The hexadehydro-Diels-Alder (HDDA) cycloisomerization reaction proceeds by a stepwise mechanism

Tao Wang, Dawen Niu, and Thomas R. Hoye*

Department of Chemistry, University of Minnesota, 207 Pleasant St. SE, Minneapolis, MN 55455

*Email: hoye@umn.edu

Contents

I. General Experimental Protocols

NMR (^{1}H and ^{13}C) spectra were recorded on Bruker Avance 500 (500 MHz) spectrometers. ^{1}H NMR chemical shifts ($C_6D_5CD_3$ or $CDCl_3$) are referenced to $C_6D_5CHD_2$ (2.09 ppm) or TMS (0.00 ppm), respectively. The "nfom" designation is used to indicate non-first order multiplets. ^{13}C NMR chemical shifts are referenced to the *C*DCl_3 resonance at 77.23 ppm. The following format is used to report each proton resonance: chemical shift in ppm {multiplicity, *J* values [coupling constant(s)] in Hz, integral value, and assignment}. Coupling constant analysis was performed using protocols we have reported elsewhere.[1]

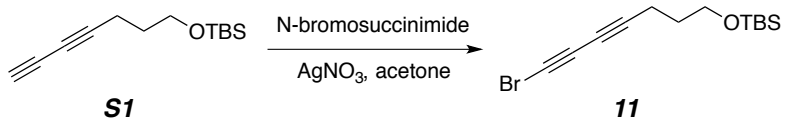
Infrared (IR) spectra were taken of thin film samples on a ZnSe ATR plate with a Prospect MIDAC FT-IR spectrometer. Absorption bands are reported in cm^{-1}.

Medium pressure liquid chromatography (MPLC, 50-200 psi) was performed on hand-packed silica gel columns (25-35 μm, 60 Å pores). A Waters HPLC pump fitted with a Waters R401 differential refractive index detector was used to detect the eluants. Flash column chromatography (FCC) was performed on columns packed with silica gel (40-63 μm).

Mass spectrometric measurements were performed: i) at low mass accuracy with an Agilent 5975 GC-MS instrument (electron impact ionization (EI) at 70 eV) and ii) at high mass accuracy on a Bruker BioTOF II instrument (<5 ppm mass accuracy) using electrospray ionization (ESI) and PEG as the internal calibrant.

Experiments requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon in oven- or flame-dried glassware. Anhydrous THF, toluene, diethyl ether, and methylene chloride were collected immediately prior to use by being passed through an activated alumina column.

II. Preparation procedures and characterization data for all key compounds



S1 ***11***

Preparation of ((7-bromohepta-4,6-diyn-1-yl)oxy)(*tert*-butyl)dimethylsilane (11).

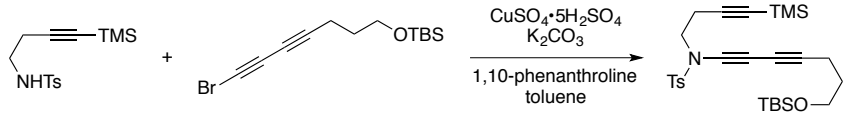
In a round bottom flask (100 mL) wrapped with aluminum foil was added *tert*-butyl(hepta-4,6-diyn-1-yloxy)dimethylsilane[2] (**S1**, 2.2 g, 10 mmol), acetone (50 mL), *N*-bromosuccinimide (2.2 g, 12 mmol), and silver nitrate (170 mg, 1 mmol) at room temperature. The heterogeneous mixture was stirred overnight, filtered, and concentrated to give a light yellow oil. The crude product was then subjected to column chromatography with silica gel (hexanes:ethyl acetate = 12:1) to give ((7-bromohepta-4,6-diyn-1-yl)oxy)(*tert*-butyl)dimethylsilane (**11**, 2.5 g, 8.3 mmol, 83%) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (t, *J* = 5.9 Hz, 2H, -C*H*$_2$OTBS), 2.35 (t, *J* = 7.0 Hz, 2H, -C≡CC*H*$_2$CH$_2$-), 1.72 (tt, *J* = 7.1, 6.1 Hz, 2H, -CH$_2$C*H*$_2$CH$_2$OTBS), 0.89 [s, 9H, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$], and 0.05 [s, 6H, -Si(C*H*$_3$)$_2$C(CH$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 74.7, 66.0, 65.7, 61.5, 37.1, 31.3, 26.1, 18.5, 15.8, and -5.2 ppm.

IR (neat) 2954, 2930, 2857, 2369, 2144, 1471, 1462, 1388, 1361, 1252, 1105, 970, 838, and 776 cm^{-1}.

GC-LRMS (ES, 70 eV): t_R = 7.96 min. *m/z*: 245, 243 (M^+-^{t}Bu), 185, 187 (M^+-TBS).



10 ***11*** ***12***

Preparation of *N*-(7-((*tert*-Butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methyl-*N*-(4-(trimethylsilyl)but-3-yn-1-yl)benzenesulfonamide (12).

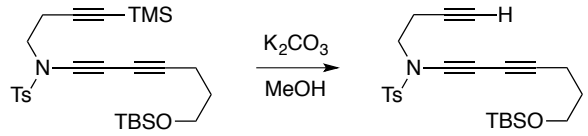
4-Methyl-*N*-(4-(trimethylsilyl)but-3-yn-1-yl)benzenesulfonamide[3] (**10**, 720 mg, 2.4 mmol), K_2CO_3 (1 g, 7.2 mmol), $CuSO_4$•$5H_2O$ (61 mg, 0.24 mmol), 1,10-phenanthroline (88 mg, 0.49 mmol), and toluene (3.5 mL) were combined in a glass vial. Neat ((7-bromohepta-4,6-diyn-1-yl)oxy)(tert-butyl)dimethylsilane (**11**, 1.1 g, 3.65 mmol) was added with stirring at room temperature. The vial was sealed with a Teflon-lined cap and placed in a 65 °C oil bath with stirring for 15 h. The crude reaction mixture was directly subjected to column chromatography with silica gel (hexanes:ethyl acetate = 12:1) to give *N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methyl-*N*-(4-(trimethylsilyl)but-3-yn-1-yl)benzenesulfonamide (**12**) as an orange-red oil (1.0 g, 80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz, 2H, -SO$_2$Ar*H*$_{ortho}$), 7.36 (d, *J* = 7.9 Hz, 2H, -SO$_2$Ar*H*$_{meta}$), 3.68 (t, *J* = 5.9 Hz, 2H, -C*H*$_2$OTBS), 3.49 [t, *J* = 7.7 Hz, 2H, -N(Ts)C*H*$_2$CH$_2$], 2.55 [t, *J* = 7.7 Hz, 2H, -N(Ts)CH$_2$C*H*$_2$], 2.46 (s, 3H, -SO$_2$ArC*H*$_3$), 2.40 (t, *J* = 7.0 Hz, 2H, -C*H*$_2$CH$_2$CH$_2$OTBS), 1.73 (tt, *J* = 5.9, 7.1 Hz, 2H, -CH$_2$C*H*$_2$CH$_2$OTBS), 0.90 [s, 9H, -Si(CH$_3$)$_2$C(C*H*$_3$)$_3$], 0.13 [s, 9H, -Si(C*H*$_3$)$_3$], and 0.06 [s, 6H, -Si(C*H*$_3$)$_2$C(CH$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 134.8, 130.2, 127.7, 101.7, 87.6, 84.2, 66.8, 64.6, 61.6, 59.1, 50.5, 31.5, 26.1, 21.9, 20.1, 18.5, 16.3, 0.1, and -5.1 ppm.

IR (neat) 2954, 2930, 2858, 2252, 2178, 1598, 1375, 1251, 1171, 1093, 970, and 841 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{27}H_{41}NNaO_3SSi_2)^+$ 538.2238; found: 538.2243.



12 ***7a***

Preparation *N*-(but-3-yn-1-yl)-*N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylbenzenesulfonamide (7a).

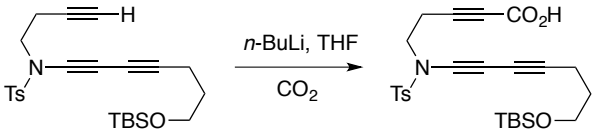
N-(7-((*tert*-Butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methyl-*N*-(4-(trimethylsilyl)but-3-yn-1-yl)benzenesulfonamide (**12**, 700 mg, 1.36 mmol), K_2CO_3 (200 mg, 1.45 mmol), and methanol (3 mL) were combined in a glass vial. The vial was capped and the contents were stirred at room temperature for 4 h. The crude mixture was partitioned between ethyl acetate and brine. The organic layer was dried over Na_2SO_4, concentrated, and purified with column chromatography on silica gel (hexanes:ethyl acetate = 12:1) to give *N*-(but-3-yn-1-yl)-*N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylbenzenesulfonamide (**7a**) as a pale yellow oil (501 mg, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 7.9 Hz, 2H, -SO_2ArH_{ortho}), 7.36 (d, J = 8.0 Hz, 2H, -SO_2ArH_{meta}), 3.68 (t, J = 5.9 Hz, 2H, -CH_2OTBS), 3.50 [t, J = 7.7 Hz, 2H, -N(Ts)CH_2CH$_2$], 2.52 [dt, J = 3.1, 7.9 Hz, 2H, -N(Ts)CH$_2$CH_2], 2.46 (s, 3H, -SO_2ArCH_3), 2.40 (t, J = 7.0 Hz, 2H, -CH_2CH$_2$CH$_2$OTBS), 1.97 (t, J = 2.7 Hz, 1H, -C≡CH), 1.73 (tt, J = 5.9, 7.1 Hz, 2H, -CH$_2$CH_2CH$_2$OTBS), 0.90 [s, 9H, -Si(CH$_3$)$_2$C(CH_3)$_3$], and 0.06 [s, 6H, -Si(CH_3)$_2$C(CH$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 134.7, 130.2, 127.8, 84.3, 79.6, 70.9, 66.6, 64.5, 61.6, 59.3, 50.2, 31.5, 26.1, 21.9, 18.6, 18.5, 16.3, and -5.1 ppm.

IR (neat) 3290, 2952, 2933, 2860, 2252, 2165, 1598, 1373, 1250, 1171, 1093, 1057, 1033, 970, and 838 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{24}H_{33}NNaO_3SSi)^+$ 466.1843. Found: 466.1857.



7a ***S2***

Preparation of 5-((*N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylphenyl)sulfonamido)pent-2-ynoic acid (S2).

In a glass vial was added *N*-(but-3-yn-1-yl)-*N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylbenzenesulfonamide (**7a**, 100 mg, 0.22 mmol) and THF (3 mL). The vial was sealed with a septum, fitted with an Ar balloon, and cooled to -78 °C in a dry-ice acetone bath. A solution of *n*-BuLi (0.15 mL, 2.5 M in hexanes) was added and the mixture was stirred at -78 °C for 1 h. A balloon filled with anhydrous CO_2 (from a lecture cylinder) was attached and the solution was allowed to warm to room temperature and stirred overnight. The color of the acetylide solution dissipated in the first few minutes. The crude mixture was partitioned between ethyl acetate and 1:1 HCl (3M, aq)/NH_4Cl (aq) solution. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified with column chromatography (hexanes:ethyl acetate:methanol = 5:5:1) to give 5-((*N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylphenyl)sulfonamido)pent-2-ynoic acid (**S2**, 77.9 mg, 71%) as a yellow oil. A portion of the starting terminal alkyne was also recovered (15.0 mg, 15%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (br s, 1H, CO_2H), 7.79 (d, J = 8.0 Hz, 2H, -SO_2ArH_{ortho}), 7.37 (d, J = 8.1 Hz, 2H, -SO_2ArH_{meta}), 3.69 (t, J = 5.9 Hz, 2H, -CH_2OTBS), 3.55 [br t, J = 7.4 Hz, 2H, -N(Ts)CH_2CH$_2$], 2.65 [br t, J = 7.2 Hz,

2H, -N(Ts)CH_2CH_2], 2.45 (s, 3H, -SO_2ArCH_3), 2.40 (t, J = 7.1 Hz, 2H, -$CH_2CH_2CH_2$OTBS), 1.73 (tt, J = 6.3, 6.3 Hz, 2H, -$CH_2CH_2CH_2$OTBS), 0.90 [s, 9H, -$Si(CH_3)_2C(CH_3)_3$], and 0.07 [s, 6H, -$Si(CH_3)_2C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3 (br), 145.6, 134.3, 130.3, 127.8, 84.7 (br), 84.5, 75.6 (br), 66.2, 64.4, 61.7, 59.7, 49.3 (br), 31.4, 26.1, 21.9, 18.9, 18.5, 16.2, and -5.2 ppm.

IR (neat) 2953, 2930, 2857, 2245, 2165, 1713 (w), 1696 (w), 1596, 1372, 1252, 1170, 1093, 966, and 837 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{25}H_{33}NNaO_5SSi)^+$ 510.1741. Found: 510.1731.

S2 ***7b***

Preparation of 5-((*N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylphenyl)sulfonamido)-*N*,*N*-diethylpent-2-ynamide (7b).

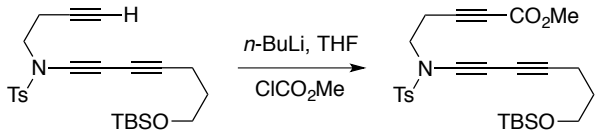
In a glass vial (2 mL) was added 5-((*N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylphenyl)sulfonamido)pent-2-ynoic acid (**S2**, 50 mg, 0.1 mmol), dimethylformamide (0.2 mL), diethylamine (20 μL, 0.2 mmol), 4-dimethylaminopyridine (4 mg, 0.03 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 40 mg, 0.2 mmol) at room temperature. This mixture was stirred overnight and then partitioned between ethyl acetate and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography (silica gel, hexanes:ethyl acetate = 1:1) to give 5-((*N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylphenyl)sulfonamido)-*N*,*N*-diethylpent-2-ynamide (**7b**, 30.4 mg, 0.06 mmol, 57%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2H, -SO_2ArH_{ortho}), 7.37 (d, J = 8.1 Hz, 2H, -SO_2ArH_{meta}), 3.68 (t, J = 5.9 Hz, 2H, -CH_2OTBS), 3.57 [q, J = 7.1 Hz, 2H, -$N(CH_2CH_3)_a(CH_2CH_3)_b$], 3.53 [t, J = 7.3 Hz, 2H, -N(Ts)CH_2CH_2], 3.40 [q, J = 7.2 Hz, 2H, -$N(CH_2CH_3)_a(CH_2CH_3)_b$], 2.72 [t, J = 7.3 Hz, 2H, -N(Ts)CH_2CH_2], 2.46 (s, 3H, -SO_2ArCH_3), 2.40 (t, J = 7.0 Hz, 2H, -$CH_2CH_2CH_2$OTBS), 1.73 (tt, J = 7.0, 6.1 Hz, 2H, -$CH_2CH_2CH_2$OTBS), 1.21 [t, J = 7.1 Hz, 3H, -$N(CH_2CH_3)_a(CH_2CH_3)_b$], 1.13 [t, J = 7.1 Hz, 3H, -$N(CH_2CH_3)_a(CH_2CH_3)_b$], 0.90 [s, 9H, -$Si(CH_3)_2C(CH_3)_3$], and 0.06 [s, 6H, -$Si(CH_3)_2C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 145.5, 134.4, 130.3, 127.8, 86.3, 84.5, 76.5, 66.4, 64.4, 61.6, 59.5, 49.6, 43.7, 39.3, 31.5, 26.1, 21.9, 19.1, 18.5, 16.2, 14.5, 13.0, and -5.2 ppm.

IR (neat) 2953, 2932, 2857, 2252, 2165, 1627, 1428, 1373, 1281, 1171, 1092, 969, and 838 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{29}H_{42}N_2NaO_4SSi)^+$ 565.2527. Found: 565.2533.



7a *7c*

Preparation of methyl 5-((*N*-(7-((tert-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylphenyl)sulfonamido)pent-2-ynoate (7c).

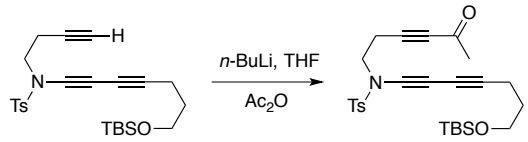
In a glass vial was added *N*-(but-3-yn-1-yl)-*N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylbenzenesulfonamide (**7a**, 50 mg, 0.11 mmol) and THF (1.5 mL). The vial was sealed with a septum, connected to an Ar balloon, and cooled to -78 °C in a dry-ice acetone bath. A solution of *n*-BuLi (0.07 mL, 2.5 M in hexanes) was added and the solution was stirred at -78 °C for 1 h. Methyl chloroformate ($ClCO_2Me$, 0.03 mL) was added. The reaction vial was allowed to warm to room temperature and stirred overnight. The crude mixture was partitioned between ethyl acetate and NH_4Cl (aq) solution. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography (silica gel, hexanes:ethyl acetate = 5:1) to give methyl 5-((*N*-(7-((tert-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylphenyl)sulfonamido) pent-2-ynoate (**7c**, 36.2 mg, 64%) as a yellow oil. Some starting material (10.4 mg, 20%) was also recovered.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.1 Hz, 2H, -$SO_2Ar\mathit{H}_{ortho}$), 7.37 (d, J = 8.1 Hz, 2H, -$SO_2Ar\mathit{H}_{meta}$), 3.76 (s, 3H, $CO_2C\mathit{H}_3$), 3.68 (t, J = 5.9 Hz, 2H, -$C\mathit{H}_2$OTBS), 3.55 [t, J = 7.5 Hz, 2H, -N(Ts)$C\mathit{H}_2CH_2$], 2.68 [t, J = 7.7 Hz, 2H, -N(Ts)$CH_2C\mathit{H}_2$], 2.46 (s, 3H, -$SO_2ArC\mathit{H}_3$), 2.41 (t, J = 7.0 Hz, 2H, -$C\mathit{H}_2CH_2CH_2$OTBS), 1.73 (tt, J = 6.5, 6.4 Hz, 2H, -$CH_2C\mathit{H}_2CH_2$OTBS), 0.90 [s, 9H, -$Si(CH_3)_2C(C\mathit{H}_3)_3$], and 0.06 [s, 6H, -$Si(C\mathit{H}_3)_2C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 145.5, 134.4, 130.2, 127.8, 84.6, 84.1, 74.7, 66.2, 64.3, 61.5, 59.7, 52.9, 49.2, 31.4, 26.1, 21.9, 18.8, 18.5, 16.2, and -5.2 ppm.

IR (neat) 2952, 2931, 2858, 2246, 2165, 1717, 1597, 1435, 1373, 1257, 1171, 1091, 966, and 838 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{26}H_{35}NNaO_5SSi)^+$ 524.1897. Found: 524.1951.



7a *7d*

Preparation of *N*-(7-((tert-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methyl-*N*-(5-oxohex-3-yn-1-yl)benzenesulfonamide (7d).

In a glass vial was added *N*-(but-3-yn-1-yl)-*N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylbenzenesulfonamide (**7a**, 100 mg, 0.22 mmol) and THF (3 mL). The vial was then sealed with a septum, connected to an Ar balloon, and cooled to -78 °C in a dry-ice acetone bath. A solution of *n*-BuLi (0.15 mL, 2.5 M in hexanes) was added. This solution was stirred at -78 °C for 1 h. The reaction mixture was then taken up in a syringe and added dropwise to an ambient temperature solution of acetic anhydride (0.1 mL) in THF (1 mL). This mixture was stirred overnight and then partitioned between ethyl acetate and NH_4Cl (aq) solution. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified with column chromatography (silica gel, hexanes:ethyl acetate = 5:1) to give **7d** (55.4 mg, 51%) as a yellow oil. Some starting material was also recovered (30 mg, 30%).

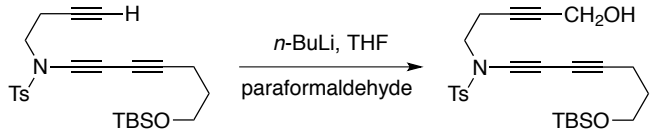
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 7.4 Hz, 2H, -$SO_2Ar\mathit{H}_{ortho}$), 7.37 (d, J = 7.9 Hz, 2H, -$SO_2Ar\mathit{H}_{meta}$), 3.68 (t, J = 5.9 Hz, 2H, -$C\mathit{H}_2$OTBS), 3.55 [t, J = 6.9 Hz, 2H, -N(Ts)$C\mathit{H}_2CH_2$], 2.72 [t, J = 6.9 Hz, 2H, -N(Ts)$CH_2C\mathit{H}_2$], 2.46 (s,

3H, -SO_2ArCH_3), 2.40 (t, J = 6.7 Hz, 2H, -$CH_2CH_2CH_2OTBS$), 2.31 (s, 3H, -$COCH_3$), 1.73 (tt, J = 7.1, 5.9 Hz, 2H, -$CH_2CH_2CH_2OTBS$), 0.90 [s, 9H, -$Si(CH_3)_2C(CH_3)_3$], and 0.06 [s, 6H, -$Si(CH_3)_2C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 145.5, 134.5, 130.3, 127.8, 88.1, 84.7, 82.9, 66.5, 64.4, 61.6, 59.6, 49.5, 32.8, 31.5, 26.1, 21.9, 19.3, 18.5, 16.2, and -5.2 ppm.

IR (neat) 2953, 2930, 2857, 2216, 2164, 1679, 1373, 1250, 1232, 1170, 1092, 969, and 837 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{26}H_{35}NNaO_4SSi)^+$ 508.1948. Found: 508.1962.



7a ***S3***

Preparation of *N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-*N*-(5-hydroxypent-3-yn-1-yl)-4-methylbenzenesulfonamide (S3).

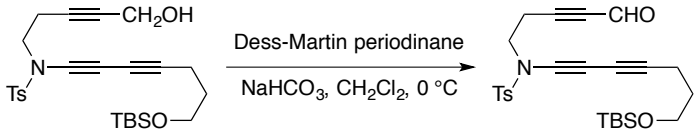
In a glass vial was added *N*-(but-3-yn-1-yl)-*N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methylbenzenesulfonamide (**7a**, 100 mg, 0.22 mmol) and THF (3 mL). The vial was then sealed with a septum, connected with an Ar balloon, and cooled to -78 °C in a dry-ice acetone bath. A solution of *n*-BuLi (0.15 mL, 2.5 M in hexanes) was added and the solution was stirred at -78 °C for 1 h. Solid paraformaldehyde (30 mg, 1.0 mmol) was added in one portion. The reaction vial was allowed to warm to room temperature overnight. The crude mixture was partitioned between ethyl acetate and NH_4Cl (aq) solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified with column chromatography (silica gel, hexanes:ethyl acetate = 5:1) to give *N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-*N*-(5-hydroxypent-3-yn-1-yl)-4-methylbenzenesulfonamide (**S3**, 41.0 mg, 38%) as a yellow oil. Some starting material was also recovered (25.3 mg, 25%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.1 Hz, 2H, -$SO_2Ar\mathit{H}_{ortho}$), 7.37 (d, J = 8.1 Hz, 2H, -$SO_2Ar\mathit{H}_{meta}$), 4.19 (s, 2H, CH_2OH), 3.68 (t, J = 5.9 Hz, 2H, -CH_2OTBS), 3.49 [t, J = 7.4 Hz, 2H, -N(Ts)CH_2CH_2], 2.55 [tt, J = 7.5, 2.1 Hz, 2H, -N(Ts)CH_2CH_2], 2.46 (s, 3H, -SO_2ArCH_3), 2.40 (t, J = 7.0 Hz, 2H, -$CH_2CH_2CH_2OTBS$), 1.73 (tt, J = 6.6, 6.3 Hz, 2H, -$CH_2CH_2CH_2OTBS$), 0.90 [s, 9H, -$Si(CH_3)_2C(CH_3)_3$], and 0.06 [s, 6H, -$Si(CH_3)_2C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 134.7, 130.1, 127.7, 84.4, 81.6, 81.1, 66.8, 64.5, 61.6, 59.2, 51.3, 50.4, 31.5, 26.1, 21.9, 19.0, 18.5, 16.2, and -5.2 ppm.

IR (neat) 3450 (br), 2952, 2929, 2857, 2251, 2165, 1597, 1372, 1252, 1171, 1093, 1017, 967, and 838 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{25}H_{35}NNaO_4SSi)^+$ 496.1948. Found: 496.1959.



S3 ***7e***

Preparation of *N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methyl-*N*-(5-oxopent-3-yn-1-yl)benzenesulfonamide (7e).

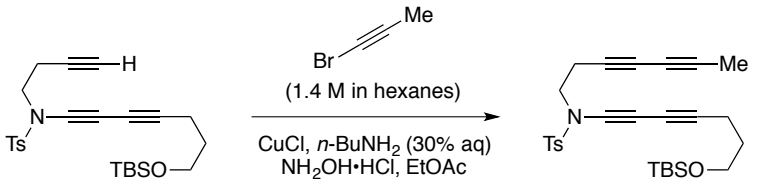
In a glass vial was added alcohol **S3** (45 mg, 0.09 mmol), CH_2Cl_2 (2 mL), and $NaHCO_3$ (84 mg, 1 mmol). The vial was cooled to 0 °C and Dess-Martin periodinane (85 mg, 0.2 mmol) was added in a single portion. The mixture was stirred at 0 °C for 3 h and a 1:1 mixture of $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq) was added. The aqueous phase was extracted 2 times with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified with column chromatography (silica gel, hexanes:ethyl acetate = 5:1) to give *N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methyl-*N*-(5-oxopent-3-yn-1-yl)benzenesulfonamide (**7e**, 40.8 mg, 0.09 mmol, 91%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (t, *J* = 0.9 Hz, 1H, -C*H*O), 7.80 (d, *J* = 8.4 Hz, 2H, -SO_2ArH_{ortho}), 7.37 (d, *J* = 8.0 Hz, 2H, -SO_2ArH_{meta}), 3.68 (t, *J* = 5.9 Hz, 2H, -CH_2OTBS), 3.58 [t, *J* = 7.4 Hz, 2H, -N(Ts)CH_2CH_2], 2.77 [dt, *J* = 0.9, 7.5 Hz, 2H, -N(Ts)CH_2CH_2], 2.46 (s, 3H, -SO_2ArCH_3), 2.41 (t, *J* = 7.1 Hz, 2H, -CH_2CH_2CH_2OTBS), 1.73 (tt, *J* = 7.1, 5.9 Hz, 2H, -CH_2CH_2CH_2OTBS), 0.90 [s, 9H, -Si(CH_3)$_2$C(CH_3)$_3$], and 0.06 [s, 6H, -Si(CH_3)$_2$C(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 145.6, 134.4, 130.3, 127.8, 93.1, 84.8, 82.9, 66.2, 64.3, 61.6, 59.8, 49.2, 31.4, 26.1, 21.9, 19.3, 18.5, 16.2, and -5.2 ppm.

IR (neat) 2952, 2930, 2858, 2207, 2165, 1669, 1372, 1252, 1170, 1092, 967, and 838 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{26}H_{37}NNaO_5SSi)^+$ ($M+CH_3OH+Na^+$) 526.2054. Found: 526.2077.



7a ***7f***

Preparation of *N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-*N*-(hepta-3,5-diyn-1-yl)-4-methylbenzenesulfonamide (7f)

In a glass vial (2 mL) was added CuCl (1 mg, 0.01 mmol), NH_2OH•HCl (10 mg), and *n*-$BuNH_2$ (0.6 mL, 30% aq solution). The reaction was cooled to 0 °C before addition of alkyne **7a** (50 mg, 0.11 mmol) as an ethyl acetate (0.6 mL) solution. A solution of 1-bromopropyne[4] (160 μL, 1.4 M in hexanes) was added. The vial was sealed with a Teflon-lined cap. After 5 min of stirring at 0 °C, the cooling bath was removed. The reaction was allowed to stir at room temperature for 1 h and saturated NH_4Cl (aq) solution was added. The aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, hexanes:ethyl acetate = 12:1) to give *N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-*N*-(hepta-3,5-diyn-1-yl)-4-methylbenzenesulfonamide (**7f**, 49.3 mg, 0.1 mmol, 91%) as a pale yellow oil.

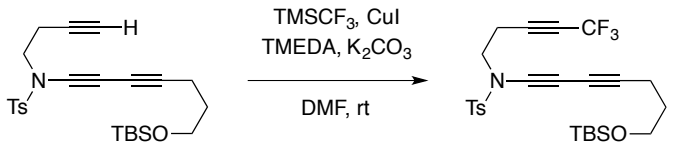
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H, -SO_2ArH_{ortho}), 7.36 (d, *J* = 8.0 Hz, 2H, -SO_2ArH_{meta}), 3.68 (t, *J*

= 5.9 Hz, 2H, -CH_2OTBS), 3.49 [t, J = 7.4 Hz, 2H, -N(Ts)CH_2CH$_2$], 2.57 [tq, J = 6.9, 1.2 Hz, 2H, -N(Ts)CH$_2$CH_2], 2.46 (s, 3H, -SO$_2$ArCH_3), 2.40 (t, J = 7.1 Hz, 2H, -CH_2CH$_2$CH$_2$OTBS), 1.90 (t, J = 1.2 Hz, 3H, -C≡CCH_3), 1.73 (tt, J = 7.1, 5.9 Hz, 2H, -CH$_2$CH_2CH$_2$OTBS), 0.90 [s, 9H, -Si(CH$_3$)$_2$C(CH_3)$_3$], and 0.06 [s, 6H, -Si(CH_3)$_2$C(CH$_3$)$_3$].

^{13}C NMR (125 MHz, CDCl$_3$) δ 145.3, 134.5, 130.2, 127.8, 84.4, 74.5, 71.3, 67.8, 66.4, 64.5, 64.3, 61.6, 59.4, 49.9, 31.5, 26.1, 21.9, 19.3, 18.5, 16.2, 4.4, and -5.2 ppm.

IR (neat) 2953, 2929, 2857, 2252, 2165, 1372, 1171, 1092, 967, and 838 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{27}H_{35}NNaO_3SSi)^+$ 504.1999. Found: 504.2018.



7a ***7g***

Preparation of *N*-(7-((*tert*-butyldimethylsilyl)oxy)hepta-1,3-diyn-1-yl)-4-methyl-*N*-(5,5,5-trifluoropent-3-yn-1-yl)benzenesulfonamide (7g).

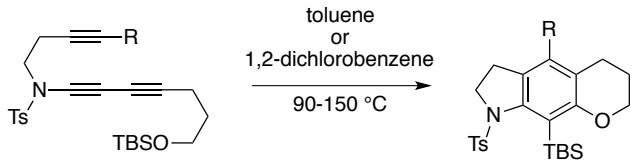
CuI (64 mg, 0.34 mmol, 1.7 eq.), K$_2$CO$_3$ (93 mg, 0.68 mmol, 3.4 eq.), and dry DMF (1.0 mL, ca. 5 mL•mmol^{-1} of alkyne substrate) were combined in a 20 mL scintillation vial equipped with a stir bar and capped with a rubber septum. A balloon filled with dry air was attached. The mixture was stirred vigorously at room temperature while anhydrous TMEDA was introduced via syringe. The white suspension immediately turned blue. This suspension was allowed to stir at ambient temperature for 15 min before addition of TMSCF$_3$ (70 μL, 2.4 eq.) The resulting deep green solution was allowed to stir at room temperature for an additional 5 min before being cooled to 0 °C in an ice-water bath. A solution of triyne **7a** (90 mg, 0.20 mmol) and TMSCF$_3$ (70 μL, 2.4 equiv) in dry DMF (1.0 mL, ca. 5 mL•mmol^{-1} of alkyne substrate) was slowly added over 10 min at 0 °C. The deep green reaction mixture was allowed to warm to room temperature overnight with stirring. After 15 h TLC analysis confirmed full consumption of starting material. The resulting mixture was partitioned between ethyl acetate and brine. The organic layer was washed with brine twice, dried over anhydrous Na$_2$SO$_4$, and concentrated. The residue was purified with column chromatography on silica gel (hexanes:ethyl acetate = 5:1) to give the trifluoromethylated triyne **7g** (89 mg, 0.17 mmol, 86%) as a pale yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80 (d, J = 8.4 Hz, 2H, -SO$_2$ArH_{ortho}), 7.37 (d, J = 8.6 Hz, 2H, -SO$_2$ArH_{meta}), 3.68 (t, J = 5.9 Hz, 2H, -CH_2OTBS), 3.56 [br d, J = 7.4 Hz, 2H, -N(Ts)CH_2CH$_2$], 2.68 [br tq, J = 7.4, 3.6 Hz, 2H, -N(Ts)CH$_2$CH_2], 2.46 (s, 3H, -SO$_2$ArCH_3), 2.41 (t, J = 7.1 Hz, 2H, -CH_2CH$_2$CH$_2$OTBS), 1.73 (tt, J = 5.9, 7.1 Hz, 2H, -CH$_2$CH_2CH$_2$OTBS), 0.90 [s, 9H, -Si(CH$_3$)$_2$C(CH_3)$_3$], and 0.06 [s, 6H, -Si(CH_3)$_2$C(CH$_3$)$_3$].

^{13}C NMR (125 MHz, CDCl$_3$) δ 145.6, 134.5, 130.3, 127.8, 114.0 (q, J = 257.0 Hz), 84.8, 84.2 (q, J = 6.4 Hz), 70.6 (q, J = 52.4 Hz), 66.2, 64.3, 61.6, 59.9, 49.0, 31.5, 26.1, 21.9, 18.54, 18.52, 16.3, and -5.1 ppm.

IR (neat) 2954, 2930, 2858, 2274, 2256, 2165, 1597, 1375, 1286, 1171, 1141, 1092, 970, and 838 cm^{-1}.

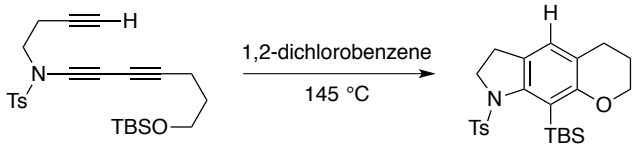
HRMS (ESI-TOF): Calcd for $(C_{25}H_{32}F_3NNaO_3SSi)^+$ 534.1716. Found: 534.1724.



7a-g ***9a-g***

General procedure for the hexadehydro-Diels-Alder reaction

Triyne precursor **7a-g**, a stir bar, and degassed (N_2 sparge) toluene or, for experiments performed at >140 °C, 1,2-dichlorobenzene (100 mL/1 mmol triyne precursor) were combined in a glass vial. The headspace was flushed with N_2, and the vial was closed with a Teflon-lined cap and placed in a hot oil bath, pre-equilibrated to the indicated temperature, for 16–24 h. The crude reaction mixture was concentrated and directly subjected to flash column chromatography (FCC) on silica gel to obtain the purified product. It should be noted that the NMR data for these products suggest that the sulfonamide nitrogen atom is puckered and that inversion of that atom is slow on the NMR time scale. Namely, this stereogenic center renders each of the methylene group geminal protons (and the TBS-methyl resonances) diastereotopic and, therefore, inequivalent in chemical shift in the ^{1}H (and ^{13}C) NMR spectrum for each compound.



7a ***9a***

Preparation of 9-(*tert*-butyldimethylsilyl)-8-tosyl-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indole (9a).

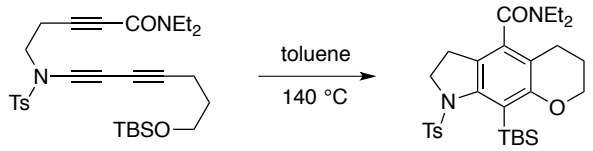
The general HDDA reaction procedure was followed using: 12 mg (27 μmol) of triyne **7a**, 1,2-dichlorobenzene, 145 °C oil bath, 15 h reaction time, and FCC elution with hexanes:ethyl acetate = 5:1. Product: 9-(*tert*-butyldimethylsilyl)-8-tosyl-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indole (**9a**, 6 mg, 14 μmol, 50%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.1 Hz, 2H, -SO_2ArH_{ortho}), 7.12 (d, J = 8.0 Hz, 2H, -SO_2ArH_{meta}), 6.66 (t, J = 1.0 Hz, 1H, Ar-H), 4.23 (dddd, J = 10.6, 6.7, 3.2, 0.9 Hz, 1H, -OC$H_a$$H_b$-), 4.10 (ddd, J = 10.7, 7.9, 3.0 Hz, 1H, -OC$H_a$$H_b$-), 4.00 [ddd, J = 13.1, 7.9, 0.9 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 3.70 [ddd, J = 13.1, 11.9, 8.3 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 2.77 (ddd, J = 16.2, 6.0, 6.0 Hz, 1H, -$OCH_2CH_2CH_aH_b$Ar-), 2.72 (ddd, J = 16.4, 7.1, 6.2 Hz, 1H, -$OCH_2CH_2CH_aH_b$Ar-), 2.38 (s, 3H, -SO_2ArCH_3), 2.09 (dd, J = 15.1, 8.2 Hz, 1H, -N(Ts)$CH_2CH_aH_b$-), 2.06 (ddddd, J = 13.8, 9.4, 7.8, 6.1, 3.4 Hz, 1H, -$OCH_2CH_aH_b$-), 1.94 (ddddd, J = 13.4, 6.5, 6.5, 6.5, 3.1 Hz, 1H, -$OCH_2CH_aH_b$-), 1.59 (dddd, J = 15.2, 11.9, 7.9, 1.2 Hz, 1H, -N(Ts)$CH_2CH_aH_b$-), 1.03 [s, 9H, -$Si(CH_3)_2C(CH_3)_3$], 0.53 [s, 3H, -$Si(CH_3)_a(CH_3)_bC(CH_3)_3$], and 0.25 [s, 3H, -$Si(CH_3)_a(CH_3)_bC(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 146.9, 143.7, 134.8, 129.4, 128.8, 128.2, 126.2, 122.3, 119.7, 65.8, 52.0, 29.3, 27.7, 25.5, 22.4, 21.8, 17.8, 0.098, and 0.084 ppm.

IR (neat) 2951, 2929, 2856, 1571, 1461, 1401, 1351, 1242, 1164, 1087, 1021, and 865 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{24}H_{33}NNaO_3SSi)^+$ 466.1843. Found: 466.1852.



7b ***9b***

Preparation of 9-(*tert*-butyldimethylsilyl)-*N*,*N*-diethyl-8-tosyl-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indole-5-carboxamide (9b).

The general HDDA reaction procedure was followed using: 12 mg (24 μmol) of triyne **7b**, 140 °C bath temperature, 24 h reaction time, and FCC elution with hexanes:ethyl acetate:methanol = 10:10:1. Product: 9-(*tert*-butyldimethylsilyl)-*N*,*N*-diethyl-8-tosyl-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indole-5-carboxamide (**9b**, 5 mg, 10 μmol, 42%) as a pale yellow oil. The compound was an ca. 4:1 mixture of diastereomeric atropisomers, presumably involving slow inversion about a puckered NTs nitrogen atom along with slow rotation about the Ar–CO bond, that interconverted slowly on the NMR time scale but rapidly on the chromatography time scale; hence it eluted from the silica column as a single spot.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 2H, -SO_2ArH_{ortho}), 7.14 (d, *J* = 8.0 Hz, 2H, -SO_2ArH_{meta}), 4.23 (dddd, *J* = 10.6, 6.5, 3.4, 0.8 Hz, 1H, -OC$H_a$$H_b$-), 4.14 [ddd, *J* = 13.0, 7.9, 0.8 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 4.11 (dddd, *J* = 10.9, 8.1, 2.9, 0.6 Hz, 1H, -OC$H_a$$H_b$-), 3.78 [ddd, *J* = 13.1, 11.9, 8.3 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 3.51 [dq, *J* = 13.7, 7.1 Hz, -N(C$H_a$$H_b$$CH_3$)$_x$($CH_2CH_3$)$_y$], 3.34 [dq, *J* = 13.6, 7.1 Hz, -N(C$H_a$$H_b$$CH_3$)$_x$($CH_2CH_3$)$_y$], 2.79 (ddd, *J* = 16.5, 8.1, 6.0 Hz, 1H, -OCH_2CH_2C$H_a$$H_b$Ar-), 2.73 [dq, *J* = 14.2, 7.2 Hz, -N(CH_2CH_3)$_x$(C$H_a$$H_b$$CH_3$)$_y$], 2.63 [dq, *J* = 14.2, 7.1 Hz, -N(CH_2CH_3)$_x$(C$H_a$$H_b$$CH_3$)$_y$], 2.46 (ddd, *J* = 16.6, 5.7, 5.7 Hz, 1H, -$OCH_2CH_2CH_a$$H_b$Ar-), 2.36 (s, 3H, -$SO_2ArCH_3$), 2.19 (ddd, *J* = 15.1, 8.0, 0.8 Hz, 1H, -N(Ts)CH_2C$H_a$$H_b$-), 2.04 (ddddd, *J* = 16.1, 9.0, 8.1, 5.8, 3.4 Hz, 1H, -OCH_2C$H_a$$H_b$-), 1.94 (ddddd, *J* = 17.0, 6.4, 6.4, 6.4, 3.2 Hz, 1H, -$OCH_2CH_a$$H_b$-), 1.66 (ddd, *J* = 15.2, 11.9, 8.1 Hz, 1H, -N(Ts)$CH_2CH_a$$H_b$-), 1.11 [t, *J* = 7.2 Hz, -N(CH_2CH_3)$_x$(CH_2CH_3)$_y$], 1.10 [s, 9H, -Si(CH_3)$_2$C(CH_3)$_3$], 0.90 [t, *J* = 7.1 Hz, -N(CH_2CH_3)$_x$(CH_2CH_3)$_y$], 0.52 [s, 3H, -Si(CH_3)$_a$(CH_3)$_b$C(CH_3)$_3$], and 0.15 [s, 3H, -Si(CH_3)$_a$(CH_3)$_b$C(CH_3)$_3$].

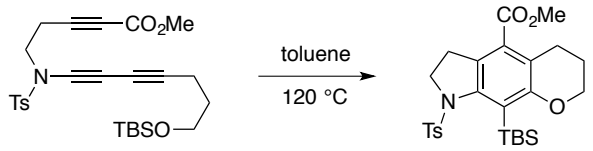
^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 159.9, 146.8, 143.5, 135.8, 134.5, 129.6, 128.3, 128.0, 124.9, 115.7, 65.7, 52.1, 42.1, 38.4, 29.5, 26.3, 22.7, 21.9, 21.8, 17.7, 14.6, 13.0, 0.6, and 0.2 ppm.

IR (neat) 2932, 2854, 1633, 1354, 1164, 1098, and 841 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{29}H_{42}N_2NaO_4SSi)^+$ 565.2527. Found: 565.2544.

The following NMR data are have been extracted from the minor set of resonances (ca. 4:1 major:minor species) present in the proton spectrum of the purified material:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.2 Hz, 2H, -SO_2ArH_{ortho}), 7.18 (d, *J* = 8.2 Hz, 2H, -SO_2ArH_{meta}), 4.26 (dddd, *J* = 10.8, 6.5, 3.3, 1.0 Hz, 1H, -OC$H_a$$H_b$-), 4.09 (ddd, *J* = 10.6, 8.4, 2.9 Hz, 1H, -OC$H_a$$H_b$-), 3.97 [ddd, *J* = 13.1, 8.2, 0.8 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 3.70 [ddd, *J* = 13.0, 12.1, 8.1 Hz, 1H, -N(Ts)C$H_a$$H_b$-], resonances for the following protons in the range of 3.6–2.4 ppm were too severely overlapped with those of the major isomer to explicitly discern: -N(C$H_a$$H_b$$CH_3$)$_x$($CH_2CH_3$)$_y$, -$OCH_2CH_2CH_a$$H_b$Ar, -N($CH_2CH_3$)$_x$(C$H_a$$H_b$$CH_3$)$_y$; 2.37 (s, 3H, -$SO_2ArCH_3$), resonances for the following protons in the range of 2.2–1.6 ppm were too severely overlapped with those of the major isomer to explicitly discern: -N(Ts)CH_2C$H_a$$H_b$- and -$OCH_2CH_a$$H_b$-; 1.14 [t, *J* = 7.1 Hz, -N(CH_2CH_3)$_x$(CH_2CH_3)$_y$], 0.99 [s, 9H, -Si(CH_3)$_2$C(CH_3)$_3$], 0.95 [t, *J* = 7.1 Hz, -N(CH_2CH_3)$_x$(CH_2CH_3)$_y$], 0.54 [s, 3H, -Si(CH_3)$_a$(CH_3)$_b$C(CH_3)$_3$], and 0.31 [s, 3H, -Si(CH_3)$_a$(CH_3)$_b$C(CH_3)$_3$].



7c ***9c***

Preparation of methyl 9-(*tert*-butyldimethylsilyl)-8-tosyl-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indole-5-carboxylate (9c).

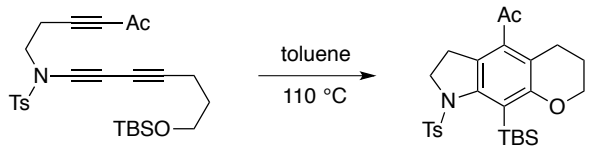
The general HDDA reaction procedure was followed using: 11 mg (22 μmol) of triyne **7c**, 120 °C oil bath, 24 h reaction time, and FCC elution with hexanes:ethyl acetate = 3:1. Product: methyl 9-(*tert*-butyldimethylsilyl)-8-tosyl-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indole-5-carboxylate (**9c**, 7 mg, 14 μmol, 64%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.2 Hz, 2H, -SO_2ArH_{ortho}), 7.14 (d, *J* = 7.9 Hz, 2H, -SO_2ArH_{meta}), 4.27 (dddd, *J* = 10.6, 6.0, 3.4, 1.2 Hz, 1H, -OC$H_a$$H_b$-), 4.08 (ddd, *J* = 10.6, 8.6, 2.8 Hz, 1H, -OC$H_a$$H_b$-), 3.97 [ddd, *J* = 13.1, 8.3, 1.2 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 3.73 (s, 3H, CO_2CH_3), 3.69 [ddd, *J* = 13.1, 11.9, 8.4 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 2.94 (ddd, *J* = 17.3, 8.6, 6.1 Hz, 1H, -$OCH_2CH_2CH_a$$H_b$Ar-), 2.87 (dddd, *J* = 17.3, 5.9, 5.9, 1.1 Hz, 1H, -$OCH_2CH_2CH_a$$H_b$Ar-), 2.39 (s, 3H, -$SO_2ArCH_3$), 2.30 (ddd, *J* = 16.2, 8.4, 0.9 Hz, 1H, -N(Ts)$CH_2CH_a$$H_b$-), 2.04 (ddddd, *J* = 13.7, 9.3, 8.5, 5.8, 3.4 Hz, 1H, -$OCH_2CH_a$$H_b$-), 1.96 (ddddd, *J* = 13.7, 6.0, 6.0, 6.0, 2.9 Hz, 1H, -$OCH_2CH_a$$H_b$-), 1.64 (ddd, *J* = 16.2, 12.0, 8.1 Hz, 1H, -N(Ts)$CH_2CH_a$$H_b$-), 1.01 [s, 9H, -$Si(CH_3)_2C(CH_3)_3$], 0.53 [s, 3H, -$Si(CH_3)_a(CH_3)_bC(CH_3)_3$], and 0.28 [s, 3H, -$Si(CH_3)_a(CH_3)_bC(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 159.6, 147.2, 144.1, 134.3, 129.5, 128.7, 128.1, 126.5, 119.0, 65.6, 51.8, 51.4, 29.1, 28.3, 24.1, 22.1, 21.8, 18.0, 0.1 and -0.1 ppm.

IR (neat) 2950, 2861, 1719, 1442, 1357, 1251, 1164, 1102, 1054, 1033, 1010, and 834 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{26}H_{36}NO_5SSi)^+$ 502.2078. Found: 502.2060.



7d ***9d***

Preparation of 1-(9-(*tert*-butyldimethylsilyl)-8-tosyl-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indol-5-yl)ethan-1-one (9d).

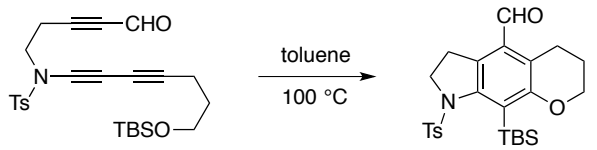
The general HDDA reaction procedure was followed using: 14 mg (28 μmol) of triyne **7d**, 110 °C heating bath, 24 h reaction time, and FCC elution with hexanes:ethyl acetate = 3:1. Product: methyl 1-(9-(*tert*-butyldimethylsilyl)-8-tosyl-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indol-5-yl)ethan-1-one (**9d**, 11 mg, 23 μmol, 80%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 2H, -SO_2ArH_{ortho}), 7.16 (d, *J* = 7.9 Hz, 2H, -SO_2ArH_{meta}), 4.28 (dddd, *J* = 10.7, 6.2, 3.4, 1.2 Hz, 1H, -OC$H_a$$H_b$-), 4.09 (dddd, *J* = 10.7, 8.5, 3.0, 0.7 Hz, 1H, -OC$H_a$$H_b$-), 4.02 [ddd, *J* = 13.2, 8.0, 1.0 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 3.68 [ddd, *J* = 13.2, 11.7, 8.3 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 2.78 (dddd, *J* = 16.7, 8.6, 6.1, 0.6 Hz, 1H, -$OCH_2CH_2CH_a$$H_b$Ar-), 2.64 (dddd, *J* = 16.6, 5.8, 5.8, 1.2 Hz, 1H, -$OCH_2CH_2CH_a$$H_b$Ar-), 2.39 (s, 3H, -$SO_2ArCH_3$), 2.15 (s, 3H, ArCOC$H_3$), 2.08 (ddd, *J* = 15.3, 8.3, 0.9 Hz, 1H, -N(Ts)$CH_2CH_a$$H_b$-), 2.04 (ddddd, *J* = 13.5, 8.9, 8.4, 5.6, 3.4 Hz, 1H, -$OCH_2CH_a$$H_b$-), 1.95 (ddddd, *J* = 13.7, 6.0, 6.0, 6.0, 2.9 Hz, 1H, -$OCH_2CH_a$$H_b$-), 1.51 (ddd, *J* = 15.4, 11.7, 8.0 Hz, 1H, -N(Ts)$CH_2CH_a$$H_b$-), 1.02 [s, 9H, -$Si(CH_3)_2C(CH_3)_3$], 0.53 [s, 3H, -$Si(CH_3)_a(CH_3)_bC(CH_3)_3$], and 0.26 [s, 3H, -$Si(CH_3)_a(CH_3)_bC(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 159.6, 147.3, 144.2, 139.0, 134.3, 129.4, 128.2, 125.0, 124.8, 115.4, 65.6, 51.6, 31.1, 29.2, 27.0, 23.3, 21.9, 21.8, 17.9, 0.02 and -0.03 ppm.

IR (neat) 2950, 2931, 2894, 2855, 1698, 1355, 1245, 1164, 1096, and 830 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{26}H_{35}NNaO_4SSi)^+$ 508.1948. Found: 508.1954.



7e ***9e***

Preparation of 9-(*tert*-butyldimethylsilyl)-8-tosyl-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indole-5-carbaldehyde (9e).

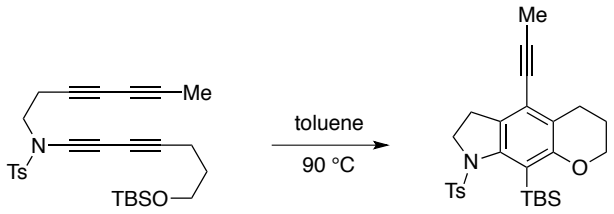
The general HDDA reaction procedure was followed using: 14 mg (29 μmol) of triyne **7e**, 100 °C heating bath, 24 h reaction time, and FCC elution with hexanes:ethyl acetate = 3:1. Product: methyl 9-(*tert*-butyldimethylsilyl)-8-tosyl-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indole-5-carbaldehyde (**9e**, 9.1 mg, 19 μmol, 66%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1H, ArC*H*O), 7.22 (d, *J* = 8.2 Hz, 2H, -SO_2ArH_{ortho}), 7.11 (d, *J* = 8.1 Hz, 2H, -SO_2ArH_{meta}), 4.30 (ddd, *J* = 10.6, 6.1, 3.3 Hz, 1H, -OC$H_a$$H_b$-), 4.12 (ddd, *J* = 10.5, 8.5, 2.9 Hz, 1H, -OC$H_a$$H_b$-), 4.07 [ddd, *J* = 13.1, 8.1, 1.0 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 3.71 [ddd, *J* = 13.2, 11.7, 8.4 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 3.19 (t, *J* = 6.4 Hz, 2H, -$OCH_2CH_2CH_2$Ar-), 2.63 (ddd, *J* = 16.8, 8.5, 1.0 Hz, 1H, -N(Ts)CH_2C$H_a$$H_b$-), 2.37 (s, 3H, -$SO_2ArCH_3$), 2.12 (ddddd, *J* = 13.8, 8.5, 7.2, 7.2, 3.4 Hz, 1H, -OCH_2C$H_a$$H_b$-), 2.03 (ddddd, *J* = 13.9, 6.1, 6.1, 6.1, 2.9 Hz, 1H, -$OCH_2CH_a$$H_b$-), 1.81 (ddd, *J* = 16.8, 11.7, 8.1 Hz, 1H, -N(Ts)$CH_2CH_a$$H_b$-), 1.03 [s, 9H, -Si$(CH_3)_2C(CH_3)_3$], 0.55 [s, 3H, -Si$(CH_3)_a(CH_3)_bC(CH_3)_3$], and 0.29 [s, 3H, -Si$(CH_3)_a(CH_3)_bC(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 159.9, 147.9, 144.4, 134.2, 132.7, 130.9, 129.7, 129.6, 128.1, 120.9, 65.5, 51.7, 29.1, 27.4, 22.8, 21.9, 21.8, 18.0, 0.1 and -0.1 ppm.

IR (neat) 2949, 2928, 2893, 2855, 1687, 1356, 1244, 1164, 1110, 1089, and 842 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{25}H_{33}NNaO_4SSi)^+$ 494.1792. Found: 494.1813.



7f ***9f***

Preparation of 9-(*tert*-butyldimethylsilyl)-5-(prop-1-yn-1-yl)-8-tosyl-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indole (9f).

The general HDDA reaction procedure was followed using: 17 mg (35 μmol) of triyne **7f**, 90 °C heating bath, 16 h reaction time, and FCC elution with hexanes:ethyl acetate = 12:1. Product: 9-(*tert*-butyldimethylsilyl)-5-(prop-1-yn-1-yl)-8-tosyl-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indole (**9f**, 14 mg, 29 μmol, 82%) as a pale yellow oil.

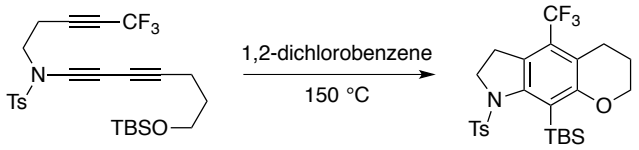
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.2 Hz, 2H, -SO_2ArH_{ortho}), 7.14 (d, *J* = 7.9 Hz, 2H, -SO_2ArH_{meta}), 4.22 (dddd, *J* = 10.6, 6.4, 3.3, 0.7 Hz, 1H, -OC$H_a$$H_b$-), 4.05 (dddd, *J* = 10.8, 8.4, 3.0, 0.4 Hz, 1H, -OC$H_a$$H_b$-), 3.98 [ddd, *J* = 13.1, 8.0, 1.0 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 3.69 [ddd, *J* = 13.1, 11.9, 8.4 Hz, 1H, -N(Ts)C$H_a$$H_b$-], 2.82 (ddd, *J* = 17.1, 6.4,

6.4 Hz, 1H, -$OCH_2CH_2CH_aH_bAr$-), 2.80 (dddd, J = 17.2, 7.5, 6.2 Hz, 1H, -$OCH_2CH_2CH_aH_bAr$-), 2.39 (s, 3H, -SO_2ArCH_3), 2.23 (ddd, J = 15.8, 8.4, 0.9 Hz, 1H, -$N(Ts)CH_2CH_aH_b$-), 2.11–2.02 (nfom, 1H, -$OCH_2CH_aH_b$-), 2.01 (t, J = 1.2 Hz, 3H, -$C{\equiv}CCH_3$), 2.00-1.92 (nfom, 1H, -$OCH_2CH_aH_b$-), 1.58 (ddd, J = 15.8, 11.8, 8.0 Hz, 1H, -$N(Ts)CH_2CH_aH_b$-), 1.01 [s, 9H, -$Si(CH_3)_2C(CH_3)_3$], 0.52 [s, 3H, -$Si(CH_3)_a(CH_3)_bC(CH_3)_3$], and 0.25 [s, 3H, -$Si(CH_3)_a(CH_3)_bC(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 146.2, 143.9, 134.6, 131.7, 129.4, 128.1, 122.5, 121.1, 121.0, 94.1, 75.8, 65.6, 51.6, 29.2, 27.9, 24.3, 22.2, 21.8, 17.9, 4.8, 0.1, and 0.0 ppm.

IR (neat) 2949, 2930, 2854, 1582, 1463, 1393, 1354, 1243, 1164, 1136, 1083, and 909 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{27}H_{35}NNaO_3SSi)^+$ 504.1999. Found: 504.1965.



7g ***9g***

Preparation of 9-(*tert*-butyldimethylsilyl)-8-tosyl-5-(trifluoromethyl)-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indole (9g)

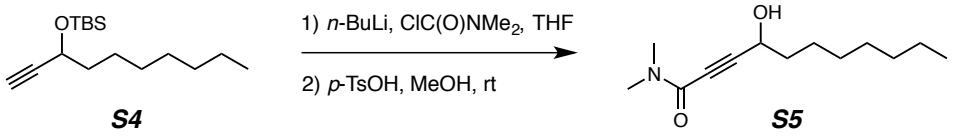
The general HDDA reaction procedure was followed using: 12 mg (23 μmol) of triyne **7g**, 1,2-dichlorobenzene as solvent, 150 °C oil bath, 14 h reaction time, and FCC elution with hexanes:ethyl acetate = 5:1. Product: methyl 9-(*tert*-butyldimethylsilyl)-8-tosyl-5-(trifluoromethyl)-2,3,4,6,7,8-hexahydropyrano[3,2-*f*]indole (**9g**, 5 mg, 10 μmol, 42%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 8.1 Hz, 2H, -$SO_2Ar{H_{ortho}}$), 7.13 (d, J = 8.4 Hz, 2H, -$SO_2Ar{H_{meta}}$), 4.27 (ddd, J = 10.5, 6.8, 3.3 Hz, 1H, -OCH_aH_b-), 4.13 (ddd, J = 10.5, 7.8, 3.0 Hz, 1H, -OCH_aH_b-), 3.98 [dd, J = 13.2, 8.0 Hz, 1H, -$N(Ts)CH_aH_b$-], 3.64 [ddd, J = 13.3, 11.6, 8.4 Hz, 1H, -$N(Ts)CH_aH_b$-], 2.92 (ddd, J = 17.8, 6.7, 6.7 Hz, 1H, -$OCH_2CH_2CH_aH_bAr$-), 2.89 (dddd, J = 17.6, 6.2, 6.2 Hz, 1H, -$OCH_2CH_2CH_aH_bAr$-), 2.39 (s, 3H, -SO_2ArCH_3), 2.30 (ddq, J = 16.7, 8.3, 3.1 Hz, 1H, -$N(Ts)CH_2CH_aH_b$-), 2.08 (ddddd, J = 13.8, 7.7, 7.7, 6.0, 3.4 Hz, 1H, -$OCH_2CH_aH_b$-), 1.97 (ddddd, J = 13.7, 6.5, 6.5, 6.5, 3.1 Hz, 1H, -$OCH_2CH_aH_b$-), 1.62 (dddq, J = 16.8, 11.2, 8.2, 2.6 Hz, 1H, -$N(Ts)CH_2CH_aH_b$-), 1.01 [s, 9H, -$Si(CH_3)_2C(CH_3)_3$], 0.54 [s, 3H, -$Si(CH_3)_a(CH_3)_bC(CH_3)_3$], and 0.30 [s, 3H, -$Si(CH_3)_a(CH_3)_bC(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 147.7, 144.4, 133.9, 129.4, 128.1, 127.8 (q, J = 2.7 Hz), 127.4, 125.6 (q, J = 30.0 Hz), 124.8 (q, J = 275 Hz), 118.0 (q, J = 1.7 Hz), 65.5, 50.9, 29.1, 28.2 (q, J = 3.6 Hz), 22.7 (q, J = 3.5 Hz), 21.8, 21.7, 18.0, 0.0, and -0.2 ppm.

IR (neat) 2951, 2930, 2895, 2857, 1727 (w), 1597, 1567, 1442, 1396, 1360, 1299, 1262, 1166, 1154, 1116, 1103, 1033, and 942 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{25}H_{32}F_3NNaO_3SSi)^+$ 534.1716. Found: 534.1744.



Preparation of 4-hydroxy-*N*,*N*-dimethylundec-2-ynamide (S5).

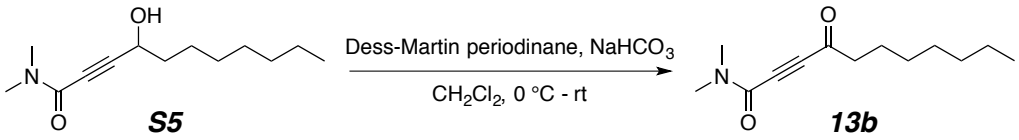
In a glass vial was added *tert*-butyl(dec-1-yn-3-yloxy)dimethylsilane[5] (**S4**, 806 mg, 3.0 mmol) and anhydrous THF (6 mL). The vial was then sealed with a septum, placed under a balloon of Ar, and cooled to -78 °C in a dry-ice acetone bath. A solution of *n*-BuLi (1.8 mL, 2.5 M in hexanes) was added, and the mixture was stirred at -78 °C for 1 h. This solution was transferred to a THF solution of dimethylcarbamoyl chloride (540 mg in 5 mL of dry THF, 5 mmol) at -78 °C with stirring. The reaction vial was allowed to warm to room temperature and stirred overnight. The crude mixture was partitioned between ethyl acetate and NH_4Cl (aq) solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was redissolved in MeOH (10 mL). Solid *p*-toluenesulfonic acid monohydrate (1.14 g, 6 mmol) was added at room temperature with stirring. This mixture was stirred at room temperature for 4 h. The reaction solution was concentrated, the residue was partitioned between EtOAc and a saturated solution of $NaHCO_3$(aq). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified with FCC on silica gel (hexanes:ethyl acetate:methanol=10:10:1) to give 4-hydroxy-*N*,*N*-dimethylundec-2-ynamide (**S5**, 601 mg, 89 % yield, 2 steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 (t, J = 6.7 Hz, 1H, -C*H*OH-), 3.20 [s, 3H, -C(O)N(CH_3)$_a$(CH$_3$)$_b$], 2.97 [s, 3H, -C(O)N(CH$_3$)$_a$(CH_3)$_b$], 1.82–1.71 [nfom, 2H, -CH(OH)CH_2], 1.52–1.42 [m, 2H, -CH(OH)CH$_2$CH_2], 1.36–1.22 [m, 8H, - CH(OH)CH$_2$CH$_2$(CH_2)$_4$-], and 0.88 (t, J = 7.2 Hz, 3H, -CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 92.9, 77.3, 62.4, 38.6, 37.3, 34.3, 31.9, 29.4, 29.3, 25.3, 22.8, and 14.3 ppm.

IR (neat) 3377 (br), 2927, 2856, 2233, 1622, 1496, 1459, 1400, 1267, 1183, and 1073 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{13}H_{23}NNaO_2)^+$ 248.1621. Found: 248.1629.



Preparation of *N*,*N*-dimethyl-4-oxoundec-2-ynamide (13b).

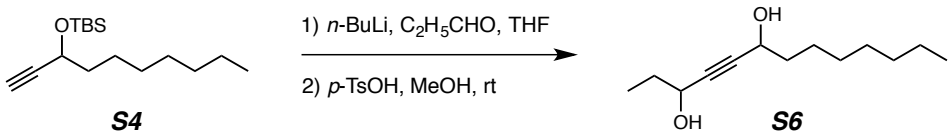
In a glass vial was added alcohol **S5** (226 mg, 1 mmol), CH_2Cl_2 (5 mL), and $NaHCO_3$ (840 mg, 10 mmol). The vial was cooled to 0 °C and Dess-Martin periodinane (640 mg, 1.5 mmol) was added in a single portion. This reaction mixture was stirred overnight, and a 1:1 mixture of $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq) was added. The aqueous phase was extracted 2 times with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by FCC (silica gel, hexanes:ethyl acetate = 1:1) to give *N*,*N*-dimethyl-4-oxoundec-2-ynamide (**13b**, 216 mg, 0.97 mmol, 97%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.21 [s, 3H, -C(O)N(CH_3)$_a$(CH$_3$)$_b$], 3.01 [s, 3H, -C(O)N(CH$_3$)$_a$(CH_3)$_b$], 2.64 [t, J = 7.4 Hz, 2H, C(O)CH_2], 1.69 [br pentet, J = 7.3 Hz, 2H, -C(O)CH$_2$CH_2], 1.36–1.23 [m, 8H, - (CH_2)$_4$CH$_3$-], and 0.88 (t, J = 7.2 Hz, 3H, -CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 186.9, 152.7, 86.0, 79.7, 45.6, 38.3, 34.4, 31.8, 29.1, 29.0, 23.8, 22.8, and 14.2 ppm.

IR (neat) 2954, 2928, 2858, 1683, 1647, 1397, 1265, 1172, and 1060 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{13}H_{21}NNaO_2)^+$ 246.1465. Found: 246.1465.



Preparation of tridec-4-yne-3,6-diol (S6).

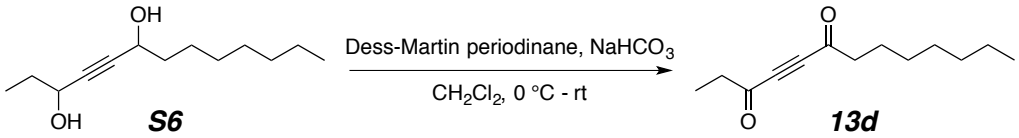
In a glass vial was added *tert*-butyl(dec-1-yn-3-yloxy)dimethylsilane (**S4**, 806 mg, 3.0 mmol) and anhydrous THF (6 mL). The vial was then sealed with a septum, placed under a balloon of Ar, and cooled to -78 °C in a dry-ice acetone bath. A solution of *n*-BuLi (1.8 mL, 2.5 M in hexanes) was added and the mixture was stirred at -78 °C for 1 h. This solution was transferred to a THF solution of propanal (870 mg in 5 mL of dry THF, 15 mmol) under -78 °C with stirring. The reaction vial was allowed to warm to room temperature and stirred overnight. The crude mixture was partitioned between ethyl acetate and NH_4Cl (aq) solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was redissolved in MeOH (10 mL). Solid *p*-toluenesulfonic acid monohydrate (1.14 g, 6 mmol) was added at room temperature with stirring. This mixture was stirred at room temperature for 4 h. The reaction solution was concentrated, the residue was partitioned between EtOAc, and saturated solution of $NaHCO_3$(aq). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by FCC on silica gel (hexanes:ethyl acetate = 3:1) to give tridec-4-yne-3,6-diol (**S6**, 561 mg, 88 % yield, 2 steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (t, *J* = 6.4 Hz, 1H, -C*H*OHCH$_2$CH$_3$), 4.36 (t, *J* = 6.2 Hz, 1H, -C*H*OHCH$_2$CH$_2$-), 1.99 (br s, 2H, two -O*H*), 1.78–1.63 [m, 4H, -CH(OH)C*H*$_2$CH$_3$ and -CH(OH)C*H*$_2$CH$_2$-], 1.48–1.39 [m, 2H, -CH(OH)CH$_2$C*H*$_2$], 1.36–1.23 [m, 8H, - CH(OH)CH$_2$CH$_2$(C*H*$_2$)$_4$-], 1.01 (dt, *J* = 7.4, 1.4 Hz, 3H, -CHOHCH$_2$C*H*$_3$), and 0.88 (t, *J* = 7.1 Hz, 3H, -C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 86.3 (br), 85.9 (br), 63.9 (br), 62.7 (br), 38.0 (br), 32.0, 31.0 (br), 29.42, 29.39, 25.4, 22.8, 14.3, and 9.6 ppm.

IR (neat) 3321 (br), 2954, 2927, 2856, 1730 (w), 1624, 1458, 1336, 1242, 1149, 1099, 1038, and 964 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{13}H_{24}NaO_2)^+$ 235.1669. Found: 235.1671.



Preparation of tridec-4-yne-3,6-dione (13d).

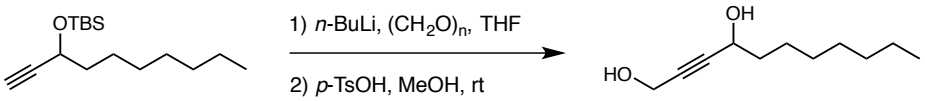
In a glass vial was added alcohol **S6** (215 mg, 1 mmol), CH_2Cl_2 (5 mL), and $NaHCO_3$ (1.7 g, 20 mmol). The vial was cooled to 0 °C and Dess-Martin periodinane (1.28 g, 3 mmol) was added in a single portion. The reaction was stirred overnight and a 1:1 mixture of $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq) was added. The aqueous phase was extracted 2 times with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified using FCC (silica gel, hexanes:ethyl acetate = 5:1) to give tridec-4-yne-3,6-dione (**13d**, 198 mg, 0.95 mmol, 95%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67 [q, *J* = 7.3 Hz, 2H, C(O)C*H*$_2$CH$_3$], 2.63 [t, *J* = 7.4 Hz, 2H, C(O)C*H*$_2$CH$_2$], 1.68 [br pentet, *J* = 7.2 Hz, 2H, -C(O)CH$_2$C*H*$_2$], 1.36–1.23 [m, 8H, - (C*H*$_2$)$_4$CH$_3$-], 1.18 [t, *J* = 7.3, 3H, C(O)CH$_2$C*H*$_3$], and 0.88 [t, *J* = 7.0 Hz, 3H, -(CH$_2$)$_6$C*H*$_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 187.1, 186.8, 84.6, 84.3, 45.5, 38.9, 31.8, 29.1, 29.0, 23.8, 22.8, 14.2, and 7.7 ppm.

IR (neat) 2954, 2929, 2858, 1685, 1459, 1405, 1151, 1088, and 1033 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{13}H_{20}NaO_2 \bullet MeOH)^+$ (M^++MeOH) 263.1618. Found: 263.1609.



S4 ***S7***

Preparation of undec-2-yne-1,4-diol (S7).

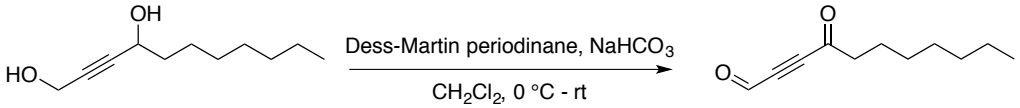
In a glass vial was added *tert*-butyl(dec-1-yn-3-yloxy)dimethylsilane (**S4**, 806 mg, 3.0 mmol) and anhydrous THF (6 mL). The vial was then sealed with a septum, placed under a balloon of Ar, and cooled to -78 °C in a dry-ice acetone bath. A solution of *n*-BuLi (1.8 mL, 2.5 M in hexanes) was added and the mixture was stirred at -78 °C for 1 h. Solid paraformaldehyde (1.8 g, 60 mmol) was added to the solution under -78 °C. The reaction vial was allowed to warm to room temperature and stirred overnight. The crude mixture was partitioned between ethyl acetate and NH_4Cl (aq) solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was redissolved in MeOH (10 mL). Solid *p*-toluenesulfonic acid monohydrate (1.14 g, 6 mmol) was added at room temperature with stirring. This mixture was stirred at room temperature for 4 h. The reaction solution was concentrated, and the residue was partitioned between EtOAc and a saturated solution of $NaHCO_3$(aq). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by FCC on silica gel (hexanes:ethyl acetate = 3:1) to give undec-2-yne-1,4-diol (**S7**, 450 mg, 82 % yield, 2 steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (br t with nfom character, J = 6.6 Hz, 1H, -C*H*OH-), 4.31–4.30 (m, *2*H, CH_2OH), 2.54 (br s, 1H, -OH_a), 2.24 (br s, 1H, -OH_b), 1.76–1.64 [m, 2H, -CH(OH)CH_2], 1.49–1.39 [m, 2H, -CH(OH)CH$_2$CH_2], 1.36–1.23 [m, 8H, - CH(OH)CH$_2$CH$_2$(CH_2)$_4$-], 1.01 (dt, J = 7.4, 1.4 Hz, 3H, -CHOHCH$_2$CH_3), and 0.88 (t, J = 7.1 Hz, 3H, -CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 87.2, 83.2, 62.7, 51.2, 37.9, 32.0, 29.44, 29.40, 25.4, 22.8, and 14.3 ppm.

IR (neat) 3305 (br), 2926, 2856, 1464, 1241, 1142, 1108, and 1019 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{11}H_{20}NaO_2)^+$ 207.1356. Found: 207.1360.



S7 ***13e***

Preparation of 4-oxoundec-2-ynal (13e).

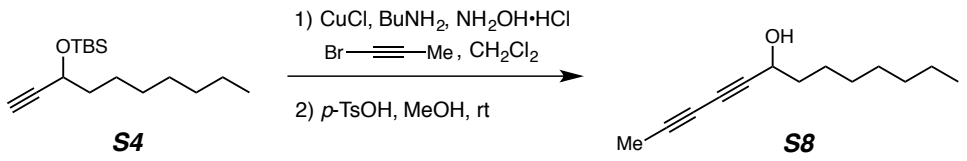
In a glass vial was added alcohol **S7** (184 mg, 1 mmol), CH_2Cl_2 (5 mL), and $NaHCO_3$ (1.7 g, 20 mmol). The vial was cooled to 0 °C and Dess-Martin periodinane (1.28 g, 3 mmol) was added in a single portion. The reaction was stirred overnight and a 1:1 mixture of $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq) was added. The aqueous phase was extracted 2 times with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude material of 4-oxoundec-2-ynal (**13e**, 140 mg, 0.78 mmol, 78%) was obtained as a red oil and was directly used without purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (s, J = 7.4 Hz, 1H, -C*H*O), 2.65 [t, J = 7.4 Hz, 2H, C(O)CH_2], 1.69 [br pentet, J = 7.2 Hz, 2H, -C(O)CH$_2$CH_2], 1.38–1.17 [m, 8H, - (CH_2)$_4$CH$_3$-], and 0.89 [t, J = 7.2 Hz, 3H, -(CH$_2$)$_6$CH_3].

^{13}C NMR (125 MHz, $CDCl_3$) δ 186.3, 175.4, 87.7, 83.5, 45.5, 31.8, 29.1, 29.0, 23.7, 22.8, and 14.2 ppm.

IR (neat) 2954, 2927, 2858, 1773 (w), 1674, 1458, 1401, 1244, 1140, 1055, 1033, and 1013 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{11}H_{16}NaO_2 \bullet MeOH)^+$ (M^++MeOH) 235.1305. Found: 235.1300.



Preparation of trideca-2,4-diyn-6-ol (S8).

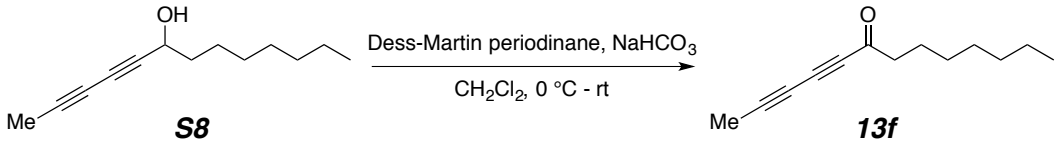
In a round bottom flash (50 mL) was added CuCl (20 mg, 0.2 mmol), NH_2OH•HCl (200 mg), and *n*-$BuNH_2$ (10 mL, 30% aq solution). The reaction mixture was cooled to 0 °C before addition of alkyne **S4** (538 mg, 2 mmol) as an ethyl acetate (10 mL) solution. A solution of 1-bromopropyne (2 mL, 1.4 M in hexanes) was added. The flask was sealed with rubber stopper and placed under a balloon filled with Ar. After 5 min of stirring at 0 °C, the cooling bath was removed. The reaction mixture was allowed to stir at room temperature for 1 h and saturated NH_4Cl (aq) solution was added. The aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was redissolved in MeOH (10 mL). Solid *p*-toluenesulfonic acid monohydrate (760 mg, 4 mmol) was added at room temperature with stirring. This mixture was stirred at room temperature for 4 h. The reaction solution was concentrated, and the residue was partitioned between EtOAc and saturated solution of $NaHCO_3$(aq). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by FCC on silica gel (hexanes:ethyl acetate = 5:1) to give trideca-2,4-diyn-6-ol (**S8**, 360 mg, 94 % yield, 2 steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.39 (tq, *J* = 6.6, 1.0 Hz, 1H, -C*H*OH-), 1.94 (d, *J* = 1.0 Hz, 3H, C-CH_3), 1.76–1.64 [nfom, 2H, -CH(OH)CH_2], 1.51–1.39 [m, 2H, -CH(OH)CH_2CH_2], 1.37–1.22 [m, 8H, - CH(OH)CH_2CH_2(CH_2)$_4$-], 0.92 (s, 1H, -O*H*), and 0.88 (t, *J* = 7.1 Hz, 3H, -CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 77.4, 76.2, 70.1, 63.9, 63.1, 37.9, 32.0, 29.41, 29.37, 25.3, 22.8, 14.3, and 4.5 ppm.

IR (neat) 3334 (br), 2926, 2855, 2258, 1732 (w), 1464, 1376, 1336, 1038, 1025, and 834 cm^{-1}.

GC-LRMS (ES, 70 eV): t_R = 7.77 min. *m/z*: 174 $(M–H_2O)^{\bullet+}$, 93 $(M–99)^+$.



Preparation of trideca-2,4-diyn-6-one (13f).

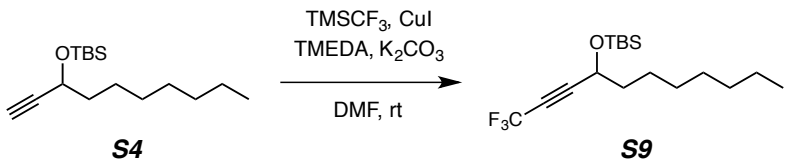
To a glass vial was added alcohol **S8** (195 mg, 1 mmol), CH_2Cl_2 (5 mL), and $NaHCO_3$ (840 mg, 10 mmol). The vial was cooled to 0 °C and Dess-Martin periodinane (640 mg, 1.5 mmol) was added in a single portion. The reaction mixture was stirred overnight, and a 1:1 mixture of $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq) was added. The aqueous phase was extracted 2 times with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by FCC (silica gel, hexanes:ethyl acetate = 12:1) to give trideca-2,4-diyn-6-one (**13f**, 186 mg, 0.98 mmol, 98%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 [t, *J* = 7.5 Hz, 2H, C(O)CH_2], 2.04 (s, 3H, C-CH_3), 1.66 [br pentet, *J* = 7.3 Hz, 2H, -C(O)CH_2CH_2], 1.34–1.22 [m, 8H, - (CH_2)$_4$$CH_3$-], and 0.88 (t, *J* = 7.1 Hz, 3H, -CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 187.6, 86.3, 76.3, 71.9, 63.3, 45.8, 31.8, 29.2, 29.1, 24.2, 22.8, 14.3, and 5.0 ppm.

IR (neat) 2955, 2928, 2857, 2238, 2150, 1671, 1458, 1272, and 1068 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{13}H_{18}NaO)^+$ 213.1250. Found: 213.1255.



S4 ***S9***

Preparation of *tert*-butyldimethyl((1,1,1-trifluorodec-2-yn-4-yl)oxy)silane (S9).

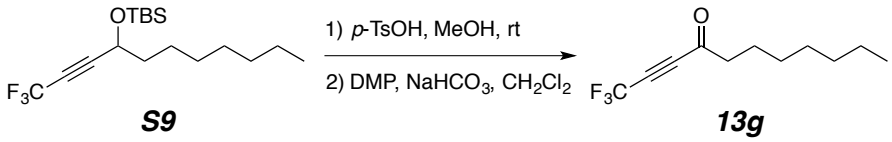
CuI (1.07 g, 5.62 mmol, 1.5 equiv), K_2CO_3 (1.54 g, 11.2 mmol, 3 equiv), and dry DMF (17 mL, ca. 5 mL•mmol^{-1} of alkyne substrate) were combined in a 200 mL round-bottomed flask equipped with a stir bar and capped with a rubber septum. A balloon filled with dry air was attached. The mixture was stirred vigorously at room temperature while anhydrous TMEDA was introduced via syringe. The white suspension immediately turned blue. This suspension was allowed to stir at ambient temperature for 15 min before addition of $TMSCF_3$ (1.1 mL, 2 equiv). The resulting deep green solution was allowed to stir at room temperature for an additional 5 min before being cooled to 0 °C in an ice-water bath. A solution of alkyne **S4** (1 g, 3.72 mmol) and $TMSCF_3$ (1.1 mL, 2 equiv) in dry DMF (17 mL, ca. 5 mL•mmol^{-1} of alkyne substrate) was slowly added over 10 min at 0 °C. The deep green reaction mixture was allowed to warm to room temperature and stirred overnight. After 15 h TLC analysis confirmed full consumption of starting material. The resulting mixture was partitioned between ethyl acetate and brine. The organic layer was washed with brine twice, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by FCC on silica gel (hexanes:ethyl acetate = 12:1) to give the trifluoromethylated alkyne **S9** (632 mg, 2 mmol, 54%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 [tq, *J* = 6.1, 3.0 Hz, 1H, -C*H*(OTBS)-], 1.72 [dddd, 13.3, 9.1, 6.4, 6.4 Hz, 1H, CH(OTBS)CH_aH$_b$], 1.70 [dddd, 13.4, 8.8, 6.3, 6.3 Hz, 1H, CH(OTBS)CH$_a$$H_b$], 1.48–1.35 (m, 2H-CH(OTBS)CH$_2$CH_2-), 1.35–1.22 [m, 8H, -(CH_2)$_4$CH$_3$], 0.90 [s, 9H, -Si(CH$_3$)$_2$C(CH_3)$_3$], 0.89 (t, *J* = 7.1 Hz, 3H, -CH$_2$CH_3), 0.13 [s, 3H, -Si(CH_3)$_a$(CH$_3$)$_b$C(CH$_3$)$_3$], and 0.11 [s, 3H, -Si(CH$_3$)$_a$(CH_3)$_b$C(CH$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$) δ 114.4 (q, *J* = 257.0 Hz), 89.4 (q, *J* = 6.4 Hz), 71.5 (q, *J* = 51.9 Hz), 62.5, 37.7, 32.0, 29.31, 29.25, 25.8, 25.0, 22.8, 18.3, 14.3, -4.5, and -4.9 ppm.

IR (neat) 2956, 2929, 2862, 1277, 1147, 1097, and 839 cm^{-1}.

GC-LRMS (ES, 70 eV): t_R = 6.39 min. *m/z*: 336 (M^+), and 279 (M^+–Bu•).



S9 ***13g***

Preparation of 1,1,1-trifluorodec-2-yn-4-one (13g).

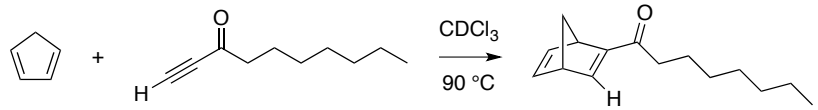
tert-Butyldimethyl((1,1,1-trifluorodec-2-yn-4-yl)oxy)silane (**S9**, 325 mg, 1 mmol), MeOH (10 mL), and *para*-toluenesulfonic acid (200 mg, 1 mmol) were combined in a 20 mL glass vial equipped with a stir bar, and the mixture was stirred at room temperature. After 2 h TLC analysis indicated completion of reaction. The crude mixture was partitioned between Et_2O and $NaHCO_3$ (aq). The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude material was then re-dissolved in CH_2Cl_2 (5 mL), and cooled to 0 °C before addition of $NaHCO_3$ (0.84 g, 10 mmol) and Dess-Martin periodinane (DMP, 0.84 g, 2 mmol). The ice bath was removed after 5 min. The reaction mixture was allowed to stir overnight at room temperature. The crude mixture was then partitioned between EtOAc and $Na_2S_2O_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 20:1) to give 1,1,1-trifluorodec-2-yn-4-one (**13g**, 165 mg, 80%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 [t, *J* = 7.4 Hz, 2H, C(O)CH_2], 1.69 (br pentet, *J* = 7.1 Hz, 2H, -C(O)CH$_2$CH_2-), 1.36–1.23 [m, 8H, -(CH_2)$_4$CH$_3$], and 0.89 (t, *J* = 7.1 Hz, 3H, -CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 185.2 (q, *J* = 2.0 Hz), 114.0 (q, *J* = 259.7 Hz), 80.9 (q, *J* = 6.6 Hz), 73.1 (q, *J* = 54.4 Hz), 45.5, 31.7, 29.1, 28.9, 23.5, 22.8, and 14.2 ppm.

IR (neat) 2960, 2931, 2862, 1701, 1257, 1221, 1155, and 1088 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{11}H_{15}F_3NaO•MeOH)^+$ (M+Na$^+$+MeOH) 275.1229. Found: 275.1240.



14 ***13a*** ***15a***

Preparation of methyl 1-(bicyclo[2.2.1]hepta-2,5-dien-2-yl)octan-1-one (15a).

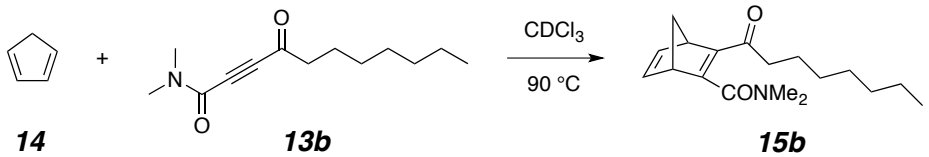
Freshly cracked cyclopentadiene (1 M solution in $CDCl_3$, 0.15 mL, 1.5 equiv) was directly added to dec-1-yn-3-one[6] (**13a**, 0.2 M solution in $CDCl_3$, 15 mg in 0.5 mL of $CDCl_3$) in an NMR tube at room temperature. ^{1}H NMR analysis was performed to monitor the reaction progress. The NMR tube was placed in a 90 °C oil bath. After 15 h the reaction was judged to be complete (>5 half-lives), and the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 12:1) to give 1-(bicyclo[2.2.1]hepta-2,5-dien-2-yl)octan-1-one (**15a**, 20 mg, 0.09 mmol, 92%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 [d, *J* = 3.2 Hz, 1H, -C*H*=C(octanoyl)-], 6.87 (dd, *J* = 5.0, 3.2 Hz, 1H, -CH_a=CH$_b$-), 6.72 (ddd, *J* = 4.8, 3.2, 0.3 Hz, 1H, -CH$_a$=CH_b-), 4.00–3.97 (br s, 1H, bridgehead H_a), 3.74–3.71 (br s, 1H, bridgehead H_b), 2.58 (ddd, *J* = 15.4, 8.0, 7.2 Hz, 1H, -C(O)CH_aH$_b$), 2.53 (ddd, *J* = 15.5, 7.7, 7.1 Hz, 1H, -C(O)CH$_a$$H_b$-), 2.09 (ddd, *J* = 6.6, 1.6, 1.6 Hz, CH_aH$_b$CHC=C), 2.07 (ddd, *J* = 6.5, 1.6, 1.6 Hz, CH$_a$$H_b$CHC=C), 1.58 (br pentet, *J* = 7.1 Hz, 2H, -C(O)CH$_2$CH_2-), 1.34–1.20 [m, 8H, -(CH_2)$_4$CH$_3$], and 0.87 (t, *J* = 7.1 Hz, 3H, -CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 158.2, 155.6, 144.0, 141.9, 73.6, 51.9, 48.9, 39.1, 31.9, 29.6, 29.3, 25.1, 22.8, and 14.3 ppm.

IR (neat) 2956, 2929, 2857, 1656, 1584, 1553, 1460, 1370, 1219, 1141, and 876 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{15}H_{22}NaO)^+$ 241.1563. Found: 241.1572.



14 ***13b*** ***15b***

Preparation of *N*,*N*-dimethyl-3-octanoylbicyclo[2.2.1]hepta-2,5-diene-2-carboxamide (15b).

Freshly cracked cyclopentadiene (1 M solution in $CDCl_3$, 0.15 mL, 1.5 equiv) was directly added to *N*,*N*-dimethyl-4-oxoundec-2-ynamide (**13b**, 0.2 M solution in $CDCl_3$, 22 mg in 0.5 mL of $CDCl_3$) in an NMR tube at room temperature. ^{1}H NMR analysis was performed to monitor the reaction progress. The NMR tube was sealed with a plastic cap, wrapped with black electrical tape, and placed in a 90 °C oil bath. After 3 h the reaction was judged to be complete (>5 half-lives), and the crude mixture was concentrated. The residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 1:1) to give *N*,*N*-dimethyl-3-octanoylbicyclo[2.2.1]hepta-2,5-diene-2-carboxamide (**15b**, 28 mg, 0.10 mmol, 97%) as a pale yellow oil.

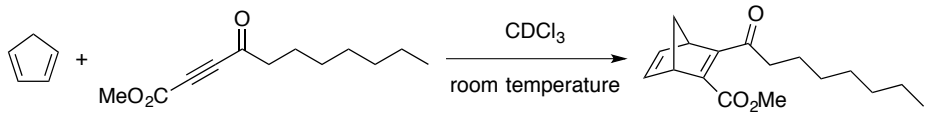
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92-6.90 (m, 2H, -C*H*=C*H*-), 4.07 (dddd, *J* = 4.0, 2.4, 1.6, 1.6 Hz, 1H, bridgehead H_a),

3.74 (dddd, J = 3.9, 2.3, 1.6, 1.6 Hz, 1H, bridgehead H_b), 3.05 (s, 3H, -CON(CH_3)$_a$(CH$_3$)$_b$], 2.84 (s, 3H, -CON(CH$_3$)$_a$(CH_3)$_b$], 2.51 [dt, J = 16.9, 7.5 Hz, 1H, -C(O)CH_aH$_b$], 2.44 [dt, J = 16.8, 7.4 Hz, 1H, -C(O)CH$_a$$H_b$], 2.26 (ddd, J = 6.8, 1.6, 1.6 Hz, 1H, CH_aH$_b$CHC=C), 2.08 (ddd, J = 6.8, 1.5, 1.5 Hz, 1H, CH$_a$$H_b$CHC=C), 1.55 [br pentet, J = 7.2 Hz, 2H, -C(O)CH$_2$CH_2-], 1.32–1.20 [m, 8H, -(CH_2)$_4$CH$_3$], and 0.87 [t, J = 7.1 Hz, 3H, -(CH$_2$)$_6$CH_3].

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 169.1, 159.7, 149.5, 142.8, 141.6, 72.0, 56.0, 50.7, 40.6, 37.5, 34.4, 31.8, 29.4, 29.2, 23.9, 22.8, and 14.2 ppm.

IR (neat) 2928, 2856, 1658, 1634, 1613, 1557, 1455, 1395, 1290, 1217, 1139, and 1042 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{18}H_{27}NNaO_2)^+$ 312.1934. Found: 312.1922.



14 ***13c*** ***15c***

Preparation of methyl 3-octanoylbicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (15c).

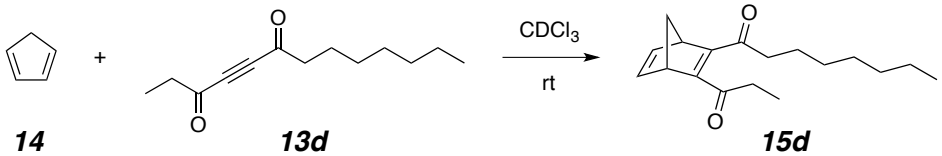
Freshly cracked cyclopentadiene (1 M solution in $CDCl_3$, 0.15 mL, 1.5 equiv) was directly added to methyl 4-oxoundec-2-ynoate[7] (**13c**, 0.2 M solution in $CDCl_3$, 21 mg in 0.5 mL of solvent) in an NMR tube at room temperature. ^{1}H NMR analysis was performed to monitor the reaction progress. After 4 h the reaction was judged to be complete (>5 half-lives), and the crude mixture was concentrated. The residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 5:1) to give methyl 3-octanoylbicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (**15c**, 25 mg, 0.09 mmol, 90%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (dd, J = 5.0, 3.2 Hz, 1H, -CH_a=CH$_b$-), 6.88 (dd, J = 5.0, 3.1 Hz, 1H, -CH$_a$=CH_b-), 4.00–3.97 (br s, 1H, bridgehead H_a), 3.86–3.83 (br s, 1H, bridgehead H_b), 3.76 (s, 3H, -CO$_2$CH_3), 2.65 (t, J = 7.3 Hz, 1H, -C(O)CH_2), 2.22 (dddd, J = 6.8, 1.7, 1.7, 0.4 Hz, CH_aH$_b$CHC=C), 2.05 (ddd, J = 6.8, 1.5, 1.5 Hz, CH$_a$$H_b$CHC=C), 1.58 (br pentet, J = 7.1 Hz, 2H, -C(O)CH$_2$CH_2-), 1.33–1.23 [m, 8H, -(CH_2)$_4$CH$_3$], and 0.88 (t, J = 7.1 Hz, 3H, -CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 165.2, 163.7, 147.2, 143.2, 142.1, 72.4, 54.7, 53.0, 52.1, 42.4, 31.9, 29.4, 29.3, 23.9, 22.8, and 14.3 ppm.

IR (neat) 2951, 2929, 2855, 1717, 1612, 1435, 1290, 1238, 1100, and 1072 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{17}H_{24}NaO_3)^+$ 299.1618. Found: 299.1625.



14 ***13d*** ***15d***

Preparation of 3-propionylbicyclo[2.2.1]hepta-2,5-dien-2-yl)octan-1-one (15d).

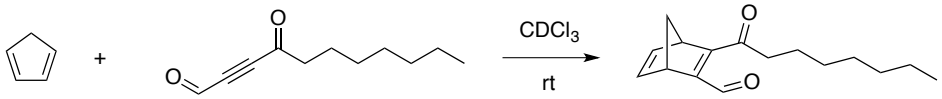
Freshly cracked cyclopentadiene (1 M solution in $CDCl_3$, 0.15 mL, 1.5 equiv) was directly added to tridec-4-yne-3,6-dione (**13d**, 0.2 M solution in $CDCl_3$, 21 mg in 0.5 mL of solvent) in an NMR tube at room temperature. ^{1}H NMR analysis was performed to monitor the reaction progress. After 1.5 h the reaction was judged to be complete (>5 half-lives), and the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 12:1) to give 3-propionylbicyclo[2.2.1]hepta-2,5-dien-2-yl)octan-1-one (**15d**, 25 mg, 0.09 mmol, 93%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93–6.91 (m, 2H, -C*H*=C*H*-), 3.93–3.88 (m, 2H, bridgehead *Hs*), 2.57 [q, *J* = 7.3 Hz, 2H, C(O)CH_2CH$_3$], 2.56–2.52 (overlapping nfoms, 2H, -C(O)CH_2), 2.20 (ddd, *J* = 6.8, 1.6, 1.6, Hz, CH_aH$_b$CHC=C), 2.07 (ddd, *J* = 6.9, 1.5, 1.5 Hz, CH$_a$$H_b$CHC=C), 1.58 [br pentet, *J* = 7.3 Hz, 2H, -C(O)CH$_2$CH_2-], 1.33–1.23 [m, 8H, -(CH_2)$_4$CH$_3$], 1.09 [t, *J* = 7.3 Hz, C(O)CH$_2$CH_3], and 0.87 (t, *J* = 7.1 Hz, 3H, -CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.90, 201.88, 158.7, 158.2, 142.7, 142.6, 71.9, 53.7, 53.6, 41.8, 35.0, 31.9, 29.4, 29.3, 23.9, 22.8, 14.3, and 7.9 ppm.

IR (neat) 2930, 2858, 1692, 1665, 1598, 1556, 1456, 1357, 1293, 1214, 1164, 1135, 1089, and 809 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{18}H_{26}NaO_2)^+$ 297.1825. Found: 297.1819.



14 ***13e*** ***15e***

Preparation of 3-octanoylbicyclo[2.2.1]hepta-2,5-diene-2-carbaldehyde (15e).

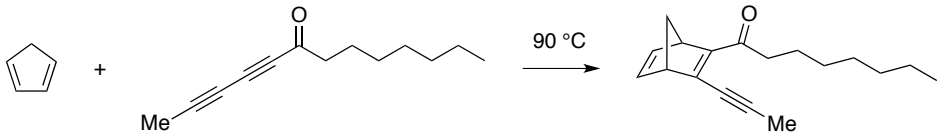
Freshly cracked cyclopentadiene (1 M solution in $CDCl_3$, 0.15 mL, 1.5 equiv) was directly added to 4-oxoundec-2-ynal (**13e**, 0.2 M solution in $CDCl_3$, 18 mg in 0.5 mL of solvent) in an NMR tube at room temperature. ^{1}H NMR analysis was performed to monitor the reaction progress. After 25 min the reaction was judged to be complete (>5 half-lives), and the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 12:1) to give 3-octanoylbicyclo[2.2.1]hepta-2,5-diene-2-carbaldehyde (**15e**, 18 mg, 0.07 mmol, 73%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.20 (s, 1H, C*H*O), 6.89 (ddd, *J* = 5.1, 2.9, 1.1 Hz, 1H, -CH_a=CH$_b$-), 6.88 (ddd, *J* = 5.1, 2.9, 1.0 Hz, 1H, -CH$_a$=CH_b-), 4.17–4.14 (dddd, *J* = 3.9, 2.8, 1.4, 1.4, 0.4 Hz, 1H, bridgehead H_a), 3.98 (dddd, *J* = 4.0, 2.6, 1.3, 1.3 Hz, 1H, bridgehead H_b), 2.71 [ddd, *J* = 16.9, 8.1, 6.7 Hz, 1H, -C(O)CH_aH$_b$], 2.63 [dt, *J* = 16.9, 8.0, 6.6 Hz, 1H, -C(O)CH$_a$$H_b$], 2.20–2.15 (m, C$H_2$CHC=C), 1.68–1.60 (m, 2H, -C(O)CH$_2$CH_2-), 1.37–1.22 [m, 8H, -(CH_2)$_4$CH$_3$], and 0.89 (t, *J* = 7.2 Hz, 3H, -CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 188.1, 166.7, 159.5, 143.3, 141.8, 72.1, 53.6, 49.2, 42.4, 31.8, 29.31, 29.28, 23.7, 22.8, and 14.3 ppm.

IR (neat) 2926, 2857, 1663, 1589, 1557, 1285, 1210, 1054, 1033, and 1015 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{17}H_{26}NaO_3)^+$ 301.1774. Found: 301.1769.



14 ***13f*** ***15f***

Preparation of 3-(prop-1-yn-1-yl)bicyclo[2.2.1]hepta-2,5-dien-2-yl)octan-1-one (15f).

Freshly cracked cyclopentadiene (0.15 mL) was directly added to trideca-2,4-diyn-6-one (**13f**, 38 mg, 0.2 mmol) in a small vial. The headspace was flushed with N_2. The vial was sealed with Teflon-lined cap and placed in a 90 °C oil bath. After 24 h the reaction mixture was concentrated, and the residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 30:1) to give 3-(prop-1-yn-1-yl)bicyclo[2.2.1]hepta-2,5-dien-2-yl)octan-1-one (**15f**, 35 mg, 1.4 mmol, 68%) as a pale yellow oil. This sample was contaminated with a small portion of coeluting **15a**,

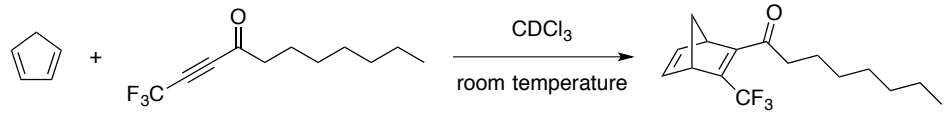
arising from a small portion of **13a** present in the starting sample of **13f.**

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (ddd, *J* = 5.2, 3.1, 0.8 Hz, 1H, -C*H*$_a$=CH$_b$-), 6.77 (ddd, *J* = 5.1, 3.1, 0.9 Hz, 1H, -CH$_a$=C*H*$_b$-), 4.08–4.06 (br s, 1H, bridgehead *H*$_a$), 3.67–3.65 (br s, 1H, bridgehead *H*$_b$), 2.87–2.76 [nfom, 2H, -C(O)C*H*$_2$], 2.17 (s, 3H, ≡C-C*H*$_3$), 2.07 (ddd, *J* = 7.0, 1.7, 1.7 Hz, C*H*$_a$H$_b$CHC=C), 2.01 (ddd, *J* = 6.8, 1.5, 1.5 Hz, CH$_a$*H*$_b$CHC=C), 1.59 (br pentet, *J* = 6.9 Hz, 2H, -C(O)CH$_2$C*H*$_2$-), 1.35–1.21 [m, 8H, -(C*H*$_2$)$_4$CH$_3$], and 0.88 (t, *J* = 7.1 Hz, 3H, -C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 155.9, 148.0, 143.2, 141.3, 106.2, 77.5, 70.7, 59.2, 50.2, 41.0, 32.0, 29.7, 29.4, 24.9, 22.9, 14.3, and 5.6 ppm.

IR (neat) 2954, 2927, 2855, 2237, 1650, 1575, 1556, 1456, 1378, and 1294 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{18}H_{24}NaO)^+$ 279.1719. Found: 279.1721.



14 ***13g*** ***15g***

Preparation of 1-((1*R*,4*S*)-3-(trifluoromethyl)bicyclo[2.2.1]hepta-2,5-dien-2-yl)decan-1-one (15g).

Freshly cracked cyclopentadiene (1 M solution in $CDCl_3$, 0.15 mL, 1.5 equiv) was directly added to 1,1,1-trifluorodec-2-yn-4-one (**13g**, 0.2 M solution in $CDCl_3$, 22 mg in 0.5 mL solvent) in an NMR tube at room temperature. ^{1}H NMR analysis was performed to monitor the reaction progress. After 40 min the reaction was judged to be complete (>5 half-lives), and the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 12:1) to give 1-(3-(trifluoromethyl)bicyclo[2.2.1]hepta-2,5-dien-2-yl)decan-1-one (**15g**, 24 mg, 0.084 mmol, 84%) as a colorless oil.

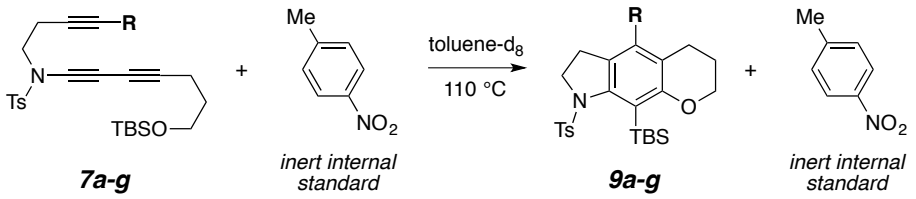
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (dd, *J* = 5.1, 1.8 Hz, 1H, -C*H*$_a$=CH$_b$-), 6.93 (dd, *J* = 5.1, 1.8 Hz, 1H, -CH$_a$=C*H*$_b$-), 3.87–3.85 (m, 2H, bridgehead *H*'s), 2.58 (dt, *J* = 16.9, 7.4 Hz, 1H, -C(O)C*H*$_a$H$_b$), 2.56 (dt, *J* = 17.0, 7.2 Hz, 1H, -C(O)CH$_a$*H*$_b$-), 2.22 (ddd, *J* = 6.9, 1.7, 1.7 Hz, C*H*$_a$H$_b$CHC=C), 2.04 (br d, *J* = 6.9 Hz, CH$_a$*H*$_b$CHC=C), 1.58 (br pentet, *J* = 7.1 Hz, 2H, -C(O)CH$_2$C*H*$_2$-), 1.33–1.21 [m, 8H, -(C*H*$_2$)$_4$CH$_3$], and 0.88 (t, *J* = 7.1 Hz, 3H, -C*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 158.7, 144.6 (q, *J* = 35.1 Hz), 142.5, 142.4 (br), 123.1 (q, *J* = 268.9 Hz), 72.2, 54.6, 52.0 (q, *J* = 1.8 Hz), 42.4 (q, *J* = 1.8 Hz), 31.8, 29.2 (2C), 23.8, 22.8, and 14.3 ppm.

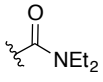
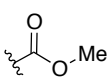
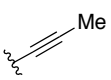
IR (neat) 2930, 2858, 1695, 1335, 1293, 1257, 1157, and 1120 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{16}H_{21}F_3NaO)^+$ 309.1437. Found: 309.1447.

III. Table S1. Relative rates of hexadehydro-Diels–Alder reactions of **7a-g**



7a-g *inert internal standard* ***9a-g*** *inert internal standard*

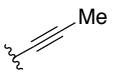
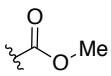
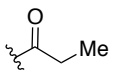
substrate	7g	7a	7b	7c	7d	7e	7f
R		H					
$t_{1/2}$ (h)	> 600	> 400	84	9.2	5.1	0.82	0.26

General procedure for measuring the relative rates of HDDA reaction of substrates 7a-g

Each of the triyne precursors **7a-g** (ca. 3 mg, 6 μmol), along with the internal standard *p*-nitrotoluene (1 mg, 7 μmol), was dissolved in 0.6 mL of toluene-d_8 and transferred to an NMR tube. A ^{1}H NMR spectrum was recorded for each sample to determine the ratio of the starting material and the inert internal standard *p*-nitrotoluene present in each. Each tube was then capped and sealed with electrical tape. All tubes were placed in a pre-equilibrated 110 °C oil bath. The reaction progress of each was monitored by periodic removal of the tube and analyzing the ^{1}H NMR spectrum. The reaction half-lives were determined based on integration of the product peaks against the internal standard peak. First order kinetics was assumed for the rate-determining, HDDA cycloisomerization of **7** to its derived benzyne **8**. The relative rate data are given in Table 1 in the manuscript.

IV. Table S2. Relative rates of bimolecular Diels–Alder reactions of **13a-g** with **14**

14 ***13a-g*** ***15a-g***

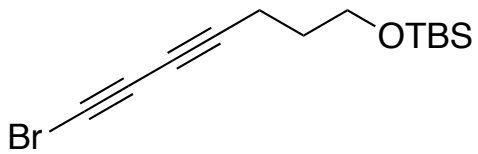
dienophile	13f	13a	13b	13c	13d	13g	13e
R		H					
k_{rel}	1	10	50	840	2,100	16,800	47,000

General procedure for measuring the relative rates of bimolecular Diels–Alder reactions of 13a-g with 14

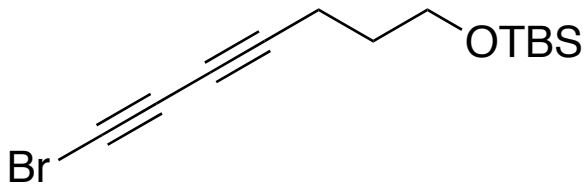
For each adjacent pair of ynones in Table S2 above (i.e. **13f** vs. **13a**, **13a** vs. **13b**, **13b** vs. **13c**, and so on), the following competition experiment was conducted: 0.1 mmol of each ynone (ca. 20 mg) was dissolved in 0.5 mL of $CDCl_3$ and the solution was transferred into an NMR tube. ^{1}H NMR analysis was then performed to determine the initial ratio of the two ynones. A solution of freshly cracked cyclopentadiene (0.1 mL, 0.1 M, 0.01 mmol) was then added to this NMR tube. The reaction progress was constantly monitored by ^{1}H NMR analysis. Heating of the NMR tube was required for several of the slower Diels–Alder reaction partners (namely, experiments involving **13f**, **13a**, or **13b** as the dienophile). The k_{rel} values shown in Table S2 are the average of two separate measurements.

V. References and Notes for Supplementary Information

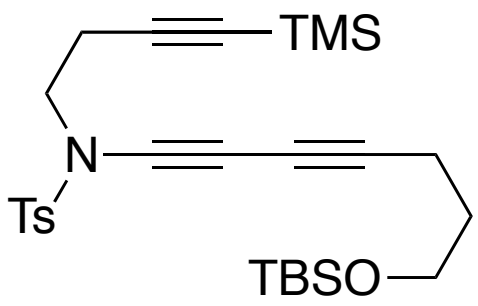
1. Hoye, T. R.; Zhao, H. *J. Org. Chem.* **2002**, *67*, 4014–4016.
2. Turlington, M.; Du, Y.; Ostrum, S. G.; Santosh, V.; Wren, K.; Lin, T.; Sabat, M.; Pu, L. *J. Am. Chem. Soc.* **2011**, 133, 11780–11794.
3. Trost, B. M.; Machacek, M.; Schnaderbeck, M. J. *Org. Lett.* **2000**, *2*, 1761–1764.
4. a) Procedure for preparation of bromopropyne[4b]:
   "A 2 L three-neck round-bottom flask containing a magnetic stir bar was charged with a solution of KOH (85% tech. grade, 260 g, 3.94 mol) in 250 mL of water, and the flask was placed in an ice-salt bath. The flask was fitted with a thermocouple, a pressure equalizing dropping funnel, and a rubber septum. When the KOH solution had cooled to –3 °C (internal temperature), bromine (40 mL, 0.78 mol, ca. 1.5 equiv) was added dropwise to the stirred solution at such a rate so that the internal temperature did not rise above 0 °C. A precipitate formed over the course of the addition. After the addition was complete, the yellow slurry was stirred for an additional 30 min at 0 °C.
   A 250 mL Erlenmeyer flask containing a ground-glass joint was charged with 150 mL of hexanes and the flask was cooled in a dry ice-acetone bath. Gaseous propyne (bp -23 °C, 95%, ca. 30 mL, 0.50 mol) was then slowly introduced via an 18 gauge syringe needle into the headspace of the flask. Condensation is more efficient if the needle tip is close to the surface of the cold hexane. Condensation was allowed to continue until the total volume of the solution had grown to ca. 180 mL. It is advisable to attach a bubbler to the headspace to ensure that the gas is not being introduced too rapidly.
   The addition funnel on 2 L the three-neck flask was replaced by a Dewar condenser filled with a dry ice-acetone mixture. The hexanes solution of propyne, still at -78 °C, was added slowly to the aqueous KOBr solution, still maintained at ≤0 °C, via cannula over approximately 1 h. Depending on the rate of addition, the internal temperature of the reaction mixture may or may not increase. The reaction mixture was allowed to warm to room temperature, using internal temperature monitoring to guide the intermittent use of the cooling bath. As the mixture warmed, propyne reflux was observed, and the rate or reflux qualitatively indicated the progress of reaction. After the cessation of propyne reflux (ca. 2 h), the reaction mixture was transferred to a 2 L separatory funnel. The aqueous layer was drained and combined with brine (100 mL) to minimize emulsion formation. The combined aqueous layers were extracted with hexanes (2x50 mL), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and filtered to give a dried stock solution of 1-bromopropyne (ca. 300 mL total volume). *Caution*: neat 1-bromopropyne (reported bp 64 °C) has been reported to ignite upon exposure to oxygen;[4c] hence, we have opted to titer the hexanes solution by ^{1}H NMR analysis of an aliquot and use that solution directly for subsequent coupling reactions. The concentration of the stock solution described here was judged to be 27 wt%. Such solutions have been stored multiple times in a freezer (ca. -20 °C) for months with no obvious loss in titer (NMR) or discoloration."[4b]
   b) Chen, J.; Palani, V.; Hoye, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 4318–4321.
   c) Brandsma, L.; Verkruijsse, H. D. *Synthesis* **1990**, 984–985.
5. Jung, M. E.; Min, S.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10834–10835.
6. Yan, W.; Li, Z.; Kishi, Y. *J. Am. Chem. Soc.* **2015**, *137*, 6219–6225.
7. Yue, Y.; Yu, X.-Q.; Pu, L. *Chem. Eur. J.* **2009**, *15*, 5104–5107.



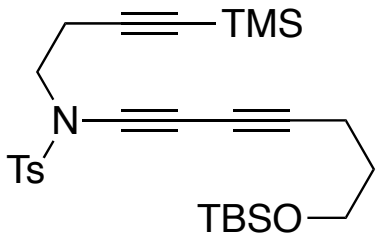
11



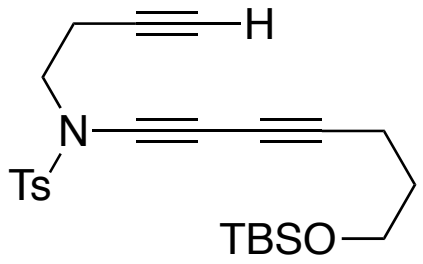
11



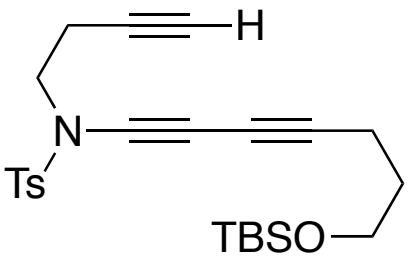
12



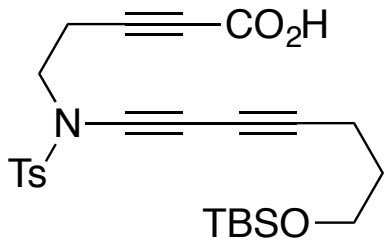
12



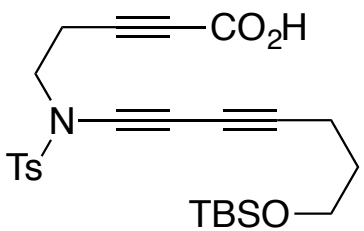
7a



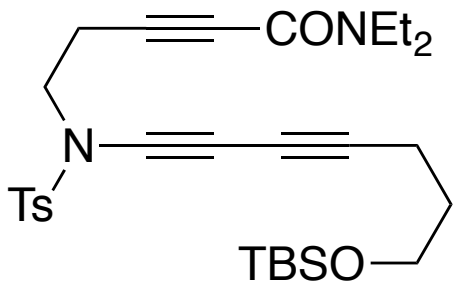
7a



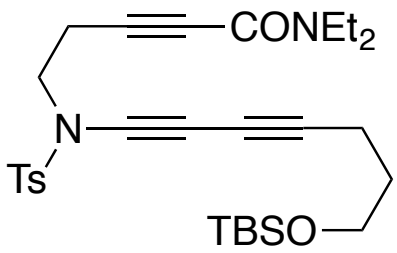
S2



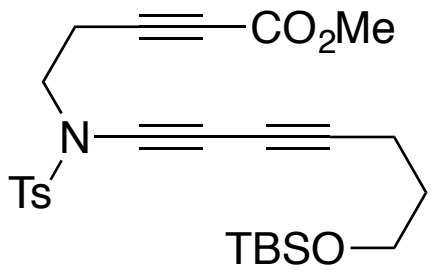
S2



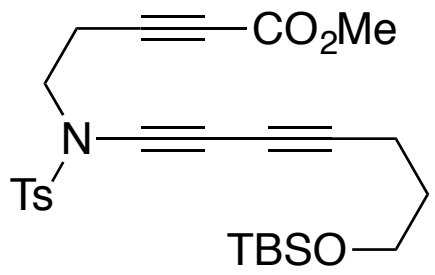
7b



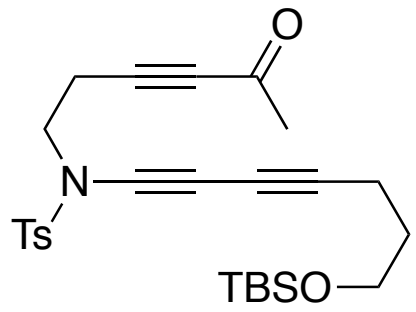
7b



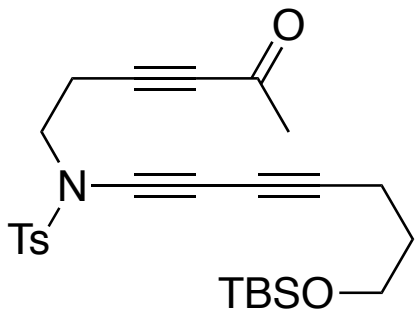
7c



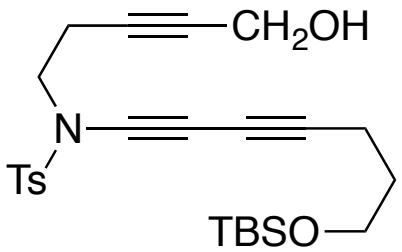
7c



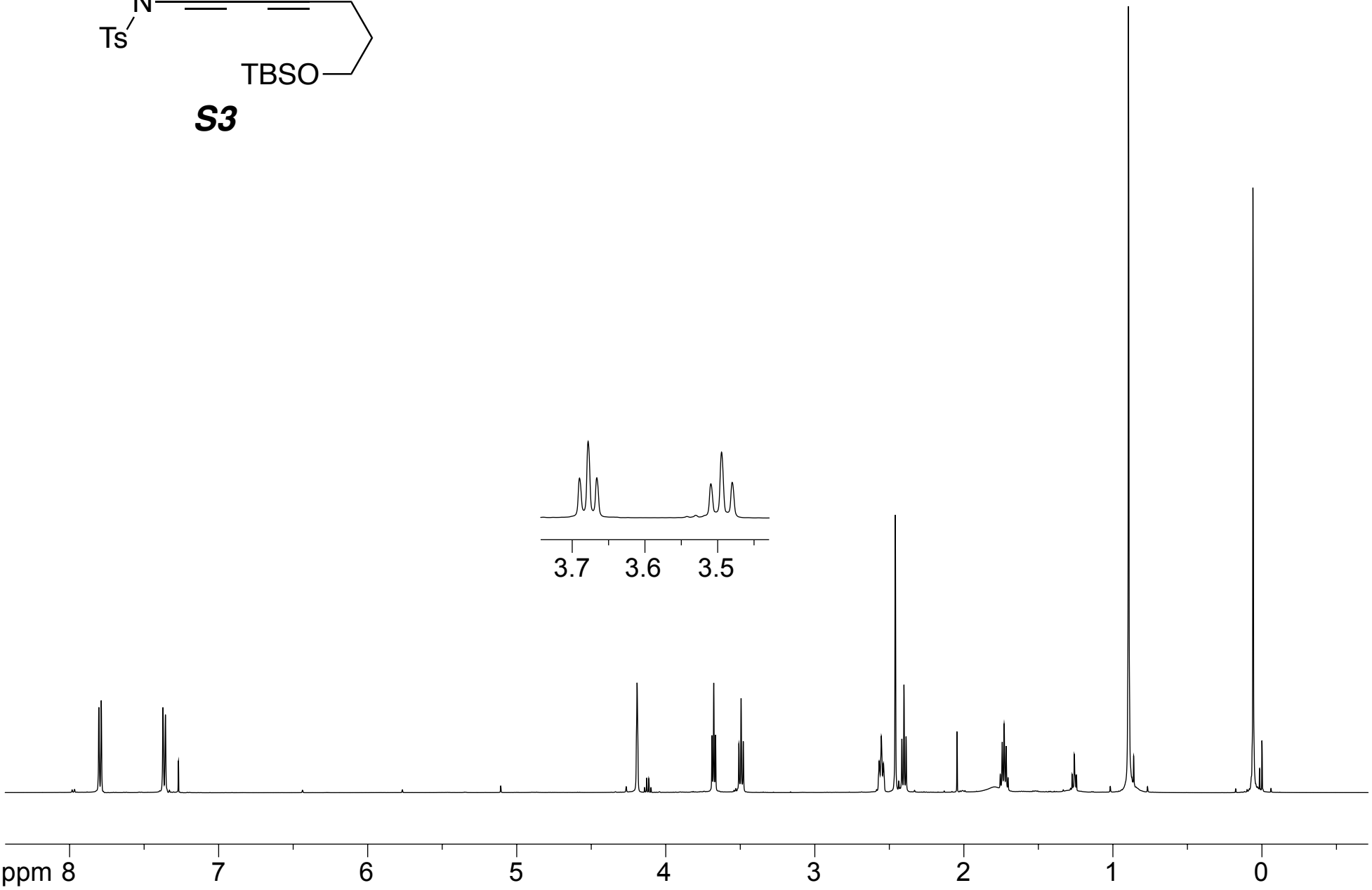
7d

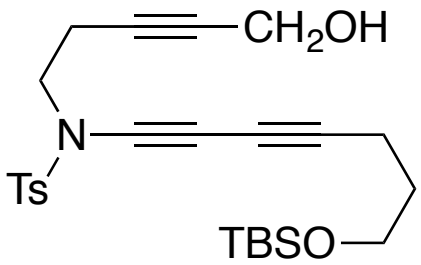


7d

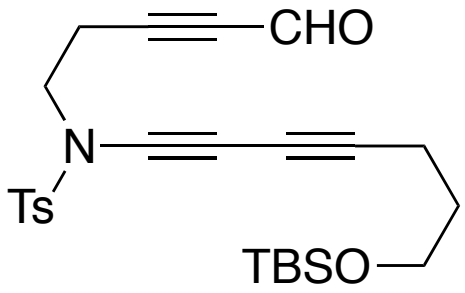


S3

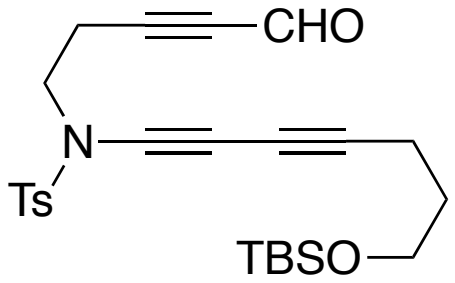




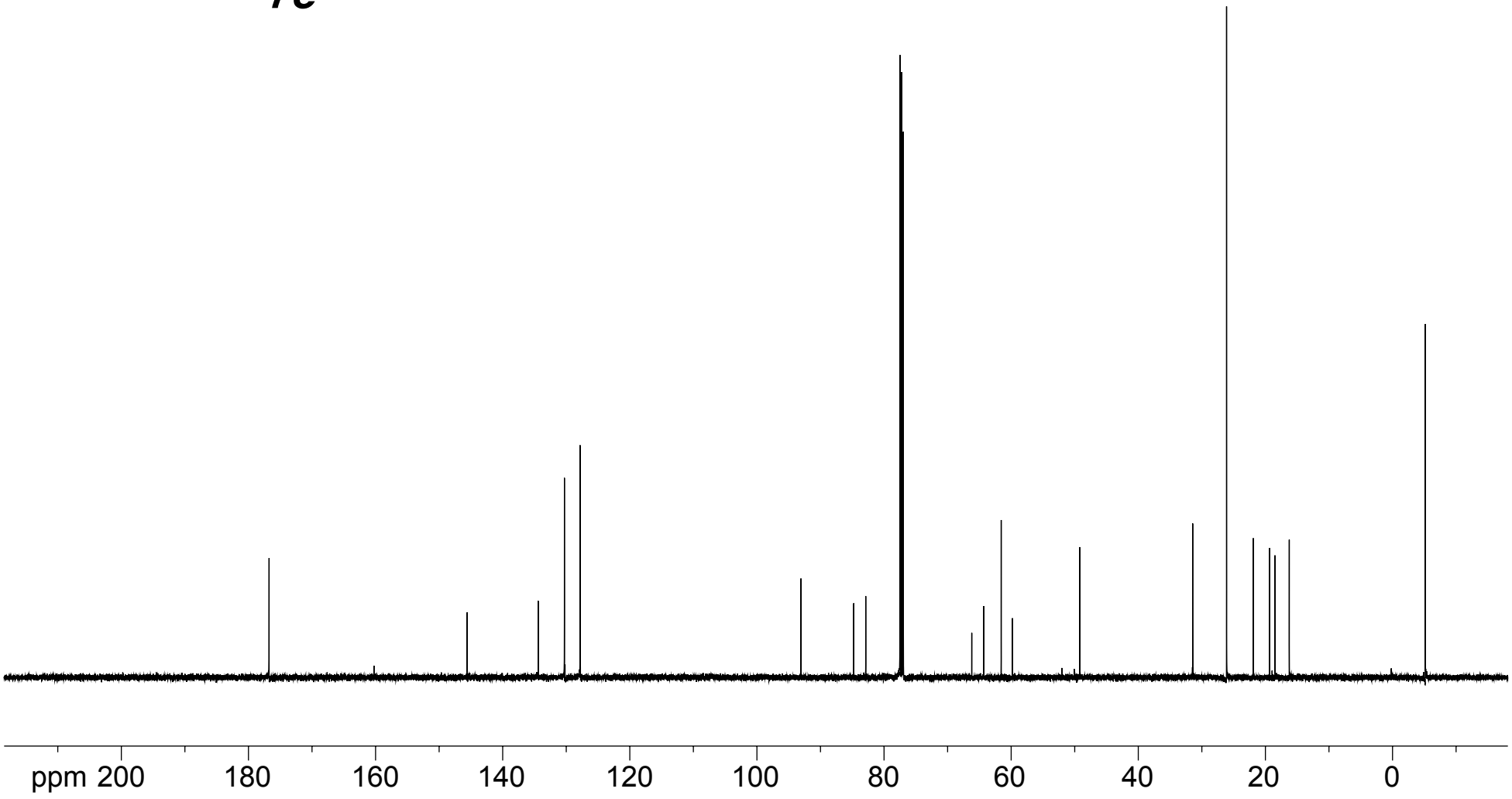
S3

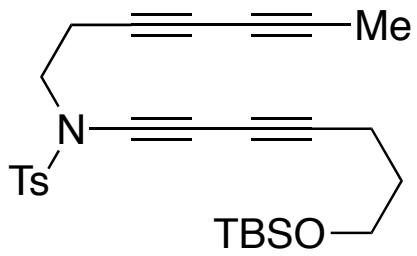


7e

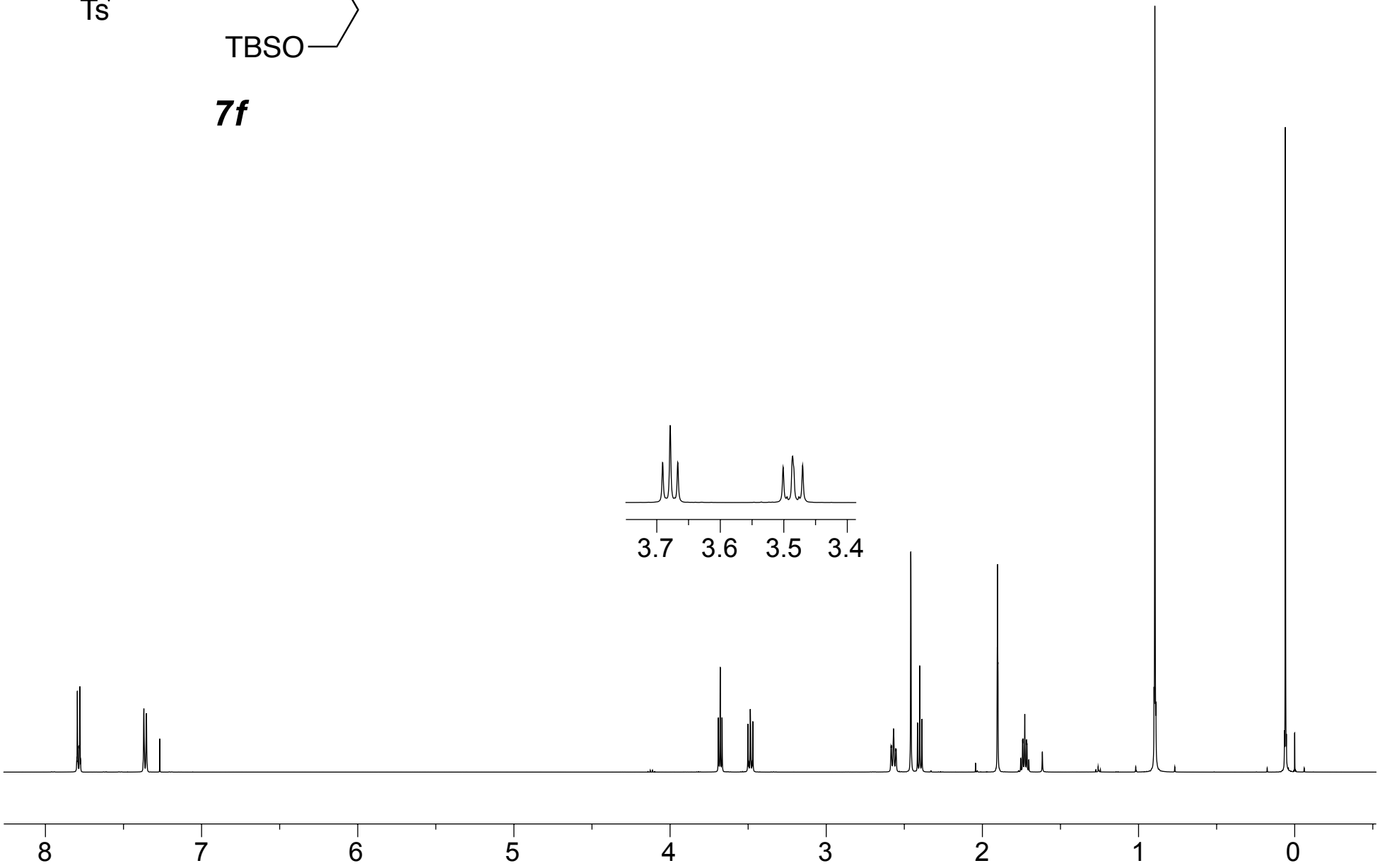


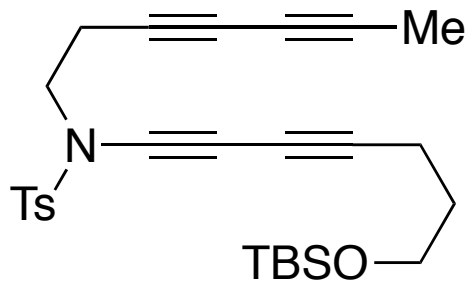
7e



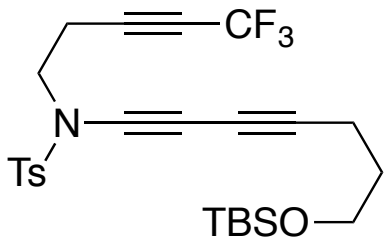


7f

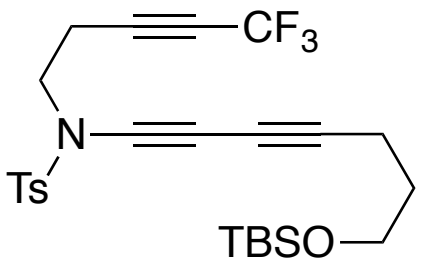




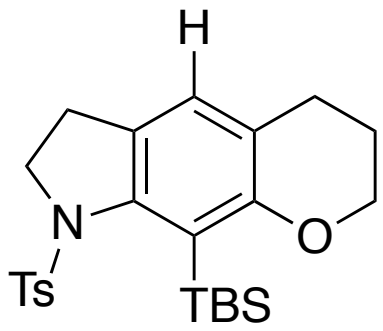
7f



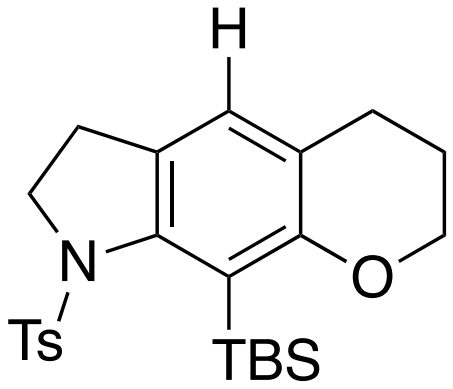
7g



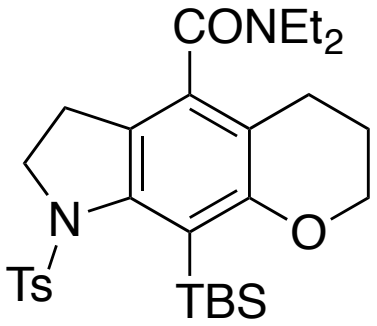
7g



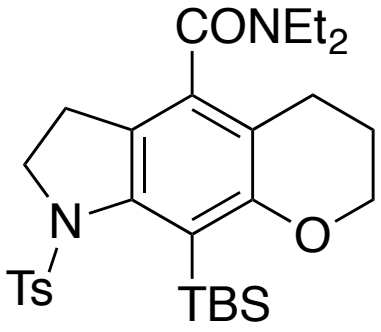
9a



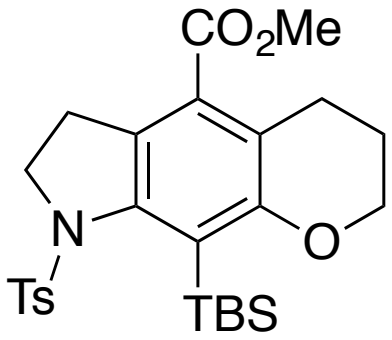
9a



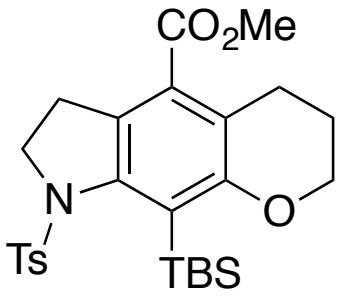
9b



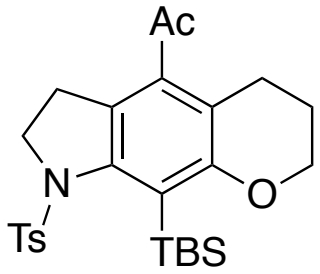
9b



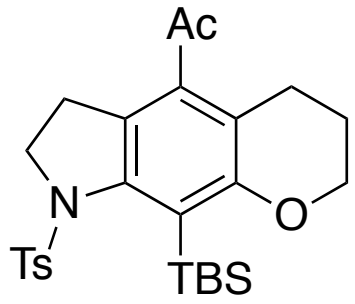
9c



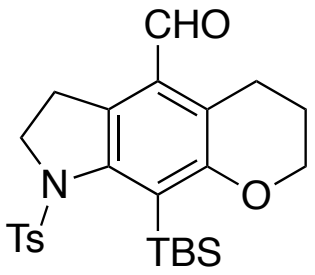
9c



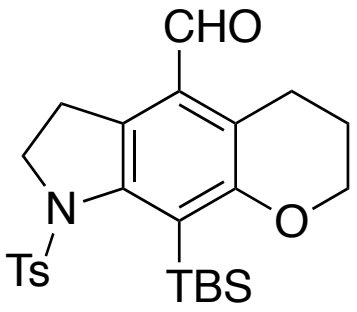
9d



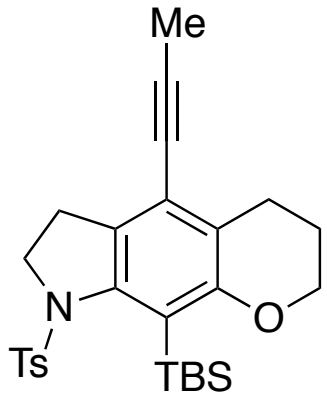
9d



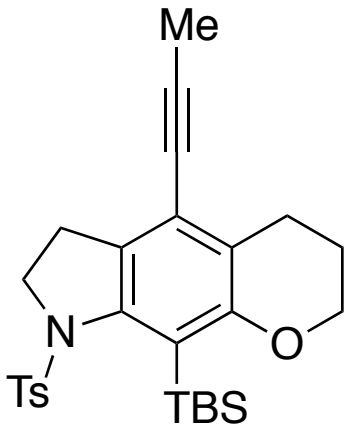
9e



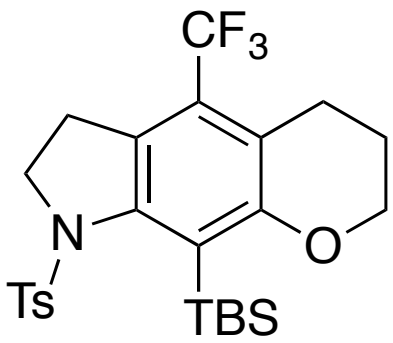
9e



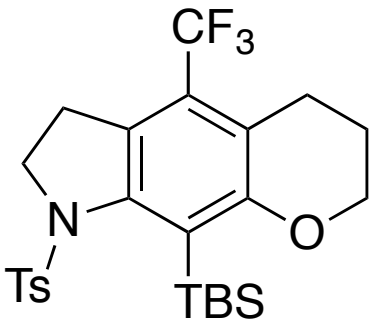
9f



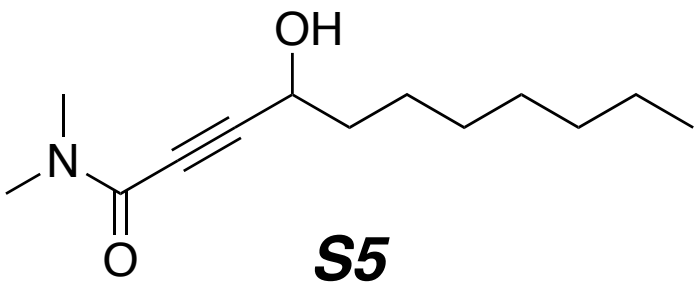
9f



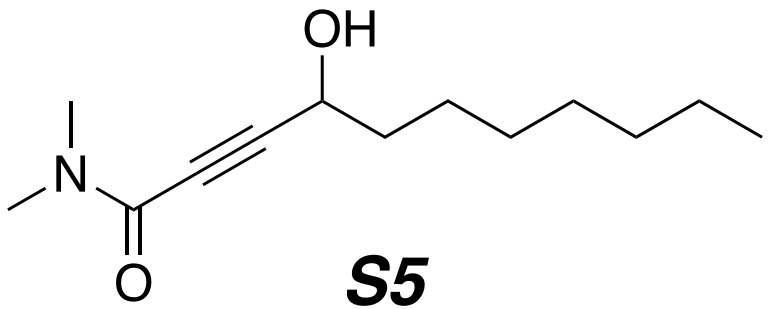
9g



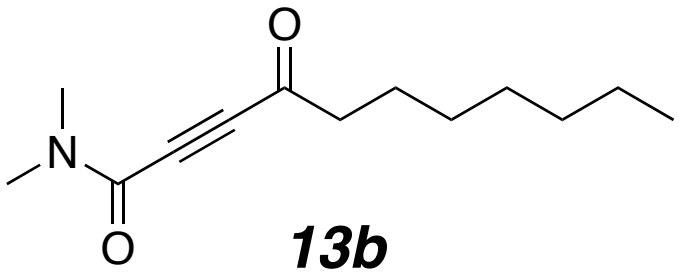
9g



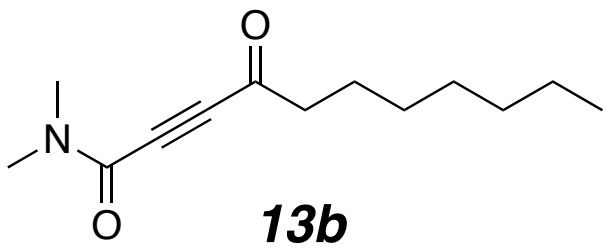
S5



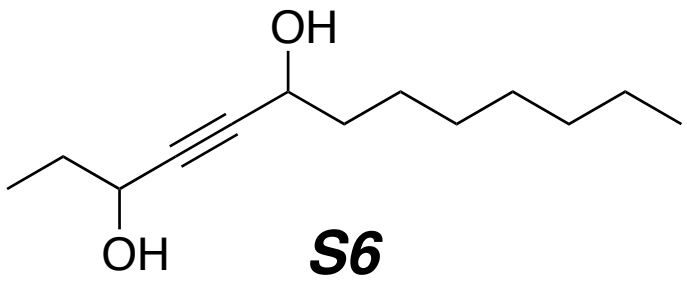
S5



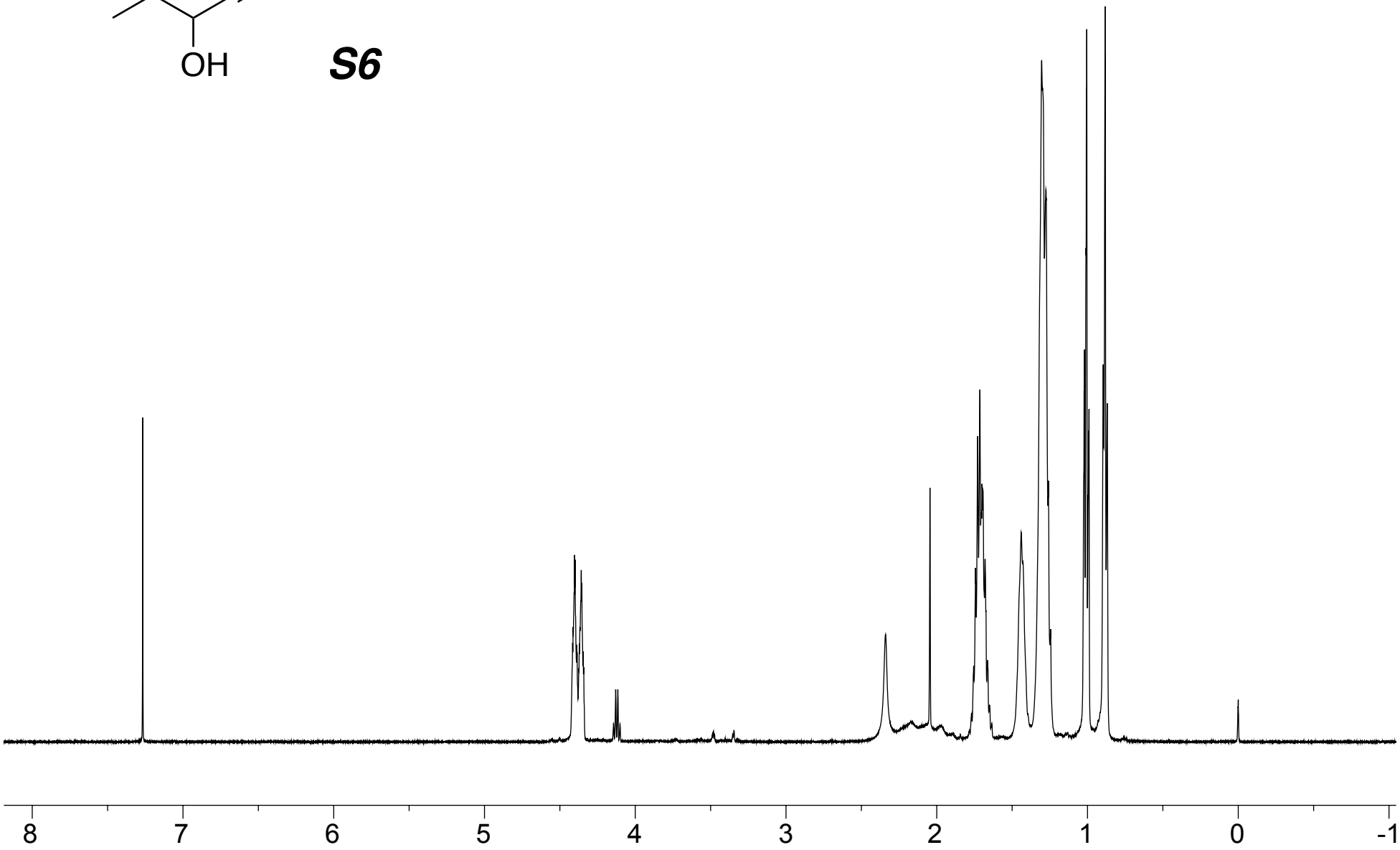
13b

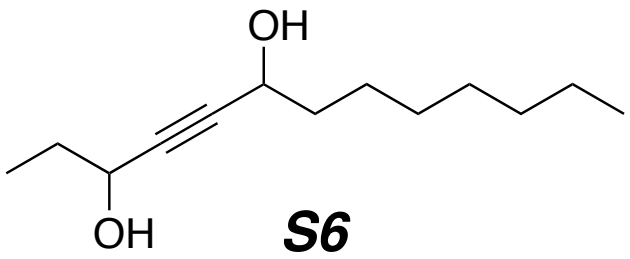


13b

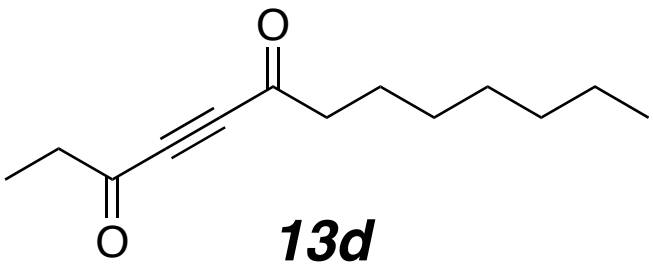


S6

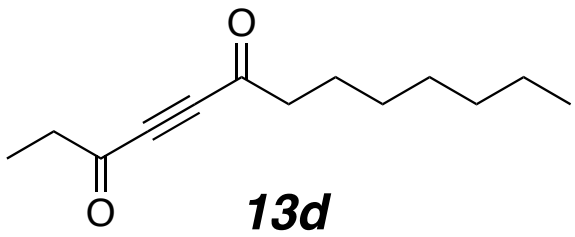




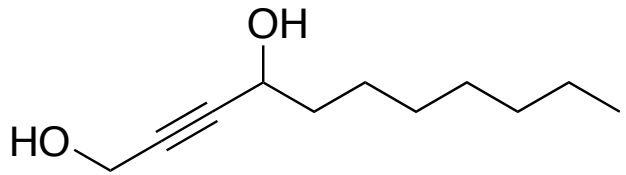
S6



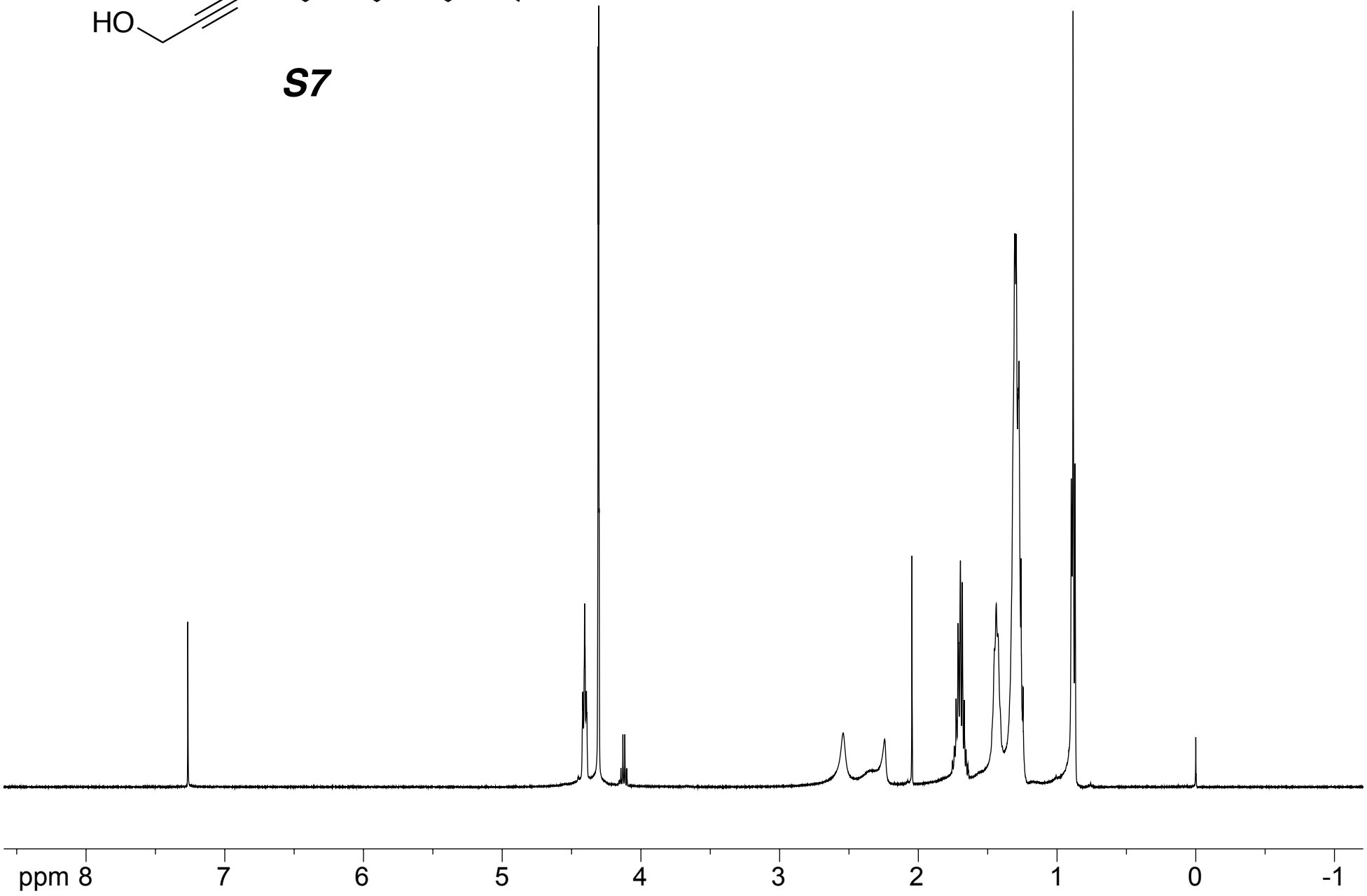
13d

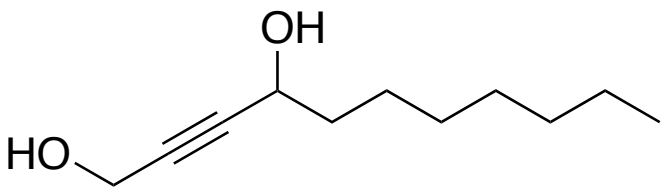


13d

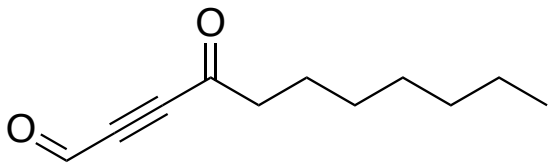


S7

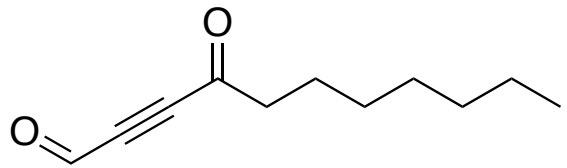




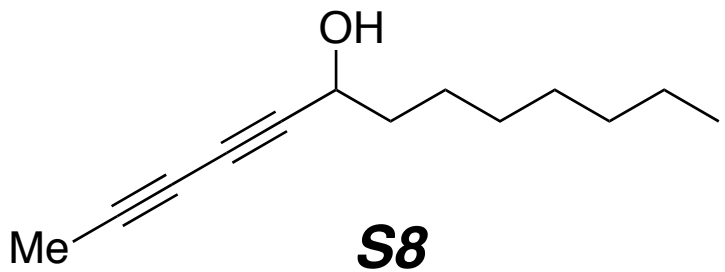
S7



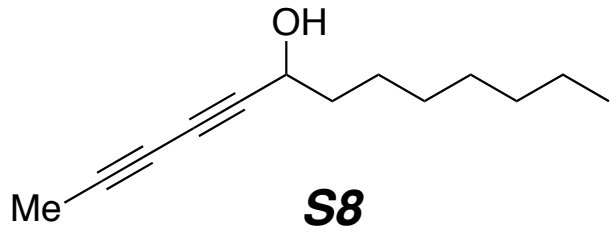
13e



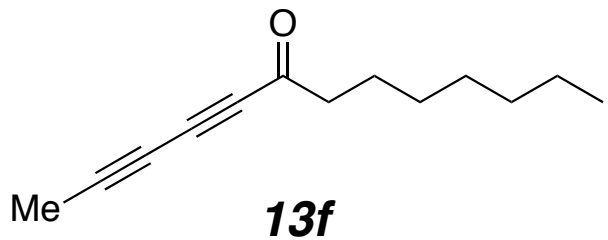
13e



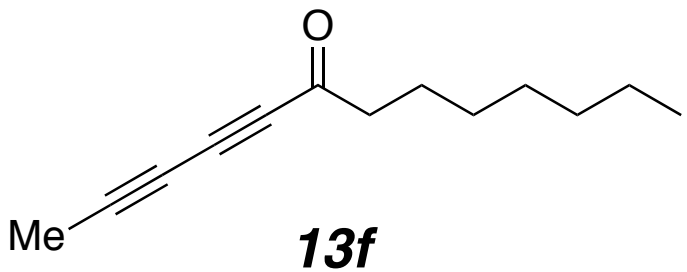
S8



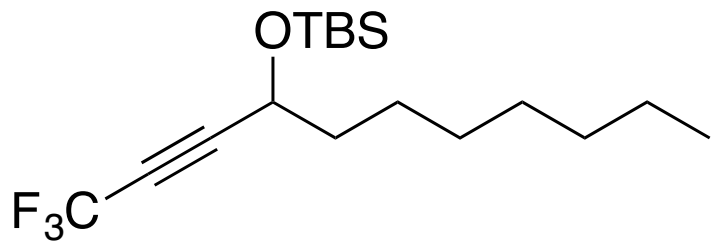
S8



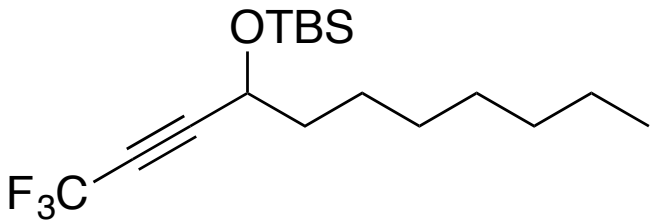
13f



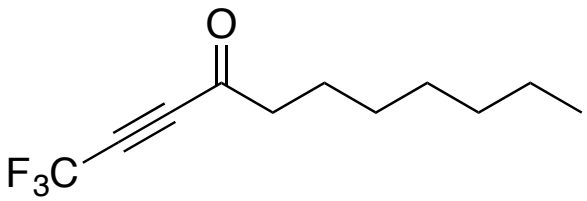
13f



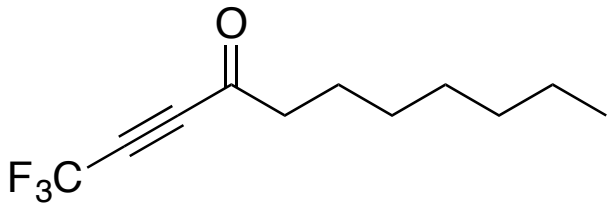
S9



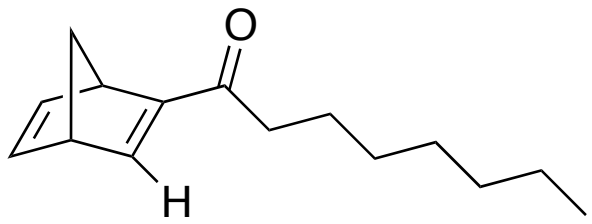
S9



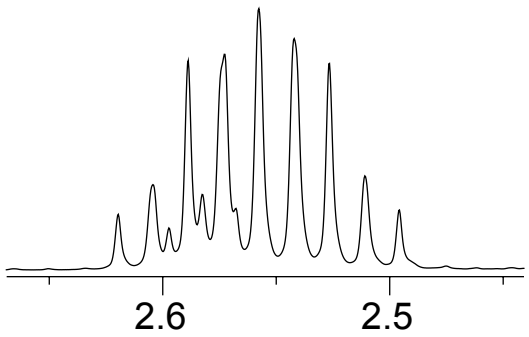
13g

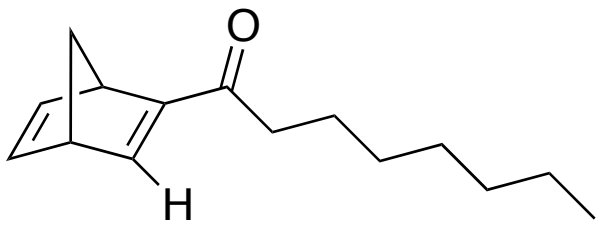


13g

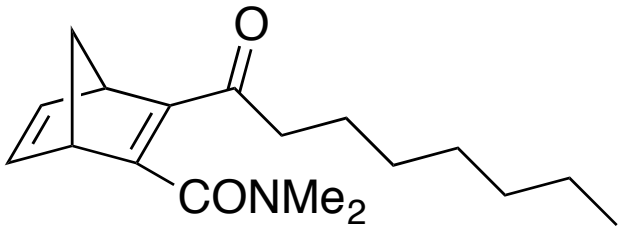


15a

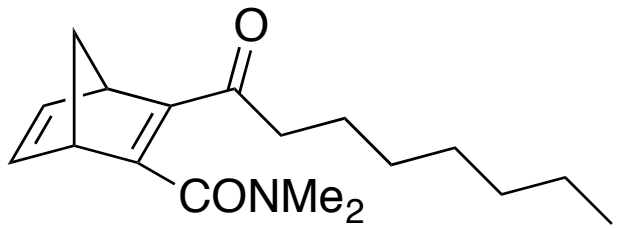




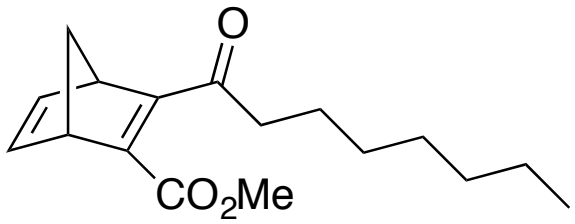
15a



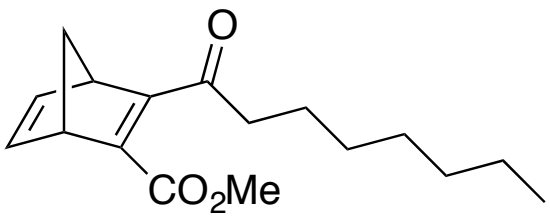
15b



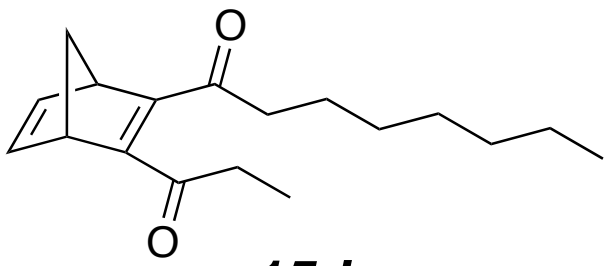
15b



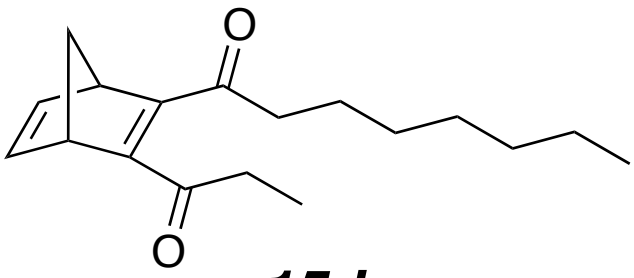
15c



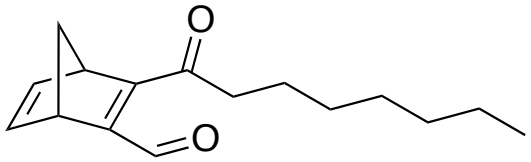
15c



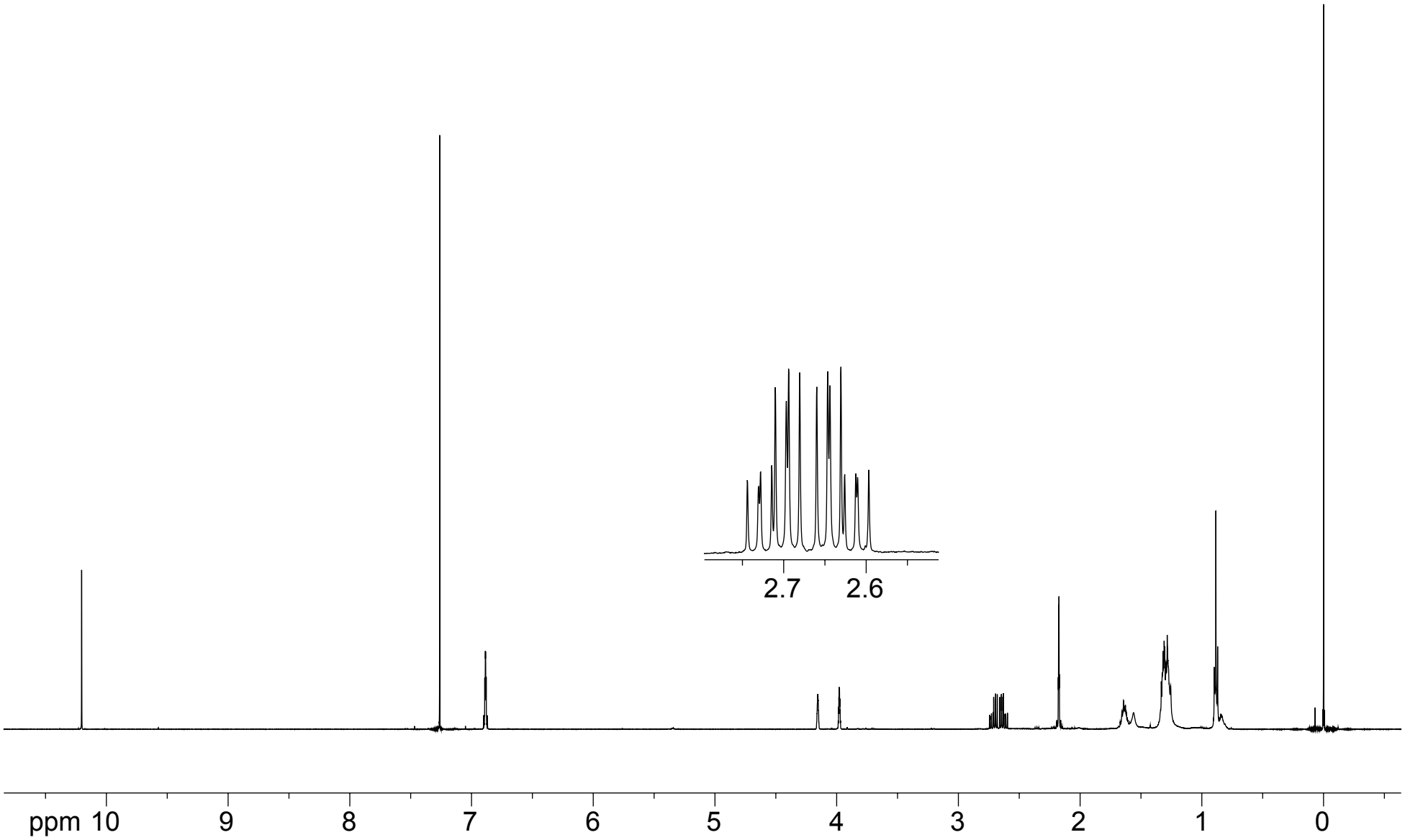
15d

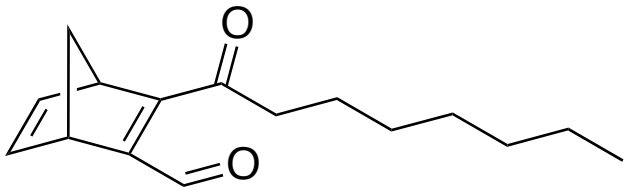


15d

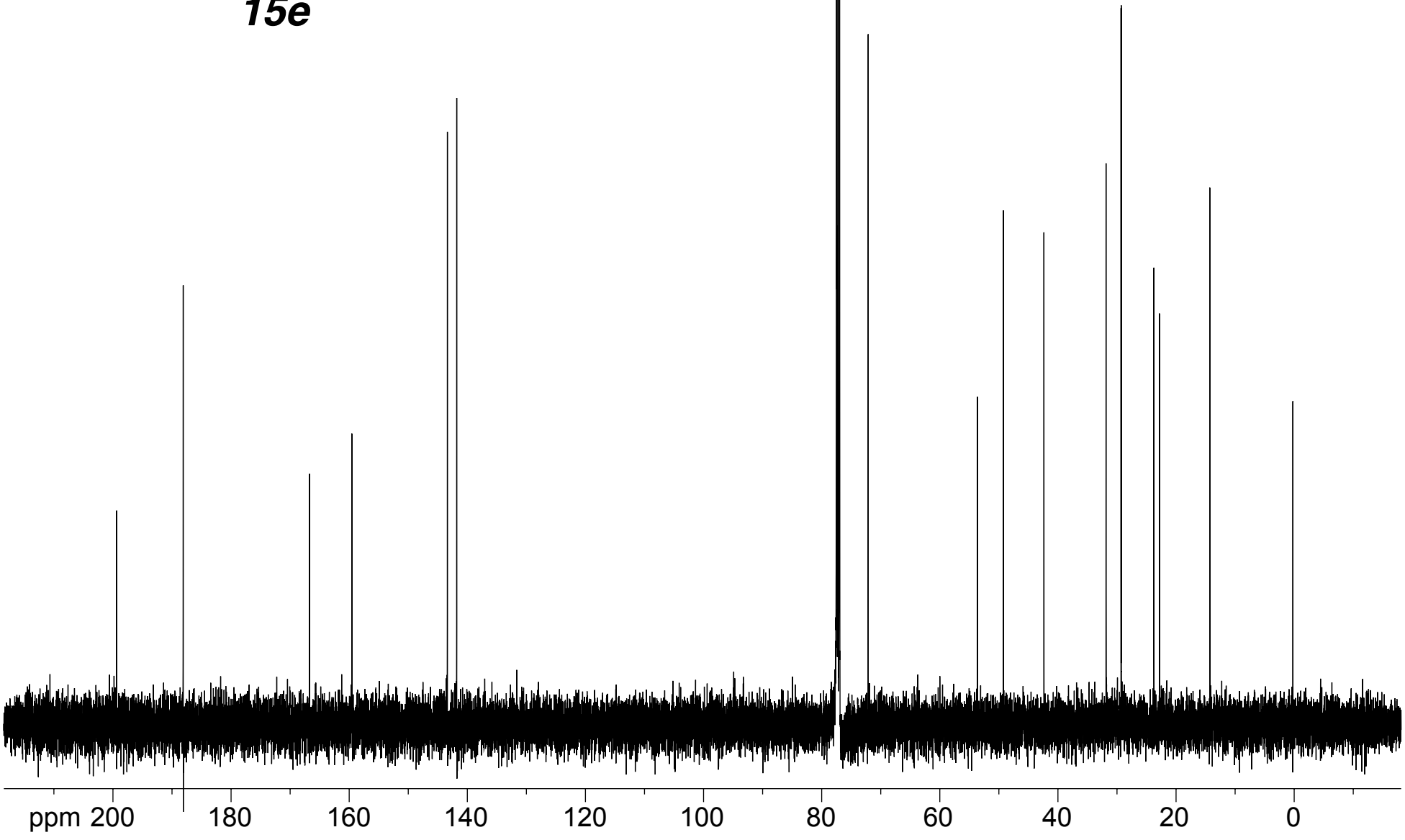


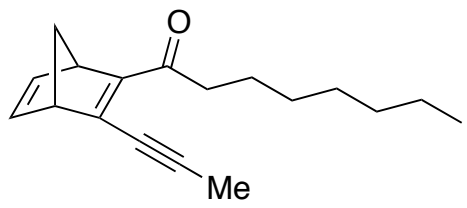
15e



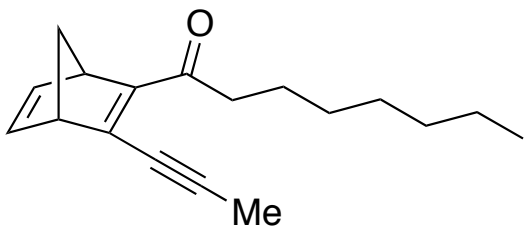


15e

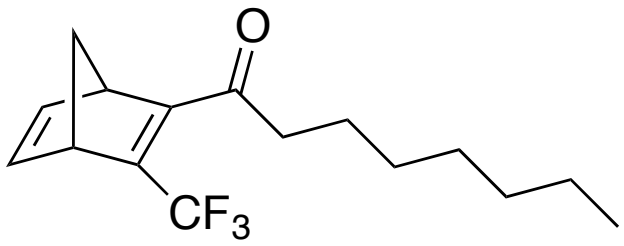




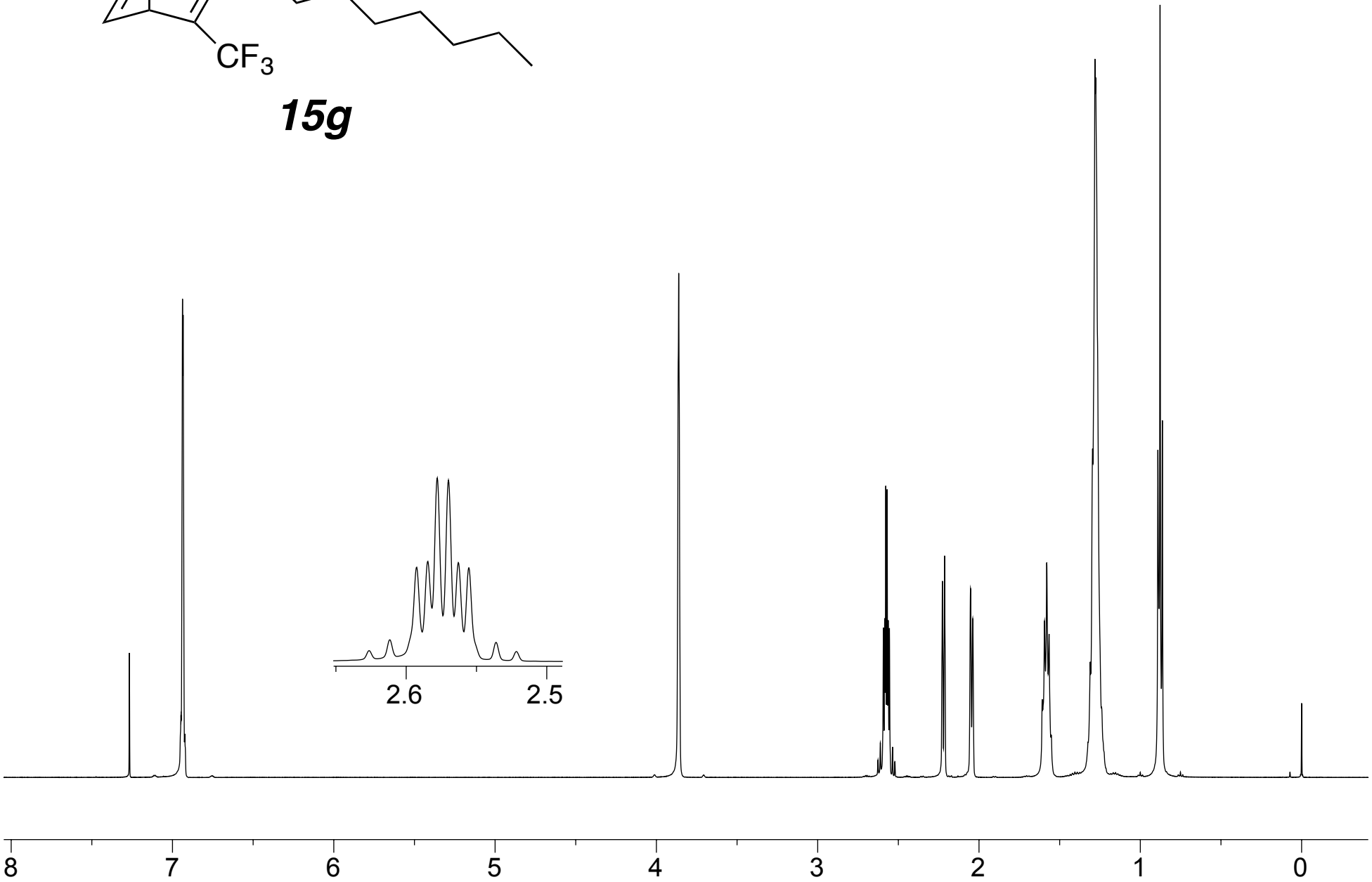
15f

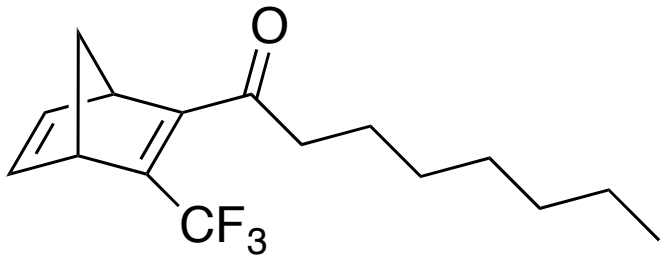


15f



15g





15g