trimethylsilane **4b** (205 mg, 1 mmol). After purification by flash chromatography over silica gel (petroleum ether/diethyl ether 95:5 to 85:15), **2n** was obtained (199 mg, 84%).

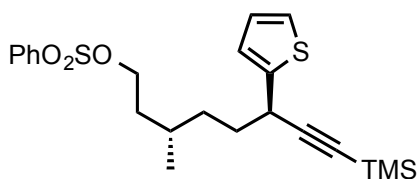
Alcohol **2n** was dissolved in DCM (10 mL) and NaHCO₃ (141 mg, 2 equiv.) followed by Dess-Martin periodinane (534 mg, 1.5 equiv.) were added. After 3 hours the TLC showed no remaining alcohol **2n** and the residue was filtrated over silica, evaporated to dryness and purified by chromatography over silica gel (petroleum ether/diethyl ether 95:5 to 85:15) to deliver **5a** (159 mg, 81%, 95% ee).



¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 7.31 (d, $J = 2.0$ Hz, 1H), 6.60 (d, $J = 2.0$ Hz, 1H), 4.73 (q, $J = 7.2$ Hz, 1H), 2.40 (s, 3H), 1.47 (d, $J = 7.2$ Hz, 3H), 0.13 (s, 9H). **¹³C NMR** (CDCl₃, 100 MHz, δ (ppm)) 193.9, 159.3, 141.0, 119.7, 110.4, 110.4, 105.2, 85.5, 29.2, 25.8, 20.4, 0.0. **IR (thin film)** $\nu = 3102, 3076, 2944, 2917, 2896, 2858, 2135, 1658, 1558, 1492, 1426, 1401, 1379, 1340, 1293, 1273, 1231$. $[\alpha]_{25}^D = 94.5$. **Chiral HPLC**: Chiralpak® IB, 0.1% isopropanol in heptane, 0.6 mL.min⁻¹, $\lambda = 254$ nm, $t_R = 20.5$ (major), 22.7 (minor). **HRMS** Calcd for C₁₃H₁₈O₂Si+H⁺: 235.1154, found: 235.1145.

(2*S*,5*R*)-2-methyl-5-(thiophen-2-yl)-7-(trimethylsilyl)hept-6-yn-1-ylbenzene sulfonate **2o**

Product **2o** was prepared according to general procedure **C** using thiophene **1c** (402 mg, 3 mmol), CuCN (134 mg, 1 mmol) and (3*S*,6*S*)-6-bromo-3-methyl-8-(trimethylsilyl)oct-7-yn-1-yl benzenesulfonate **4c** (647 mg, 1.5 mmol). After purification by flash chromatography over silica gel (petroleum ether/ethyl acetate 95:5 to 85:15), **2o** was obtained (535 mg, 82%, dr > 95:5).

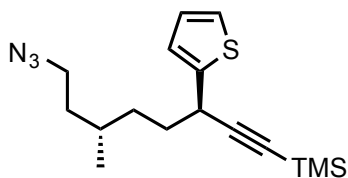


¹H NMR (CDCl₃, 500 MHz, δ (ppm)) 7.93-7.89 (m, 2H), 7.67-7.62 (m, 1H), 7.58-7.53 (m, 2H), 7.17 (dd, $J = 5$ Hz, $J = 1.5$ Hz, 1H), 6.95-6.91 (m, 2H), 4.12-4.04 (m, 2H), 3.85 (dd, $J = 6$ Hz, $J = 8.3$ Hz, 1H), 1.80-1.64 (m, 3H), 1.60-1.50 (m, 1H), 1.48-1.24 (m, 4H), 0.81 (d, $J = 6.5$ Hz, 3H), 0.18 (s, 9H).

¹³C NMR (CDCl₃, 125 MHz, δ (ppm)) 145.1, 136.1, 133.6, 129.2, 127.8, 126.5, 124.3, 123.8, 107.0, 87.4, 69.1, 35.7, 35.6, 33.9, 33.6, 28.8, 18.9, 0.0. $[\alpha]_{25}^D = -14.0$ ($c = 1.0$ in CHCl₃). **MS** Calcd for C₂₂H₃₀O₃S₂Si+Na⁺: 457.1, found: 457.1.

(3*S*,6*R*)-3-methyl-6-(thiophen-2-yl)-8-(trimethylsilyl)oct-7-yn-1-ylbenzene sulfonate **5b**

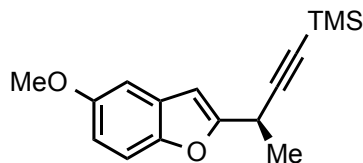
Sulfonate **2o** (217 mg, 0.5 mmol) was dissolved in dry DMF (3 mL) and NaN₃ (98 mg, 3 equiv.) was added. The resulting mixture was heated to 90°C for 1.5 hours. After work up (Et₂O, H₂O), the residue was purified by flash chromatography over silica gel (petroleum ether/diethyl ether 95:5) to deliver **5b** (142 mg, 89%, dr > 95:5).



¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 7.20-7.15 (m, 1H), 7.00-6.91 (m, 2H), 3.93 (t, *J* = 7.2 Hz, 1H), 3.36-3.19 (m, 2H), 1.90-1.77 (m, 4H), 1.69-1.28 (m, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.20 (s, 9H). **¹³C NMR** (CDCl₃, 100 MHz, δ (ppm)) 145.2, 126.5, 124.3, 123.8, 107.1, 87.4, 49.4, 35.7, 35.6, 33.9, 33.6, 29.9, 19.2, 0.0. **IR (thin film)** ν = 2917, 2832, 2225, 2141, 1440, 1360, 1232, 1026. **[α]_D²⁵** = -19.4 (c = 1.0 in CHCl₃). **HRMS** Calcd for C₁₆H₂₅N₃SSi+H⁺: 320.1616, found: 320.1599.

(*R*)-(3-(5-methoxybenzofuran-2-yl)but-1-yn-1-yl)trimethylsilane **2p**

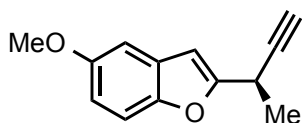
Product **2p** was prepared according to general procedure **C** using 5-methoxybenzofuran **1d** (889 mg, 6 mmol), CuCN (267 mg, 3 mmol) and (*S*)-(3-bromobut-1-yn-1-yl)trimethylsilane **4b** (616 mg, 3 mmol). After purification by flash chromatography over silica gel (petroleum ether/diethyl 99:1 to 97:3), **2p** was obtained (646 mg, 79%, 96% ee).



¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 7.36-7.31 (m, 1H), 7.0 (d, *J* = 2.6 Hz, 1H), 6.85 (dd, *J* = 8.8 Hz, *J* = 2.6 Hz, 1H), 6.58-6.55 (m, 1H), 3.97 (qd, *J* = 8.4 Hz, *J* = 1.2 Hz, 1H), 3.84 (s, 3H), 1.61 (d, *J* = 8.4 Hz, 3H), 0.22 (s, 9H). **¹³C NMR** (CDCl₃, 100 MHz, δ (ppm)) 159.2, 155.8, 149.9, 129.0, 112.0, 111.3, 105.8, 103.4, 102.2, 86.2, 55.8, 27.3, 20.4, 0.0. **IR (thin film)** ν = 3005, 2944, 2916, 2858, 2792, 2141, 1595, 1579, 1445, 1429, 1232, 1210. **[α]_D²⁵** = -0.6 (c = 1.0 in CHCl₃). **Chiral HPLC**: Chiralpak® IC, 0.5% isopropanol in heptane, 0.8 mL.min⁻¹, λ = 254 nm, t_R = 8.1 min (minor), 9.1 min (major). **HRMS** Calcd for C₁₆H₂₀O₂Si⁺: 272.1233, found: 272.1236.

(*R*)-2-(but-3-yn-2-yl)-5-methoxybenzofuran

TMS-alkyne **2p** (409 mg, 1.5 mmol) was dissolved in THF (5 mL) and AcOH (58 μL, 1 mmol) followed by TBAF (1M in THF, 1.8 mL, 1.8 mmol). When the TLC showed full conversion, the reaction medium was quenched with water and worked-up. The residue was evaporated to dryness and purified by flash chromatography over silica gel (petroleum ether/diethyl 98:2 to 96:4) to deliver the terminal alkyne (288 mg, 96%).

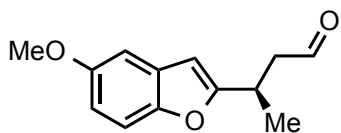


¹H NMR (CDCl₃, 400 MHz, δ (ppm)) 7.36-7.31 (m, 1H), 7.0 (d, *J* = 2.8 Hz, 1H), 6.85 (dd, *J* = 8.8 Hz, *J* = 2.8 Hz, 1H), 6.58-6.55 (m, 1H), 3.99-3.90 (m, 1H), 3.84 (s, 3H), 2.29 (dq, *J* =

2.8 Hz, $J = 0.4$ Hz, 1H), 1.63 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz, δ (ppm)) 158.7, 155.8, 149.9, 128.9, 112.2, 111.4, 103.4, 102.2, 83.8, 70.0, 55.9, 26.1, 20.2. IR (thin film) $\nu = 3248, 2947, 2897, 2793, 1593, 1580, 1455, 1429, 1270, 1189, 1164, 1120$. $[\alpha]_{25}^{\text{D}} = 1.4$ ($c = 1.0$ in CHCl_3).

(R)-3-(5-methoxybenzofuran-2-yl)butanal 5c

The previously obtained terminal alkyne (200 mg, 1 mmol) was dissolved in dry THF (2 mL) and cooled to -20°C . A suspension of dicyclohexylborane (2 mmol) in dry THF (2 mL) was added and the resulting mixture was warmed to room temperature and stirred for 2 additional hours at room temperature at which point a solution of NaOH (1M, 5.5 mL) followed by H_2O_2 (30%, 1.9 mL) were added. The biphasic mixture was vigorously stirred for 3 hours at room temperature and after usual work up, the residue was purified by flash chromatography over silica gel (petroleum ether/diethyl 95:5 to 80:20) to afford aldehyde **5c**¹⁸ (181 mg, 83%, 96%).

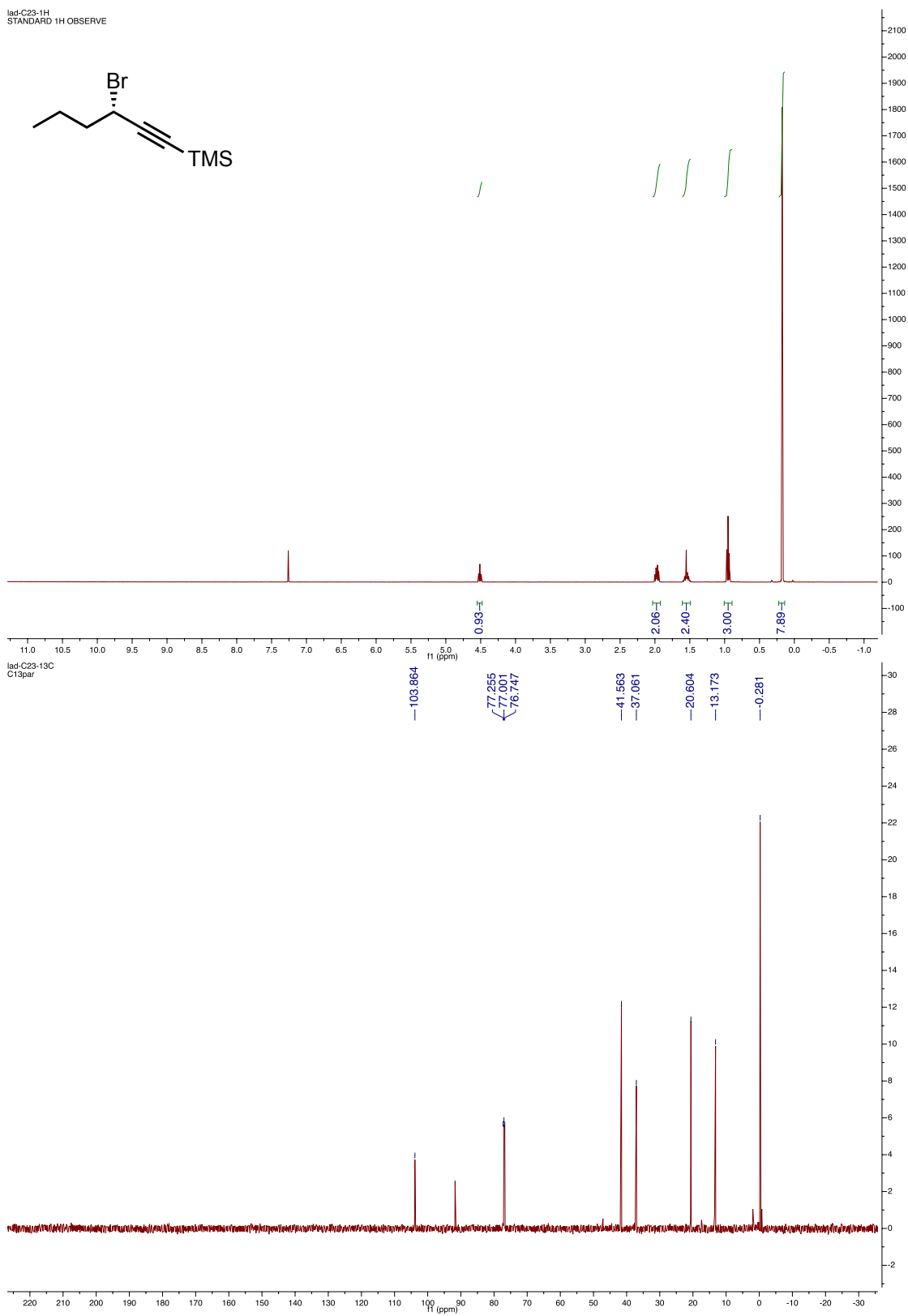
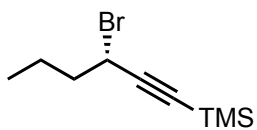


^1H NMR (CDCl_3 , 400 MHz, δ (ppm)) 9.81 (t, $J = 1.8$ Hz, 1H), 7.31-7.27 (m, 1H), 6.96 (d, $J = 2,4$ Hz, 1H), 6.83 (dd, $J = 8.8$ Hz, $J = 2.8$ Hz, 1H), 6.37-6.35 (m, 1H), 3.83 (s, 3H), 3.60-3.48 (m, 1H), 2.80 (ddd, $J = 17.3$ Hz, $J = 6.6$ Hz, $J = 1.8$ Hz, 2H), 1.40 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz, δ (ppm)) 200.9, 162.1, 155.8, 149.6, 129.0, 112.0, 111.2, 103.3, 101.5, 55.9, 48.8, 28.2, 18.8. IR (thin film) $\nu = 2998, 2893, 2792, 2687, 1701, 1600, 1593, 1456, 1429, 1188, 1016$. $[\alpha]_{25}^{\text{D}} = -12.8$ ($c = 1.0$ in CHCl_3). Chiral HPLC: Chiralpak® IC, 2% isopropanol in heptane, $0.8 \text{ mL}\cdot\text{min}^{-1}$, $\lambda = 254 \text{ nm}$, $t_{\text{R}} = 19.0 \text{ min}$ (minor), 21.1 min (major).

¹⁸ Reiter, M.; Torssell, S.; Lee, S.; MacMillan, D. W. C. *Chem. Sci.* **2010**, *1*, 37.

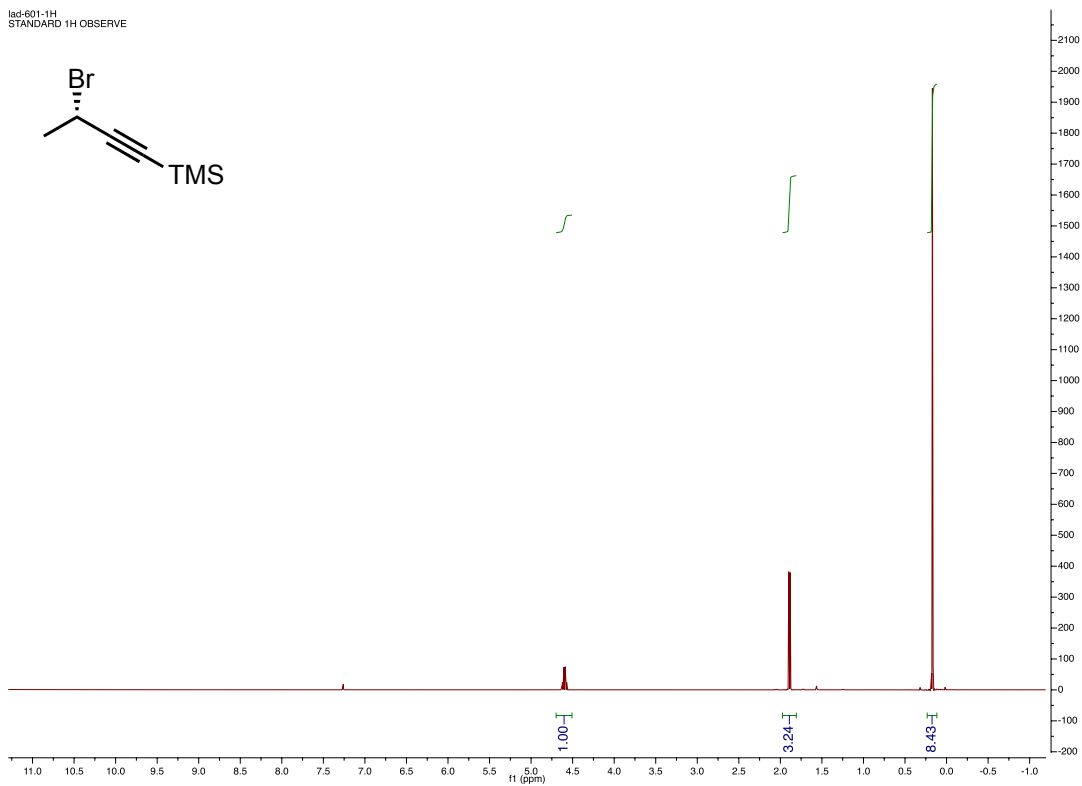
Compound 4a

lad-C23-1H
STANDARD 1H OBSERVE

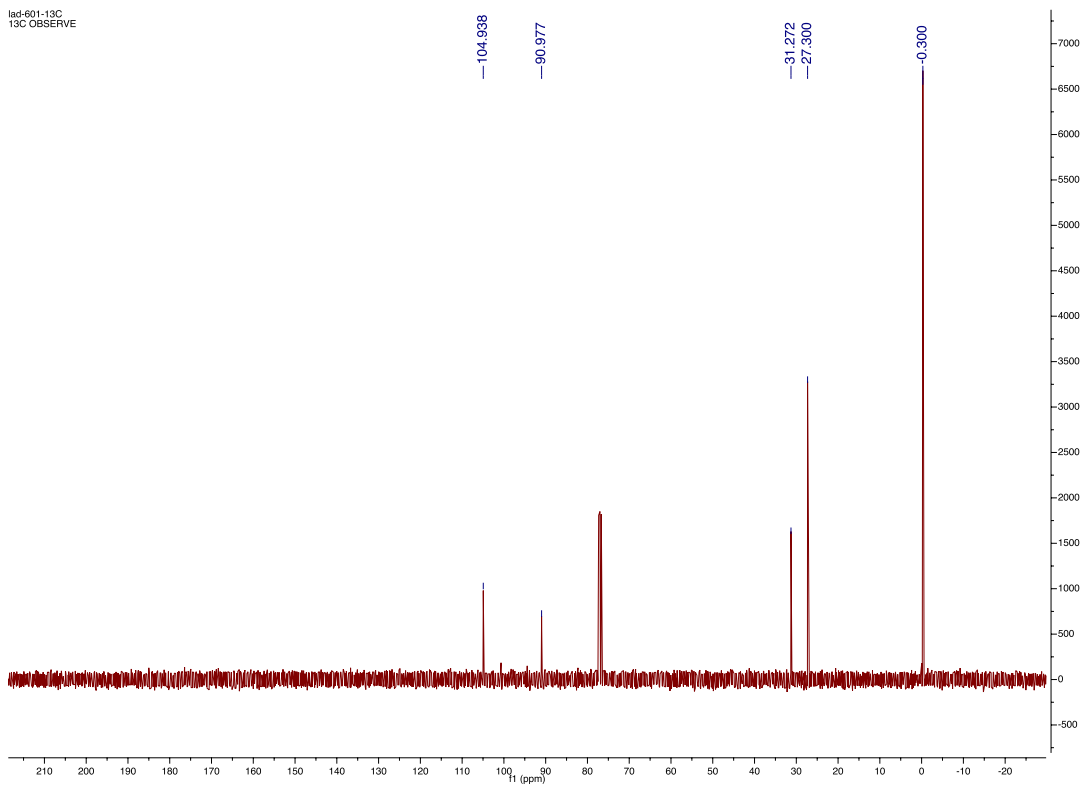


Compound 4b

lad-601-1H
STANDARD 1H OBSERVE

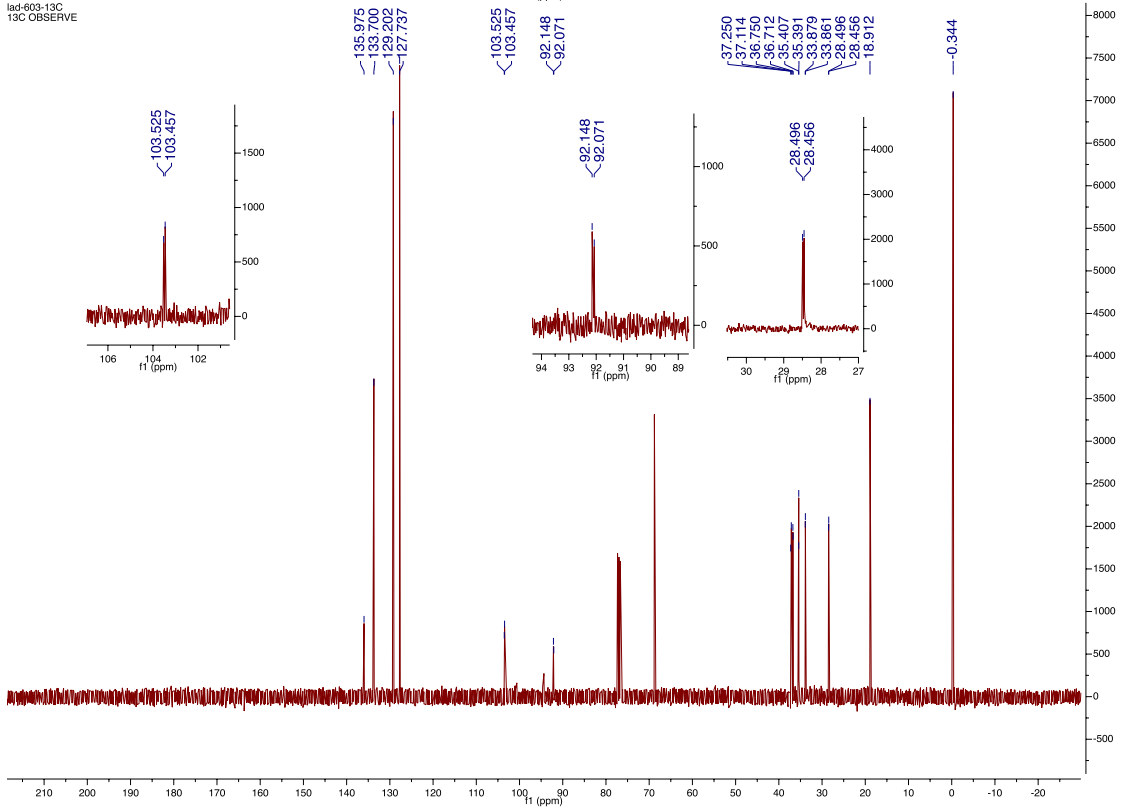
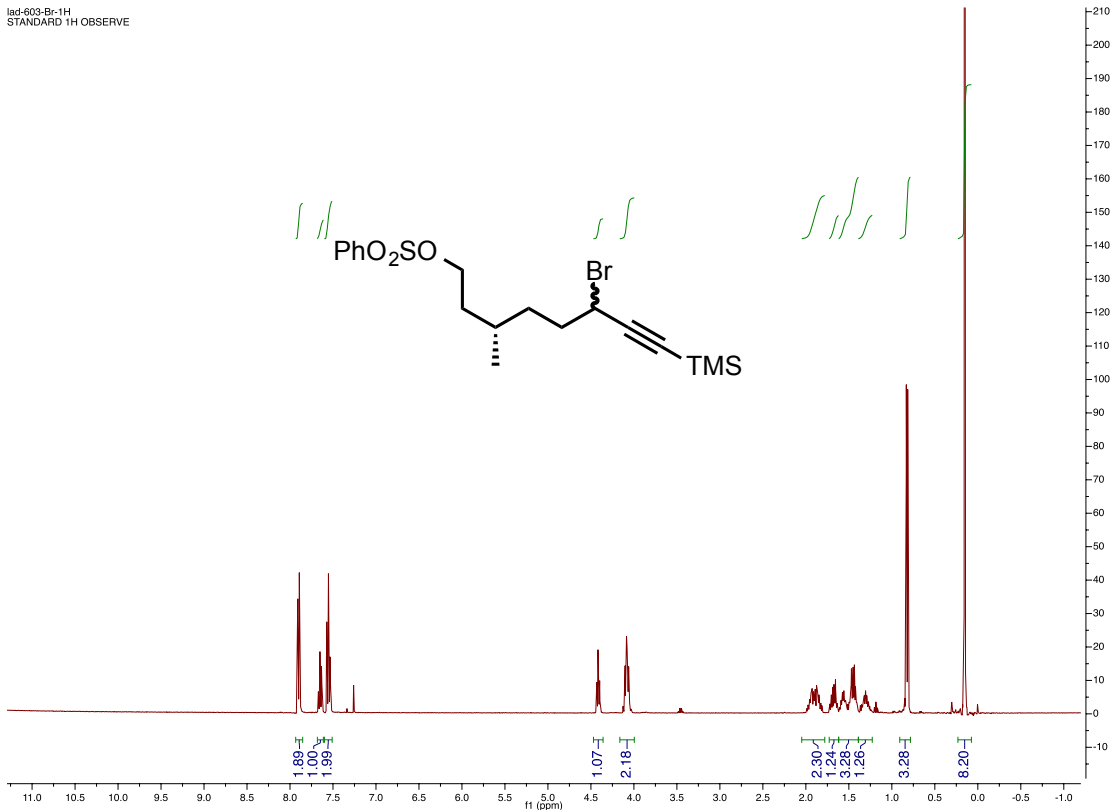


lad-601-13C
13C OBSERVE



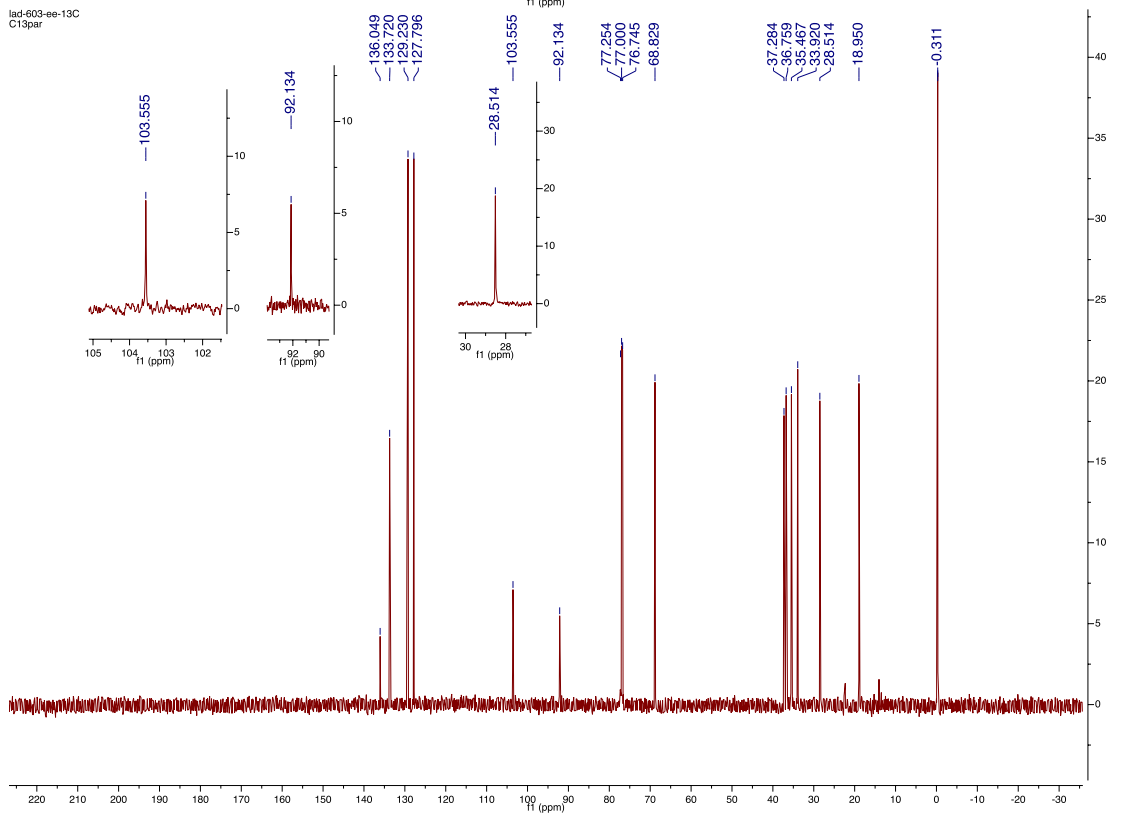
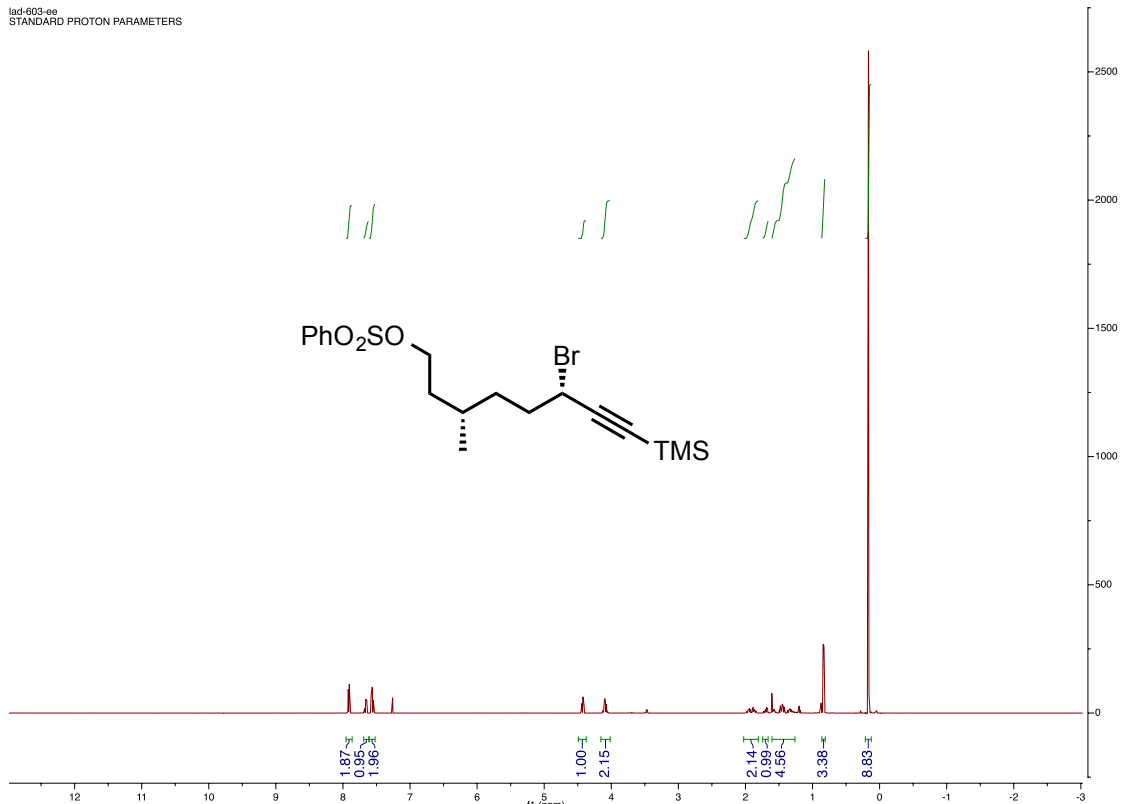
Compound 4c dr = 1:1

lad-603-B-1H
STANDARD 1H OBSERVE



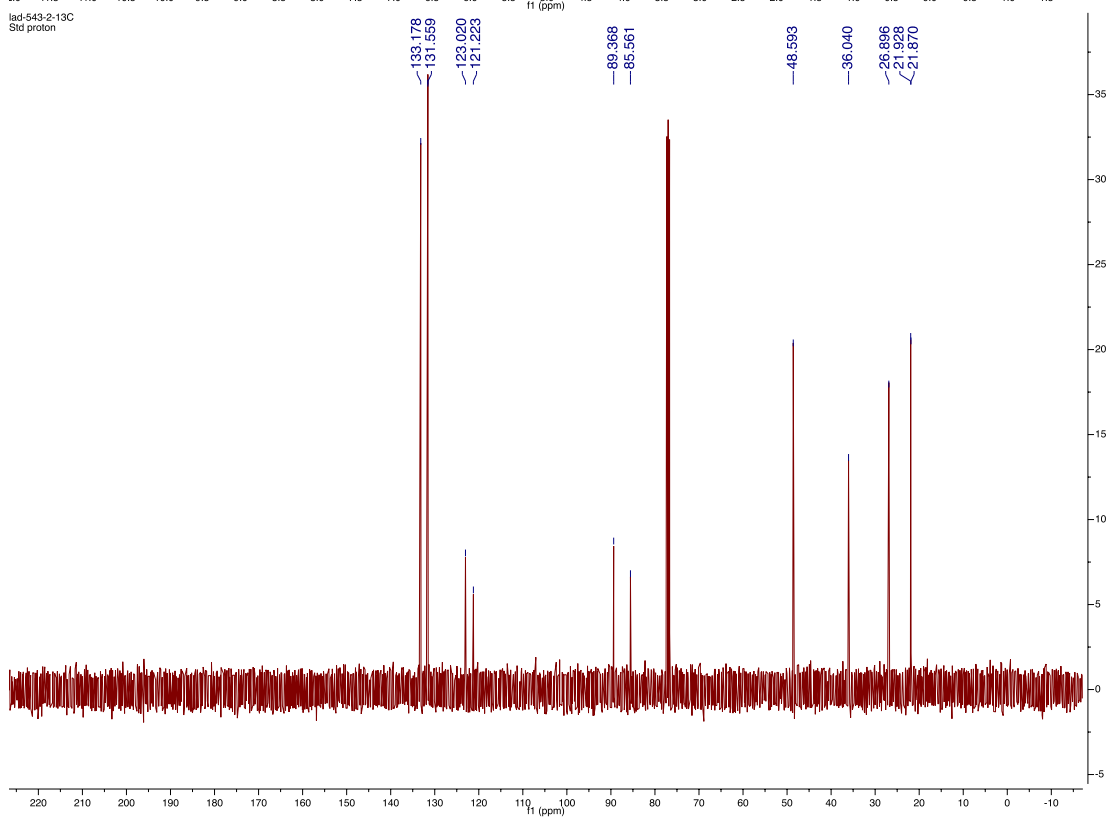
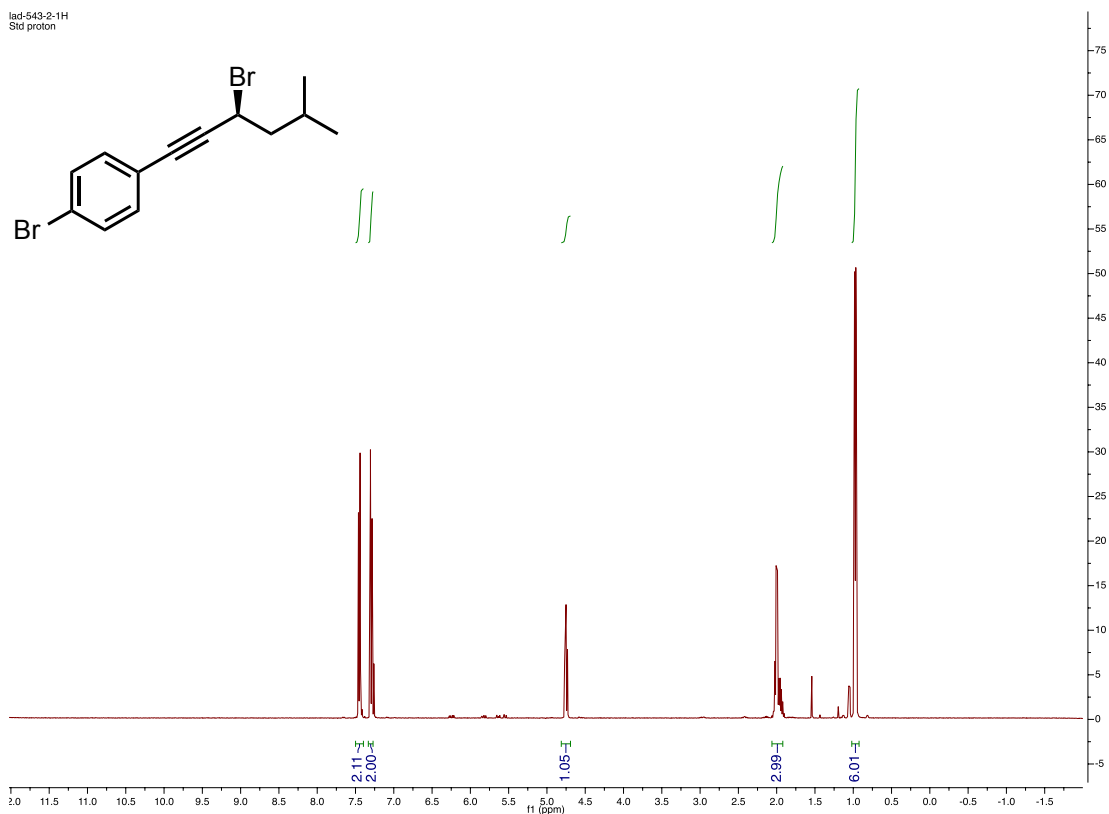
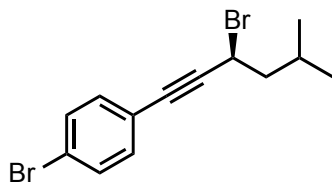
Compound 4c dr > 95:5

lad-603-ee
STANDARD PROTON PARAMETERS



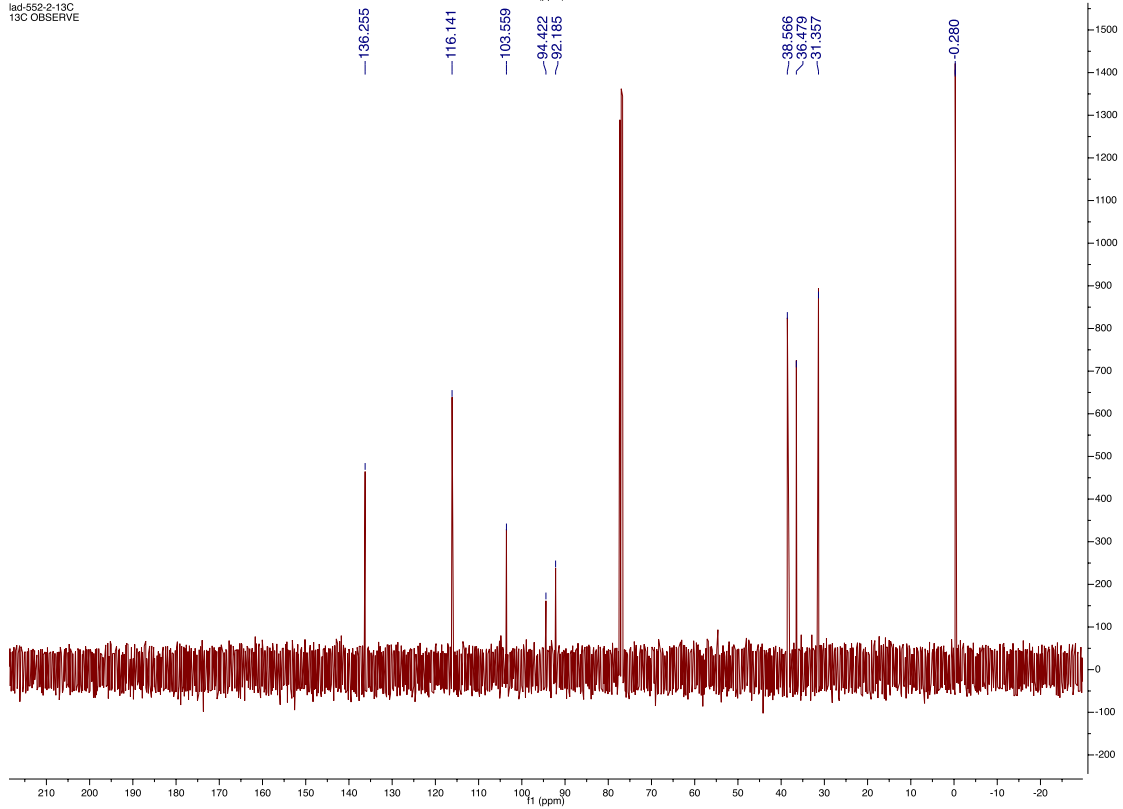
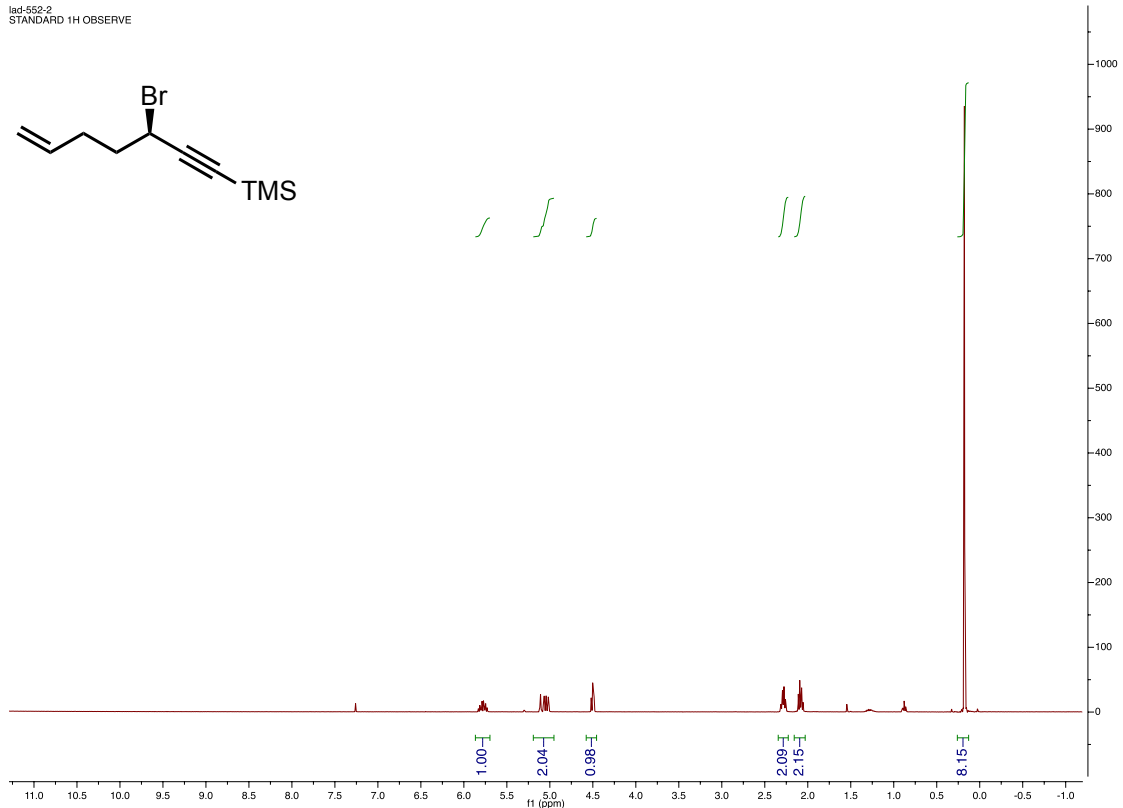
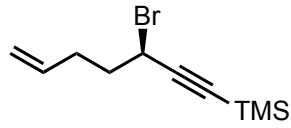
Compound 4d

lad-543-2-1H
Std proton



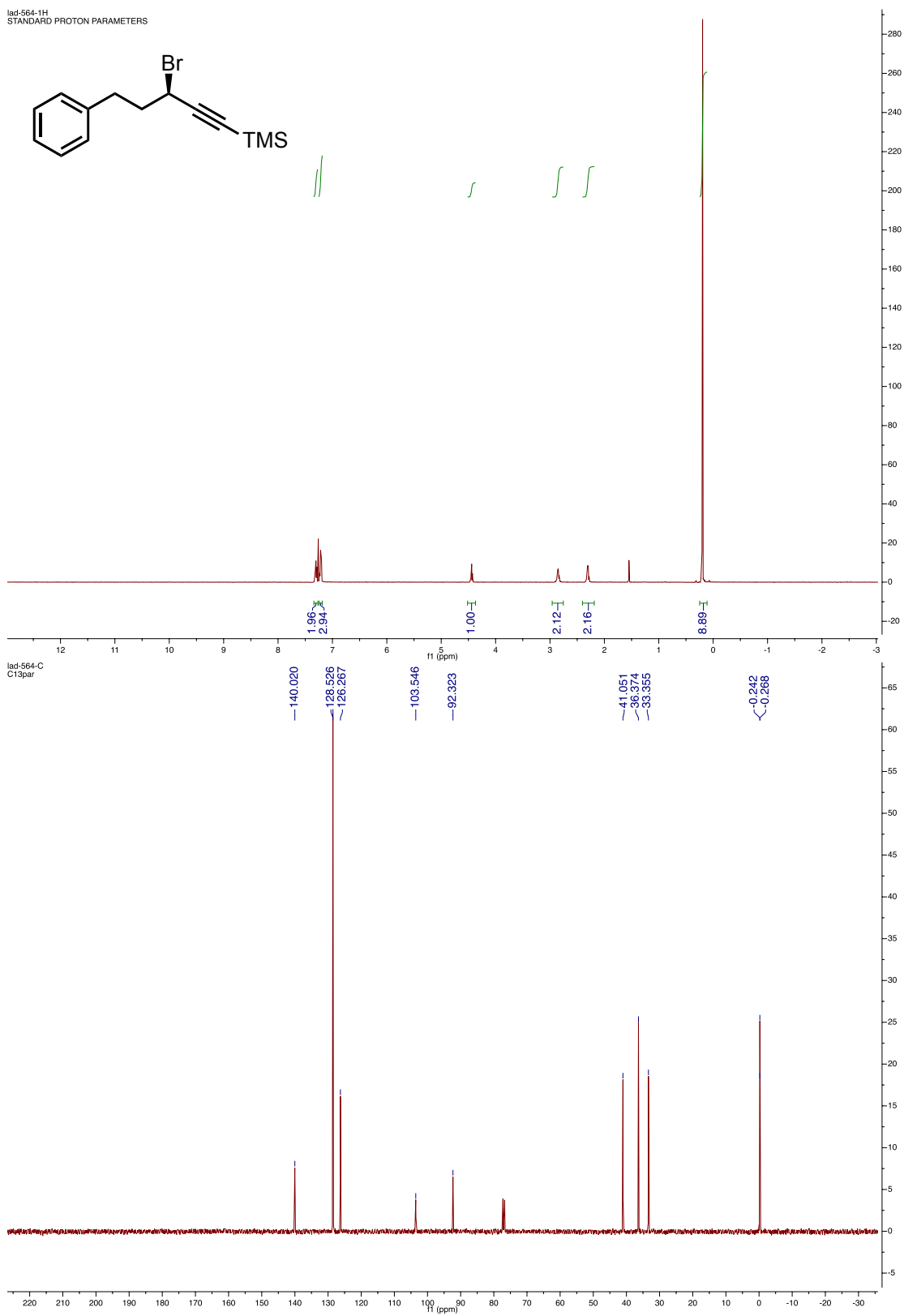
Compound 4e

lad-552-2
STANDARD 1H OBSERVE



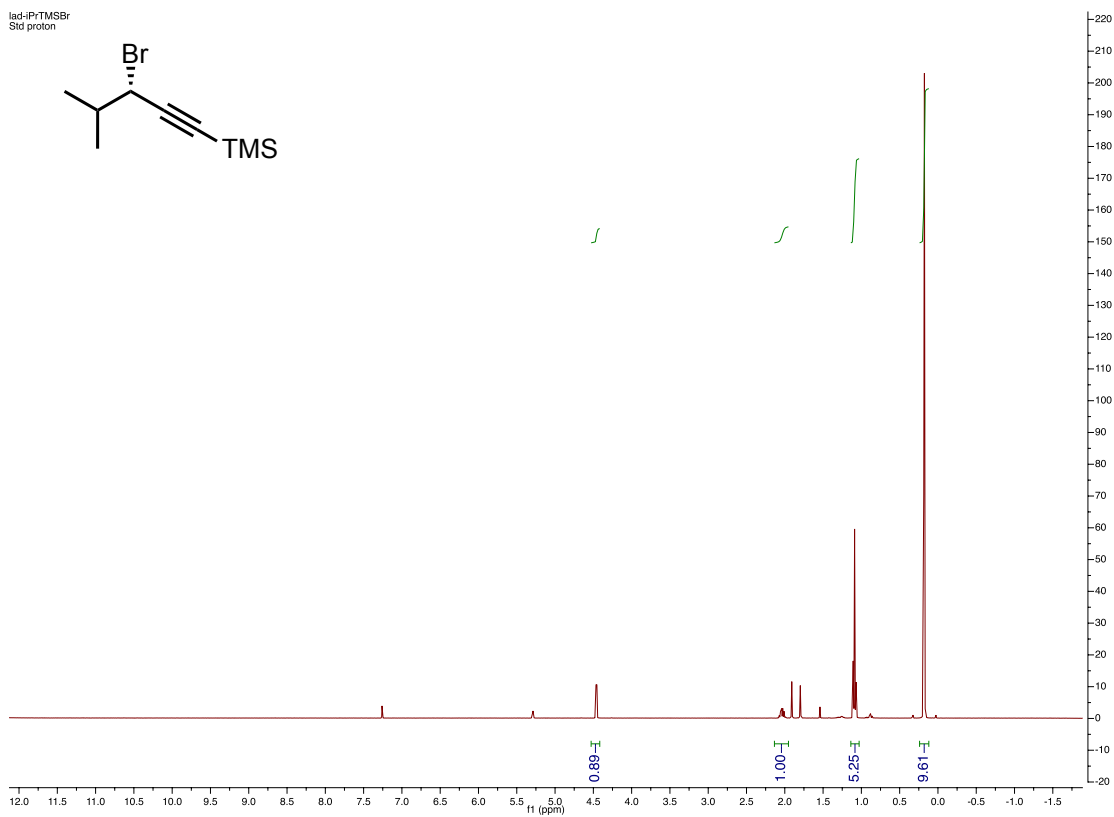
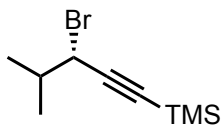
Compound 4f

lad-564-1H
STANDARD PROTON PARAMETERS

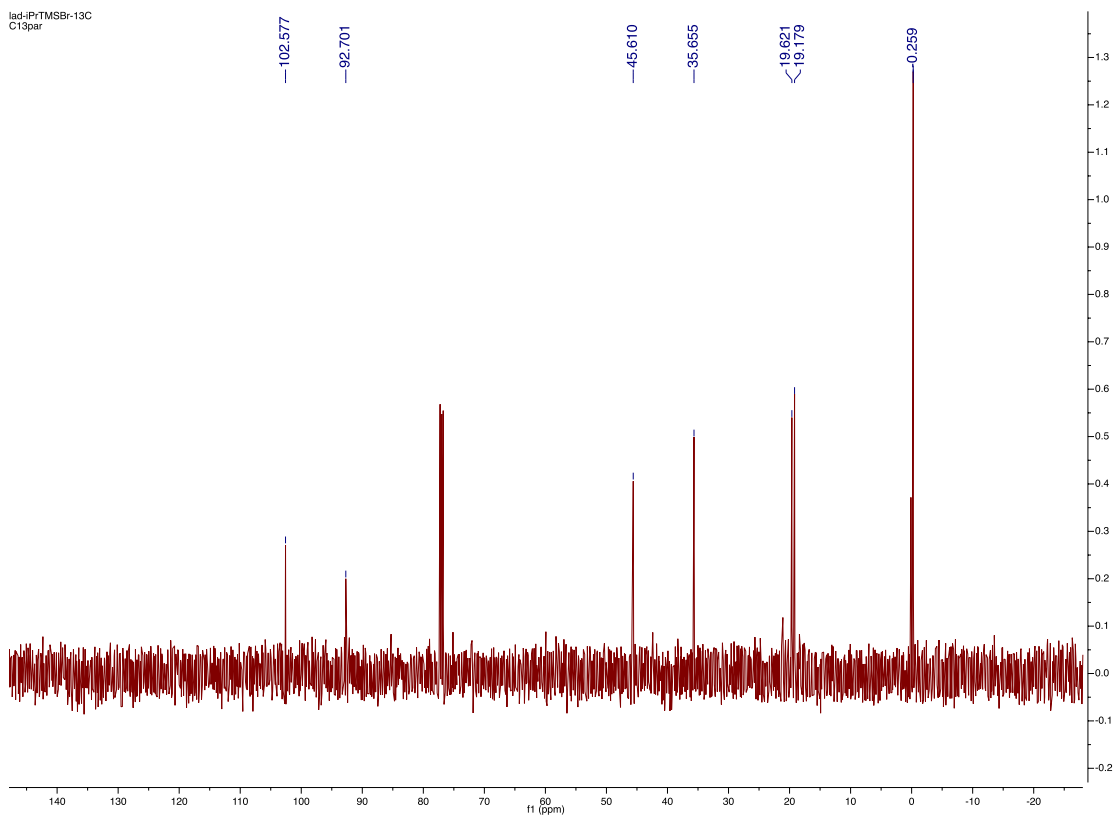


Compound 4g

lad-iPrTMSBr
Std proton

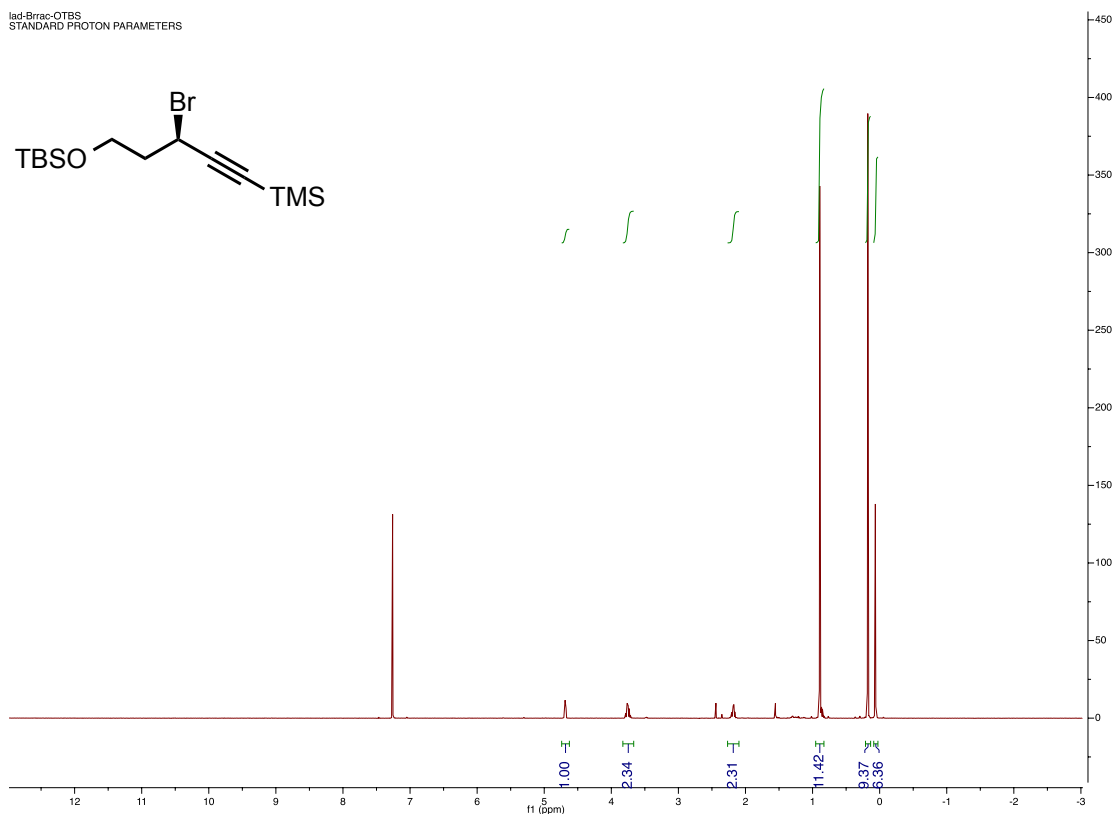
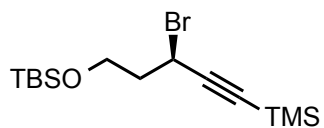


lad-iPrTMSBr-13C
C13par

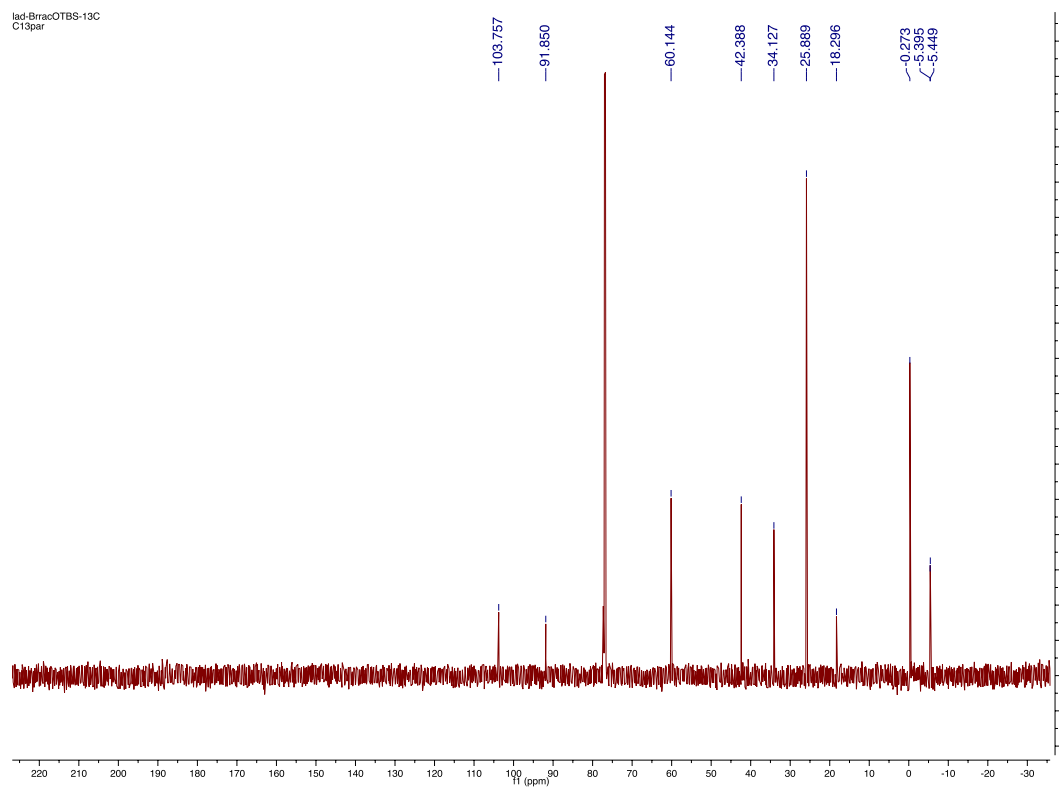


Compound 4h

lad-Brrac-OTBS
STANDARD PROTON PARAMETERS

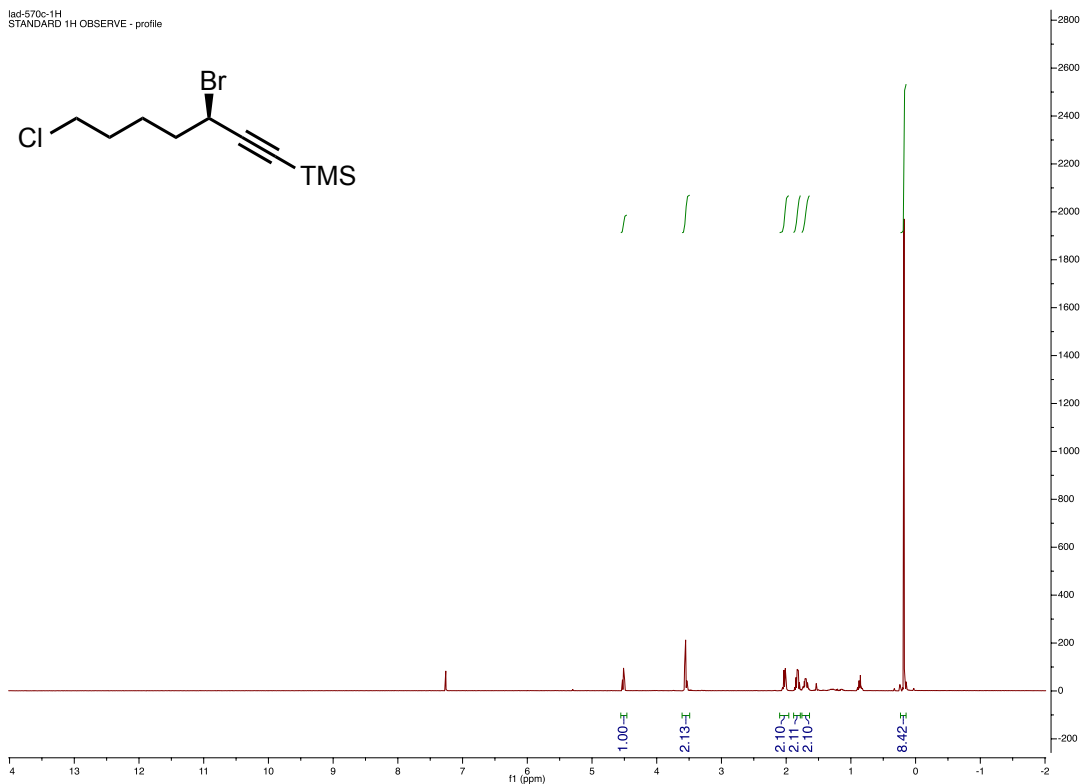
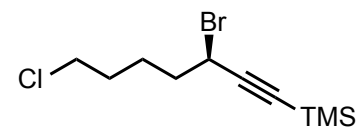


lad-BrracOTBS-13C
C13par

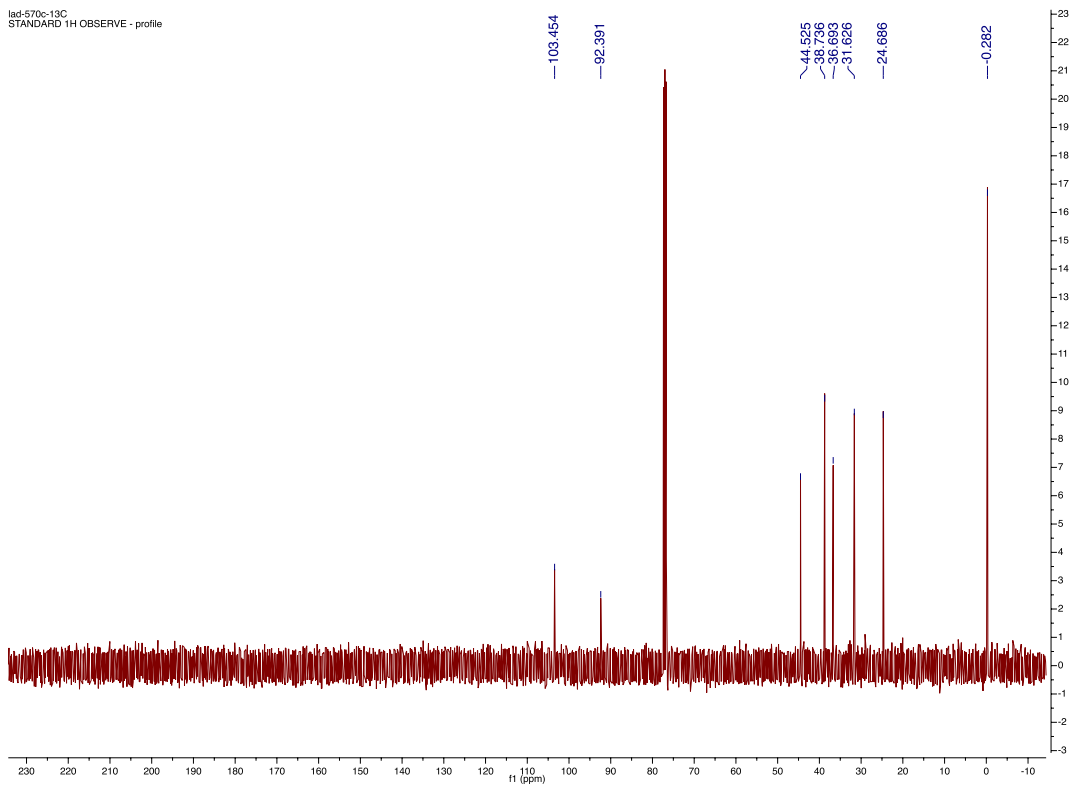


Compound 4i

lad-570c-1H
STANDARD 1H OBSERVE - profile

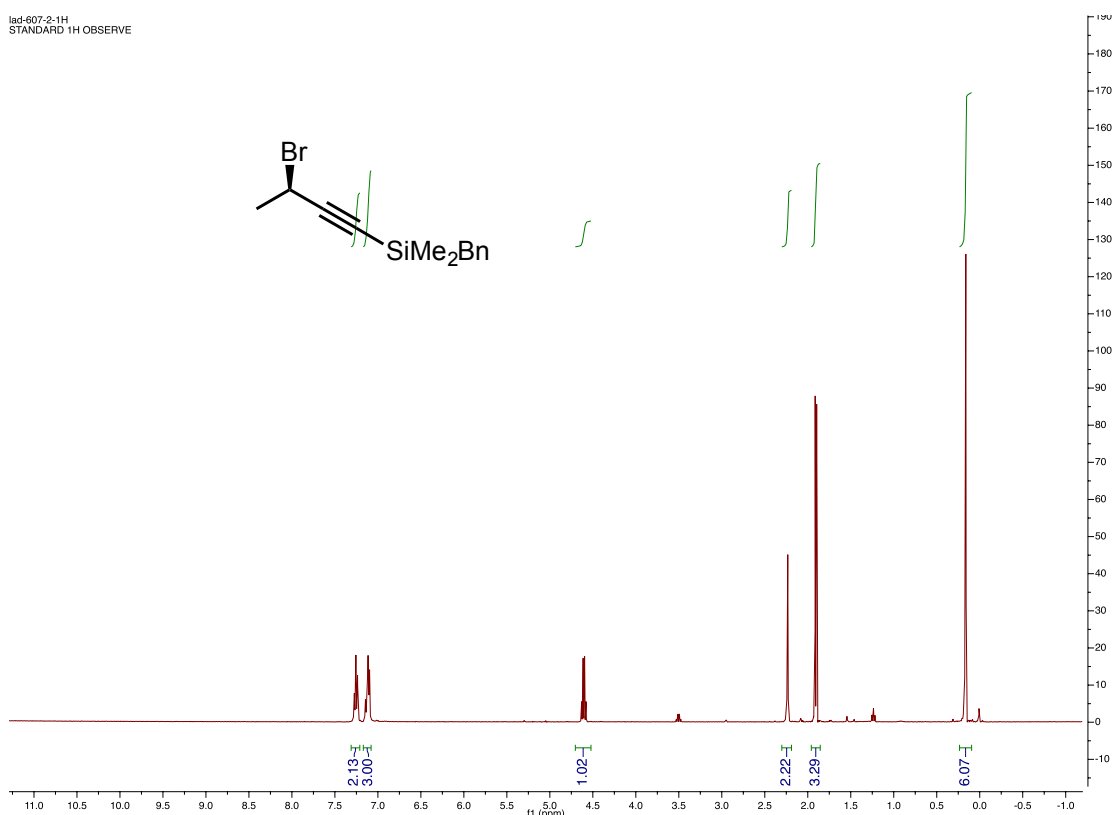
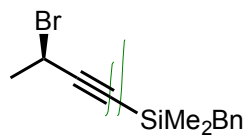


lad-570c-13C
STANDARD 1H OBSERVE - profile

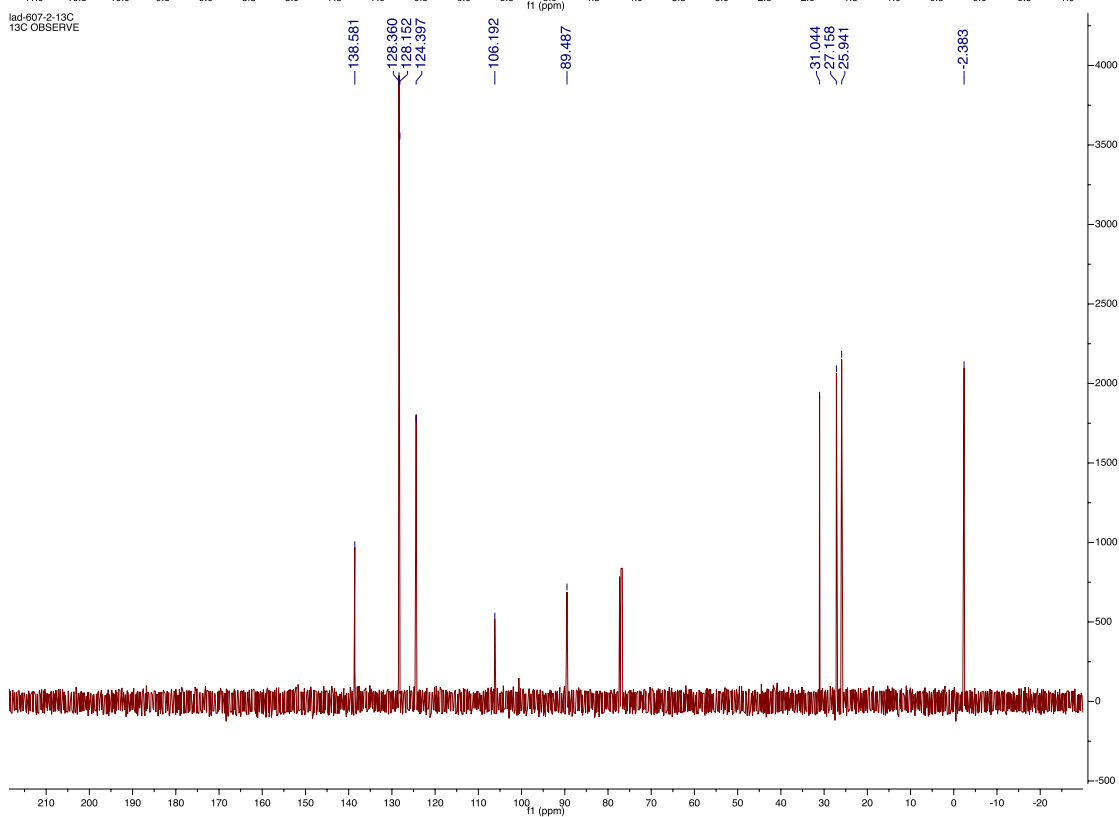


Compound 4j

lad-607-2-1H
STANDARD 1H OBSERVE

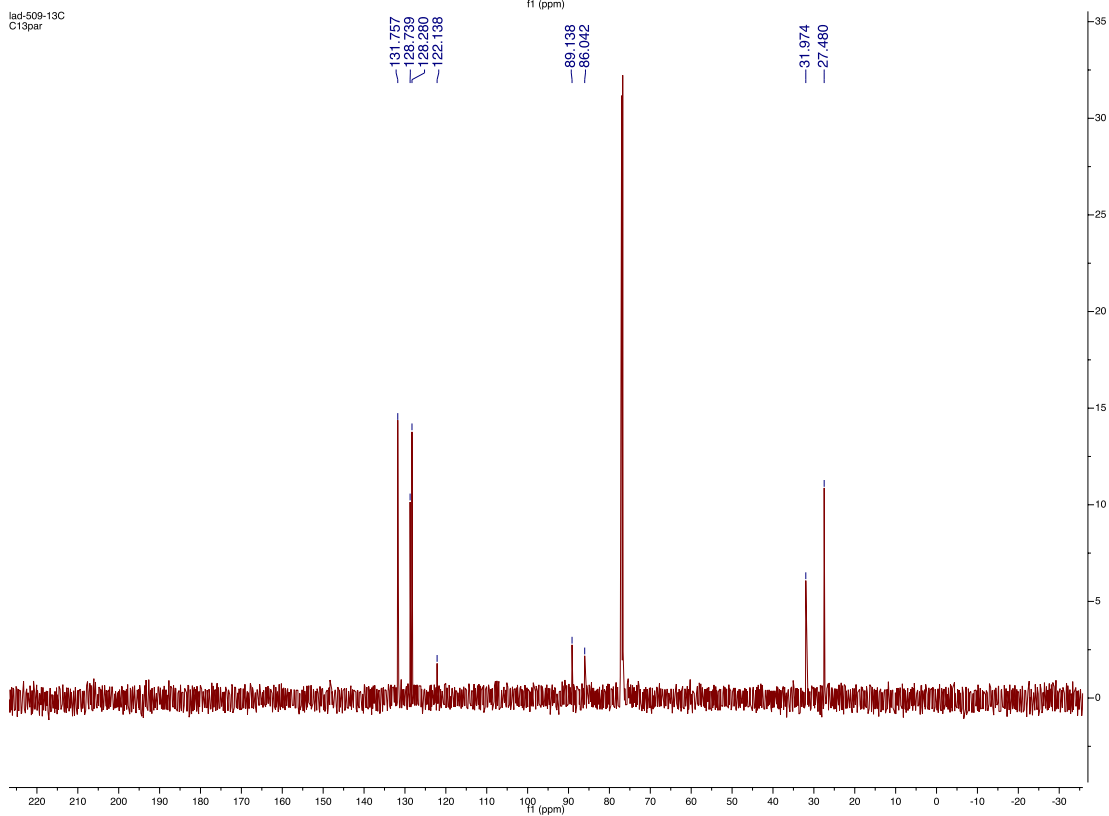
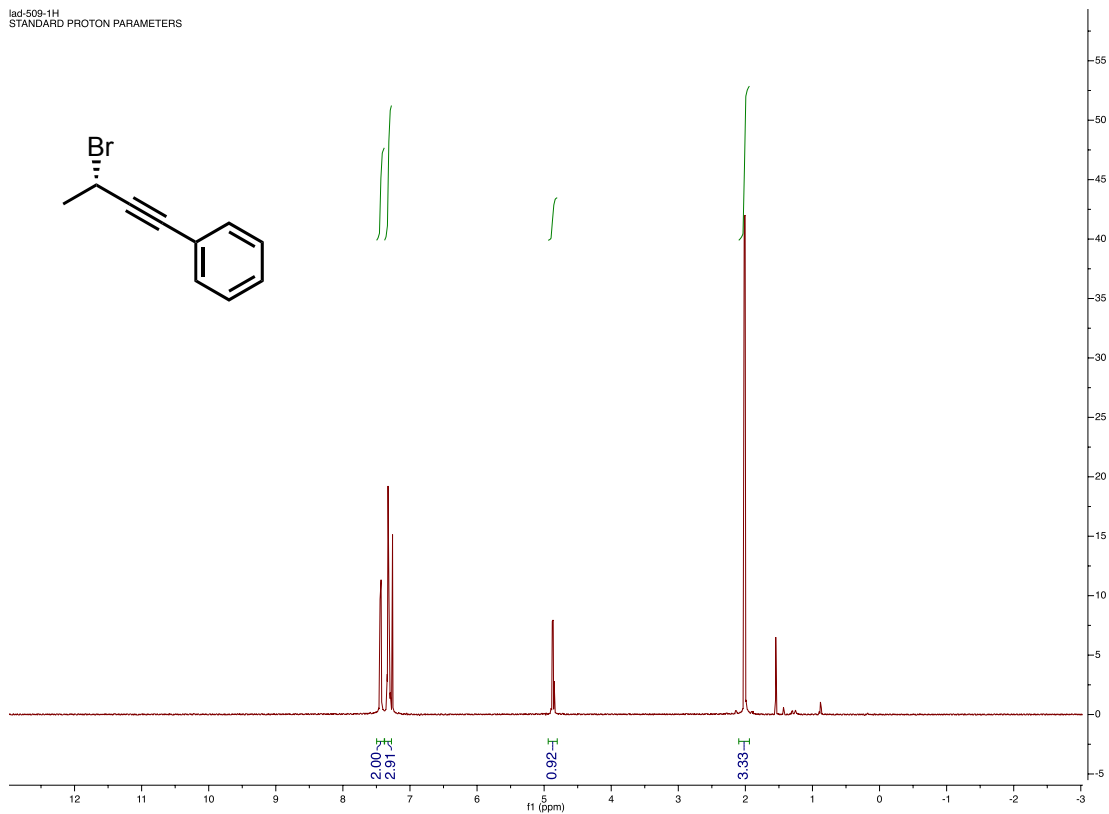


lad-607-2-13C
13C OBSERVE



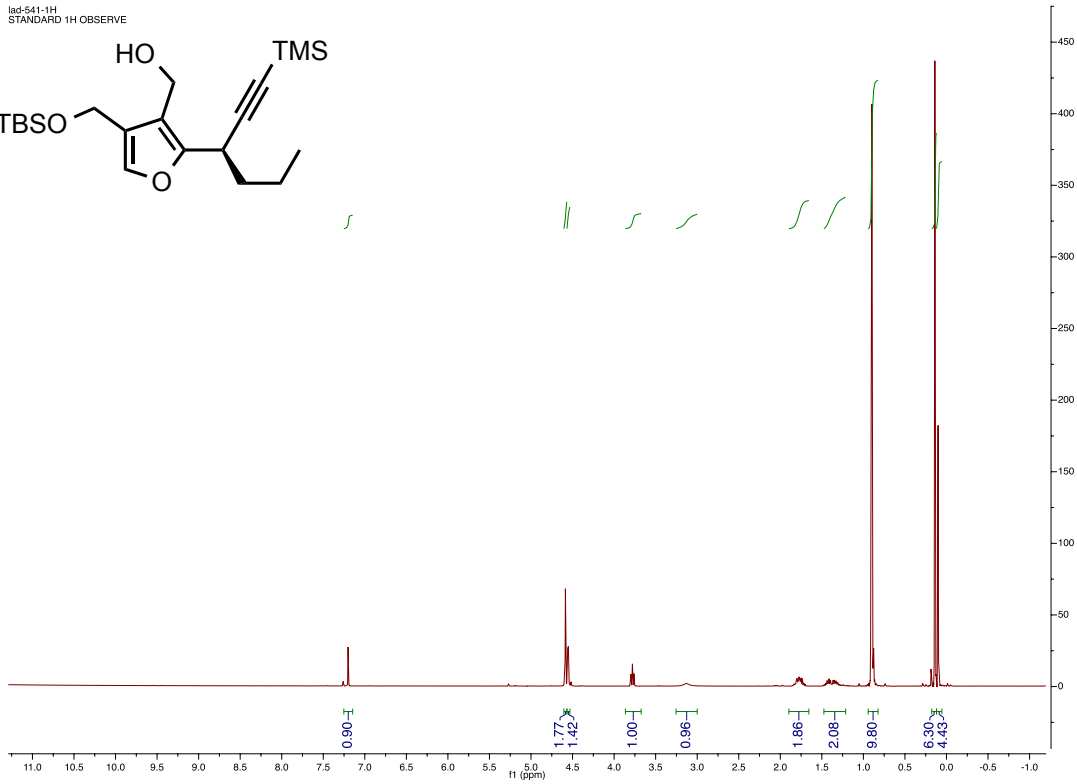
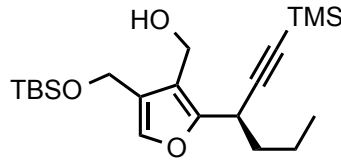
Compound 4k

lad-509-1H
STANDARD PROTON PARAMETERS

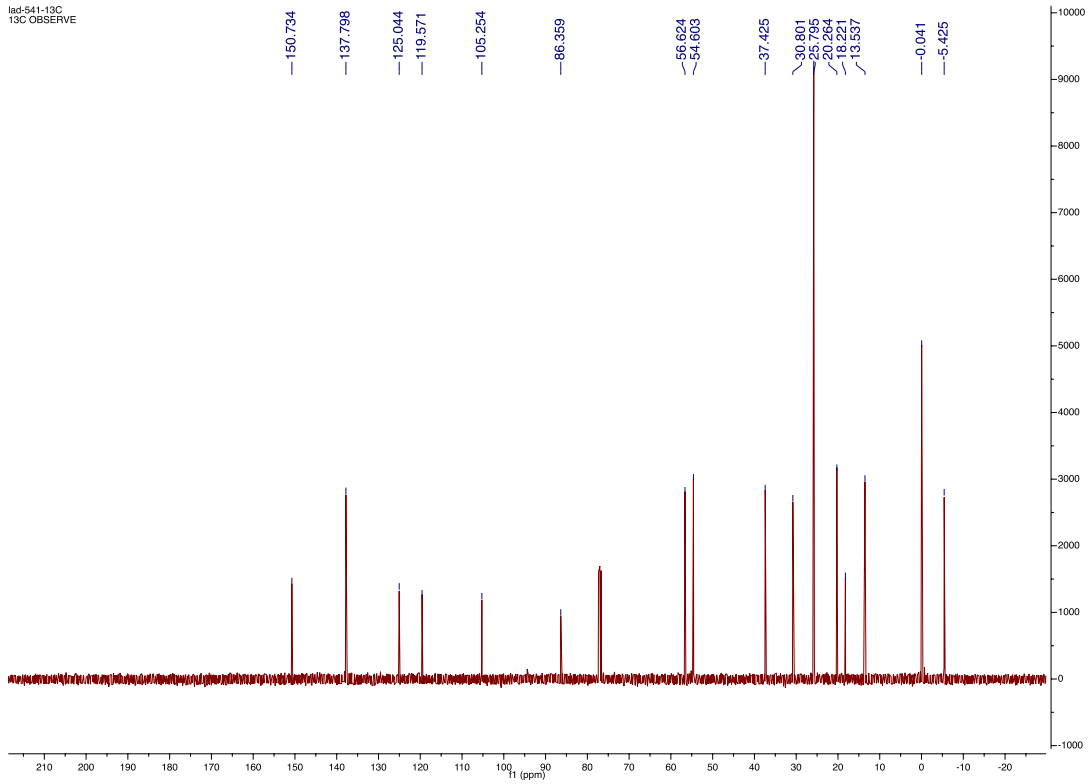


Compound 2a

lad-541-1H
STANDARD 1H OBSERVE

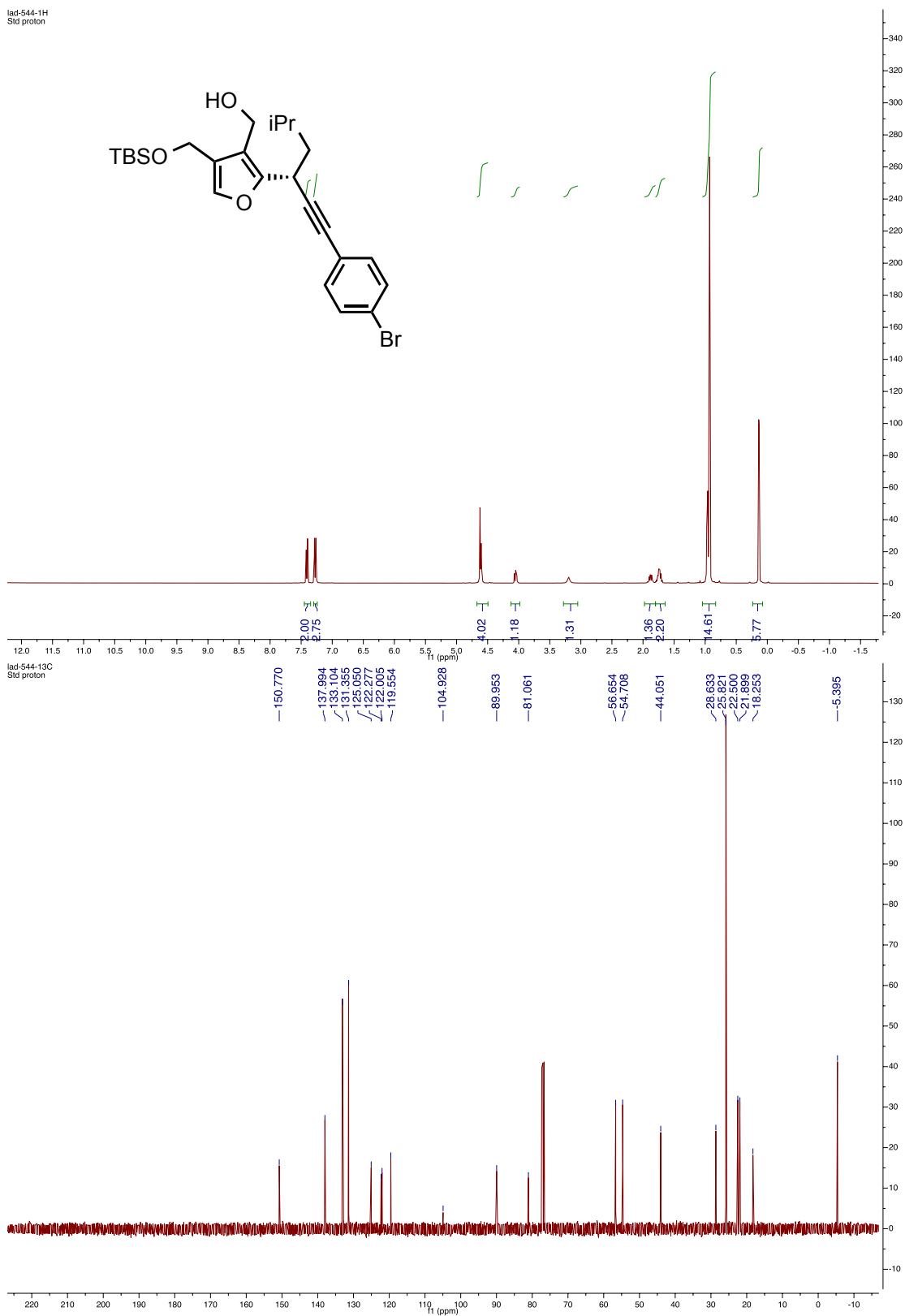


lad-541-13C
13C OBSERVE



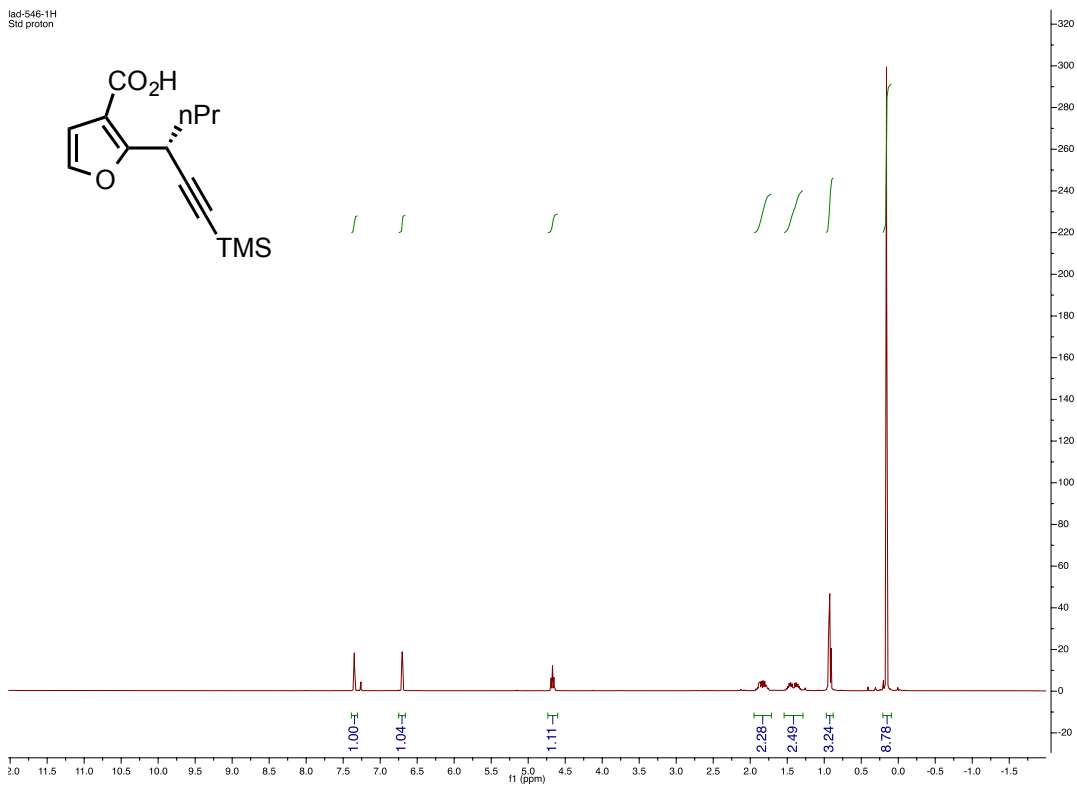
Compound 2b

lad-544-1H
Std proton

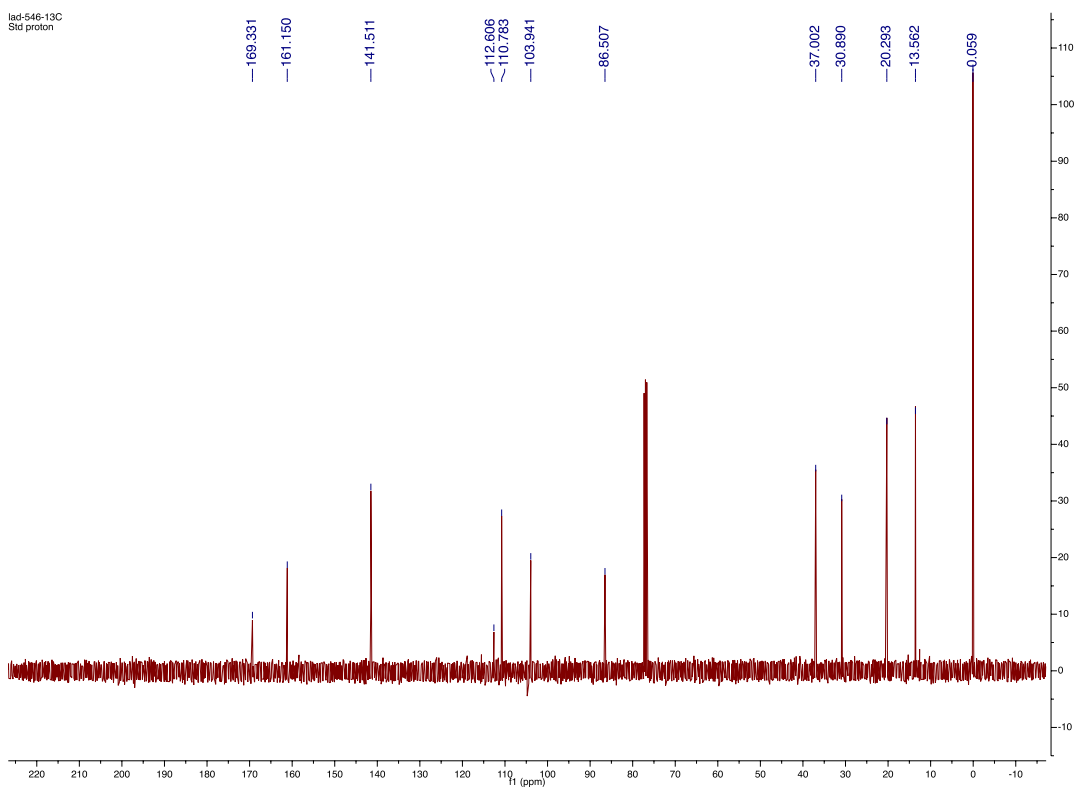


Compound 2c

lad-546-1H
Std proton

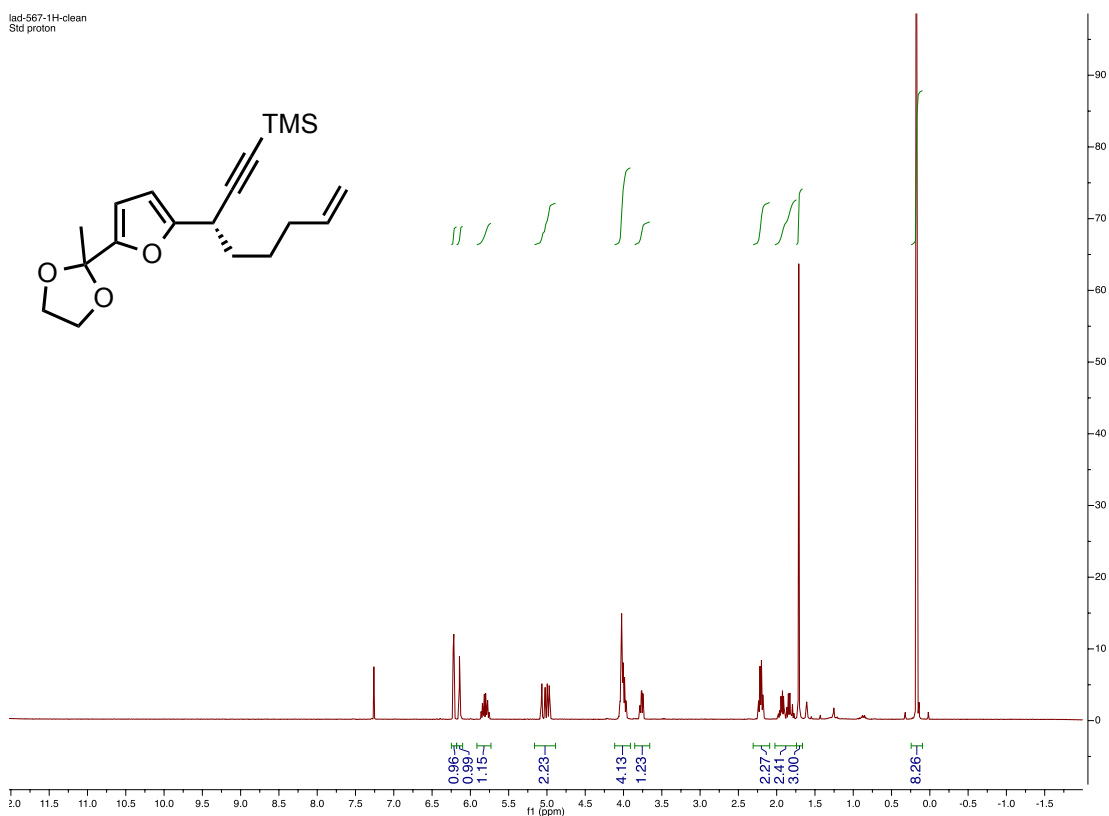


lad-546-13C
Std proton

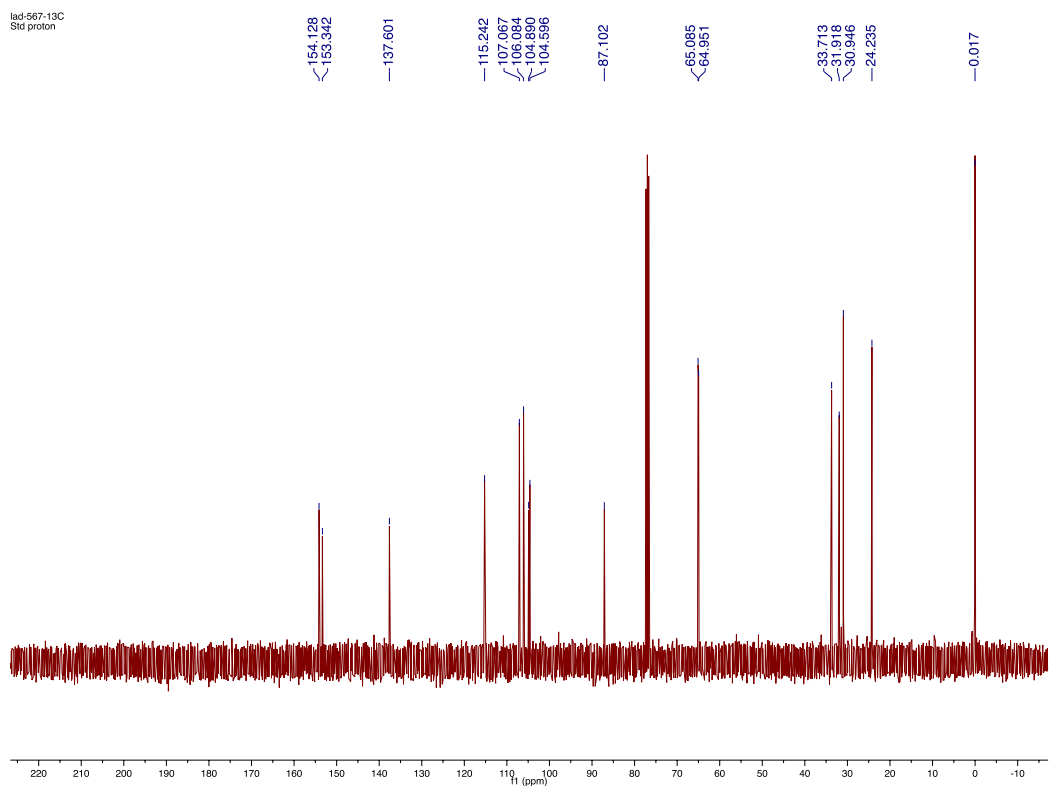


Compound 2d

lad-567-1H-clean
Std proton

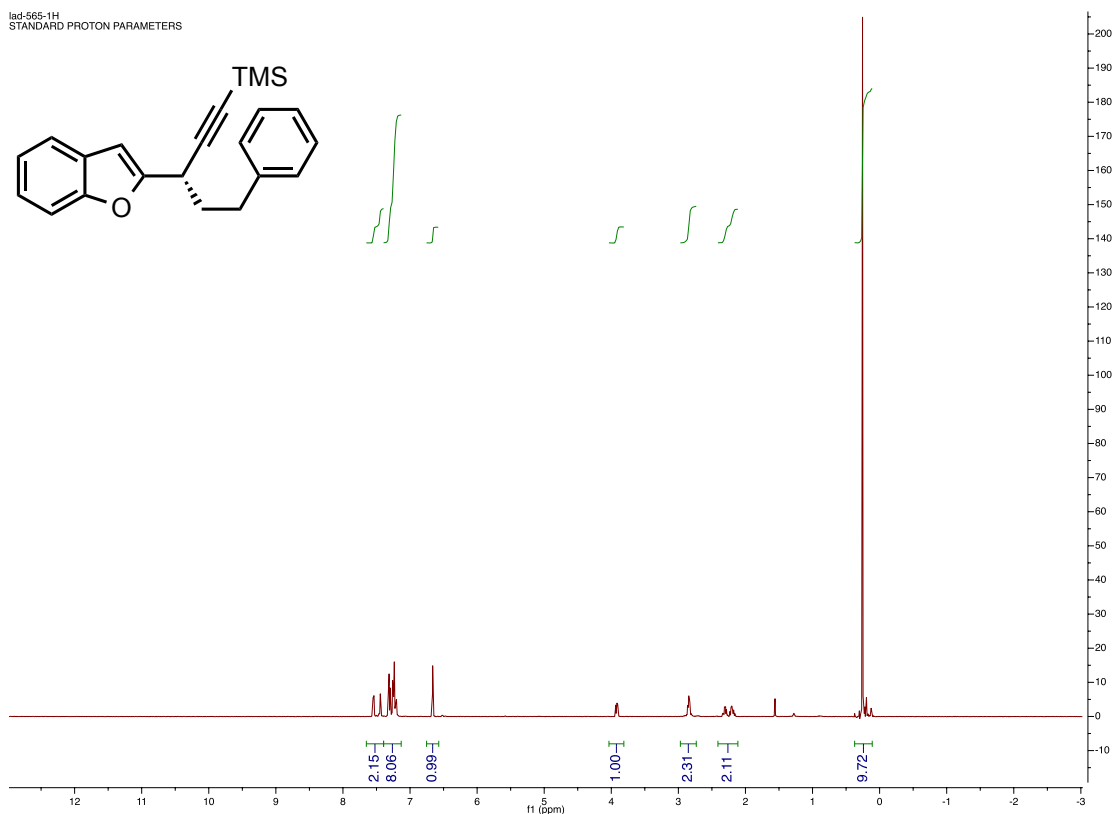
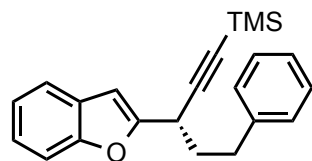


lad-567-13C
Std proton

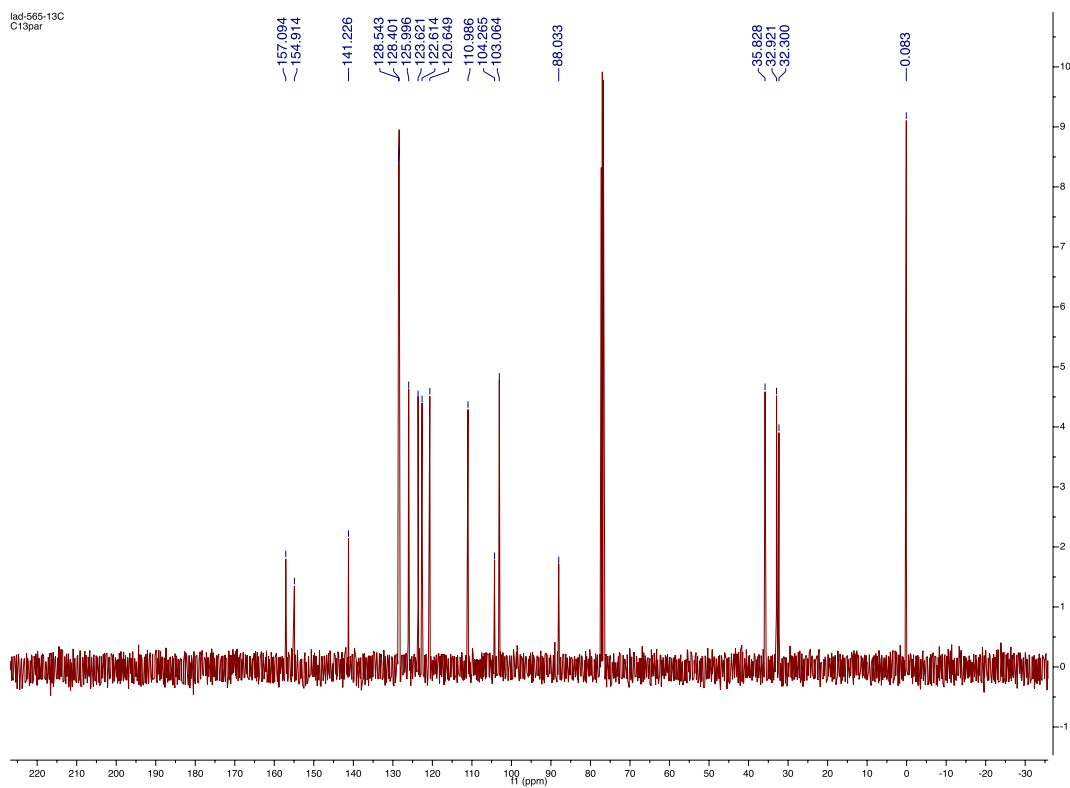


Compound 2e

lad-565-1H
STANDARD PROTON PARAMETERS

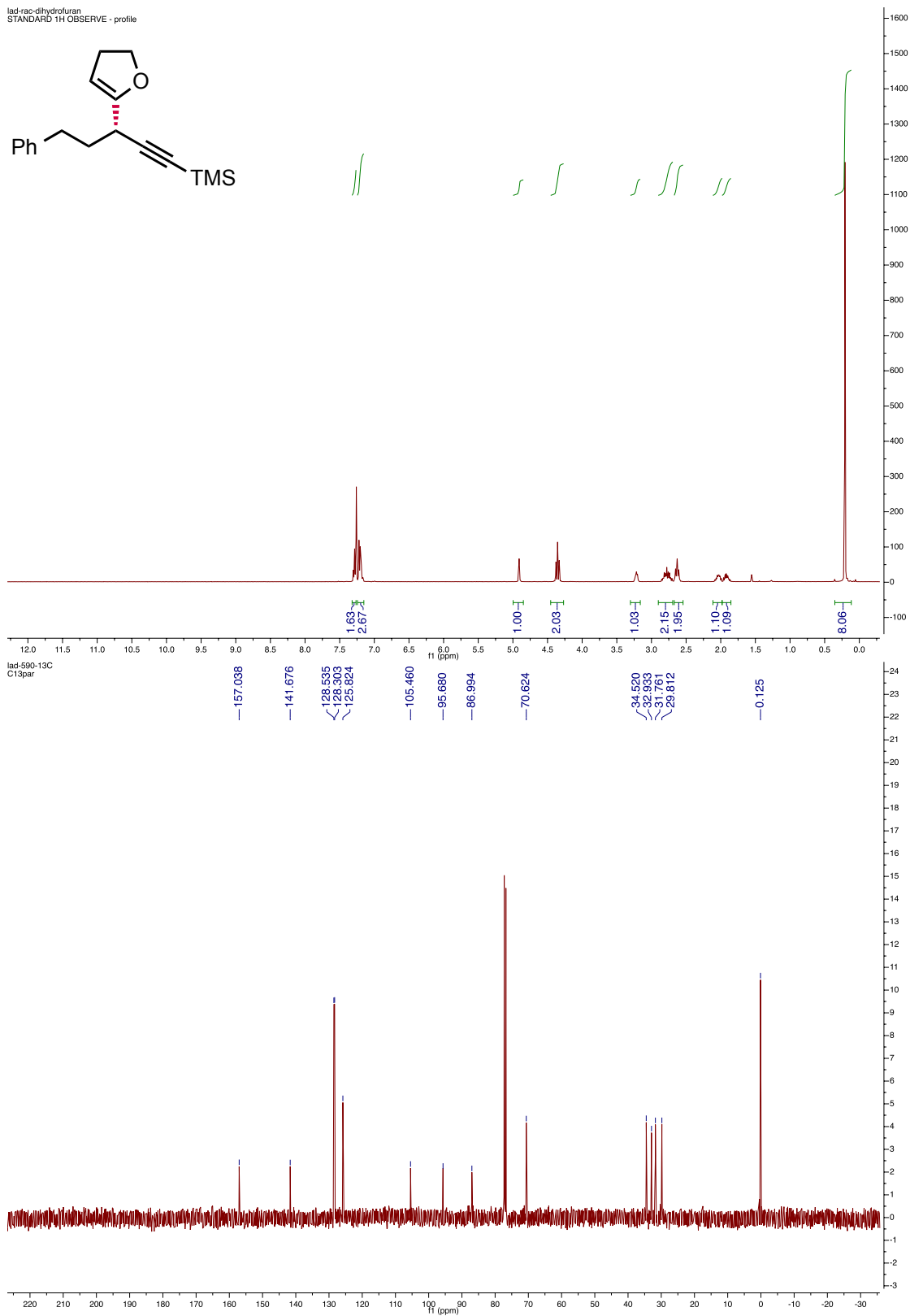
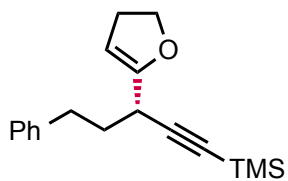


lad-565-13C
C13par



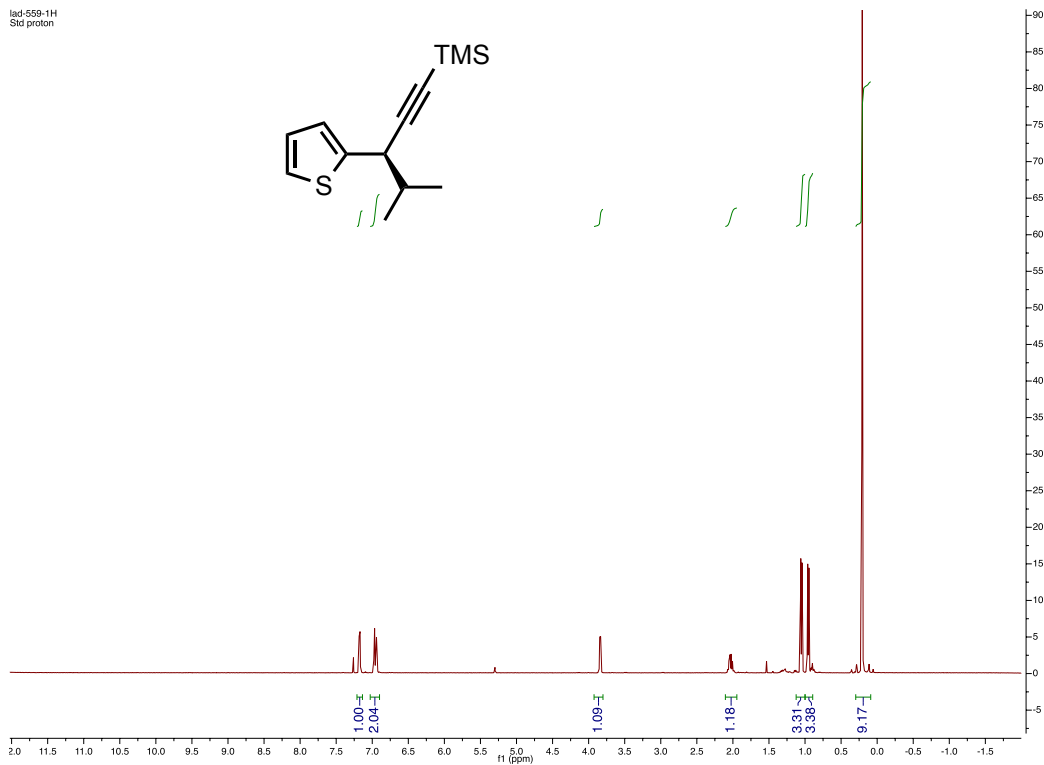
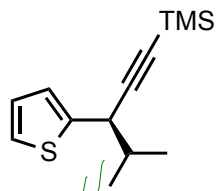
Compound 2f

lad-rac-dihydrofuran
STANDARD 1H OBSERVE - profile

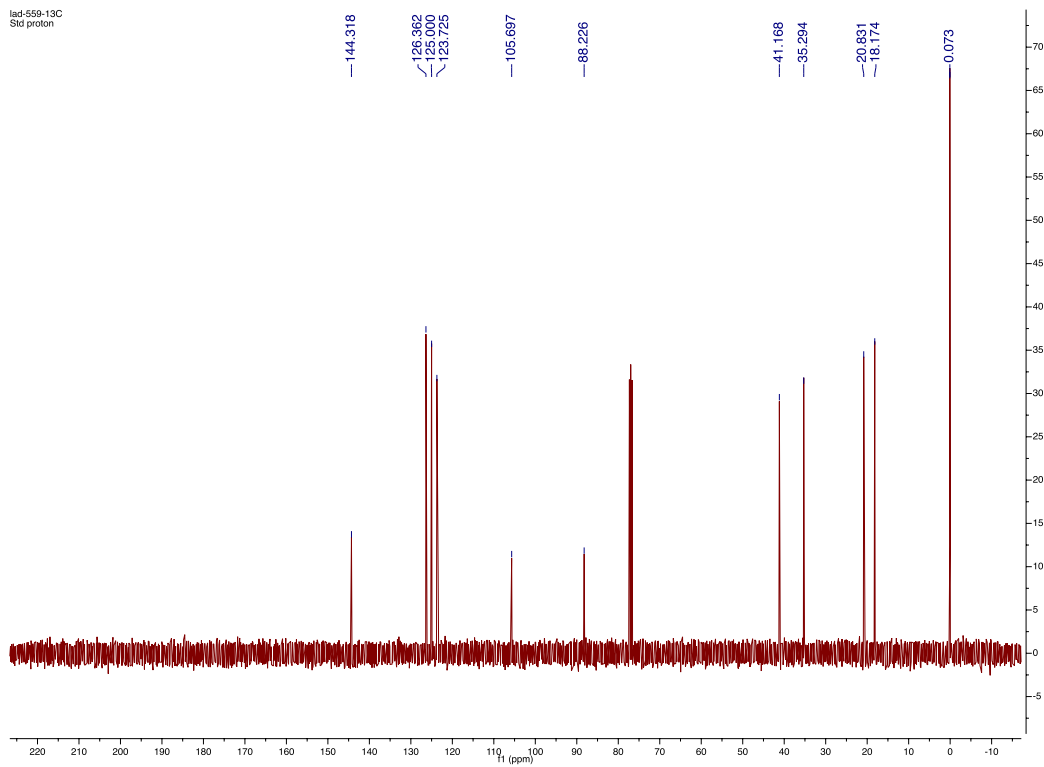


Compound 2g

lad-559-1H
Std proton

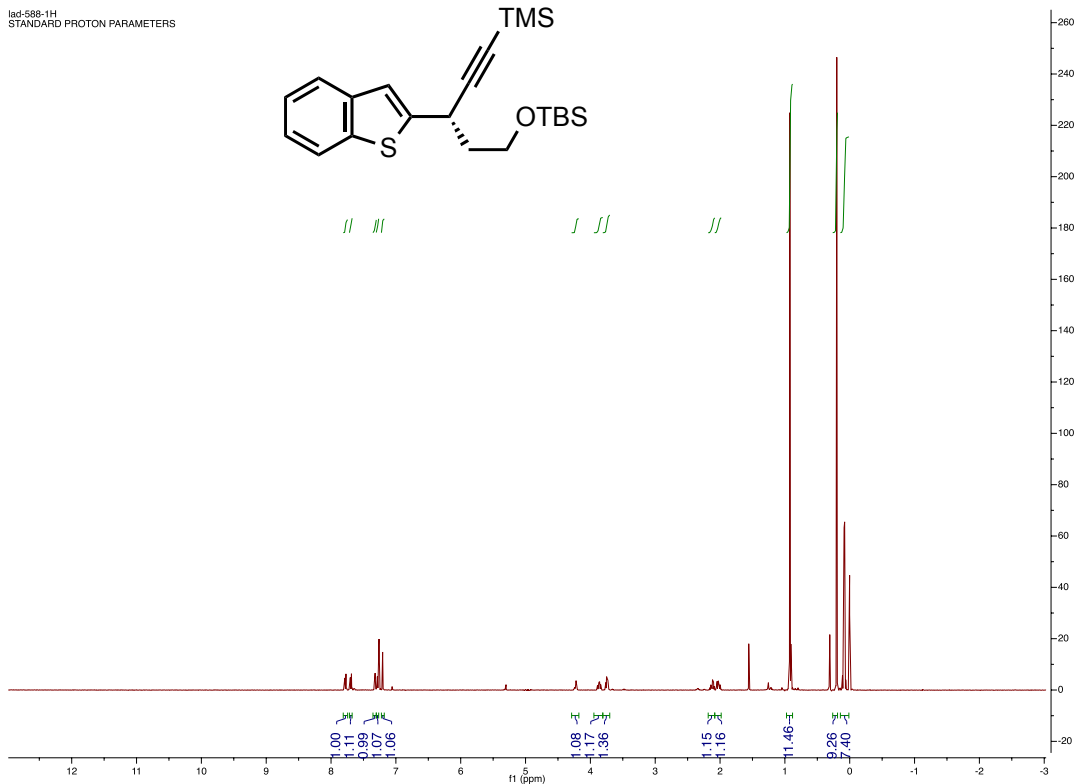


lad-559-13C
Std proton

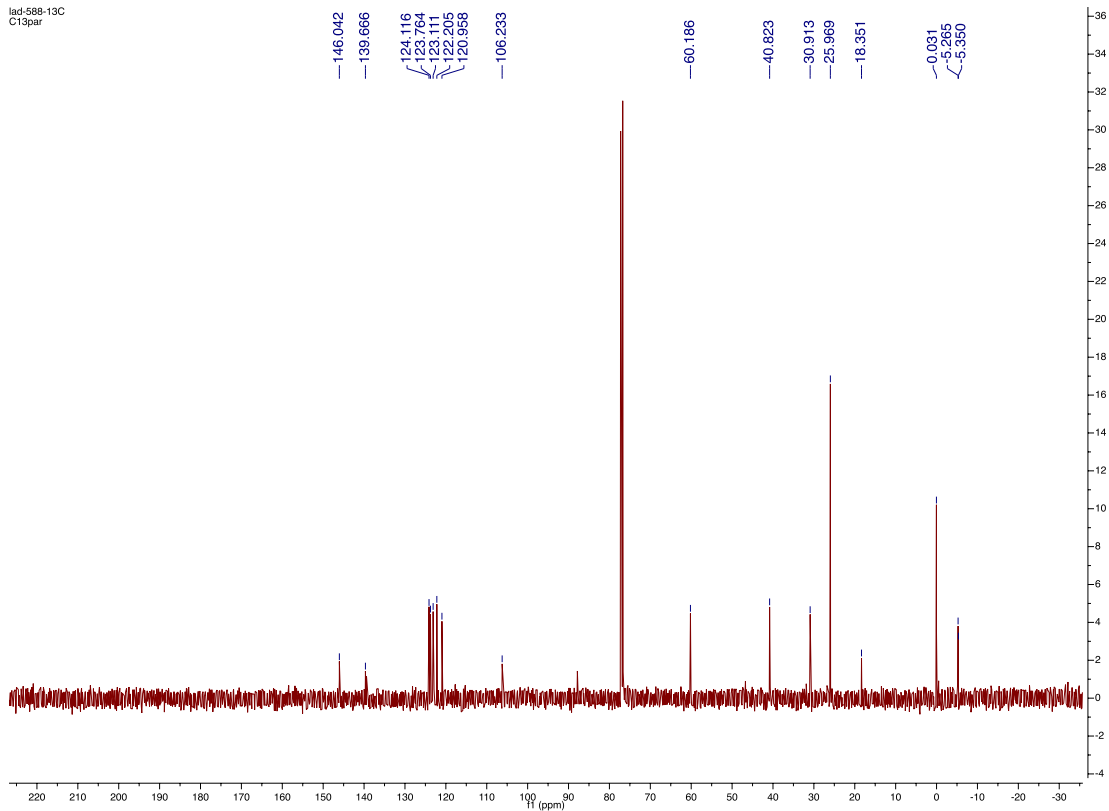


Compound 2h

lad-588-1H
STANDARD PROTON PARAMETERS

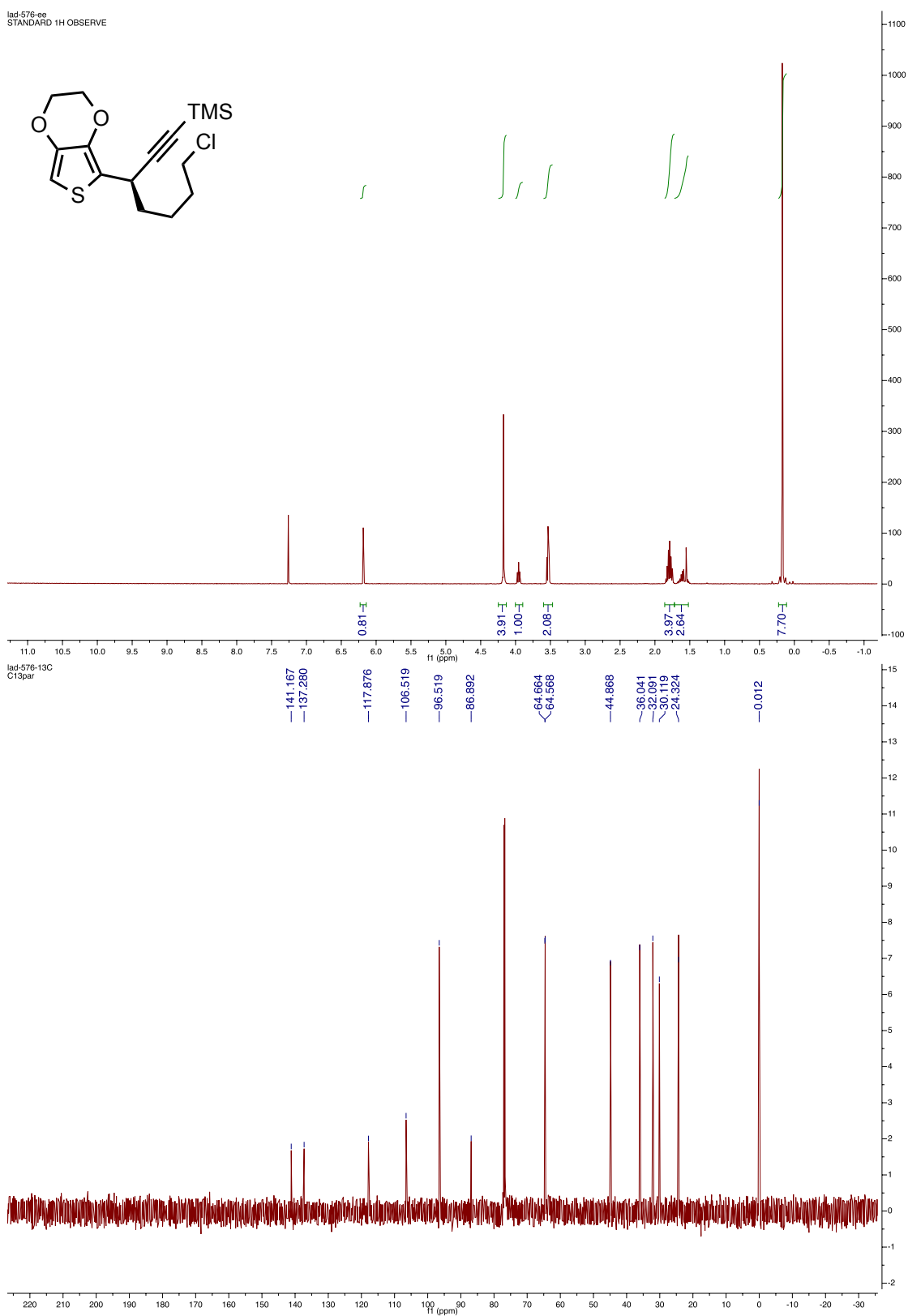


lad-588-13C
C13par



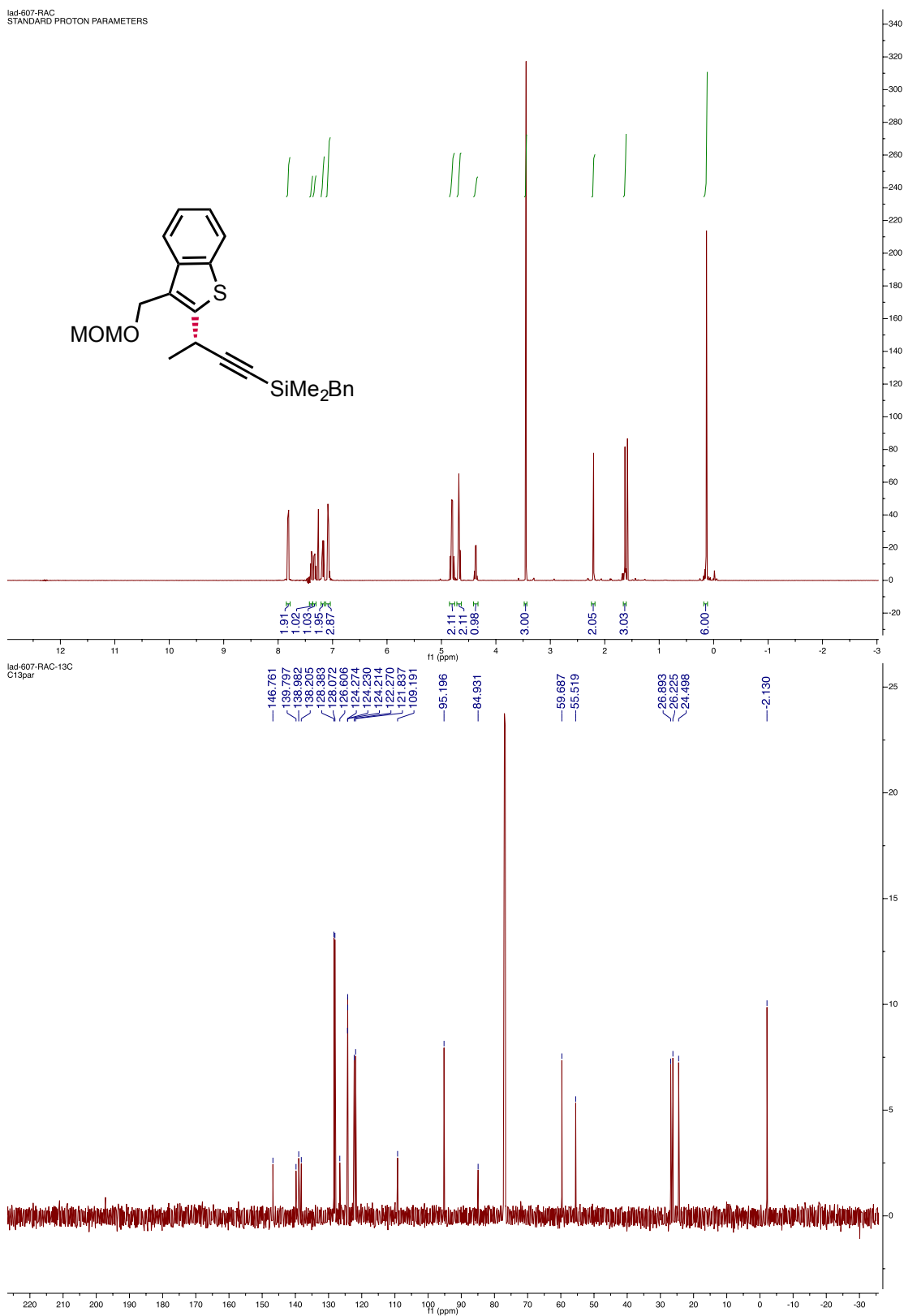
Compound 2i

lad-576-es
STANDARD 1H OBSERVE



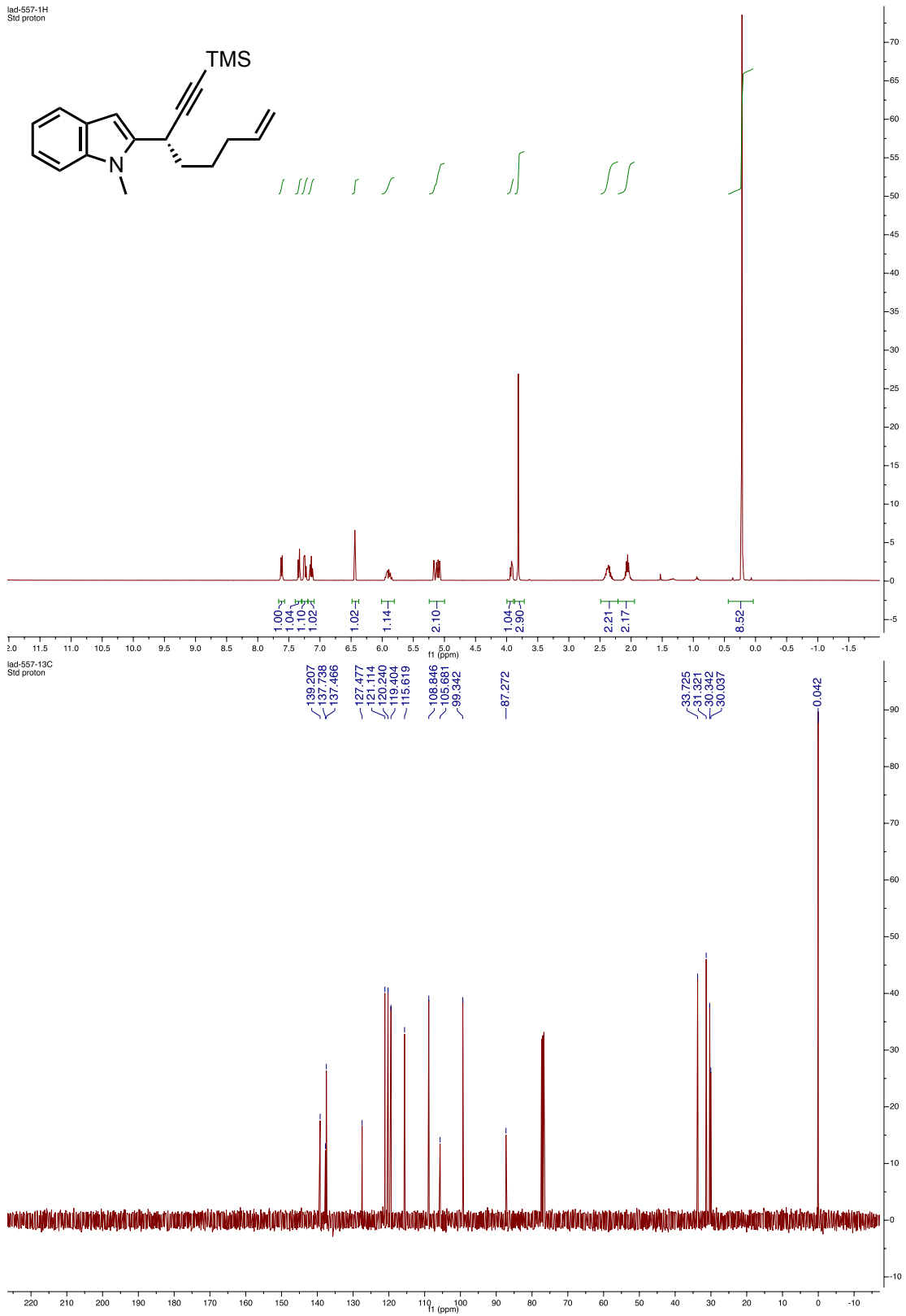
Compound 2j

lad-607-RAC
STANDARD PROTON PARAMETERS



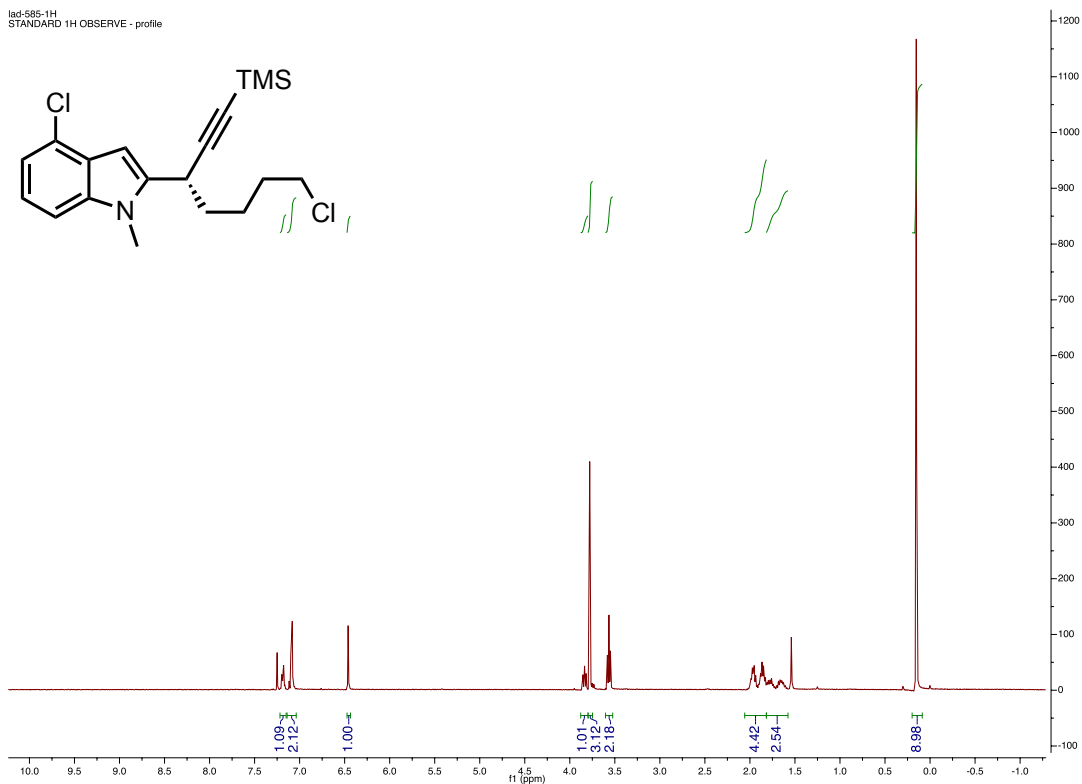
Compound 2k

lad-557-1H
Std proton

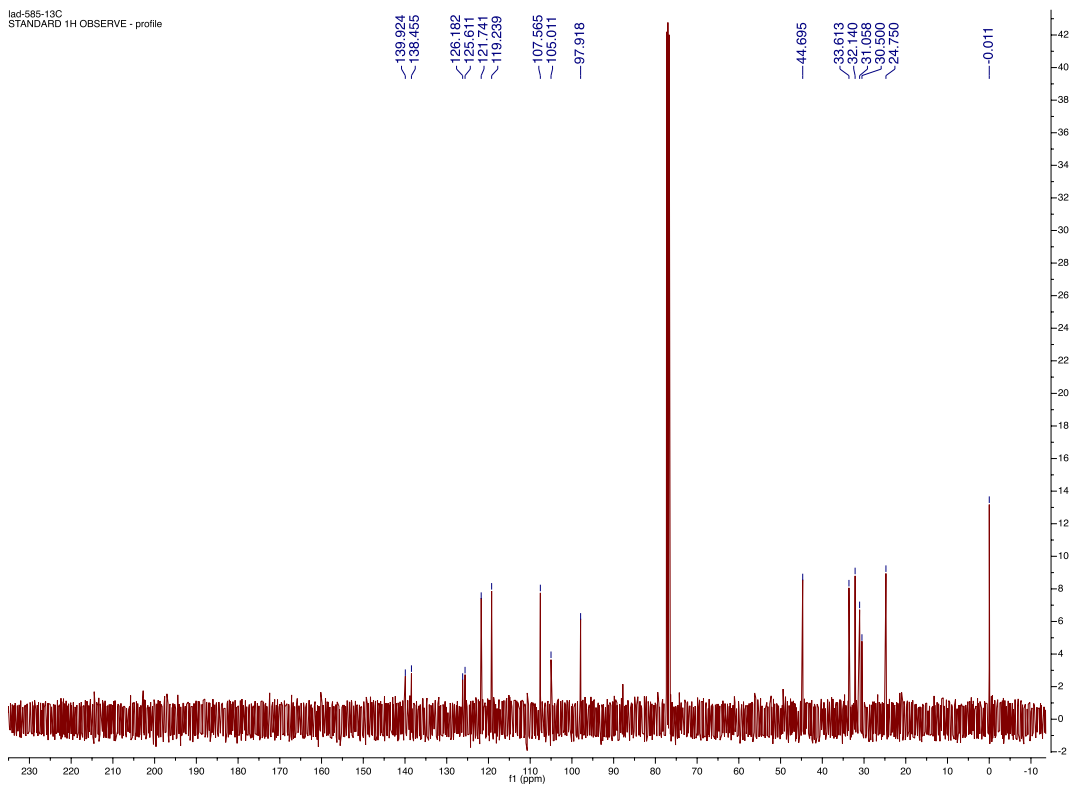


Compound 2l

lad-585-1H
STANDARD 1H OBSERVE - profile

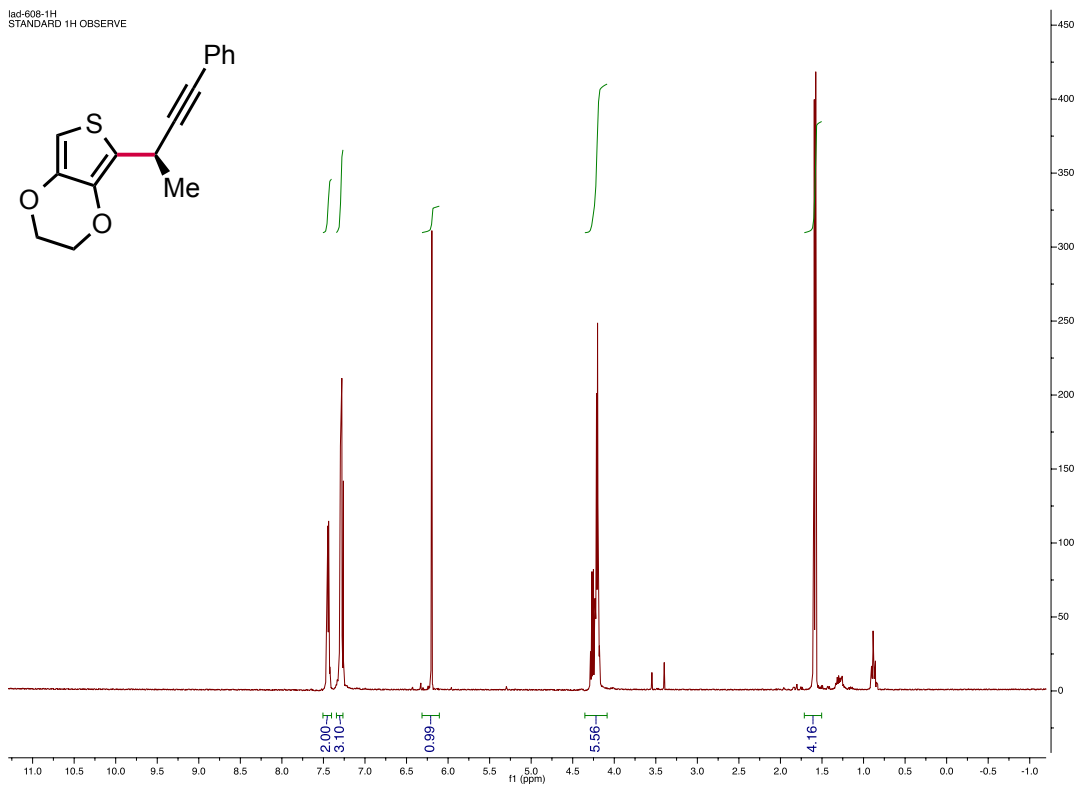
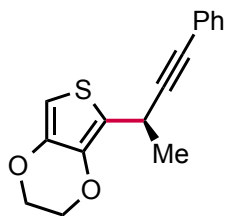


lad-585-13C
STANDARD 1H OBSERVE - profile

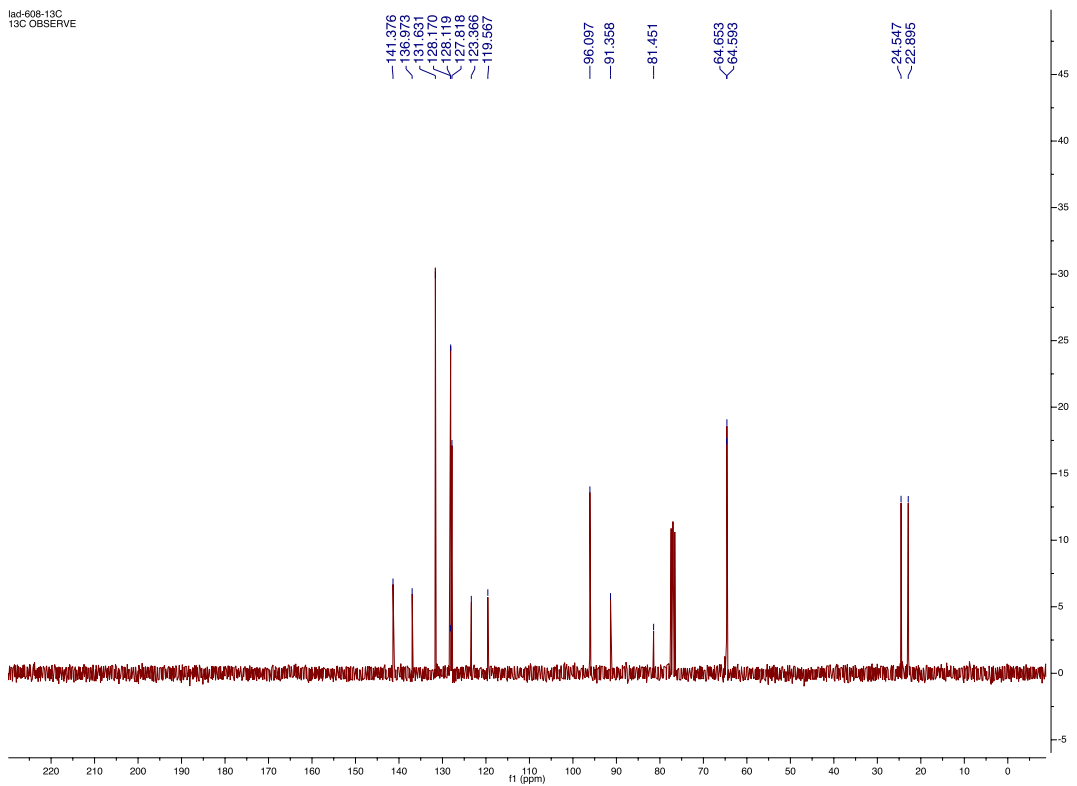


Compound 2m

lad-608-1H
STANDARD 1H OBSERVE

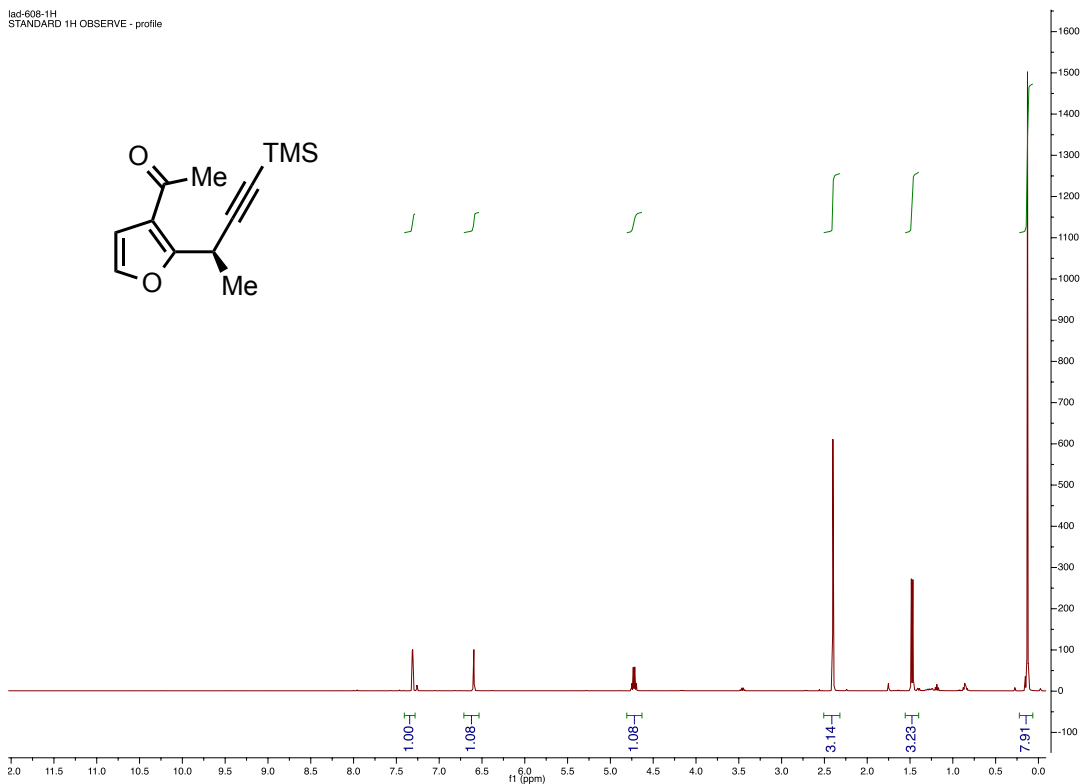


lad-608-13C
13C OBSERVE

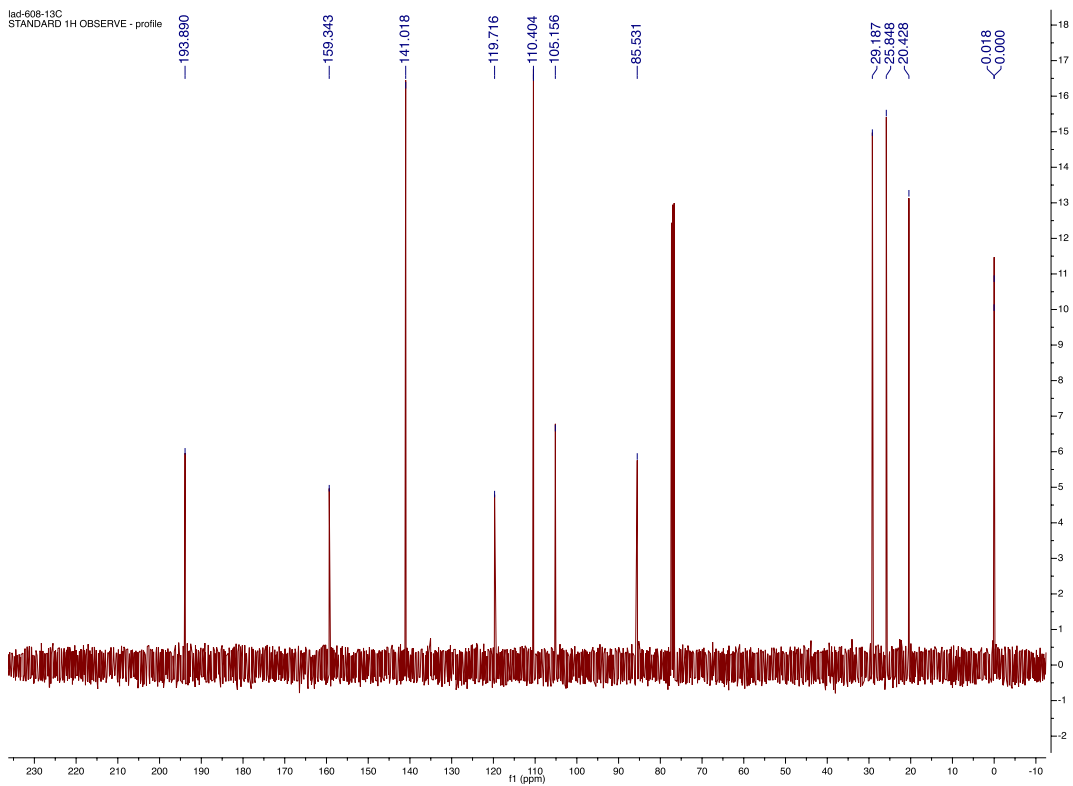


Compound 5a

lad-608-1H
STANDARD 1H OBSERVE - profile

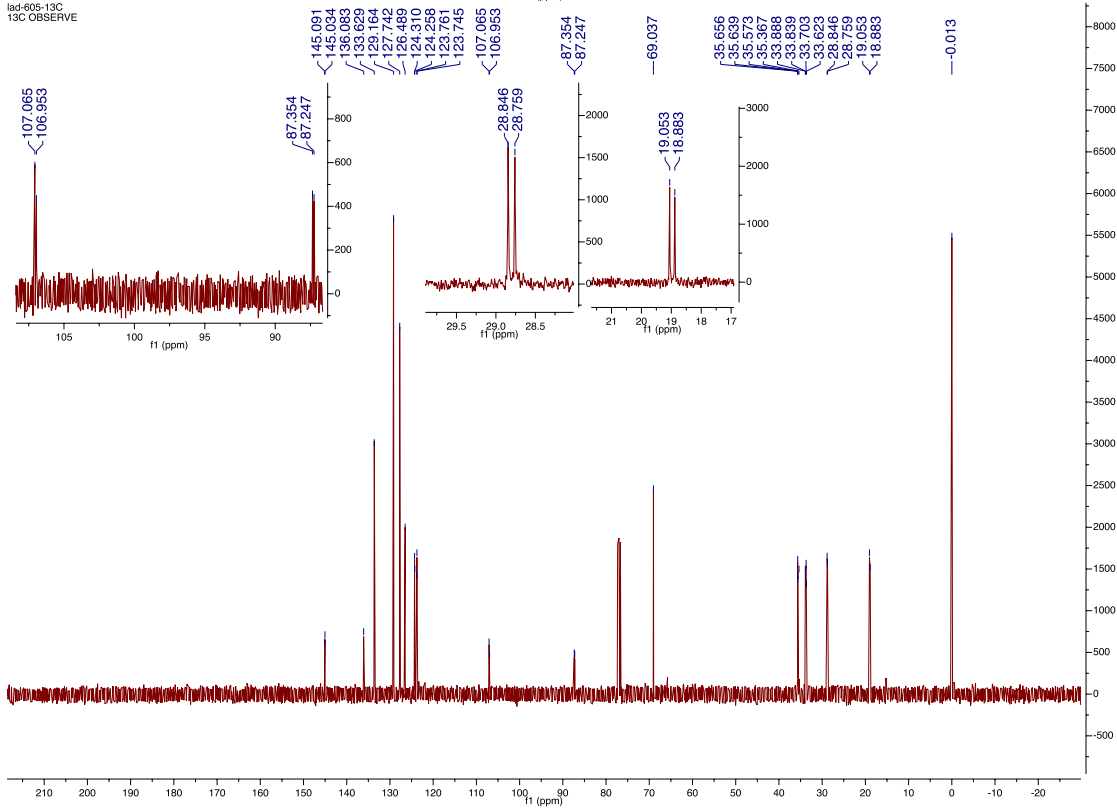
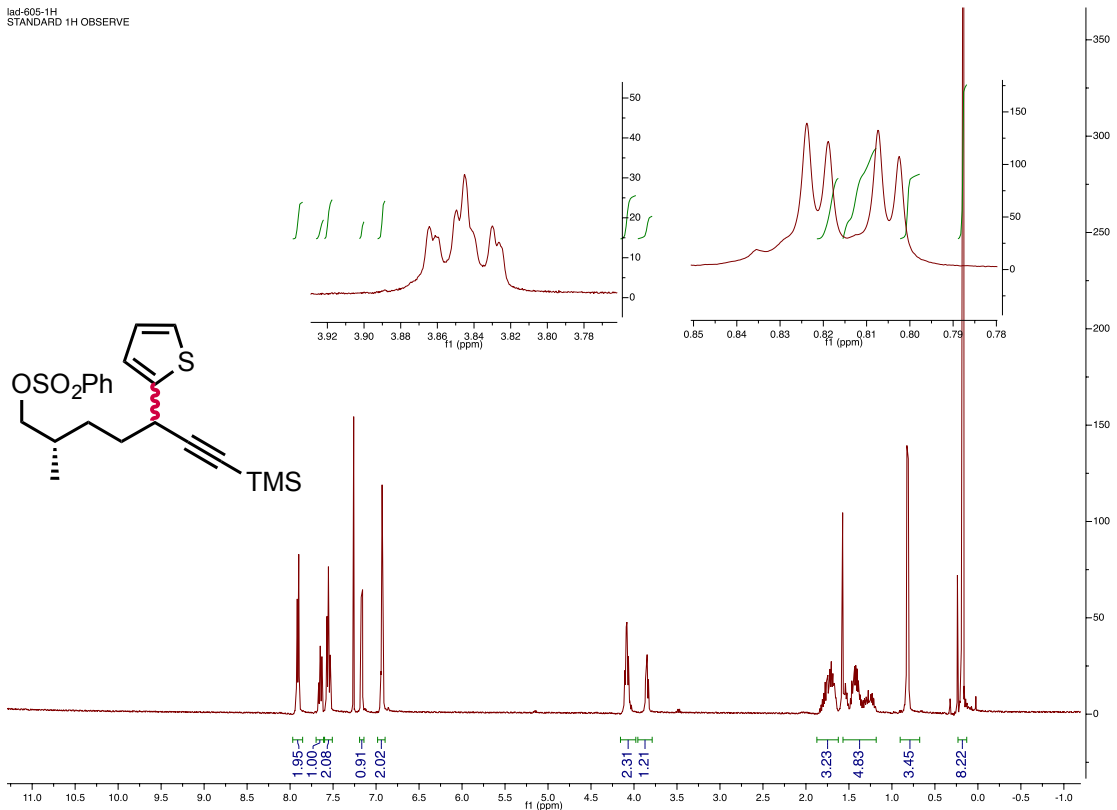


lad-608-13C
STANDARD 1H OBSERVE - profile



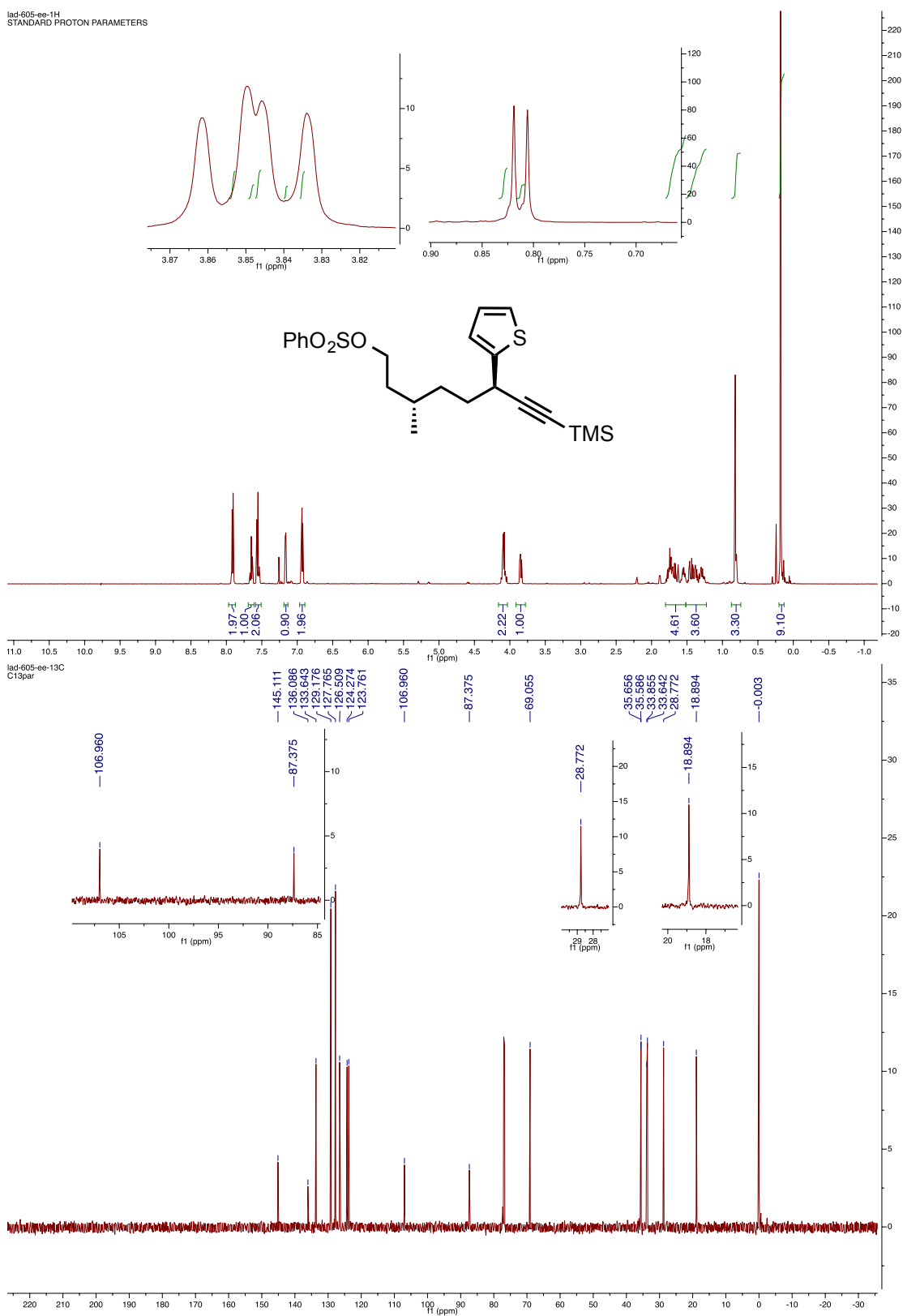
Compound 2o dr = 1:1

lad-605-1H
STANDARD 1H OBSERVE



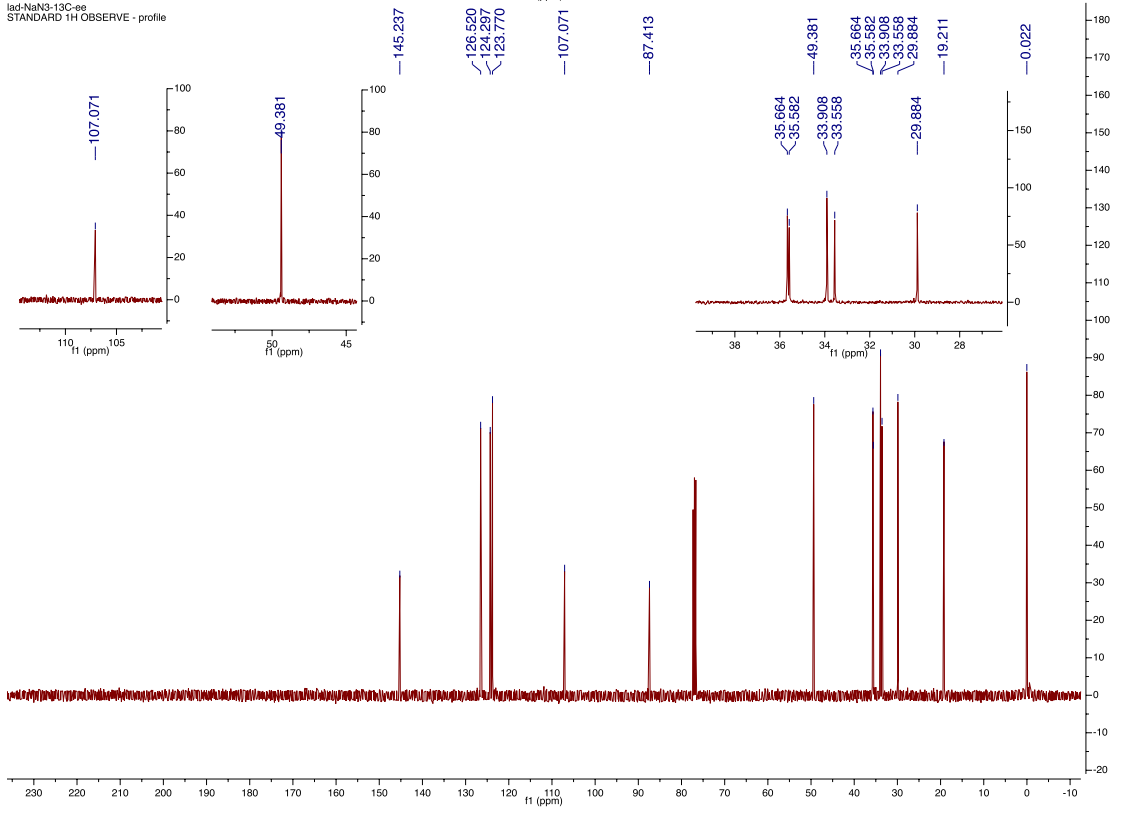
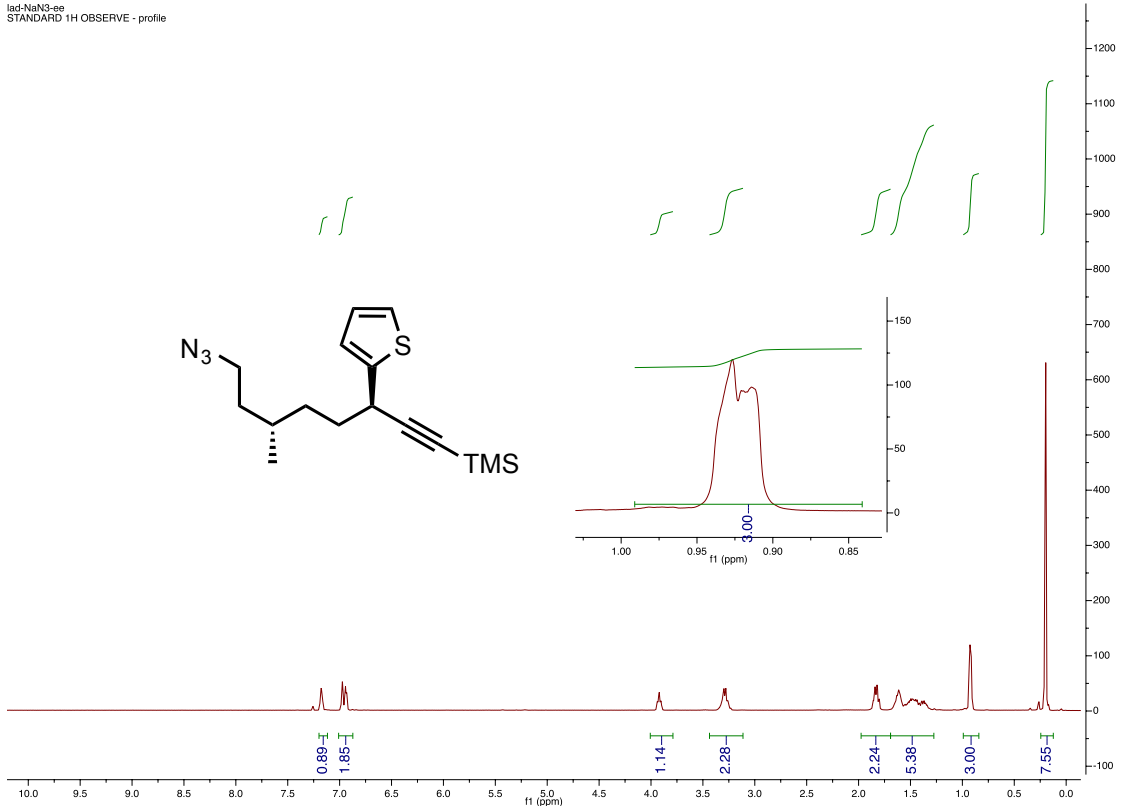
Compound 2o dr > 95:5

lad-605-ee-1H
STANDARD PROTON PARAMETERS



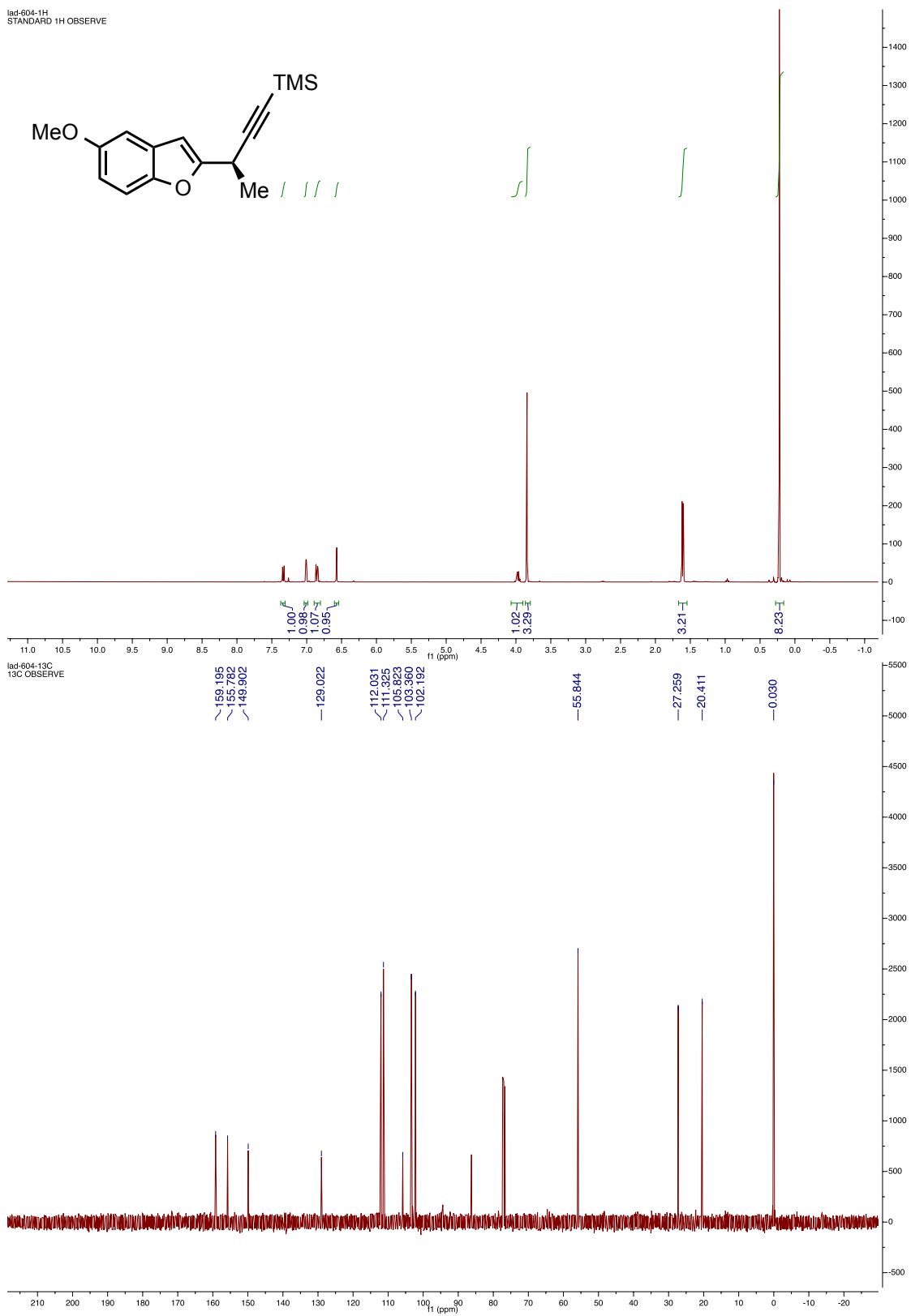
Compound 5b dr > 95:5

lad-Na3-ee
STANDARD 1H OBSERVE - profile

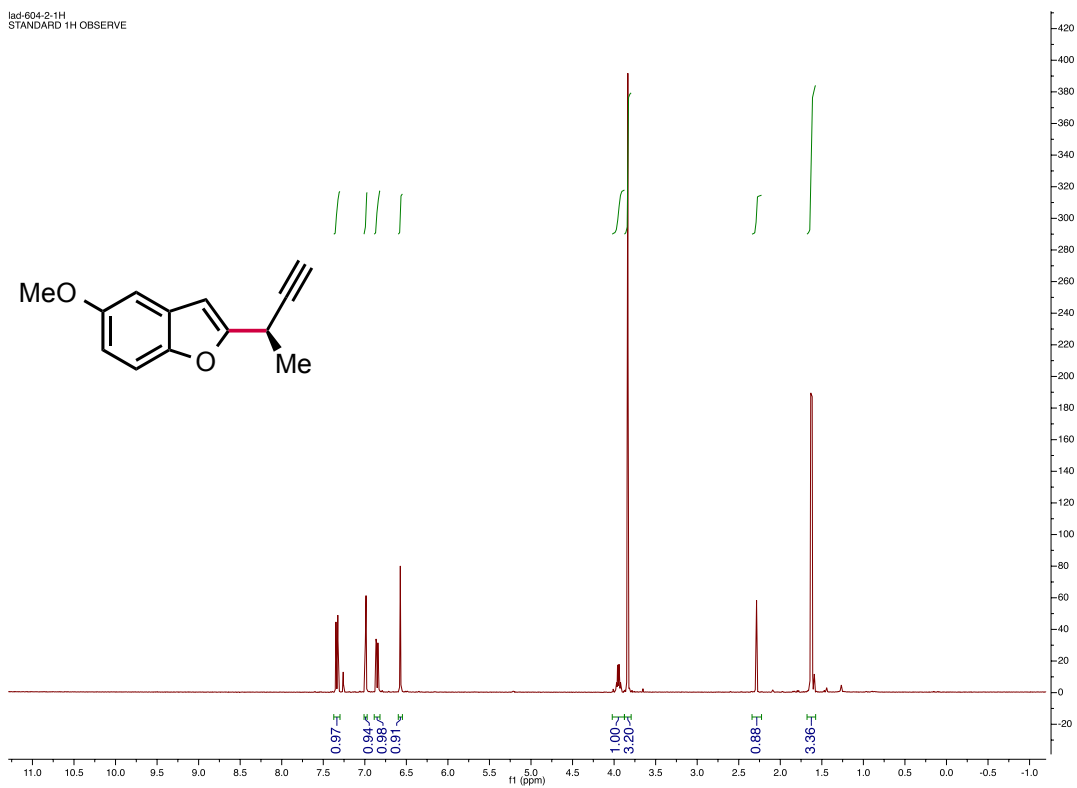


Compound 2p

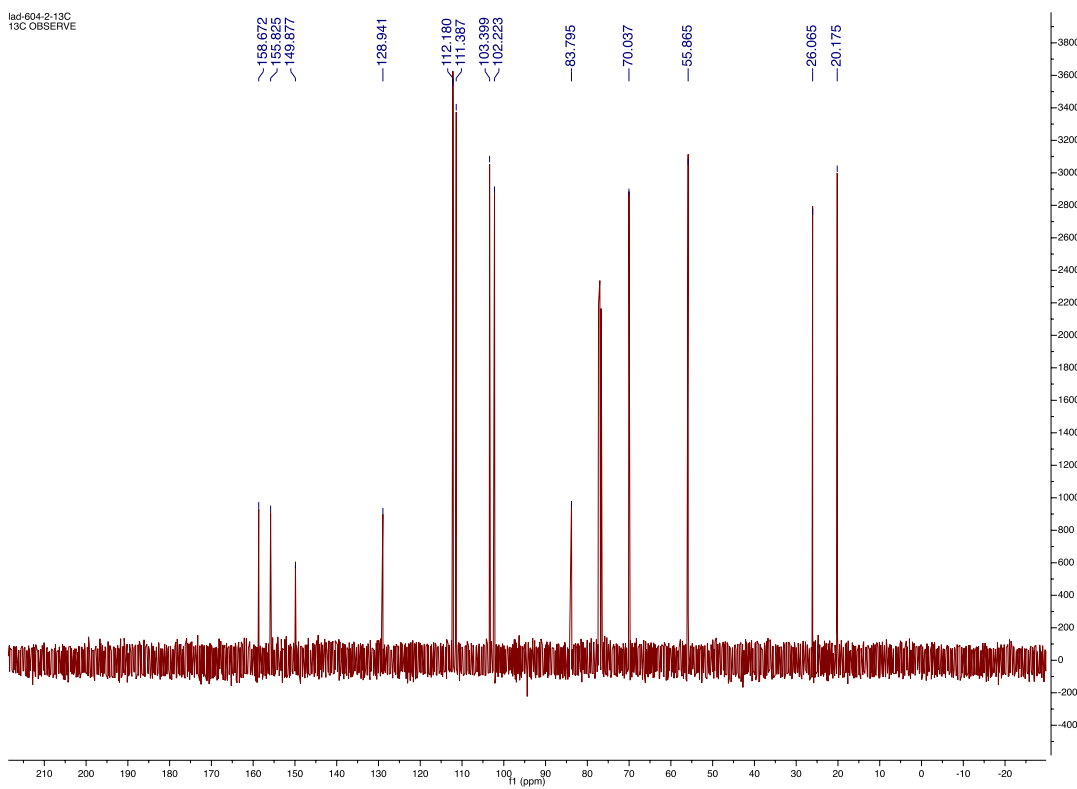
lad-604-1H
STANDARD 1H OBSERVE



lad-604-2-1H
STANDARD 1H OBSERVE



lad-604-2-13C
13C OBSERVE



Compound 5c

lad-606-1H
STANDARD 1H OBSERVE

