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Drastic fluorine effect: complete reversal of the selectivity in the Au-catalyzed hydroalkoxylation reaction of haloalkynes

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1. General information

The following includes general experimental procedures, specific details for representative reactions, isolation and spectroscopic information for the new compounds prepared. All commercial compounds were used as received. Solvents were used as purchased unless stated as dry. Et_2O, THF, CH_3CN, CH_2Cl_2 and toluene were purified using a Vacuum Atmospheres Inc. Solvent Purification System. All air and water sensitive reactions were carried out under argon atmosphere. Reactions were monitored by TLC on precoated plates (Silicycle silica gel 60 Å F254 230-240 mesh) and products were visualised under 254 nm UV light followed by staining with $KMnO_4$ stain or CAM (Cerium Ammonium Molybdate stain) when appropriate. Purification by flash column chromatography was carried out manually on silica gel (Silicycle silica gel 60 Å F254) or automatically using a Biotage Isolera One Flash Chromatography System with SiliaSep silica gel cartridges. NMR spectra were recorded on an Agilent DD2 500 spectrometer in the indicated solvent at 298 K. Chemical shifts for ^{1}H, ^{13}C or ^{19}F spectra are reported on the delta scale in ppm and were referenced to residual solvent references (^{1}H or ^{13}C), internal TMS reference (^{1}H or ^{13}C) or external $CFCl_3$ (^{19}F). Resonances are reported as follows: chemical shift (δ ppm), multiplicity (s = singulet, d = doublet, t = triplet, q =quartet, p = quintet, m = multiplet, br. s = broad signal), coupling constant (Hz), integration. High-resolution mass (HRMS) spectra were obtained on a LC/MS-TOF Agilent 6210 using electrospray ionization (ESI) in positive mode. Infrared spectra were recorded on an ABB MB3000 FT-IR spectrometer. Melting points were measured on a Stanford Research System OptiMelt MPA100 automated melting point apparatus.

2. General procedures for the synthesis of haloalkyne *gem*-difluorides

Procedure A: To a 0 °C solution of aldehyde (1 equiv.) in THF (0.3 M) was slowly added ethynylmagnesium bromide (0.5 M in THF, 1.2 equiv.). The resulting mixture was stirred at 0 °C for 30 minutes, and then at room temperature for 3 hours. Saturated NH_4Cl was added and the mixture was extracted with Et_2O (3x), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The propargylic alcohol was isolated after purification by flash column chromatography using EtOAc/hexanes as eluent.

Procedure B: To a 30 °C solution of propargylic alcohol (1 equiv.) in DMSO/THF (4:1, 0.1 M) was added 2-iodobenzoic acid (3 equiv.). The resulting mixture was stirred at 30 °C for 5 hours. The solution was then cooled down to room temperature, after which water was added and stirring was continued for 15 minutes. The suspension was filtered to remove the solids. It was then extracted with Et_2O (3x), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The propargylic ketone was isolated after purification by flash column chromatography using EtOAc/hexanes as eluent.

Procedure C: The propargylic ketone (1 equiv.) was dissolved in the minimum amount of CH_2Cl_2. Me-DAST (2.5 equiv.) was added at room temperature followed by the careful addition of a drop of EtOH. The mixture was stirred at 55 °C for 5 hours. It was brought back to 0 °C, diluted with EtOAc and poured into a stirring mixture of EtOAc and saturated $NaHCO_3$. The mixture was stirred for 30 minutes, after which the organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo*. The propargylic *gem*-difluorides was isolated after purification by flash column chromatography using EtOAc/hexanes as eluent.

Procedure D: To a −78 °C solution of propargylic *gem*-difluorides (1 equiv.) in THF (0.1 M) was added *n*-BuLi (2.5 M in hexanes, 1.5 equiv.) and the mixture was stirred at −78 °C for 30 minutes, and then at room temperature for 15 minutes. NCS was added (1.5 equiv.) and the mixture was stirred for 18 hours at room temperature. Saturated NH_4Cl was added and the mixture was extracted with Et_2O (3x), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The chloroalkyne was isolated after purification by flash column chromatography using EtOAc/hexanes as eluent.

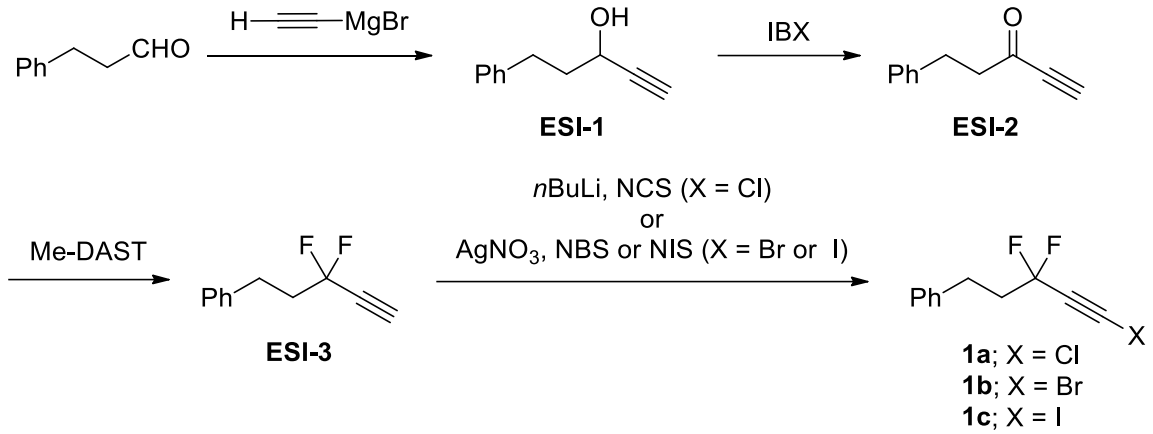
Procedure E: To a solution of *gem*-difluorure propargylic (1 equiv.) in *n*PrOH (0.5 M) was added K_2CO_3 (0.5 equiv.), NCS (52.3 mg, 0.392 mmol, 2 equiv.) and Ag_2CO_3 on Celite (0.1 equiv., 50 wt. % loading). After 18 hours at 50 °C, the solution was cooled down to room temperature, brine was added, and the resulting mixture was extracted with EtOAc (3x). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The chloroalkyne was isolated after purification by flash column chromatography using EtOAc/hexanes as eluent.

Procedure F: To a stirred mixture of propargylic *gem*-difluorides (1 equiv.) in acetone (0.2 M) at room temperature was added $AgNO_3$ (0.1 equiv.) followed by NBS (1.2 equiv.) and stirred for 18 hours. Saturated NH_4Cl was added and the mixture was extracted with Et_2O (3x), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The desired bromoalkyne was isolated after purification by flash column chromatography using EtOAc/hexanes as eluent.

Procedure G: To a -78 °C solution of oxalyl chloride (1.2 equiv.) in CH_2Cl_2 (0.1 M) was added DMSO (2.4 equiv.) and stirring was continued at −78 °C for 15 minutes. A solution of alcohol (1 equiv.) in CH_2Cl_2 (0.5 M) was slowly added and the resulting solution was stirred at −78 °C for 15 minutes. Et_3N (6 equiv.) was added, and the solution was stirred at −78 °C for 30 minutes, and the allowed to reach room temperature over 45 minutes. Saturated $NaHCO_3$ was added and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4 and concentrated *in vacuo*. The desired ketone was isolated after purification by flash column chromatography using EtOAc/hexanes.

Procedure H: To a solution of carboxylic acid (1 equiv.) at −20 °C in CH_2Cl_2 (0.15 M) was added *N*-methylmorpholine (1.1 equiv.) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.1 equiv.). To the stirring mixture at −20 °C was added for 30 minutes *N*-(3-dimethylaminopropryl)-*N*-ethylcarbodiimide hydrochloride (EDC, 1 equiv.). The mixture was stirred for 4 hours at −20 °C. At 0 °C, HCl 3 N was added and the mixture was extracted with CH_2Cl_2 (3x), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. To a 0 °C solution of the crude Weinreb amide (1 equiv.) in THF (0.3 M) was slowly added ethynylmagnesium bromide (0.5 M in THF, 1.2 equiv.). The resulting

mixture was stirred at 0 °C for 30 minutes, and then at room temperature for 3 hours. Saturated NH_4Cl was added and the mixture was extracted with Et_2O (3x), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The desired propargylic ketone was isolated after purification by flash column chromatography using EtOAc/hexanes as eluent.



5-Phenylpent-1-yn-3-ol (ESI-1). Preparing according to the general procedure A on a 10.00 mmol of hydrocinnamaldehyde, the desired compound (1.48 g, 9.24 mmol, 92%) was isolated as a colourless oil after purification by flash column chromatography (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.31-7.28 (m, 2H), 7.23-7.19 (m, 3H), 4.38 (qd, *J* = 6.6, 2.0 Hz, 1H), 2.82 (t, *J* = 7.8 Hz, 2H), 2.52 (d, *J* = 2.1 Hz, 1H), 2.10-1.99 (m, 2H), 1.82 (d, *J* = 5.6 Hz, 1H). Data are in accordance with the one described in the literature.[1]

5-Phenylpent-1-yn-3-one (ESI-2). Preparing according to the general procedure B on a 9.24 mmol of **ESI-1**, the desired compound (1.30 g, 8.22 mmol 89%) was isolated as a colourless oil after purification by flash column chromatography (15% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.31-7.27 (m, 2H), 7.23-7.18 (m, 3H), 3.23 (s, 1H), 3.02-2.98 (m, 2H), 2.95-2.91 (m, 2H). Data are in accordance with the one described in the literature.[2]

[1] Pacheco, C. M.; Gouverneur, V. *Org. Lett.* **2005**, *7*, 1267-1270.
[2] Niphakis, M. J.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6793-6805.

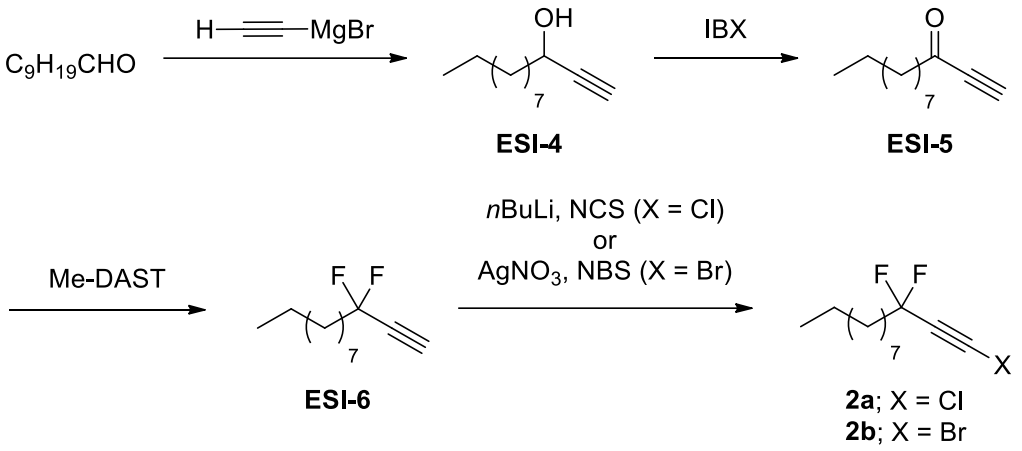
(3,3-Difluoropent-4-yn-1-yl)benzene (ESI-3). Preparing according to the general procedure C on a 8.22 mmol of **ESI-2**, the desired compound (597 mg, 3.31 mmol, 40%) was isolated as a colourless oil after purification by flash column chromatography (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.33-7.29 (m, 2H), 7.24-7.20 (m, 3H), 2.90-2.87 (m, 2H), 2.81 (t, *J* = 5.0 Hz, 1H), 2.41-2.32 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –84.7 (td, *J* = 15.1, 4.9 Hz, 2F). Data are in accordance with the one described in the literature.[3]

(5-Chloro-3,3-difluoropent-4-yn-1-yl)benzene (1a). Preparing according to the general procedure D on a 0.832 mmol of **ESI-3**, the desired compound (140 mg, 0.650 mmol, 78%) was isolated as a colourless oil after purification by flash column chromatography (hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3030, 2937, 2239, 1456, 1306, 1175, 1119, 1047, 885, 868; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.33-7.29 (m, 2H), 7.24-7.20 (m, 3H), 2.88-2.85 (m, 2H), 2.40-2.31 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 139.7, 128.8, 128.4, 126.6, 114.2 (t, J_{C-F} = 234.4 Hz), 68.2 (t, J_{C-F} = 8.3 Hz), 62.9 (t, J_{C-F} = 42.5 Hz), 41.1 (t, J_{C-F} = 26.2 Hz), 29.1 (t, J_{C-F} = 3.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –82.9 (t, *J* = 14.7 Hz, 2F); HRMS-ESI m/z calcd for $C_{11}H_{13}ClF_2N$ $[M+NH_4]^+$ 232.0699, found 232.0715.

(5-Bromo-3,3-difluoropent-4-yn-1-yl)benzene (1b). Preparing according to the general procedure F on a 0.832 mmol of **ESI-3**, the desired compound (190 mg, 0.732 mmol, 88%) was isolated as a pale-yellow oil after purification by flash column chromatography (2% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3030, 2937, 2218, 1456, 1306, 1173, 1115, 1045, 962, 849; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.33-7.29 (m, 2H), 7.24-7.20 (m, 3H), 2.89-2.85 (m, 2H), 2.41-2.31 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 139.7, 128.8, 158.5, 126.6, 114.3 (t, J_{C-F} = 234.6 Hz), 73.7 (t, J_{C-F} = 42.4 Hz), 51.4 (t, J_{C-F} = 9.1 Hz), 41.1 (t, J_{C-F} = 6.0 Hz), 29.1 (t, J_{C-F} = 4.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –83.1 (t, *J* = 14.9 Hz, 2F); HRMS-ESI m/z calcd for $C_{11}H_{13}BrF_2N$ $[M+NH_4]^+$ 276.0194, found 276.0202.

[3] Hamel, J.-D.; Hayashi, T.; Cloutier, M.; Savoie, P. R.; Thibeault, O.; Beaudoin, M.; Paquin, J.-F. *Org. Biomol. Chem*. **2017**, *15*, 9830-9836.

(5-Iodo-3,3-difluoropent-4-yn-1-yl)benzene (1c). Preparing according to the general procedure F using NIS as the reagent instead on a 0.832 mmol of **ESI-3**, the desired compound (227 mg, 0.741 mmol, 89%) was isolated as a colourless oil after purification by flash column chromatography (2% EtOAc/hexanes). The product was slightly contaminated with residual CH_2Cl_2. IR (ATR, Diamond) ν (cm^{-1}) = 3029, 2937, 2191, 1497, 1454, 1304, 1169, 1115, 1044, 958; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.32-7.29 (m, 2H), 7.24-7.19 (m, 3H), 2.88-2.85 (m, 2H), 2.40-2.31 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 139.8, 128.8, 128.5, 126.6, 114.2 (t, $J_{C\text{-}F}$ = 235.6 Hz), 87.8 (t, $J_{C\text{-}F}$ = 41.7 Hz), 41.1 (t, $J_{C\text{-}F}$ = 26.0 Hz), 29.1 (t, $J_{C\text{-}F}$ = 3.9 Hz), 10.4 (t, $J_{C\text{-}F}$ = 9.6 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –83.1 (t, J = 14.8 Hz, 2F); HRMS-ESI m/z calcd for $C_{11}H_{13}F_2IN$ $[M+NH_4]^+$ 324.0054, found 324.0055.



Dodec-1-yn-3-ol (ESI-4). Preparing according to the general procedure A on a 5.00 mmol of decanal, the desired compound (861 mg, 4.72 mmol, 94%) was isolated as a colourless oil after purification by flash column chromatography (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.37 (qd, J = 6.6, 2.1 Hz, 1H), 2.47 (d, J = 2.1 Hz, 1H), 1.76-1.69 (m, 2H), 1.50-1.42 (m, 2H), 1.34-1.26 (m, 12H), 0.88 (t, J = 7.0 Hz, 3H). Data are in accordance with the one described in the literature.[4]

Dodec-1-yn-3-one (ESI-5). Preparing according to the general procedure B on a 4.66 mmol of **ESI-4**, the desired compound (545 mg, 3.02 mmol, 65%) was isolated as a

[4] (a) McLaughlin, E. C.; Doyle, M. P. *J. Org. Chem.* **2008**, *73*, 4317-4319. (b) Satoh, T.; Hayashi, Y.; Yamakawa, K. *Bull. Chem. Soc. Jpn*. **1991**, *64*, 2153-2158.

colourless oil after purification by flash column chromatography (2% EtOAc/hexanes). The product was slightly contaminated with residual CH_2Cl_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 3.20 (s, 1H), 2.58 (t, *J* = 7.4 Hz, 2 H), 1.68 (p, *J* = 7.4 Hz, 2H), 1.33-1.25 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H). Data are in accordance with the one described in the literature.[5]

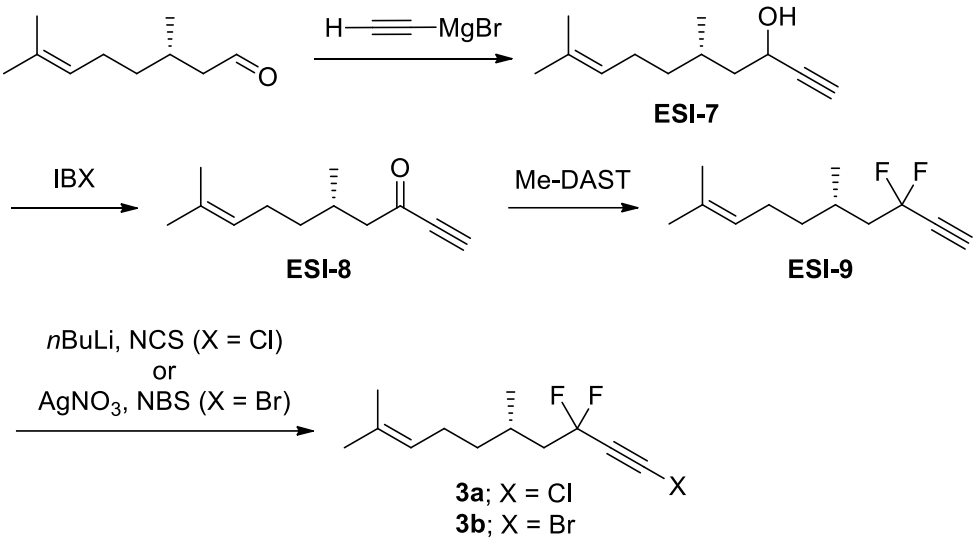
3,3-Difluorododec-1-yne (ESI-6). Preparing according to the general procedure C on a 2.91 mmol of **ESI-5**, the desired compound (252 mg, 1.25 mmol, 43%) was isolated as a colourless oil after purification by flash column chromatography (hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3329, 2949, 2869, 2149, 1488, 1299, 1244, 1210, 1158, 1131; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 2.74 (t, *J* = 4.9 Hz, 1H), 2.07-1.98 (m, 2H), 1.59-1.52 (m, 2H), 1.38-1.24 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 114.6 (t, J_{C-F} = 232.7 Hz), 75.1 (t, J_{C-F} = 6.9 Hz), 39.2 (t, J_{C-F} = 25.4 Hz), 32.0, 29.53, 29.45, 29.4, 29.1, 25.8, 22.82, 22.77 (t, J_{C-F} = 3.6 Hz), 14.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –84.0 (td, *J* = 14.6, 5.2 Hz, 2F); HRMS-ESI m/z calcd for $C_{12}H_{20}F$ $[M\text{-}F]^+$ 183.1544, found 183.1551.

1-Chloro-3,3-difluorododec-1-yne (2a). Preparing according to the general procedure D on a 0.618 mmol of **ESI-6**, the desired compound (125 mg, 0.527 mmol, 85%) was isolated as a colourless oil after purification by flash column chromatography (hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2926, 2856, 2237, 1468, 1317, 1171, 1090, 1013, 876, 758; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 2.06-1.97 (m, 2H), 1.56-1.50 (m, 2H), 1.36-1.27 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 114.9 (t, J_{C-F} = 233.7 Hz), 67.5 (t, J_{C-F} = 8.3 Hz), 63.2 (t, J_{C-F} = 42.7 Hz), 39.4 (t, J_{C-F} = 25.7 Hz), 32.0, 29.5, 29.44, 29.39, 29.1, 28.82, 28.78 (t, J_{C-F} = 3.7 Hz), 14.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –82.2 (t, *J* = 14.9 Hz, 2F); HRMS-ESI m/z calcd for $C_{12}H_{19}ClF$ $[M\text{-}F]^+$ 217.1154, found 217.1168.

1-Bromo-3,3-difluorododec-1-yne (2b). Preparing according to the general procedure F on a 0.618 mmol of **ESI-6**, the desired compound (142 mg, 0.505 mmol, 81%) was isolated as a colourless oil after purification by flash column chromatography (hexanes). IR (ATR,

[5] Ma, S.; Liu, J.; Li, S.; Chen, B.; Cheng, J.; Kuang, J.; Liu, Y.; Wan, B.; Wang, Y.; Ye, J.; Yu, Q.; Yuan, W.; Yu, S. *Adv. Synth. Catal.* **2011**, *353*, 1005-1017.

Diamond) ν (cm^{-1}) = 2926, 2856, 2220, 1468, 1313, 1171, 1086, 1009, 957, 837; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 2.06-1.97 (m, 2H), 1.57-1.50 (m, 2H), 1.38-1.25 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 115.0 (t, J_{C-F} = 233.9 Hz), 74.0 (t, J_{C-F} = 42.7 Hz), 50.6 (t, J_{C-F} = 9.1 Hz), 39.3 (t, J_{C-F} = 25.6 Hz), 32.0, 29.5, 29.44, 29.39, 29.1, 22.82, 22.77 (t, J_{C-F} = 3.6 Hz), 14.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –82.5 (t, *J* = 14.7 Hz, 2F); HRMS-ESI m/z calcd for $C_{12}H_{19}BrF$ $[M-F]^+$ 261.0649, found 261.0642.



(5*S*)-5,9-Dimethyldec-8-en-1-yn-3-ol (ESI-7). Preparing according to the general procedure A on a 5.00 mmol of (*S*)-3,7-dimethyloct-6-enal, the desired compound (839 mg, 4.65 mmol, 93%) was isolated as a colourless oil after purification by flash column chromatography (20% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3310, 2964, 2914, 2854, 1452, 1377, 1055, 1020, 908, 837; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 5.10 (tdq, *J* = 7.1, 2.9, 1.6 Hz, 1H), 4.46-4.42 (m, 1H), 2.47-2.46 (m, 1H), 2.03-1.92 (m, 2H), 1.81-1.69 (m, 2H), 1.64 (d, *J* = 38.1 Hz, 6H), 1.59-1.48 (m, 1H), 1.42-1.32 (m, 1H), 1.27-1.16 (m, 1H), 0.94 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 131.5, 124.7, 85.6, 85.2, 73.1, 77.8, 61.2, 60.7, 45.2, 45.0, 37.19, 37.17, 29.5, 29.0, 25.9, 25.47, 25.45, 19.7, 19.4, 17.83, 17.81; HRMS-ESI m/z calcd for $C_{12}H_{19}$ $[(M+H)-(H_2O)]^+$ 163.1481, found 163.1463.

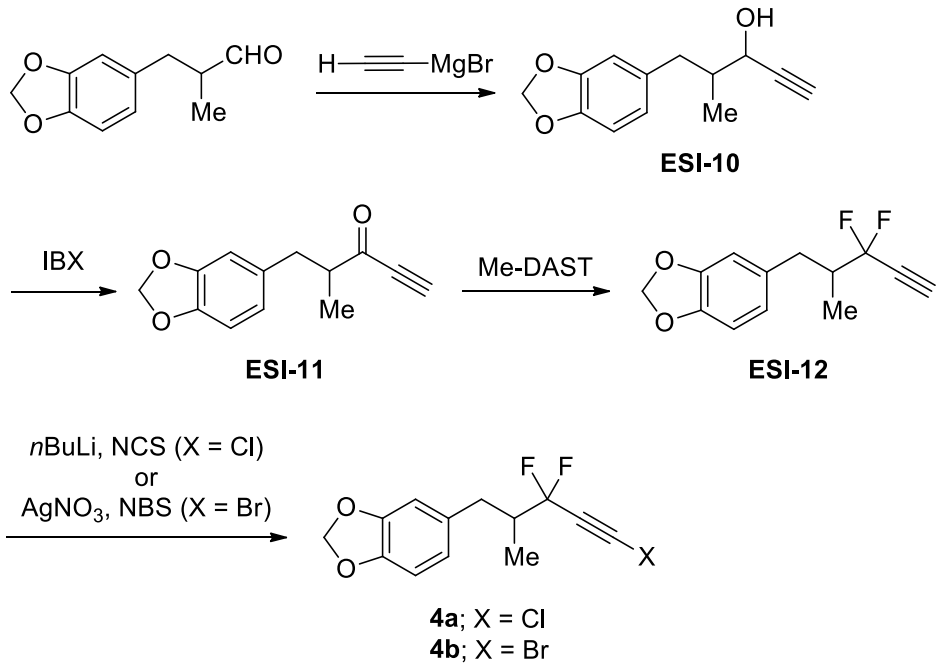
(5*S*)-5,9-Dimethyldec-8-en-1-yn-3-one (ESI-8). Preparing according to the general procedure B on a 4.44 mmol of **ESI-7**, the desired compound (570 mg, 3.20 mmol, 72%) was isolated as a colourless oil after purification by flash column chromatography (5% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2964, 2914, 2854, 2093, 1680, 1452, 1377, 1236, 1063, 889; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 5.08 (tdq, *J* = 6.8, 2.6, 1.3 Hz, 1H), 3.20 (s, 1H), 2.59 (dd, *J* = 15.5, 5.7, 1H), 2.39 (dd, *J* = 15.5, 8.2 Hz, 1H), 2.19-2.10 (m, 1H), 2.06-1.93 (m, 2H), 1.64 (d, *J* = 39.3 Hz, 6H), 1.36 (ddt, *J* = 13.5, 9.3, 6.2 Hz, 1H), 1.24 (dddd, *J* = 13.6, 9.3, 7.7, 6.1 Hz, 1H), 0.95 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 187.5, 131.9, 124.2, 81.9, 78.3, 52.6, 36.9, 79.4, 25.9, 25.5, 19.7, 17.8; HRMS-ESI m/z calcd for $C_{12}H_{19}O$ $[M+H]^+$ 179.1430, found 179.1418.

(*S*)-3,3-Difluoro-5,9-dimethyldec-8-en-1-yne (ESI-9). Preparing according to the general procedure C on a 3.09 mmol of **ESI-8**, the desired compound (200 mg, 0.991 mmol, 32%) was isolated as a colourless oil after purification by flash column chromatography (hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3308, 2924, 2137, 1657, 1456, 1377, 1277, 1178, 1059, 1009; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 5.09 (tdq, *J* = 7.0, 2.7, 1.4, 1H), 2.76 (t, *J* = 5.0 Hz, 1H), 2.12-1.99 (m, 2H), 1.97-1.82 (m, 2H), 1.65 (d, *J* = 38.7 Hz, 6H), 1.42 (ddt, *J* = 11.8, 9.4, 5.9 Hz, 1H), 1.26 (ddt, *J* = 13.4, 9.4, 6.7 Hz, 2H), 1.02 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 131.8, 124.3, 114.7 (t, J_{C-F} = 233.4 Hz), 77.1 (t, J_{C-F} = 40.9 Hz), 75.3 (t, J_{C-F} = 6.9 Hz), 45.5 (t, J_{C-F} = 24.3 Hz), 37.4, 28.2 (t, J_{C-F} = 2.9 Hz), 25.9, 25.3, 20.2, 17.8.; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –80.0 (dtd, *J* = 275.2, 5.3 Hz, 1F), -81.2 (dddd, *J* = 274.4, 18.2, 14.3, 5.4 H, 1F); HRMS-ESI m/z calcd for $C_{12}H_{18}F$ $[M-F]^+$ 181.1387, found 181.1380.

(*S*)-1-Chloro-3,3-difluoro-5,9-dimethyldec-8-en-1-yne (3a). Preparing according to the general procedure D on a 0.500 mmol of **ESI-9**, the desired compound (46.9 mg, 0.200 mmol, 40%) was isolated as a colourless oil after purification by flash column chromatography (hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2966, 2924, 2237, 1452, 1377, 1283, 1069, 1009, 858, 663; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 5.09 (tdq, *J* = 7.1, 2.9, 1.4 Hz, 1H), 2.11-1.96 (m, 2H), 1.92-1.82 (m, 2H), 1.65 (d, *J* = 40.7 Hz, 6H), 1.44-1.37 (m, 1H), 1.29-1.22 (m, 1H), 1.01 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 131.9, 124.2, 115.0 (t, J_{C-F} = 234.4 Hz), 67.7 (t, J_{C-F} = 8.1 Hz), 61.3 (t, J_{C-F} = 42.5 Hz),

45.7 (t, $J_{C\text{-}F}$ = 24.6 Hz), 37.4, 28.1 (t, $J_{C\text{-}F}$ = 2.8 Hz), 25.9, 25.3, 20.3, 17.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –78.2 (dt, *J* = 272.2, 14.6 Hz, 1F), –79.4 (ddd, *J* = 272.1, 18.7, 13.5 Hz, 1F); HRMS-ESI m/z calcd for $C_{12}H_{17}ClF$ $[M\text{-}F]^+$ 215.0997, found 215.1010.

(*S*)-1-Bromo-3,3-difluoro-5,9-dimethyldec-8-en-1-yne (3b). Preparing according to the general procedure F on a 0.500 mmol of **ESI-9**, the desired compound (79.7 mg, 0.285 mmol, 57%) was isolated as a colourless oil after purification by flash column chromatography (hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2966, 2924, 2218, 1452, 1377, 1279, 1061, 1009, 831, 648; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 5.09 (tdq, *J* = 6.9, 2.7, 1.3 Hz, 1H), 2.11-1.96 (m, 2H), 1.92-1.82 (m, 2H), 1.65 (d, *J* = 41.7 Hz, 6H), 1.44-1.38 (m, 1H), 1.26 (ddt, *J* = 13.2, 9.2, 6.6 Hz, 2H), 1.01 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 131.9, 124.3, 115.1 (t, $J_{C\text{-}F}$ = 234.4 Hz), 74.2 (t, $J_{C\text{-}F}$ = 42.3 Hz), 50.9 (t, $J_{C\text{-}F}$ = 8.9 Hz), 45.6 (t, $J_{C\text{-}F}$ = 24.4 Hz), 37.4, 28.1 (t, $J_{C\text{-}F}$ = 2.8 Hz), 25.9, 25.3, 20.6, 17.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –78.5 (dt, *J* = 272.9, 14.8 Hz, 1F), –79.1 (ddd, *J* = 271.8, 19.1, 13.5 Hz, 1F); HRMS-ESI m/z calcd for $C_{12}H_{17}BrF$ $[M\text{-}F]^+$ 259.0492, found 259.0512.



5-(Benzo[*d*][1,3]dioxol5-yl)-4-methylpent-1-yn-3-ol (ESI-10). Preparing according to the general procedure A on a 5.00 mmol of 3-(benzo[*d*][1,3]dioxol-5-yl)2-methylpropanal, the desired compound (1.01 g, 4.63 mmol, 93%) was isolated as a colourless oil after

purification by flash column chromatography (20% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3292, 2893, 2249, 1489, 1441, 1244, 1188, 1036, 908, 810; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.73 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.69 (dd, *J* = 4.4, 1.7 Hz, 1H), 6.64 (ddd, *J* = 7.8, 5.8, 1.7 Hz, 1H), 5.92 (s, 2H), 4.27 (dtd, *J* = 12.7, 5.3, 4.8, 2.1 Hz, 1H), 2.80 (ddd, *J* = 54.5, 13.6, 6.4 Hz, 1H), 2.51 (dd, *J* = 9.3, 2.2 Hz, 1H), 2.43 (dt, *J* = 13.6, 8.5 Hz, 1H), 2.03-1.95 (m, 1H), 1.93-1.85 (m, 1H), 0.99 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 147.70, 147.67, 145.93, 145.92, 134.2, 133.9, 122.2, 122.1, 109.7, 109.6, 108.3, 108.2, 100.9, 83.9, 83.1, 74.5, 74.1, 66.0, 65.7, 41.6, 41.4, 38.9, 38.2, 14.7, 14.4; HRMS-ESI m/z calcd for $C_{13}H_{13}O_2$ $[(M+H)-(H_2O)]^+$ 201.0910, found 201.0897.

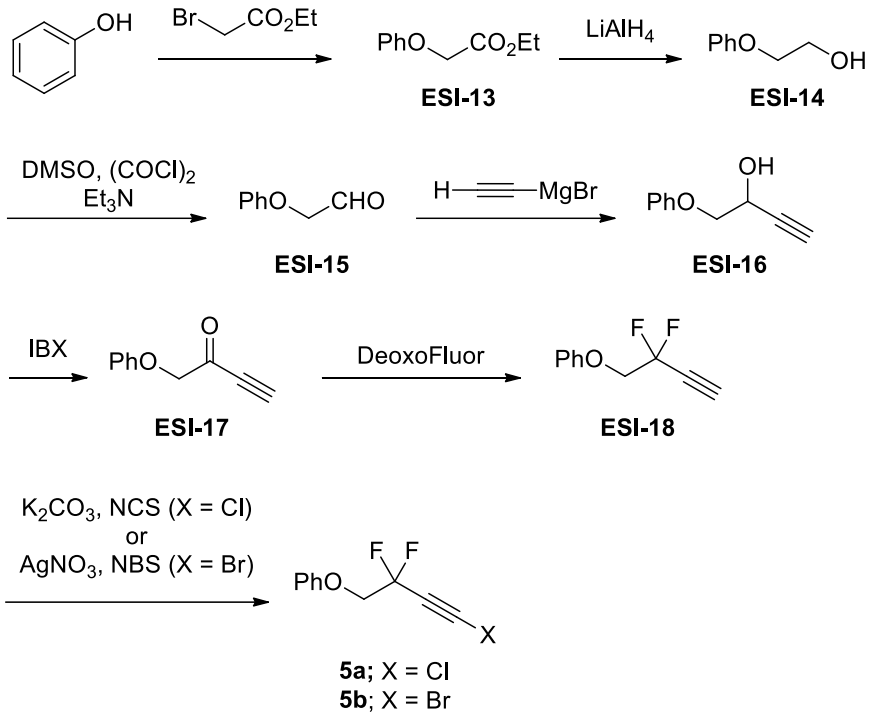
5-(Benzo[*d*][1,3]dioxol-5-yl)-4-methylpent-1-yn-3-one (ESI-11). Preparing according to the general procedure B on a 4.58 mmol of **ESI-10**, the desired compound (823 mg, 3.80 mmol, 83%) was isolated as a pale-yellow oil after purification by flash column chromatography (10% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3265, 2893, 2363, 2091, 1676, 1489, 1244, 1034, 928, 810; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.73 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 1.7 Hz, 1H), 6.62 (dd, *J* = 1.7 Hz, 1H), 5.93 (s, 2H), 3.27 (s, 1H), 3.09 (dd, *J* = 13.9, 6.3 Hz, 1H), 2.87-2.80 (m, 1H), 2.59 (dd, *J* = 13.9, 8.0 Hz, 1H), 1.17 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 190.5, 147.8, 146.3, 132.5, 121.2, 109.5, 108.4, 101.0, 80.8, 79.8, 50.6, 38.2, 15.5; HRMS-ESI m/z calcd for $C_{13}H_{13}O_2$ $[M+H]^+$ 217.0859, found 217.0866.

5-(3,3-Difluoro-2-methylpent-4-yn-1-yl)benzo[*d*][1,3]dioxole (ESI-12). Preparing according to the general procedure C on a 3.47 mmol of **ESI-11**, the desired compound (278 mg, 1.17 mmol, 34%) was isolated as a colourless oil after purification by flash column chromatography (5% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2896, 2110, 1521, 1473, 1456, 1271, 1201, 1139, 1005, 957; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.74 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 1.8 Hz, 1H), 6.62 (dd, *J* = 8.0, 1.7 Hz, 1H), 5.94 (s, 2H), 3.09-3.06 (m, 1H), 2.81 (t, *J* = 5.0 Hz, 1H), 2.34-2.29 (m, 1H), 3.21-2.23 (m, 1H), 1.00 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 147.8, 146.2, 132.7, 122.3, 116.5 (t, J_{C-F} = 235. 8 Hz), 109.6, 108.4, 101.1, 76.2 (t, J_{C-F} = 6.9 Hz), 75.8 (t, J_{C-F} = 41.0 Hz), 44.1 (t, J_{C-F} = 23.6 Hz), 36.1 (t, J_{C-F} = 3.6 Hz), 12.7; ^{19}F NMR (470 MHz,

$CDCl_3$) δ (ppm) = –89.9 (ddd, *J* = 272.6, 10.9, 4.9 Hz, 1F), –90.6 (ddd, *J* = 272.6, 11.1, 4.9 Hz, 1F); HRMS-ESI m/z calcd for $C_{13}H_{13}F_2O_2$ $[M+H]^+$ 239.0878, found 239.0891.

5-(5-Chloro-3,3-Difluoro-2-methylpent-4-yn-1-yl)benzo[*d*][1,3]dioxole (4a). Preparing according to the general procedure D on a 0.525 mmol of **ESI-12**, the desired compound (119 mg, 0.438 mmol, 83%) was isolated as a colourless oil after purification by flash column chromatography (5% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2939, 2885, 2233, 1489, 1443, 1246, 1190, 1036, 930, 806; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.74 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 1.7 Hz, 1H), 6.62 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.94 (s, 2H), 3.06-3.03 (m, 1H), 2.33-2.28 (m, 1H), 2.30-2.24 (m, 1H), 0.99 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 147.8, 146.2, 132.6, 122.3, 116.8 (t, J_{C-F} = 236.8 Hz), 109.5, 108.4, 101.1, 68.4 (t, J_{C-F} = 8.1 Hz), 62.3 (t, J_{C-F} = 42.4 Hz), 44.3 (t, J_{C-F} = 24.1 Hz), 36.1 (t, J_{C-F} = 3.3 Hz), 12.8 (t, J_{C-F} = 3.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –88.1 (dd, *J* = 267.9, 11.2 Hz, 1F), –88.8 (dd, *J* = 267.91 11.2 Hz, 1F); HRMS-ESI m/z calcd for $C_{13}H_{12}ClF_2O_2$ $[M+H]^+$ 273.0494, found 273.0471.

5-(5-Bromo-3,3-difluoro-2-methylpent-4-yn-1-yl)benzo[*d*][1,3]dioxole (4b). Preparing according to the general procedure F on a 0.525 mmol of **ESI-12**, the desired compound (154 mg, 0.484 mmol, 92%) was isolated as a colourless oil after purification by flash column chromatography (5% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2939, 2883, 2214, 1491, 1443, 1246, 1190, 1036, 930, 810; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.74 (d, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 1.7 Hz, 1H), 6.62 (dd, *J* = 8.0, 1.9 Hz, 1H), 5.94 (s, 2H), 3.06-3.03 (m, 1H), 2.33-2.28 (m, 1H), 2.30-2.24 (m, 1H), 0.99 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 147.8, 146.2, 132.6, 122.6, 116.8 (t, J_{C-F} = 237.0 Hz), 109.6, 108.4, 101.1, 73.0 (t, J_{C-F} = 42.4 Hz), 51.5 (t, J_{C-F} = 9.1 Hz), 44.3 (t, J_{C-F} = 23.9 Hz), 36.0 (t, J_{C-F} = 3.4 Hz), 12.8 (t, J_{C-F} = 3.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –88.4 (dd, *J* = 272.6, 10.9 Hz, 1F), –89.0 (dd, *J* = 272.6, 10.4 Hz, 1F); HRMS-ESI m/z calcd for $C_{13}H_{12}BrF_2O_2$ $[M+H]^+$ 316.9988, found 316.9985.



Ethyl 2-phenoxyacetate (ESI-13). To a solution of phenol (1.5 mL, 17.21 mmol, 1 equiv.) in acetone (57.4 mL, 0.3 M) was added ethyl bromo acetate (2.2 mL, 18.93 mmol, 1.1 equiv.) and K_2CO_3 (23.8 g, 172.1 mmol, 10 equiv.) and the suspension was stirred at room temperature for 3 hours. The solid was filtered and the solution was concentrated *in vacuo*. The desired compound (3.10 g, 17.20 mmol, 99%) was isolated as a colourless oil after purification by flash column chromatography (10 to 20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.32-7.27 (m, 2H), 7.00 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.93-6.90 (m, 2H), 4.62 (s, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). The product was slightly contaminated with residual CH_2Cl_2. Data are in accordance with the one reported in the literature.[6]

2-Phenoxyethan-1-ol (ESI-14). To a solution of **ESI-13** (3.10 g, 17.20 mmol, 1 equiv.) in Et_2O (172 mL, 0.1 M) at 0 °C was slowly added $LiAlH_4$ (2.61 g, 68.8 mmol, 4 equiv.) and the reaction mixture was stirred at 0 C for 3 hours. Water then aq. HCl 1 N were carefully added at 0 °C and the mixture was extracted with Et_2O (3x). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The

[6] Lee, K.; Goo, J.-I.; Jung, H. Y.; Kim, M.; Boovanahalli, S. K.; Park, H. R.; Kim, M.-O.; Kim, D.-H.; Lee, H. S.; Choi, Y. *Bioorg. Med. Chem*. **2012**, *22*, 7456-7460.

desired compound (2.33 g, 16.86 mmol, 98%) was isolated as a colourless oil by a short pad of silica. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.33-7.27 (m, 2H), 6.97 (m, 1H), 6.94-6.91 (m, 2H), 4.10-4.08 (m, 2H), 3.97 (dd, *J* = 14.1, 4.9 Hz, 2H), 2.09 (t, *J* = 4.9 Hz, 1H). Data are in accordance with the one described in the literature.[7]

2-Phenoxyacetaldehyde (ESI-15). Preparing according to the general procedure G on a 16.65 mmol of **ESI-14**, the desired compound was directly used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 9.88 (t, *J* = 1.1 Hz, 1H), 7.34-7.31 (m, 2H), 7.03 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.92-6.90 (m, 2H), 4.58 (d, *J* = 1.1 Hz, 2H). The product was slightly contaminated with residual CH_2Cl_2. Data are in accordance with the one described in the literature.[8]

1-Phenoxybut-3-yn-2-ol (ESI-16). Preparing according to the general procedure A on a 2.92 mmol of **ESI-15**, the desired compound (331 mg, 2.04 mmol, 70% over 2 steps) was isolated as a colourless oil after purification by flash column chromatography (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.32-7.29 (m, 2H), 7.00 (app tt, *J* = 7.5, 1.0 Hz, 1H), 6.95-6.93 (m, 2H), 4.77 (dddd, *J* = 7.4, 5.7, 3.5, 2.2 Hz, 1H), 4.16 (dd, *J* = 9.6, 3.6 Hz, 1H), 4.09 (dd, *J* = 9.5, 7.1 Hz, 1H), 2.54 (d, *J* = 2.3 Hz, 1H), 2.53 (d, *J* = 5.4 Hz, 1H). Data are in accordance with the one described in the literature.[8]

1-Phenoxybut-3-yn-2-one (ESI-17). Preparing according to the general procedure B on a 2.92 mmol of **ESI-16**, the desired compound (315 mg, 1.97 mmol, 97%) was isolated as a pale-yellow oil after purification by flash column chromatography (20% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3263, 3024, 2970, 2947, 2098, 1736, 1705, 1597, 1497, 1366, 1219, 1049, 756; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.32-7.28 (m, 2H), 7.01 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.91-6.88 (m, 2H), 4.74 (s, 2H), 3.39 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 182.8, 157.6, 129.8, 122.2, 114.9, 82.6, 79.2, 73.6; HRMS-ESI m/z calcd for $C_{10}H_9O_2$ $[M+H]^+$ 161.0597, found 161.0582.

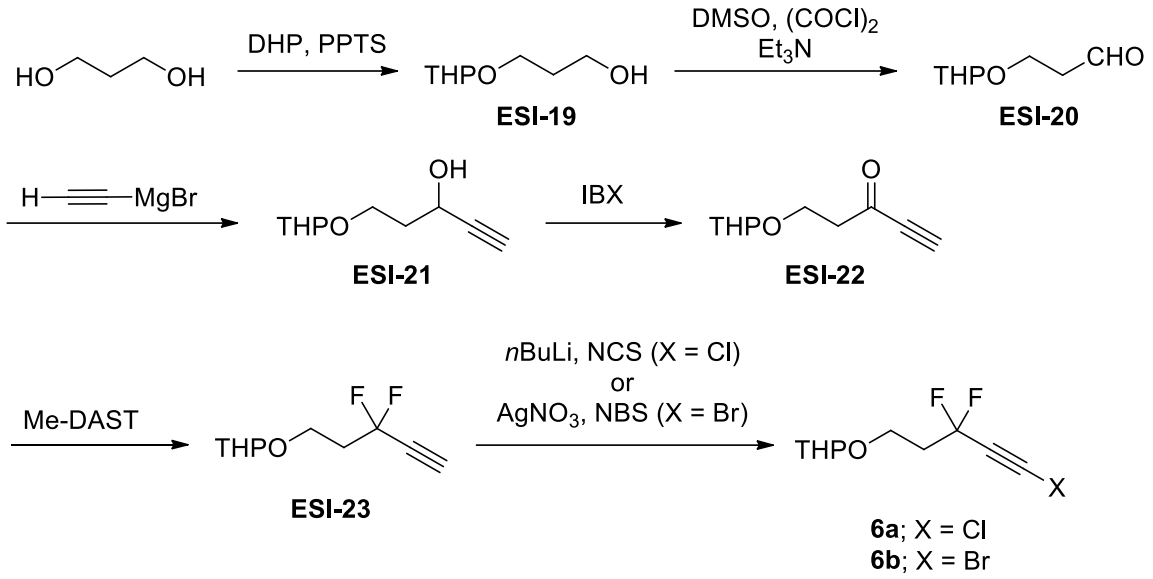
((2,2-Difluorobut-3-yn-1-yl)oxy)benzene (ESI-18). Preparing according to the general procedure C on 4.20 mmol of **ESI-17** using DeoxoFluor® as reagent instead for 18 hours, the desired compound (245 mg, 1.35 mmol, 32%) was isolated as a colourless oil after

[7] Liu, Y.; Park, S. K.; Chae, J. *Org. Biomol. Chem.* **2014**, *12*, 4747-4753.
[8] Hon, Y.-S.; Wong, Y.-C.; Chang, C.-P; Hsieh, C.-H. *Tetrahedron* **2017**, *63*, 11325-11340.

purification by flash column chromatography (10% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3024, 2970, 2932, 2361, 1736, 1435, 1366, 1019; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.33-7.30 (m, 2H), 7.03 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.97-6.95 (m, 2H), 4.30 (t, *J* = 11.2 Hz, 2H), 2.86 (t, *J* = 5.1 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 157.9, 129.8, 122.3, 115.2, 111.0 (t, J_{C-F} = 235.7 Hz), 77.2 (t, J_{C-F} = 7.0 Hz), 74.7 (t, J_{C-F} = 38.8 Hz), 70.3 (t, J_{C-F} = 32.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –93.4 (td, *J* = 11.4, 5.1 Hz, 2F); HRMS-ESI m/z calcd for $C_{10}H_9F_2O$ $[M+H]^+$ 183.0616, found 183.0609.

((4-Chloro-2,2-difluorobut-3-yn-1-yl)oxy)benzene (5a). Preparing according to the general procedure E on 0.518 mmol of **ESI-18**, the desired compound (74.1 mg, 0.342 mmol, 66%) was isolated as a colourless oil after purification by flash column chromatography (5% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3032, 2932, 2237, 1597, 1497, 1250, 1211, 1157, 1072, 748, 687; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.33-7.29 (m, 2H), 7.03 (m, 1H), 6.96-6.93 (m, 2H), 4.27 (t, *J* = 11.0 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 157.9, 129.8, 122.3, 115.2, 111.3 (t, J_{C-F} = 236.5 Hz), 70.3 (t, J_{C-F} = 33.1 Hz), 69.8 (t, J_{C-F} = 8.2 Hz), 61.2 (t, J_{C-F} = 40.7 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –91.4 (td, *J* = 11.2, 3.6 Hz, 2F); HRMS-ESI m/z calcd for $C_{10}H_7ClFO$ $[M-F]^+$ 197.0169, found: 197.0151.

((4-Bromo-2,2-difluorobut-3-yn-1-yl)oxy)benzene (5b). Preparing according to the general procedure F on 0.901 mmol of **ESI-18**, the desired compound (174 mg, 0.666 mmol, 74%) was isolated as a colourless oil after purification by flash column chromatography (10% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3063, 3040, 2932, 2878, 2222, 1597, 1497, 1288, 1250, 1196, 1157, 1072, 756; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.33-7.29 (m, 2H), 7.02 (tt, *J* = 7.5, 1.1 Hz, 1H), 6.96-6.93 (m, 2H), 4.27 (t, *J* = 11.1 Hz,2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 157.9, 129.8, 122.3, 115.2, 111.4 (t, J_{C-F} = 236.7 Hz), 72.0 (t, J_{C-F} = 40.3 Hz), 70.3 (t, J_{C-F} = 32.9 Hz), 53.3 (t, J_{C-F} = 9.1 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –91.6 (t, *J* = 11.2 Hz, 2F); HRMS-ESI m/z calcd for $C_{10}H_7BrFO$ $[M-F]^+$ 236.9667, found: 236.9650.



3-((Tetrahydro-*2H*-pyran-2-yl)oxy)propan-1-ol (ESI-19). To a stirred solution of propane-1-3-diol (3.3 mL, 45.0 mmol, 1.5 equiv.) in CH_2Cl_2 (113 mL, 0.4 M) at room temperature was added PPTS (113 mg, 0.450 mmol, 0.15 equiv.). DHP (2.7 mL, 30.0 mmol, 1 equiv.) in CH_2Cl_2 (10.0 mL) was slowly added for 1 hour and the resulting solution was stirred at room temperature for 18 hours. The mixture was washed with water and NaCl (1x), dried over Na_2SO_4 and concentrated *in vacuo*. The desired compound (3.48 g, 21.72 mmol, 72%) was isolated as a yellow oil after purification by flash column chromatography (5% MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 4.60 (dd, *J* = 4.5, 2.6 Hz, 1H), 3.94 (ddd, *J* = 9.8, 7.1, 5.2 Hz, 1H), 3.88 (m, 1H), 3.82-3.77 (m, 2H), 3.60 (ddd, *J* = 9.8, 6.1, 5.0 Hz, 1H), 3.53 (m, 1H), 2.48 (t, *J* = 5.6 Hz, 1H), 1.89-1.53 (m, 8H). Data are in accordance with the one described in the literature.[9]

3-((Tetrahydro-*2H*-pyran-2-yl)oxy)propanal (ESI-20). Preparing according to the general procedure G on a 21.53 mmol of **ESI-19**, the desired compound (2.95 g, 18.65 mmol, 86%) was isolated as a yellow oil after purification by flash column chromatography (15% acetone/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.82 (t, *J* = 1.9, 1H), 4.63 (t, *J* = 3.5 Hz, 1H), 4.10 (dt, *J* = 10.3, 6.0 Hz, 1H), 3.84 (ddd, *J* = 11.2, 7.9, 3.1 Hz, 1H), 3.76 (dt, *J* = 10.3, 6.0 Hz, 1H), 3.53 (m, 1H), 2.70 (td, *J* = 6.1, 1.9, 2H), 1.82-1.51 (m, 6H).

[9] Petroski, R. J. *Synth. Comm*. **2003**, *33*, 3251-3259.

The product was slightly contaminated with residual CH_2Cl_2. Data are in accordance with the one described in the literature.[9]

5-((Tetrahydro-*2H*-pyran-2-yl)oxy)pent-1-yn-3-ol (ESI-21). Preparing according to the general procedure A on a 18.65 mmol of **ESI-20**, the desired compound (3.07 g, 16.66 mmol, 89%) was isolated as a yellow oil after purification by flash column chromatography (25% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3290, 2941, 2116, 1354, 1200, 1119, 1020, 986, 866, 808; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.65-4.61 (m, 2H), 4.16-3.96 (m, 1Hz), 3.89 (dddd, *J* = 32.4, 11.3, 8.4, 2.9 Hz, 1H), 3.81-3.60 (m, 1H), 3.55-3.52 (m, 1H), 3.29-3.10 (m, 1H), 2.48 (m, 1H), 2.14-2.07 (m, 1H.), 2.01-1.92 (m, 1H), 1.82-1.70 (m, 2H), 1.61-1.53 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 99.2, 99.1, 84.5, 84.4, 73.11, 73.05, 64.9, 64.7, 61.54, 61.49, 61.15, 61.12, 36.71, 36.66, 30.64, 30.63, 25.5, 25.4, 19.6, 19.5; HRMS-ESI m/z calcd for $C_{10}H_{15}O_2$ $[(M+H)-(H_2O)]^+$ 167.1067, found 167.1056.

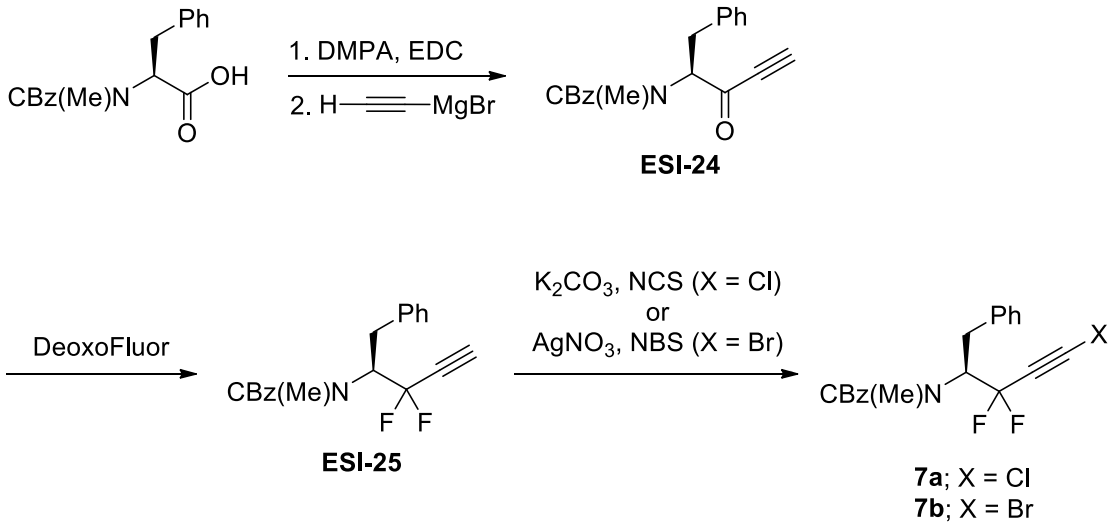
5-((Tetrahydro-*2H*-pyran-2-yl)oxy)pent-1-yn-3-one (ESI-22). Preparing according to the general procedure B on a 16.28 mmol of **ESI-21**, the desired compound (1.85 g, 10.15 mmol, 62%) was isolated as a yellow oil after purification by flash column chromatography (20% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3254, 2943, 2091,1684, 1387, 1202, 1119, 1028, 870, 814; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.63 (t, *J* = 3.5 Hz, 1H), 4.08 (dt, *J* = 10.3, 6.1 Hz, 1H), 3.85 (ddd, *J* = 11.6, 8.6, 3.1 Hz, 1H), 3.78 (dt, *J* = 10.3, 6.1 Hz, 1H), 3.54-3.49 (m, 1H), 3.25 (s, 1H), 2.87 (t, *J* = 6.1 Hz, 2H), 1.83-1.49 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 185.4, 99.1, 81.4, 78.9, 62.3, 62.1, 45.7, 30.6, 25.5, 19.4; HRMS-ESI m/z calcd for $C_{10}H_{15}O_3$ $[M+H]^+$ 183.1016, found 183.1008.

2-((3,3-Difluoropent-4-yn-1-yl)oxy)tetrahydro-*2H*-pyran (ESI-23). Preparing according to the general procedure C on a 10.15 mmol of **ESI-22**, the desired compound (780.8 mg, 3.82 mmol, 38%) was isolated as a yellow oil after purification by flash column chromatography (10% EtOAc/hexanes). IR (ATR, Diamond): ν (cm^{-1}) = 3244, 2945, 2359, 2131, 1356, 1182, 1124, 1024, 972, 870; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.63 (t, *J* = 3.5 Hz, 1H), 3.99 (ddd, *J* = 10.3, 7.4, 6.6 Hz, 1H), 3.87 (ddd, *J* = 11.4, 8.7, 6.6 Hz, 1H), 3.66 (ddd, *J* = 10.3, 7.3, 6.7 Hz, 1H), 3.53 (m, 1H), 2.80 (t, *J* = 5.1 Hz, 1H), 2.42 (ttd, *J* = 14.7, 7.2, 2.2 Hz, 2H), 1.86-1.52 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 113.1

(t, J_{C-F} = 234.4 Hz), 99.0, 76.5 (t, J_{C-F} = 40.3 Hz), 75.7 (t, J_{C-F} = 6.7 Hz), 62.3, 61.4 (t, J_{C-F} = 5 Hz), 39.5 (t, J_{C-F} = 25.7 Hz), 30.6, 25.5, 19.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –82.9 (td, *J* = 14.8, 5.0 Hz, 2F); HRMS-ESI m/z calcd for $C_{10}H_{18}F_2NO_2$ $[M+NH_4]^+$ 222.1300, found 222.1319.

2-((5-Chloro-3,3-difluoropent-4-yn-1-yl)oxy)tetrahydro-*2H*-pyran (6a). Preparing according to the general procedure D on a 0.979 mmol of **ESI-23**, the desired compound (115 mg, 0.482 mmol, 49%) was isolated as a pale-yellow oil after purification by flash column chromatography (10% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2943, 2237, 1356, 1202, 1124, 1078, 1028, 968, 868, 816; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.62 (t, *J* = 3.6 Hz, 1H), 3.96 (dt, *J* = 10.4, 6.8 Hz, 1H), 3.86 (ddd, *J* = 11.3, 8.6, 3.0 Hz, 1H), 3.62 (dt, *J* = 10.4, 6.8, 0.8 1H), 3.53 (m, 1H), 2.40 (ttd, *J* = 14.0, 6.8, 2.4 Hz, 2H), 1.86-1.51 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 113.4 (t, J_{C-F} = 234.1 Hz), 99.0, 68.2 (t, J_{C-F} = 8.3 Hz), 62.9 (t, J_{C-F} = 42.1 Hz), 62.2, 61.4 (t, J_{C-F} = 4.9 Hz), 39.7 (t, J_{C-F} = 26.0 Hz), 30.6, 25.5, 19.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –81.1 (t, *J* = 14.6 Hz, 2F); HRMS-ESI m/z calcd for $C_{10}H_{14}ClF_2O_2$ $[M+H]^+$ 239.0645, found 239.0657.

2-((5-Bromo-3,3-difluoropent-4-yn-1-yl)oxy)tetrahydro-*2H*-pyran (6b). Preparing according to the general procedure D on a 0.979 mmol of **ESI-23**, the desired compound (146 mg, 0.514 mmol, 52%) was isolated as a pale-yellow oil after purification by flash column chromatography (10% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2943, 2218, 1356, 1184, 1124, 1032, 970, 906, 870, 812; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.63 (t, *J* = 3.5 Hz, 1H), 3.97 (dt, *J* = 10.4, 6.8 Hz, 1H), 3.86 (ddd, *J* = 11.4, 8.7, 3.1 Hz, 1H), 3.62 (dt, *J* = 10.4, 6.8 Hz, 1H), 3.53 (m, 1H), 2.40 (ttd, *J* = 14.3, 6.8, 2.5 Hz, 2H), 1.86-1.52 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 113.5 (t, J_{C-F} = 234.4 Hz), 99.9, 73.6 (t, J_{C-F} = 42.0 Hz), 62.1, 61.4, (t, J_{C-F} = 4.9 Hz), 51.4 (t, J_{C-F} = 9.1 Hz), 39.6 (t, J_{C-F} = 26.1 Hz), 30.6, 25.6, 19.4.). ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –81.3 (t, *J* = 14.5 Hz, 2F); HRMS-ESI m/z calcd for $C_{10}H_{17}BrF_2NO_2$ $[M+NH_4]^+$ 300.0411, found 300.0385.



Benzyl (*S*)-methyl-(3-oxo-1-phenylpent-4-yn-2-yl)carbamate (ESI-24). Preparing according to the general procedure H on 4.24 mmol of *N*-((Benzyloxy)carbonyl)-*N*-methyl-(*S*)-phenylalanine,[10] the desired compound (1.20 g, 3.73 mmol, 88% overall yield) was isolated as a yellow oil after purification by flash column chromatography (30% EtOAc/hexanes). The product was isolated as a mixture (55:45) of rotamers. $[\alpha]_D$ –36.8 (*c* = 0.1, $CHCl_3$); IR (ATR, Diamond) ν (cm^{-1}) = 3271, 3032, 2970, 2947, 2091, 1736, 1690, 1450, 1366, 1211, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.36-7.08 (m, 20H), 5.13 (s, 2H), 5.11 (d, *J* = 6.7 Hz, 1H), 5.01 (d, *J* = 12.2 Hz, 1H), 4.75 (dd, *J* = 10.7, 4.8 Hz, 1H), 4.54 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.44 (dd, *J* = 14.6, 4.8 Hz, 1H), 3.37 (dd, *J* = 14.5, 4.4 Hz, 1H), 3.18 (s, 1H), 3.15 (s, 1H), 3.00 (dd, *J* = 14.6, 10.7 Hz, 1H), 2.91 (dd, *J* = 14.5, 10.6 Hz, 1H), 2.80 (s, 3H), 2.76 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 184.9, 184.7, 156.6, 155.8, 137.0, 136.7, 136.0, 129.0, 128.8, 128.7, 128.6, 128.5, 128.3, 128.3, 128.1, 127.9, 126.9, 126.8, 80.6, 80.3, 80.2, 80.0, 69.1, 68.7, 67.8, 67.5, 33.8, 33.7, 33.2, 33.1; HRMS-ESI m/z calcd for $C_{20}H_{20}NO_3$ $[M+H]^+$ 322.1438, found 322.1407.

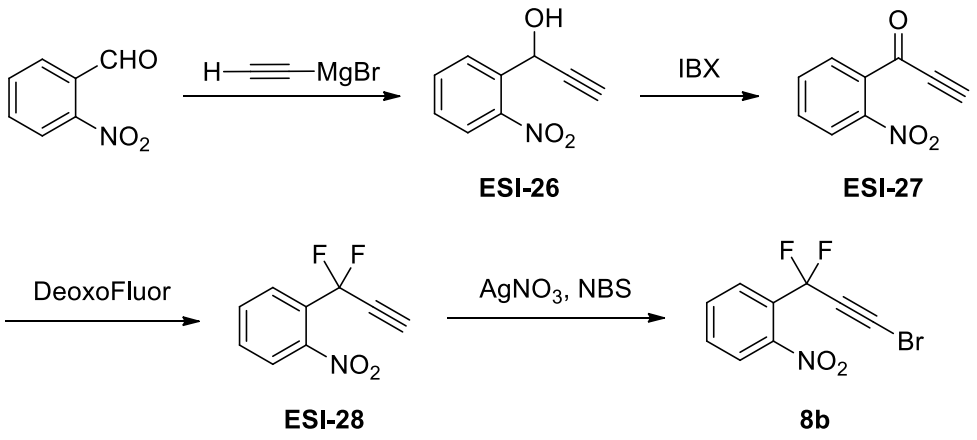
Benzyl (*S*)-(3,3-difluoro-1-phenylpent-4-yn-2-yl)(methyl)carbamate (ESI-25). Preparing according to the general procedure C using DeoxoFluor® as reagent instead on 1.34 mmol of **ESI-24**, the desired compound (74.1 mg, 0.228 mmol, 17%) was isolated as a yellow oil after purification by flash column chromatography (20% EtOAc/hexanes). The product was isolated as a mixture (52:48) of rotamers and contained trace amounts of

[10] Pfizebnamayer, A. J.; Ramanjulu, J. M.; Vera, M. D.; Ding, X.; Xiao, D.; Chen, W.-C.; Jouillé, M. M. *Tetrahedron* **1999**, *55*, 313-334.

inseparable and unknown impurities. $[\alpha]_D$ –5.8 (*c* = 0.12, $CHCl_3$); IR (ATR, Diamond) ν (cm^{-1}) = 3286, 3225, 3032, 2970, 2947, 2129, 1736, 1705, 1404, 1373, 1319, 1211, 1041, 694; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.31-7.11 (m, 20H), 5.23-5.14 (m, 1H), 5.05 (s, 2H), 5.01 (d, *J* = 12.4 Hz, 1H), 4.96 (d, *J* = 12.4 Hz, 1H), 4.95-4.88 (m, 1H), 3.23 (dd, *J* = 15.1, 3.9 Hz, 1H), 3.13 (dd, *J* = 14.8, 3.4 Hz, 1H), 3.00-2.96 (m, 2H), 2.94 (s, 3H), 2.87 (s, 3H), 2.73 (t, *J* = 5.2 Hz, 1H), 2.70 (t, *J* = 5.2 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 157.2, 156.3, 136.8, 136.4, 136.3, 136.1, 128.80, 128.78, 128.7, 128.51, 128.50, 128.1, 128.0, 127.9, 127.7, 127.0, 126.9, 113.7 (t, J_{C-F} = 240.6 Hz), 113.4 (t, J_{C-F} = 240.8 Hz), 77.4 (t, J_{C-F} = 6.7 Hz), 77.2 (t, J_{C-F} = 6.7 Hz), 75.1 (t, J_{C-F} = 39.4 Hz), 75.0 (t, J_{C-F} = 39.5 Hz), 67.5, 67.4, 61.0 (t, J_{C-F} = 27.5, 26.6 Hz), 60.1 (t, J_{C-F} = 26.8 Hz), 30.8, 30.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = major rotamer: –90.1 (d, *J* = 278.9 Hz, 1F), –92.1 (d, *J* = 279.6 Hz, 1F) and minor rotamer: –89.3 (m, 1F), –91.9 (m, 1F); HRMS-ESI m/z calcd for $C_{20}H_{20}F_2NO_2$ $[M+H]^+$ 344.1457, found 344.1428.

Benzyl (*S*)-(5-chloro-3,3-difluoro-1-phenylpent-4-yn-2-yl)(methyl)carbamate (7a). Preparing according to the general procedure E on 0.198 mmol of **ESI-25**, the desired compound (57.2 mg, 0.151 mmol, 76%) was isolated as a colourless oil after purification by flash column chromatography (15% EtOAc/hexanes). The product was isolated as a mixture (55:45) of two rotamers. $[\alpha]_D$ –10.4 (*c* = 0.63, $CHCl_3$); IR (ATR, Diamond) ν (cm^{-1}) = 3032, 2970, 2361, 2237, 1705, 1319, 1219, 1142, 1041, 748; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.33-7.12 (m, 20H), 5.18 (bs, 1H), 5.08 (d, *J* = 12.6 Hz, 1H), 5.06 (d, *J* = 12.8 Hz, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 4.96 (d, *J* = 12.4 Hz, 1H), 4.95-4.87 (m, 1H), 3.22 (dd, *J* = 15.1, 4.1 Hz, 1H), 3.12 (dd, *J* = 14.8, 3.7 Hz, 1H), 3.00-2.96 (m, 2H), 2.93 (s, 3H), 2.86 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 157.1, 156.2, 136.7, 136.4, 136.1, 136.0, 128.74, 128.72, 128.68, 128.53, 128.50, 128.0, 127.9, 127.7, 127.5, 127.0, 126.9, 114.0 (t, J_{C-F} = 241.5 Hz), 113.8 (t, J_{C-F} = 241.8 Hz), 69.9 (t, J_{C-F} = 8.0 Hz), 69.6 (t, J_{C-F} = 8.1 Hz), 67.6, 67.4, 61.5 (t, J_{C-F} = 40.8 Hz), 61.4 (t, J_{C-F} = 41.0 Hz), 61.2 (dd, J_{C-F} = 28.6, 25.6 Hz), 60.2, 30.9, 30.8, 29.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = major rotamer: –88.5 (d, *J* = 274.6 Hz, 1F), –90.3 (d, *J* = 278.6 Hz, 1F) and minor rotamer: –87.6 (dd, *J* = 276.2, 9.7 Hz, 1F), –90.4 (dd, *J* = 276.3, 14.8 Hz, 1F); HRMS-ESI m/z calcd for $C_{20}H_{19}ClF_2NO_2$ $[M+H]^+$ 378.1067, found 378.1057.

Benzyl (*S*)-(5-bromo-3,3-difluoro-1-phenylpent-4-yn-2-yl)(methyl)carbamate (7b). Preparing according to the general procedure F on 0.108 mmol of **ESI-25**, the desired compound (34.2 mg, 0.081 mmol, 75%) was isolated as a colourless oil after purification by flash column chromatography (15% EtOAc/hexanes). The product was isolated as a mixture (55:45) of two rotamers. $[\alpha]_D$ –8.0 (*c* = 0.1, $CHCl_3$); IR (ATR, Diamond) ν (cm^{-1}) = 3024, 2970, 2947, 1736, 1450, 1366, 2111; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.32-7.12 (m, 20H), 5.21-5.18 (bs, 1H), 5.08 (d, *J* = 12.6 Hz, 1H), 5.05 (d, *J* = 12.6 Hz, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 4.95 (d, *J* = 12.5 Hz, 1H), 4.96-4.87 (m, 1H), 3.22 (dd, *J* = 15.1, 4.1 Hz, 1H), 3.12 (dd, *J* = 14.8, 3.6 Hz, 1H), 2.99-2.95 (m, 2H), 2.93 (s, 3H), 2.86 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 157.2, 156.3, 136.7, 136.4, 136.2, 136.0, 128.79, 128.77, 128.74, 128.73, 128.59, 128.57, 128.04, 127.98, 127.7, 127.6, 127.1, 127.0, 114.1 (t, J_{C-F} = 241.6 Hz), 113.8 (t, J_{C-F} = 242.0 Hz), 72.4 (t, J_{C-F} = 40.8 Hz), 72.2 (t, J_{C-F} = 40.8 Hz), 67.6, 67.5, 61.1 (dd, J_{C-F} = 28.5, 26.6 Hz), 60.1, 53.4 (t, J_{C-F} = 8.8 Hz), 53.2 (t, J_{C-F} = 8.9 Hz), 30.9, 29.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = major rotamer: –89.0 (d, *J* = 276.4 Hz, 1F), –90.4 (d, *J* = 273.8 Hz, 1F) and minor rotamer: –87.9 (dd, *J* = 276.7, 9.8 Hz, 1F), –90.7 (dd, *J* = 276.5, 14.8 Hz, 1F); HRMS-ESI m/z calcd for $C_{20}H_{19}BrF_2NO_2$ $[M+H]^+$ 422.0562, found 422.0532.



1-(2-Nitrophenyl)prop2-yn-1-ol (ESI-26). Preparing according to the general procedure A on a 10.00 mmol of 2-nitrobenzaldehyde, the desired compound (1.72 g, 9.71 mmol, 97%) was isolated as a pale-brown solid after purification by flash column chromatography (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 8.00 (d, *J* = 8.3 Hz, 1H),

7.98 (d, *J* = 7.4 Hz, 1H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 6.03 (d, *J* = 3.7 Hz, 1H), 3.21 (d, *J* = 5.5 Hz, 1H), 2.65 (d, *J* = 2.3 Hz, 1H). Data are in accordance with the one described in the literature.[11]

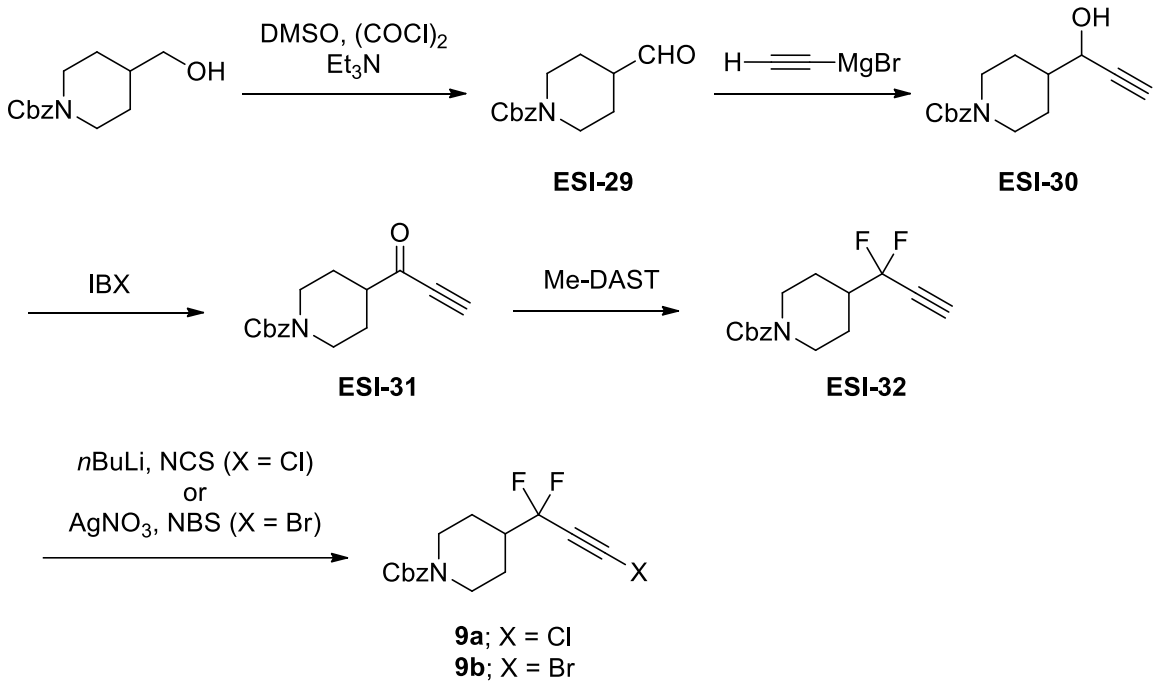
1-(2-Nitrophenyl)prop2-yn-1-one (ESI-27). Preparing according to the general procedure B on a 9.03 mmol of **ESI-26**, the desired compound (1.45 g, 8.28 mmol, 92%) was isolated as a pale-brown solid after purification by flash column chromatography (10% EtOAc/hexanes). m. p. 46.6-47.8 °C; IR (ATR, Diamond) ν (cm^{-1}) = 3269, 3103, 2832, 2096, 1657, 1526, 1348, 1242, 1229, 1005; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.95-7.93 (m, 1H), 7.84-7.82 (m, 1H), 7.74 (td, *J* = 7.5,1.4 Hz, 1H); 7.70 (td, *J* = 7.7, 1.7 Hz, 1H), 3.47 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 175.4, 133.3, 133.0, 130.3, 124.4, 82.3, 80.1; HRMS-ESI m/z calcd for $C_9H_6NO_3$ $[M+H]^+$ 176.0342, found 176.0335.

1-(1,1-Difluoroprop-2-yn-1-yl)-2-nitrobenzene (ESI-28). Preparing according to the general procedure C using DeoxoFluor® as reagent instead on a 8.28 mmol of **ESI-27**, the desired compound (690 mg, 3.50 mmol, 42%) was isolated as a yellow oil after purification by flash column chromatography (10% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3290, 2926, 2135, 1533, 1348, 1242, 1097, 999, 854, 747; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.87-7.84 (m, 2H), 7.73-7.69 (m, 1H), 7.68-7.65 (m, 1H), 3.02 (t, *J* = 5.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 132.7, 132.1, 127.6 (t, J_{C-F} = 7.6 Hz), 125.1, 109.1 (t, J_{C-F} = 235.8 Hz), 77.8 (t, J_{C-F} = 6.2 Hz), 75.6 (t, J_{C-F} = 41.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –78.2 (d, *J* = 5.4 Hz, 2F); HRMS-ESI m/z calcd for $C_9H_6F_2NO_2$ $[M+H]^+$ 198.0361, found 198.0360.

1-(3-Bromo-1,1-difluoroprop-2-yn-1-yl)-2-nitrobenzene (8b). Preparing according to the general procedure F on a 0.507 mmol of **ESI-28**, the desired compound (103 mg, 0.371 mmol, 73%) was isolated as a pale-yellow oil after purification by flash column chromatography (10% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2924, 2220, 1541, 1360, 1246, 1167, 1061, 1034, 1009; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.86 (d, *J* = 7.8 Hz, 1H), 7.82 (m, 1H), 7.72-7.64 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 132.7, 132.0, 127.5 (t, J_{C-F} = 7.4 Hz), 125.1, 109.4 (t, J_{C-F} = 237.2 Hz), 72.9 (t, J_{C-F} = 42.5

[11] Salgado-Zamora, H.; Hernandez, J.; Campos, E.; Jimenez, R. *J. Prakt. Chem*. **1999**, *5*, 461-465.

Hz), 54.4 (t, J_{C-F} = 8.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –76.9 (s, 2F); HRMS-ESI m/z calcd for $C_9H_5BrF_2NO_2$ $[M+H]^+$ 275.9466, found 275.9459.



Benzyl 4-formylpiperidine-1-carboxylate (ESI-29). Preparing according to the general procedure G on a 16.04 mmol of benzyl 4-(hydroxymethyl)piperidine-1-carboxylate,[12] the desired compound (2.38 g, 9.62 mmol, 60%) was isolated as a colourless oil after purification by flash column chromatography (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 9.66 (d, J = 0.8 Hz, 1H), 7.38-7.31 (m, 5H), 5.13 (s, 2H), 4.05 (bs, 2H), 3.05-3.00 (m, 2H), 2.44 (ttd, J = 10.5, 4.0, 0.8 Hz, 1H), 1.92 (bs, 2H), 1.62-1.55 (m, 2H). Data are in accordance with the one described in the literature.[12]

Benzyl 4-(1-hydroxypro-2-yn-1-yl)piperidine-1-carboxylate (ESI-30). Preparing according to the general procedure A on a 9.50 mmol of **ESI-29**, the desired compound (2.55 g, 9.33 mmol, 98%) was isolated as a colourless oil after purification by flash column chromatography (40% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3410, 2860, 2247,

[12] Boyer, N.; Gloanec, P.; De Nanteuil, G.; Jubault, P.; Quirion, J.-C. *Eur. J. Org. Chem*. **2008**, 4277-4295.

1674, 1433, 1277, 1223, 1128, 1082, 908; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.38-7.30 (m, 5H), 5.13 (s, 2H), 4.27 (bs, 2H), 2.77 (bs, 2H), 2.49 (d, *J* = 2.1 Hz, 1H), 1.93 (d, *J* = 5.3 Hz, 1H), 1.86-1.84 (m, 2H), 1.75 (m, 1H), 1.37 (bs, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 155.4, 137.0, 128.6, 128.1, 128.0, 83.2, 74.6, 67.2, 66.1, 43.91, 43.89, 42.4; HRMS-ESI m/z calcd for $C_{16}H_{18}NO_2$ [(M+H)-(H_2O)] 256.1332, found 256.1328.

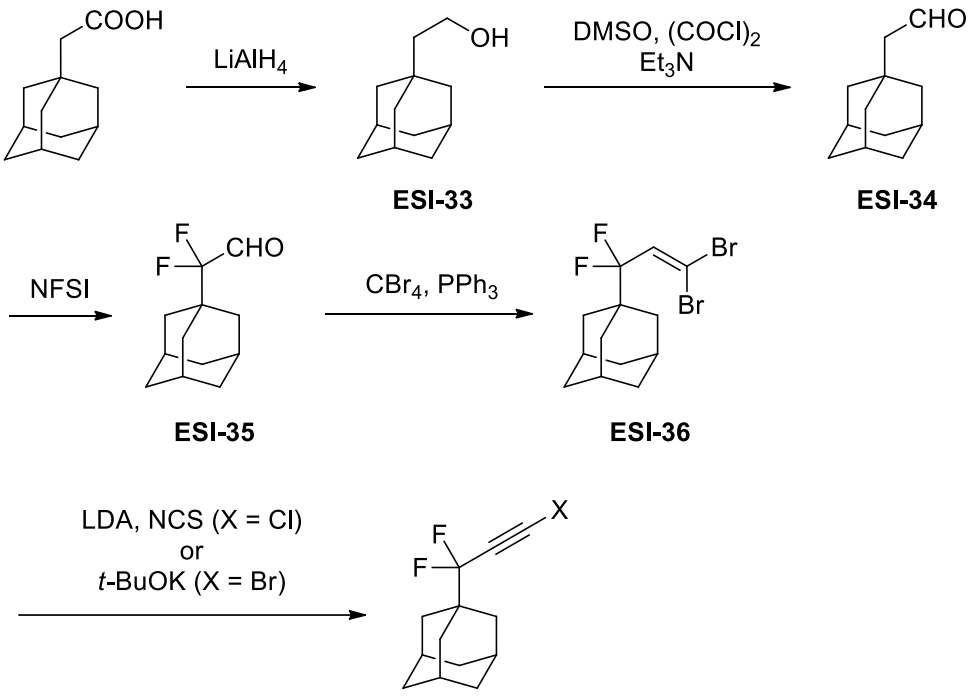
Benzyl 4-propioloylpiperidine-1-carboxylate (ESI-31). Preparing according to the general procedure B on a 9.15 mmol of **ESI-30**, the desired compound (1.19 g, 4.39 mmol, 48%) was isolated as a colourless oil after purification by flash column chromatography (30% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3261, 2949, 2858, 2539, 2089, 1674, 1429, 1225, 1136, 1014; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.38-7.30 (m, 5H), 5.13 (s, 2H), 4.13 (bs, 2H), 3.29 (s, 1H), 2.98-2.93 (m, 2H), 2.59 (tt, *J* = 10.9, 3.9 Hz, 1H), 1.99 (bs, 2H), 1.69-1.62 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 188.6, 155.3, 136.8, 128.7, 128.2, 128.0, 80.4, 80.3, 67.3, 49.9, 43.2, 27.1; HRMS-ESI m/z calcd for $C_{16}H_{18}NO_3$ $[M+H]^+$ 272.1281, found 272.1285.

Benzyl 4-(1,1-difluoroprop-2-yn-1-yl)piperidine-1-carboxylate (ESI-32). Preparing according to the general procedure C on a 3.69 mmol of **ESI-31**, the desired compound (525 mg, 1.79 mmol, 49%) was isolated as a white solid after purification by flash column chromatography (20% EtOAc/hexanes). The product contained trace amounts of inseparable and unknown impurities. m. p. 59.3-61.0 °C; IR (ATR, Diamond) ν (cm^{-1}) = 3242, 2971, 2109, 1654, 1490, 1375, 1338, 1262, 974, 835; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.39-7.30 (m, 5H), 5.14 (s, 2H), 4.32 (bs, 2H), 2.79 (t, *J* = 5.1 Hz, 1H), 2.77 (bs, 2H), 2.15-2.06 (m, 1H), 1.87 (bs, 2H), 1.50 (bs, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 155.3, 136.8, 128.7, 128.2, 128.1, 116.3 (t, J_{C-F} = 235.5 Hz), 76.6 (t, J_{C-F} = 6.9 Hz), 75.3 (t, J_{C-F} = 40.8 Hz), 67.4, 44.4 (t, J_{C-F} = 25.0 Hz), 43.2, 25.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –91.1 (ddd, *J* = 26.2, 10.4, 4.3 Hz, 2F); HRMS-ESI m/z calcd for $C_{16}H_{18}F_2NO_2$ $[M+H]^+$ 293.1305, found 294,1298.

Benzyl 4-(3-chloro-1,1-difluoropro-2-yn-1-yl)piperidine-1-carboxylate (9a). Preparing according to the general procedure D on a 0.852 mmol of **ESI-32**, the desired compound (89.4 mg, 0.273 mmol, 32%) was isolated as a colourless oil after purification by flash column chromatography (25% EtOAc/hexanes). The product contained trace amounts of

inseparable and unknown impurities. IR (ATR, Diamond) ν (cm^{-1}) = 2957, 2864, 2235, 1701, 1429, 1315, 1219, 1132, 1034, 908; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.45-7.32 (m, 5H), 5.14 (s, 2H), 4.32 (bs, 2H), 2.76 (bs, 2H), 2.09 (m, 1H), 1.86 (bs, 2H), 1.48 (bs, 2H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 155.3, 136.8, 128.7, 128.2, 128.1, 115.7 (t, J_{C-F} = 236.5 Hz), 68.9 (t, J_{C-F} = 8.1 Hz), 67.4, 61.7 (t, J_{C-F} = 42.6 Hz), 44.7 (t, J_{C-F} = 25.3 Hz), 43.2, 25.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –89.2 (dd, J = 39.9, 11.3 Hz, 2F); HRMS-ESI m/z calcd for $C_{16}H_{17}ClF_2NO_2$ $[M+H]^+$ 328.0916, found 328.0902.

Benzyl 4-(3-bromo-1,1-difluoroprop-2-yn-1-yl)piperidine-1-carboxylate (9b). Preparing according to the general procedure D on a 0.852 mmol of **ESI-32**, the desired compound (216 mg, 0.580 mmol, 68%) was isolated as a colourless oil after purification by flash column chromatography (25% EtOAc/hexanes). The product was slightly contaminated with residual EtOAc. IR (ATR, Diamond) ν (cm^{-1}) = 2957, 2864, 2216, 1690, 1429, 1313, 1217, 1132, 1034, 766; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.39-7.30 (m, 5H), 5.14 (s, 2H), 4.32 (bs, 2H), 2.76 (bs, 2H), 2.09 (m, 1H), 1.86 (bs, 2H), 1.47 (bs, 2H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 155.3, 136.8, 128.7, 128.2, 128.1, 115.7 (t, J_{C-F} = 236.1 Hz), 72.5 (t, J_{C-F} = 42.3 Hz), 67.4, 52.1 (t, J_{C-F} = 8.9 Hz), 44.7 (t, J_{C-F} = 25.2 Hz), 43.2, 25.2; ^{19}F NMR (470 MHz, CDCl3) δ (ppm) = –89.5 (dd, J = 41.5, 11.3 Hz, 2F); HRMS-ESI m/z calcd for $C_{16}H_{17}BrF_2NO_2$ $[M+H]^+$ 372.0410, found 372.0391.



10a; X = Cl
10b; X = Br

2-(1-Adamantyl)-1-ethanol (ESI-33). To a solution of suspension $LiAlH_4$ (908 mg, 23.9 mmol, 1.5 equiv.) at 0 °C in THF (43.1 mL, 0.37 M) was slowly added 1-adamantylacetic acid (3.10 g, 15.96 mmol, 1 equiv.) in THF (25.7 mL, 0.62 M). The mixture was stirred at room temperature for 18 hours. An aq. HCl solution 1 N were carefully added at 0 °C and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The desired compound (2.88 g, 15.96 mmol, 100%) was obtained as a white solid which was used without further purification. m. p. 73.1-74.0 °C; IR (ATR, Diamond) ν (cm^{-1}) = 3298, 2899, 2845, 2361, 1448, 1344, 1097, 1055, 1045, 733; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 3.72 (t, *J* = 7.2 Hz, 2H), 1.94 (bs, 3H), 1.72-1.62 (m, 6H), 1.53-1.52 (m, 6H), 1.39 (t, *J* = 7.1 Hz, 2H), 1.08 (bs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 59.0, 47.4, 42.9, 37.2, 32.0, 28.8; HRMS-ESI m/z calcd for $C_{12}H_{24}NO$ $[M+NH_4]^+$ 198.1852, found 198.1849.

2-(Adamant-1-yl)acetaldehyde (ESI-34). Preparing according to the general procedure G on a 3.57 mmol of **ESI-33**, the desired compound (558 mg, 3.13 mmol, 88%) was isolated as a colourless oil after purification by flash column chromatography (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 9.88 (t, *J* = 3.3 Hz, 1H), 2.13 (d,

J = 3.3 Hz, 2H), 1.99 (bs, 3H), 1.74-1.64 (m, 12H). Data are in accordance with the one described in the literature.[13]

2-(Adamatan-1-yl)-2,2-difluoracetaldehyde (ESI-35). A solution of **ESI-34** (2.59 g, 14.53 mmol, 1 equiv.) and (±)-proline (335 mg, 2.91 mmol, 0.2 equiv.) in dry THF (72.7 mL, 0.2 M) was stirred 15 minutes at room temperature. To this solution was added *N*-fluorobenzenesulfonimide (NFSI, 18.3 g, 58.1 mmol, 4 equiv.) and the mixture was stirred at room temperature for 18 hours. An aqueous solution of HCl 1 N was added and the product was extracted with Et_2O (3x). The combined organic layers were washed with water and NaCl (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The desired compound (2.21 g, 10.30 mmol, 71%) was isolated as a clear yellow oil after purification by flash column chromatography (20% EtOAc/hexanes). The product was slightly contaminated with residual CH_2Cl_2. IR (ATR, Diamond) ν (cm^{-1}) = 2908, 2854, 1736, 1450, 1366, 1211, 1080, 1011; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 9.62 (t, *J* = 4.1 Hz, 1H), 2.05 (bs, 3H), 1.77-1.67 (m, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 192.7 (t, J_{C-F} = 37.5 Hz), 117.8 (t, J_{C-F} = 37.5 Hz), 39.1 (t, J_{C-F} = 21.6 Hz), 36.5, 34.6 (t, J_{C-F} = 3.5 Hz), 27.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –126.1 (d, *J* = 4.3 Hz, 2F); HRMS-ESI m/z calcd for $C_{12}H_{20}F_2NO$ $[M+NH_4]^+$ 232.1507, found: 232.1508.

(3r,5r,7r)-1-(3,3-Dibromo-1,1-difluoroallyl)adamantane (ESI-36). To a solution of Ph_3P (669 mg, 2.55 mmol, 2.1 equiv.) in CH_2Cl_2 (0.93 mL, 1.3 M) at 0 °C was added CBr_4 (421 mg, 1.27 mmol, 1.05 equiv.). The orange solution was stirred at 0 °C for 20 minutes, then a solution of **ESI-35** (260 mg, 1.21 mmol, 1 equiv.) in CH_2Cl_2 (1.0 mL, 1.2 M) was added. The solution was stirred at 0 °C for 2 hours. The mixture was concentrated *in vacuo*. The desired compound (300 mg, 0.811 mmol, 67%) was isolated as a white solid after purification by flash column chromatography (hexanes). m. p. 93 °C; IR (ATR, Diamond) ν (cm^{-1}) = 3016, 2908, 2854, 1736, 1605, 1450, 1366, 1211, 1165, 1057, 1018; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.70 (t, *J* = 12.7 Hz, 1H), 2.05 (bs, 3H), 1.74-1.66 (m, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 130.6 (t, J_{C-F} = 29.3 Hz), 122.5 (t, J_{C-F} = 247.5 Hz), 95.1 (t, J_{C-F} = 7.3 Hz), 41.1 (t, J_{C-F} = 23.2 Hz), 36.6, 35.0 (t, J_{C-F} = 3.1 Hz), 27.7; ^{19}F

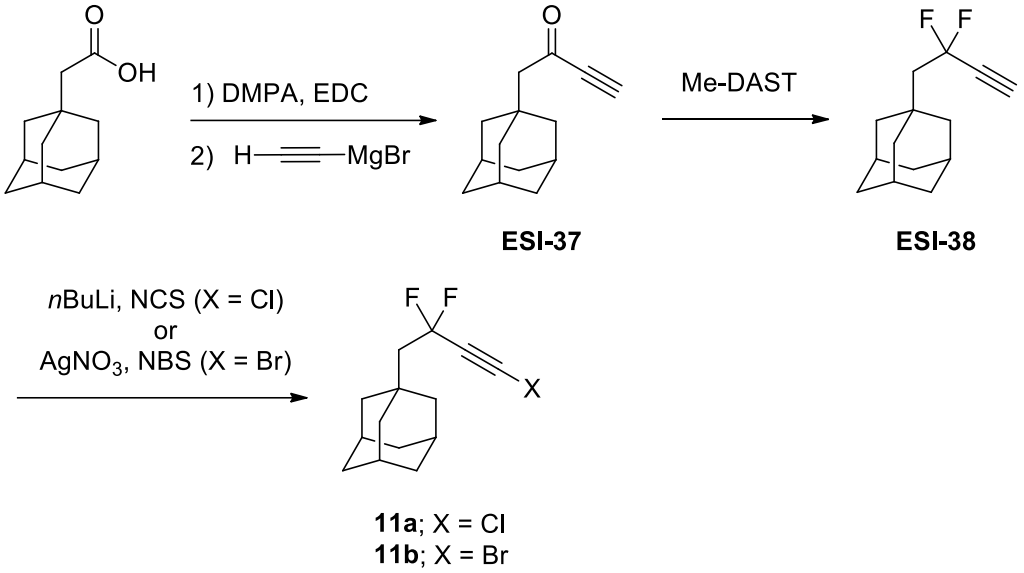
[13] Shitaba, M.; Nagata, R.; Saito, S.; Naka, H. *Chemistry Lett.* **2017**, *46*, 580-582.

NMR (470 MHz, $CDCl_3$) δ (ppm) = –110.9 (d, *J* = 12.9 Hz, 2F); HRMS-ESI m/z calcd for $C_{13}H_{20}Br_2F_2N$ $[M+NH_4]^+$ 385.9925, found 385.9928.

1-(3-Chloro-1,1-difluoroprop-2-yn-1-yl)adamantane (10a). To a solution of *i*Pr_2NH (141 mg, 1.39 mmol, 3 equiv) in dry THF (0.15 M) at –78 C was added dropwise a *n*BuLi solution (2.5 M in hexane, 558 µL, 1.39 mmol, 3 equiv). The solution was stirred for 30 minutes then a solution of **ESI-36** (172 mg, 0.46 mmol, 1 equiv) in dry THF (0.12 M) was added dropwise. The resulting mixture was stirred for 30 minutes at –78 °C. *N*-chlorosuccinimide (186 mg, 1.39 mmol, 3 equiv) was added and the mixture was stirred at –78 °C for an additional 2 hours, at which point, a 1 M aqueous HCl solution was added. The mixture was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using hexanes to afford **10a** as a colourless oil (29.7 mg, 0.121 mmol, 26%). IR (ATR, Diamond) ν (cm^{-1}) = 2908, 2854, 2237, 1450, 1273, 1219, 1165, 1057, 1026, 903; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 2.05 (bs, 3H), 1.74-1.66 (m, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 118.1 (t, J_{C-F} = 237.2 Hz), 67.7 (t, J_{C-F} = 7.9 Hz), 62.0 (t, J_{C-F} = 42.9 Hz), 40.8 (t, J_{C-F} = 23.3 Hz), 36.7, 35.1 (t, J_{C-F} = 2.4 Hz), 27.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –98.9 (s, 2F); HRMS-ESI m/z calcd for $C_{13}H_{15}ClF$ $[M-F]^+$ 225.0852, found: 225.0862.

1-(3-Bromo-1,1-difluoroprop-2-yn-1-yl)adamantane (10b). To a mixture of **ESI-36** (104 mg, 0.281 mmol, 1 equiv.) in THF (1.0 mL, 0.27 M) at –20 °C was added *t*BuOK (31.5 mg, 0.281 mmol, 1 equiv.) and the mixture was warmed to room temperature for 1 hour. Water was added, and the solution was extracted with Et_2O (3x). The combined organic layers were washed with water and NaCl (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The desired compound (78.0 mg, 0.270 mmol, 96%) was isolated as a colourless oil after purification by flash column chromatography using (hexanes. IR (ATR, Diamond) ν (cm^{-1}) = 3009, 2970, 1908, 2854, 1736, 1450, 1366, 1211, 1027; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 2.05 (bs, 3H), 1.74-1.66 (m, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 118.2 (t, J_{C-F} = 238.3, 237.4 Hz), 72.8 (t, J_{C-F} = 42.8 Hz), 50.6 (t, J_{C-F} = 9.0 Hz), 40.7 (t, J_{C-F} = 23.1 Hz), 36.6, 35.1 (t, J_{C-F} = 2.5 Hz), 27.7; ^{19}F NMR (470

MHz, $CDCl_3$) δ (ppm) = –99.2 (s, 2F); HRMS-ESI m/z calcd for $C_{13}H_{15}BrF$ $[M-F]^+$ 269.0343, found: 269.0354.



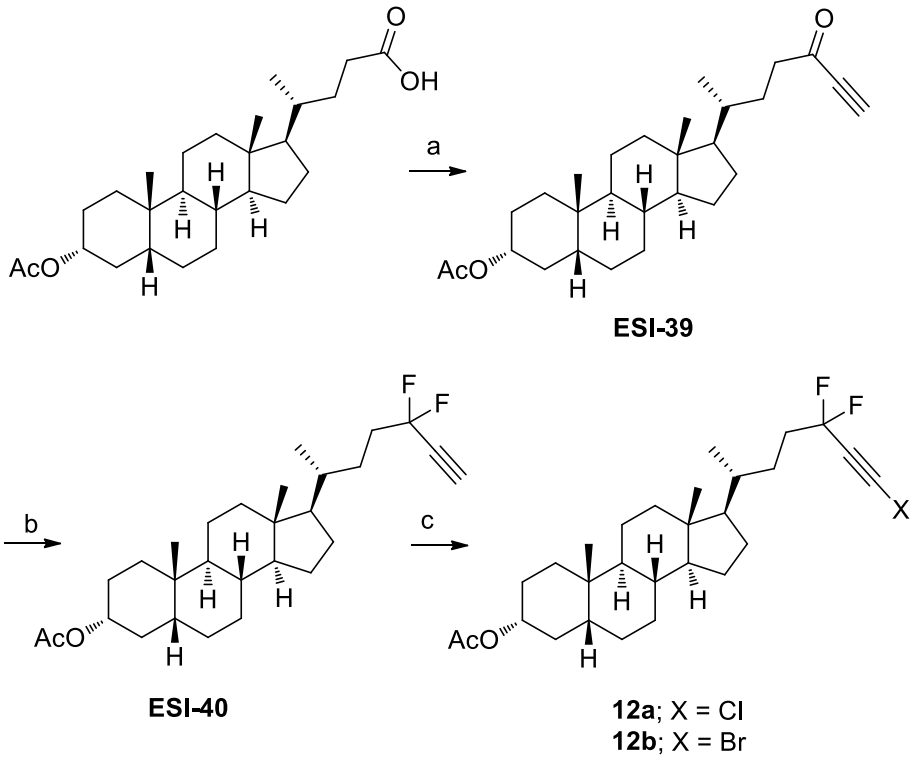
1-(Adamantan-1-yl)but-3-yn-2-one (ESI-37). Preparing according to the general procedure H on a 10.29 mmol of 1-adamantanecarboxylic acid, the desired compound (1.23 g, 6.08 mmol, 59% overall yield) was isolated as a white solid after purification by flash column chromatography (2% EtOAc/hexanes). m. p. 48.4-48.8 °C; IR (ATR, Diamond) ν (cm^{-1}) = 3211, 2976, 2802, 2069, 1715, 1467, 1204, 1157, 1150, 893; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) = 3.23 (s, 1H), 2.39 (s, 2H), 1.98 (bs, 3H), 1.72-1.63 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 187.1, 83.6, 78.2, 59.1, 42.6, 36.8, 34.5, 28.7; HRMS-ESI m/z calcd for $C_{14}H_{19}O$ $[M+H]^+$ 203.1430, found 203.1421.

1-(2,2-Difluorobut-3-yn-1-yl)adamantane (ESI-38). Preparing according to the general procedure C on a 5.68 mmol of **ESI-37**, the desired compound (259 mg, 1.15 mmol, 20%) was isolated as a colourless oil after purification by flash column chromatography (hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3306, 2901, 2851, 2135, 1452, 1254, 1142, 1115, 1051, 965; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) = 2.78 (t, J = 5.3 Hz, 1H), 1.96 (bs, 3H), 1.90 (t, J = 17.4 Hz, 2H), 1.72-1.64 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 114.0 (t, J_{C-F} = 234.9 Hz), 78.2 (t, J_{C-F} = 40.3 Hz), 75.2 (t, J_{C-F} = 6.7 Hz), 52.0 (t, J_{C-F} = 23.9 Hz), 42.8 (t, J_{C-F} = 0.9 Hz), 36.9, 32.3 (t, J_{C-F} = 2.0 Hz), 28.7; ^{19}F NMR (470 MHz,

$CDCl_3$) δ (ppm) = –76.9 (td, *J* = 18.1, 6.4 Hz, 2F); HRMS-ESI m/z calcd for $C_{14}H_{18}F$ [M-F]$^+$ 215.1387, found 215.1380.

1-(4-Chloro-2,2-difluorobut-3-yn-1-yl)adamantane (11a). Preparing according to the general procedure D on a 0.557 mmol of **ESI-38**, the desired compound (76.4 mg, 0.295 mmol, 53%) was isolated as a colourless oil after purification by flash column chromatography (hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2901, 2851, 2235, 1452, 1267, 1176, 1117, 1020, 974, 854; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.97 (bs, 3H), 1.88 (t, *J* = 17.1 Hz, 2H), 1.72-1.63 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 114.3 (t, J_{C-F} = 235.3 Hz), 67.7 (t, J_{C-F} = 8.1 Hz), 64.4 (t, J_{C-F} = 41.7 Hz), 52.2 (t, J_{C-F} = 24.1 Hz), 42.8, 36.9, 32.3 (t, J_{C-F} = 1.9 Hz), 28.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –75.3 (t, *J* = 16.9 Hz, 2F); HRMS-ESI m/z calcd for $C_{14}H_{17}ClF$ [M-F]$^+$ 239.0997, found 239.1009.

1-(4-Bromo-2,2-difluorobut-3-yn-1-yl)adamantane (11b). Preparing according to the general procedure F on a 0.557 mmol of **ESI-38**, the desired compound (140 mg, 0.462 mmol, 83%) was isolated as a pale-yellow oil after purification by flash column chromatography (hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2901, 2849, 2218, 1452, 1259, 1175, 1113, 1020, 974, 837; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.96 (s, 3H), 1.88 (t, *J* = 17.2 Hz, 2H), 1.72-1.64 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 114.5 (t, J_{C-F} = 236.1 Hz), 75.2 (t, J_{C-F} = 41.5 Hz), 52.1 (t, J_{C-F} = 24.1 Hz), 51.0 (t, J_{C-F} = 8.8 Hz), 42.8, 36.9, 32.87 (t, J_{C-F} = 2.0 Hz), 28.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –75.5 (t, *J* = 17.0 Hz, 2F); HRMS-ESI m/z calcd for $C_{14}H_{17}BrF$ [M-F]$^+$ 283.0492, found 283.0485.



a) 1. DMPA, EDC
2. Ethynylmagnesium bromide
b) DeoxoFluor;
c) K_2CO_3, NCS (X = Cl)
or $AgNO_3$, NBS (X = Br)

(3R,5R,8R,9S,10S,13R,14S,17R)-10,13-Dimethyl-17-((*R*)-5-oxohept-6-yn-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (ESI-39). Preparing according to the general procedure H on a 0.406 mmol of lithocholic acid acetate ((*R*)-4-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-Acetoxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoic acid),[14] the desired compound (163 mg, 0.382 mmol, 94% overall yield) was isolated as a white solid after purification by flash column chromatography (10% EtOAc/hexanes). The product was slightly contaminated with residual CH_2Cl_2. m. p. 161.0 °C; $[\alpha]_D$ +88.6 (*c* = 0.12, $CHCl_3$); IR (ATR, Diamond) ν (cm^{-1}) = 3294, 3248, 2939, 2870, 2091, 1736, 1682, 1450, 1381, 1242, 1026, 756; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.72 (tt, *J* = 11.4, 4.8 Hz, 1H), 3.21 (s, 1H), 2.62 (ddd, *J* = 15.9, 10.0, 5.0 Hz, 1H), 2.51 (ddd, *J* = 16.1, 9.4, 6.3 Hz, 1H), 2.03 (s, 3H), 1.96 (dt, *J* = 12.4, 3.1 Hz, 1H), 1.93-1.79 (m, 5H), 1.70-1.67 (m, 1H), 1.60-1.52 (m, 2H), 1.47-1.34 (m,

[14] Morita, Y.; Yamamoto,T.; Nagai, H.; Sgimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2015**, *137*, 7075-7078.

8H), 1.32-1.20 (m, 3H), 1.18-1.00 (m, 6H), 0.93 (s, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.64 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 188.2, 170.8, 81.7, 78.4, 74.5, 56.6, 56.1, 42.9, 42.7, 42.0, 40.5, 40.3, 35.9, 35.3, 35.2, 34.7, 32.4, 29.9, 28.3, 27.2, 26.8, 26.5, 24.3, 23.5, 21.7, 21.0, 18.5, 12.2; HRMS-ESI m/z calcd for $C_{28}H_{46}NO_3$ $[M+NH_4]^+$ 444.3472, found 444.3463.

(3R,5R,8R,9S,10S,13R,14S,17R)-17-((*R*)-5,5-Difluorohept-6-yn-2-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (ESI-40). Preparing according to the general procedure C using DeoxoFluor® as the reagent instead for 18 hours on a 0.337 mmol of **ESI-39**, the desired compound (75.6 mg, 0.169 mmol, 50%) was isolated as a colourless oil after purification by flash column chromatography (5% EtOAc/hexanes). $[\alpha]_D$ +26.2 (*c* = 0.45, $CHCl_3$); IR (ATR, Diamond) ν (cm^{-1}) = 3302, 3248, 2932, 2870, 2129, 1736, 1450, 1381, 1242, 1026; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.72 (tt, *J* = 11.5, 4.8 Hz, 1H), 2.75 (t, *J* = 4.9 Hz, 1H), 2.17-2.06 (m, 2H), 2.03 (s, 3H), 1.96 (dt, *J* = 12.6, 3.2 Hz, 1H), 1.92-1.79 (m, 5H), 1.70-1.63 (m, 1H), 1.60-1.52 (m, 2H), 1.49-1.37 (m, 8H), 1.35-1.22 (m, 3H), 1.18-1.00 (m, 6H), 0.93 (s, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.65 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 170.8, 114.9 (t, J_{C-F} = 232.8 Hz), 75.1 (t, J_{C-F} = 6.8 Hz), 74.5, 56.6, 55.9, 42.9, 42.0, 40.5, 40.3, 35.92, 35.87 (t, J_{C-F} = 25.3 Hz), 35.2, 35.1, 34.7, 32.4, 28.6 (t, J_{C-F} = 3.1 Hz), 28.3, 27.2, 26.8, 26.5, 24.3, 23.5, 21.6, 21.0, 18.6, 12.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) –83.6 (dtd, *J* = 272.6, 14.8, 5.2 Hz, 1F), –83.3 (m, 1F); HRMS-ESI m/z calcd for $C_{28}H_{46}F_2NO_2$ $[M+NH_4]^+$ 466.3491, found 466.3472.

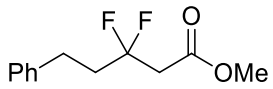
(3R,5R,8R,9S,10S,13R,14S,17R)-17-((*R*)-7-Chloro-5,5-difluorohept-6-yn-2-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (12a). Preparing according to the general procedure E on a 0.196 mmol of **ESI-40**, the desired compound (52.1 mg, 0.108 mmol, 55%) was isolated as a white foam after purification by flash column chromatography (5% EtOAc/hexanes). m. p. 54 °C; $[\alpha]_D$ +8.6 (*c* = 0.9, $CHCl_3$); IR (ATR, Diamond) ν (cm^{-1}) = 2948, 2780, 2254, 1736, 1717, 1380, 1253, 1175, 1065; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.72 (tt, *J* = 11.4, 4.7 Hz, 1H), 2.11-2.05 (m, 1H), 2.03 (s, 3H), 1.96 (dt, *J* = 12.4, 3.0 Hz, 1H), 1.93-1.79 (m, 5H), 1.69-1.52 (m, 4H), 1.47-1.38 (m, 7H), 1.33-1.23 (m, 4H), 1.18-0.99 (m, 6H), 0.94 (s, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.65

(s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 170.8, 115.2 (t, J_{C-F} = 233.7 Hz), 74.51, 67.5 (t, J_{C-F} = 8.2 Hz), 63.2 (t, J_{C-F} = 42.9 Hz), 56.6, 55.9, 42.8, 42.0, 40.5, 40.2, 36.1 (t, J_{C-F} = 25.6 Hz,), 35.9, 35.2, 35.1, 34.7, 32.4, 28.6 (t, J_{C-F} = 2.8 Hz), 28.2, 27.1, 26.8, 26.5, 24.3, 23.5, 21.6, 20.9, 18.6, 12.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –81.9 (dt, *J* = 270.6, 14.8, 13.8 Hz, 1F), –82.6 (dt, *J* = 270.6, 14.8, 14.1 Hz, 1F); HRMS-ESI m/z calcd for $C_{28}H_{45}ClF_2NO_2$ $[M+NH_4]^+$ 500.3101, found 500.3081.

(3R,5R,8R,9S,10S,13R,14S,17R)-17-((*R*)-7-Bromo-5,5-difluorohept-6-yn-2-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (12b). Preparing according to the general procedure F on a 0.156 mmol of **ESI-40**, the desired compound (45.3 mg, 0.086 mmol, 55%) was isolated as a white foam after purification by flash column chromatography (5% EtOAc/hexanes). The product was slightly contaminated with residual CH_2Cl_2. m. p. 86 °C; $[\alpha]_D$ +1.6 (c = 0.42, $CHCl_3$); IR (ATR, Diamond) ν (cm^{-1}) = 2932, 2870, 2222, 1736, 1728, 1450, 1366, 1242, 1180, 1065, 1026; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.72 (tt, *J* = 11.4, 4.7 Hz, 1H), 2.11-2.04 (m, 1H), 2.03 (s, 3H), 1.96 (dt, *J* = 12.4, 3.0 Hz, 1H), 1.93-1.80 (m, 5H), 1.69-1.53 (m, 4H), 1.46-1.38 (m, 7H), 1.31-1.23 (m, 4H), 1.17-1.00 (m, 6H), 0.93 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.65 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) = 170.8, 115.3 (t, J_{C-F} = 234.0 Hz), 74.5, 74.0 (t, J_{C-F} = 42.7 Hz), 56.6, 55.8, 50.6 (t, J_{C-F} = 9.0 Hz), 42.8, 42.0, 40.5, 40.2, 35.97 (t, J_{C-F} = 25.6 Hz), 35.9, 35.14, 35.07, 34.7, 32.5, 28.5 (t, J_{C-F} = 2.7 Hz), 28.2, 27.1, 26.7, 26.4, 24.3, 23.5, 21.6, 20.9, 18.6, 12.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –82.2 (app dt, *J* = 269.3, 15.3, 14.4 Hz, 1F), –82.9 (app dt, *J* = 270.0, 15.0, 14.2 Hz, 1F); HRMS-ESI m/z calcd for $C_{28}H_{45}BrF_2NO_2$ $[M+NH_4]^+$ 544.2596, found 544.2558.

3. Gold-catalyzed hydroalkoxylation of haloalkyne *gem*-difluorides

Procedure I: To a solution of haloalkyne (1 equiv.) in THF/H_2O (9:1, 0.1 M) was added chloro(JohnPhos)gold(I) (5 mol %) and silver trifluoromethanesulfonate (1.05 equiv.) and the vial was wrapped with aluminium foil. After 18 hours at 70 °C, the reaction mixture was cooled down to room temperature then a solution of sat. $NaHCO_3$ was added and extracted with CH_2Cl_2 (3x). The organic phases were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The desired β,β-difluoroester was isolated after purification by flash column chromatography using EtOAc/hexane as eluent.



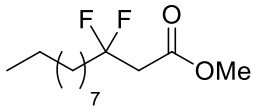
13

Methyl 3,3-difluoro-5-phenylpentanoate (13). Prepared according to the general procedure I on 30 mg scale of **1a**, the desired product (24.9 mg, 0.109 mmol, 78%) was isolated as a colourless oil after purification by flash chromatography (10% EtOAc/hexanes).

Methyl 3,3-difluoro-5-phenylpentanoate (13). Prepared according to the general procedure I on 30 mg scale of **1b**, the desired product (19.6 mg, 0.086 mmol, 74%) was isolated as a colourless oil after purification by flash chromatography (10% EtOAc/hexanes).

Methyl 3,3-difluoro-5-phenylpentanoate (13). Prepared according to the general procedure I on 30 mg scale of **1c**, the desired product (13.3 mg, 0.058 mmol, 59%) was isolated as a colourless oil after purification by flash chromatography (10% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 3030, 2955, 1744, 1437, 1229, 1136, 1051, 1005, 968, 845; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.32-7.28 (m, 2H), 7.23-7.20 (m, 3H), 3.73 (s, 3H), 2.96 (t, J = 4.6 Hz, 2H), 2.86-2.82 (m, 2H), 2.40-2.30 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 167.6 (t, J_{C-F} = 8.0 Hz), 140.4, 128.7, 126.4, 123.7, 121.8 (t, J_{C-F} = 242.9 Hz), 52.4, 41.9 (t, J_{C-F} = 28.6 Hz), 38.0 (t, J_{C-F} = 24.1 Hz), 28.5 (t,

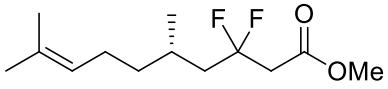
$J_{C\text{-}F}$ = 5.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –94.6 (p, *J* = 16.5 Hz, 2F); HRMS-ESI m/z calcd for $C_{12}H_{15}F_2O_2$ $[M+H]^+$ 229.1018, found 229.1035.



14

Methyl 3,3-difluorododecanoate (14). Prepared according to the general procedure I on 30 mg scale of **2a**, the desired product (25.6 mg, 0.102 mmol, 81%) was isolated as a colourless oil after purification by flash chromatography (10% EtOAc/hexanes).

Methyl 3,3-difluorododecanoate (14). Prepared according to the general procedure I on 30 mg scale of **2b**, the desired product (21.4 mg, 0.086 mmol, 80%) was isolated as a colourless oil after purification by flash chromatography (10% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2924, 2854, 2361, 1747, 1439, 1367, 1232, 1217, 1136, 1003; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 3.74 (s, 3H), 2.91 (t, *J* = 14.6 Hz, 2H), 2.05-1.96 (m, 2H), 1.51-1.45 (m, 2H), 1.34-1.26 (m, 12H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 167.7, 122.4 (t, $J_{C\text{-}F}$ = 243.0 Hz), 52.3, 41.8 (t, $J_{C\text{-}F}$ = 28.8 Hz), 36.2 (t, $J_{C\text{-}F}$ = 24.1 Hz), 32.0, 29.6, 29.5, 29.40, 29.36, 22.8, 22.3, 14.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –93.9 (p, *J* = 16.4 Hz, 2F); HRMS-ESI m/z calcd for $C_{13}H_{25}F_2O_2$ $[M+H]^+$ 251.1817, found 251.1805.

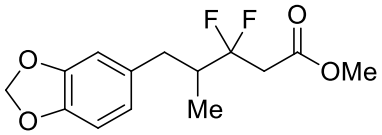


15

Methyl (*S*)-3,3-difluoro-5,9-dimethyldec-8-enoate (15). Prepared according to the general procedure I on 30 mg scale of **3a**, the desired product (13.3 mg, 0.054 mmol, 42%) was isolated as a pale-yellow oil after purification by flash chromatography (5% EtOAc/hexanes).

Methyl (*S*)-3,3-difluoro-5,9-dimethyldec-8-enoate (15). Prepared according to the general procedure I on 30 mg scale of **3b**, the desired product (10.7 mg, 0.043 mmol, 40%) was isolated as a pale-yellow oil after purification by flash chromatography (5%

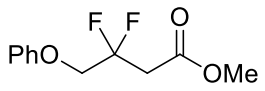
EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2959, 2924, 1747, 1643, 1439, 1375, 1213, 1140, 1117, 1001; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 5.08 (tdq, *J* = 7.1, 2.9, 1.5 Hz, 1H), 3.74 (s, 3H), 2.95-2.89 (m, 2H), 2.11-1.93 (m, 2H), 1.89-1.79 (m, 2H), 1.64 (d, *J* = 40.7 Hz, 6H), 1.43-1.36 (m, 1H), 1.28-1.17 (m, 2H), 1.00 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 167.7 (dd, J_{C-F} = 8.2, 7.0 Hz), 131.8, 124.4, 114.8, 55.9, 52.3, 42.5 (t, J_{C-F} = 28.8 Hz), 37.7, 27.6 (t, J_{C-F} = 3.1 Hz), 25.9, 25.3, 20.5 (t, J_{C-F} = 1.4 Hz), 17.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –91.1 (m, 1F), –92.3 (m, 1F); HRMS-ESI m/z calcd for $C_{13}H_{23}F_2O_2$ $[M+H]^+$ 249.1661, found 249.1663.



16

Methyl 5-(benzo[*d*][1,3]dioxol-5-yl)-3,3-difluoro-4-methylpentanoate (16). Prepared according to the general procedure I on 30 mg scale of **4a**, the desired product (23.2 mg, 0.081 mmol, 74%) was isolated as a pale-yellow oil after purification by flash chromatography (10% EtOAc/hexanes).

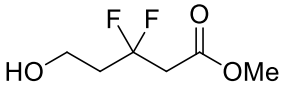
Methyl 5-(benzo[*d*][1,3]dioxol-5-yl)-3,3-difluoro-4-methylpentanoate (16). Prepared according to the general procedure I on 30 mg scale of **4b**, the desired product (17.9 mg, 0.063 mmol, 66%) was isolated as a pale-yellow oil after purification by flash chromatography (10% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2924, 1744, 1491, 1441, 1367, 1246, 1038, 989, 930, 810; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.74 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 1.4 Hz, 1H), 6.62 (dd, *J* = 8.1, 1.3 Hz, 1H), 5.93 (s, 2H), 3.75 (s, 3H), 3.03 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.97 (t, *J* = 15.5 Hz, 2H), 2.46-2.33 (m, 1H), 2.28 (dd, *J* = 13.4, 10.9 Hz, 1H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 167.4 (t, J_{C-F} = 6.8 Hz), 147.8, 146.2, 133.2, 123.5 (t, J_{C-F} = 246.1 Hz), 122.2, 109.5, 108.3, 101.2, 52.4, 41.3 (t, J_{C-F} = 22.5 Hz), 40.2 (t, J_{C-F} = 28.4 Hz), 35.6 (t, J_{C-F} = 4.8 Hz), 12.6 (t, J_{C-F} = 4.7 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –100.9 (app. dq, *J* = 248.6, 15.0 Hz, 15.0 Hz, 1F), –101.8 (app. dq, *J* = 248.8, 15.4 Hz, 1F); HRMS-ESI m/z calcd for $C_{14}H_{17}F_2O_4$ $[M+H]^+$ 287.1089, found 287.1079.



17

Methyl 3,3-difluorododecanoate (17). Prepared according to the general procedure I (X = Cl) on 30 mg scale of **5a**, the desired product (26.1 mg, 0.113 mmol, 82%) was isolated as a colourless oil after purification by flash chromatography (30% EtOAc/hexanes).

Methyl 3,3-difluorododecanoate (17). Prepared according to the general procedure I (X = Br) on 30 mg scale of **5b**, the desired product (30.0 mg, 0.099 mmol, 87%) was isolated as a colourless oil after purification by flash chromatography (30% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2955, 2926, 1744, 1599, 1497, 1244, 1122, 1078, 1009, 906; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.33-7.29 (m, 2H), 7.01 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.94-6.92 (m, 2H), 4.36 (t, *J* = 12.0 Hz, 2H), 3.73 (s, 3H), 3.19 (t, *J* = 14.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 167.4 (t, J_{C-F} = 8.1 Hz), 157.8, 129.8, 122.1, 119.8 (t, J_{C-F} = 243.3 Hz), 114.9, 67.9 (t, J_{C-F} = 33.4 Hz), 52.4, 38.8 (t, J_{C-F} = 27.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –101.2 (p, *J* = 14.1, 13.4 Hz, 2F); HRMS-ESI m/z calcd for $C_{11}H_{13}F_2O_3$ $[M+H]^+$ 231.0827, found 231.0811.

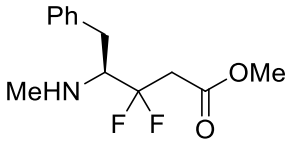


18

Methyl 3,3-difluoro-5-hydroxypentanoate (18). Prepared according to the general procedure I on 30 mg scale of **6a**, the desired product (12.3 mg, 0.073 mmol, 58%) was isolated as a pale-yellow oil after purification by flash chromatography (50% EtOAc/hexanes).

Methyl 3,3-difluoro-5-hydroxypentanoate (18). Prepared according to the general procedure I on 30 mg scale of **6b**, the desired product (11.2 mg, 0.067 mmol, 63%) was isolated as a pale-yellow oil after purification by flash chromatography (50% EtOAc/hexanes). IR (ATR, Diamond): ν (cm^{-1}) = 3433, 2955, 1747, 1441, 1377, 1205, 1107, 1055, 1013, 980; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 3.89 (dd, *J* = 16.9, 5.6 Hz,

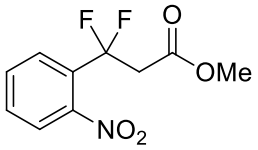
2H), 3.74 (s, 3H), 3.33 (t, J = 2.4 Hz, 1H), 3.06 (t, J = 14.9 Hz, 2H), 2.36 (tt, J = 16.7, 5.9 Hz, 2H), 1.73 (t, J = 5.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 168.0 (t, J_{C-F} = 8.3 Hz), 122.1 (t, J_{C-F} = 242.7 Hz), 57.1 (t, J_{C-F} = 5.8 Hz), 52.4, 42.2 (t, J_{C-F} = 28.6 Hz), 38.6 (t, J_{C-F} = 23.5 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –92.1 (p, J = 15.7 Hz, 2F); HRMS-ESI m/z calcd for $C_6H_9F_2O_2$ $[(M+H)-(H_2O)]^+$ 151.0565, found 151.0542.



19

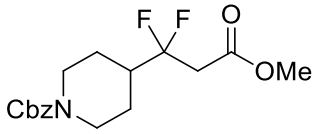
Methyl (*S*)-3,3-difluoro-4-(methylamino)-5-phenylpentanoate (19). Prepared according to the general procedure I on 30 mg scale of **7a**, the desired product (15.5 mg, 0.064 mmol, 81%) isolated as a colourless oil after purification by flash chromatography (50% EtOAc/hexanes).

Methyl (*S*)-3,3-difluoro-4-(methylamino)-5-phenylpentanoate (19). Prepared according to the general procedure I on 30 mg scale of **7b**, the desired product (14.4 mg, 0.059 mmol, 83%) was isolated as a colourless oil after purification by flash chromatography (50% EtOAc/hexanes). $[\alpha]_D$ = –6.9 (c = 0.12, $CHCl_3$); IR (ATR, Diamond) ν (cm^{-1}) = 3032, 2924, 1698, 1435, 1404, 1319, 1265, 1142, 1057, 903; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.35-7.31 (m, 2H), 7.29-7.25 (m, 1H), 7.22-7.20 (m, 2H), 4.02 (dtd, J = 17.7, 5.9, 2.9 Hz, 1H), 3.12 (dd, J = 15.0, 5.3 Hz, 1H), 2.93 (dd, J = 15.2, 6.6 Hz, 1H), 2.81 (s, 3H), 2.71 (td, J = 17.9, 5.7 Hz, 1H), 2.52 (ddd, J = 20.8, 17.5, 12.4 Hz, 1H), 1.62 (bs, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 170.0 (dd, J_{C-F} = 9.5, 3.0 Hz), 135.2, 129.5 (d, J_{C-F} = 1.7 Hz), 128.8, 127.3, 123.1 (dd, J_{C-F} = 255.2, 247.9 Hz), 72.6, 70.6 (d, J_{C-F} = 7.2 Hz), 67.8 (dd, J_{C-F} = 29.4, 25.3 Hz), 58.5, 40.0 (dd, J_{C-F} = 25.5, 23.5 Hz), 34.1 (dd, J_{C-F} = 5.1, 4.4 Hz), 28.7, 26.4 (d, J_{C-F} = 1.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –91.9 (ddd, J = 290.8, 56.6, 18.3 Hz, 2F); HRMS-ESI m/z calcd for $C_{12}H_{15}F_2NO_2$ $[M+H]^+$ 244.1140, found 244.1156.



20

Methyl 3,3-difluoro-3-(2-nitrophenyl)propanoate (20). Prepared according to the general procedure I on 30 mg scale of **8b**, the desired product (26.4 mg, 0.108 mmol, 98%) was isolated as a yellow oil after purification by flash chromatography (25% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2957, 2924, 1744, 1537, 1439, 1366, 1205, 1070, 908, 731; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.78-7.77 (m, 1H), 7.73-7.71 (m, 1H), 7.66 (tdt, *J* = 7.9, 1.5, 0.7 Hz, 1H), 7.61-7.59 (m, 1H), 3.70 (s, 3H), 3.62 (t, *J* = 15.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 166.9 (t, J_{C-F} = 6.2 Hz), 132.0, 131.5 (t, J_{C-F} = 1.1 Hz), 129.1 (t, J_{C-F} = 8.3 Hz), 124.5, 118.7 (t, J_{C-F} = 246.5 Hz), 52.4, 44.1 (t, J_{C-F} = 28.7 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –88.8 (t, *J* = 15.0 Hz, 2F); HRMS-ESI m/z calcd for $C_{10}H_{10}F_2NO_4$ $[M+H]^+$ 246.0572, found 246.0559.

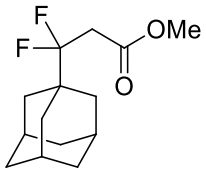


21

Benzyl-4-(1,1-difluoro-3-methoxy-3-oxopropyl)piperidine-1-carboxylate (21). Prepared according to the general procedure I on 30 mg scale of **9a**, the desired product (17.9 mg, 0.052 mmol, 57%) was isolated as a pale-yellow thick oil after purification by flash chromatography (50% EtOAc/hexanes).

Benzyl-4-(1,1-difluoro-3-methoxy-3-oxopropyl)piperidine-1-carboxylate (21). Prepared according to the general procedure I on 30 mg scale of **9b**, the desired product (20.3 mg, 0.060 mmol, 74%) was isolated as a pale-yellow thick oil after purification by flash chromatography (50% EtOAc/hexanes). The product contained trace amounts of inseparable and unknown impurities. IR (ATR, Diamond) ν (cm^{-1}) = 2926, 1744, 1697, 1437, 1366, 1327, 1236, 1138, 1041, 908; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.39-

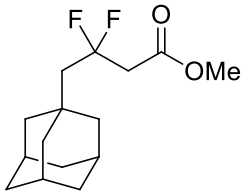
7.30 (m, 5H), 5.13 (s, 2H), 4.33-4.27 (m, 2H), 3.74 (s, 3H), 2.92 (t, J = 15.4 Hz, 2H), 2.76 (bs, 2H), 2.30-2.18 (m, 1H), 1.82-1.80 (m, 2H), 1.49-1.44 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 167.5 (t, J_{C-F} = 7.2 Hz), 155.2, 136.8, 129.3, 128.8, 128.6, 128.2, 128.1, 122.4 (t, J_{C-F} = 245.1 Hz), 72.8, 70.1, 67.3, 52.5, 43.5, 41.6 (t, J_{C-F} = 23.5 Hz), 39.7 (t, J_{C-F} = 28.6 Hz), 24.9 (t, J_{C-F} = 4.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –101.9 (ddd, J = 107.8, 44.8, 14.9 Hz, 2F); HRMS-ESI m/z calcd for $C_{17}H_{22}F_2O_4$ $[M+H]^+$ 342.1511, found 342.1484.



22

Methyl 3-(adamantan-1-yl)-3,3-difluoropropanoate (22). Prepared according to the general procedure I on 30 mg scale of **10a**, the desired product (22.7 mg, 0.088 mmol, 78%) isolated as a pale-yellow solid after purification by flash chromatography (10% EtOAc/hexanes).

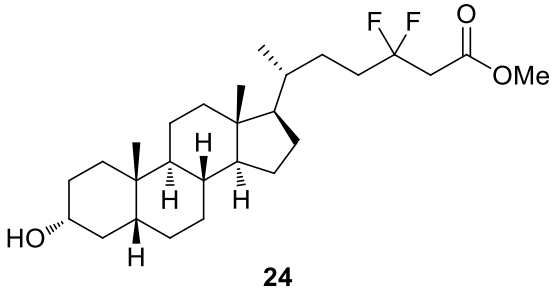
Methyl 3-(adamantan-1-yl)-3,3-difluoropropanoate (22). Prepared according to the general procedure I on 30 mg scale of **10b**, the desired product (23.1 mg, 0.089 mmol, 86%) isolated as a white solid after purification by flash chromatography (10% EtOAc/hexanes). m. p. 54.2-55.5 °C; IR (ATR, Diamond) ν (cm^{-1}) = 2908, 2854, 2361, 2260, 1736, 1435, 1219, 1065, 995, 648; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 3.75 (s, 3H), 2.85 (dd, J = 18.5, 17.6 Hz, 2H), 2.05 (bs, 3H), 1.75-1.63 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 168.2 (t, J_{C-F} = 2.1 Hz), 124.0 (t, J_{C-F} = 248.2 Hz), 52.4, 40.1 (t, J_{C-F} = 22.1 Hz), 37.3 (t, J_{C-F} = 26.6 Hz), 36.6, 35.3 (t, J_{C-F} = 3.8 Hz), 27.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –112.1 (t, J = 18.3 Hz, 2F); HRMS-ESI m/z calcd for $C_{27}H_{43}F_2O_2$ $[M+H]^+$ 259.1504, found 259.1502.



23

Methyl 3-(adamantan-1-yl)-2,2-difluoropropanoate (23). Prepared according to the general procedure I on 30 mg scale of **11a**, the desired product (22.3 mg, 0.082 mmol, 71%) was isolated as a pale-yellow oil after purification by flash chromatography (10% EtOAc/hexanes).

Methyl 3-(adamantan-1-yl)-2,2-difluoropropanoate (23). Prepared according to the general procedure I on 30 mg scale of **11b**, the desired product (18.5 mg, 0.068 mmol, 69%) was isolated as a pale-yellow oil after purification by flash chromatography (10% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2903, 1747, 1437, 1362, 1242, 1205, 1107, 1061, 1028, 976; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 3.73 (s, 3H), 2.90 (t, J = 14.9 Hz, 2H), 1.95 (bs, 3H), 1.82 (t, J = 20.3 Hz, 2H), 1.71-1.63 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 167.8 (t, J_{C-F} = 7.5 Hz), 123.1 (t, J_{C-F} = 245.9 Hz), 52.3, 49.0 (t, J_{C-F} = 22.2 Hz), 44.2 (t, J_{C-F} = 28.7 Hz), 43.0, 36.9, 32.7, 28.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –89.5 (tt, J = 20.2, 14.7 Hz, 2F); HRMS-ESI m/z calcd for $C_{15}H_{23}F_2O_2$ $[M+H]^+$ 273.1661, found 273.1678.

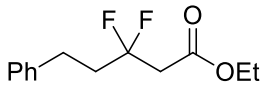


24

(*R*)-methyl 3,3-difluoro-6-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)heptanoate (24). Prepared according to the general procedure I on 30 mg scale of **12a**, the desired product

(26.5 mg, 0.058 mmol, 94%) was isolated as a white solid after purification by flash chromatography (40% EtOAc/hexanes).

(*R*)-methyl 3,3-difluoro-6-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)heptanoate (24). Prepared according to the general procedure I on 30 mg scale of **12b**, the desired product (24.6 mg, 0.054 mmol, 95%) was isolated as a white solid after purification by flash chromatography (40% EtOAc/hexanes). m. p. 69.0-70.8 °C; $[\alpha]_D$ = 16.7 (*c* = 0.17, $CHCl_3$); IR (ATR, Diamond) ν (cm^{-1}) = 2928, 2864, 1749, 1701, 1437, 1364, 1238, 1115, 1040, 1013; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 3.74 (s, 3H), 3.67-3.59 (m, 1H), 2.91 (t, *J* = 14.7 Hz, 2H), 1.96 (dt, *J* = 12.2, 2.9 Hz, 1H), 1.88-1.81 (m, 3H), 1.75 (m, 1H), 1.63-1.58 (m, 4H), 1.43-1.40 (m, 8H), 1.29-1.20 (m, 6H), 1.17-1.09 (m, 6H), 0.93-0.92 (m, 6H), 0.65 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 167.7 (t, J_{C-F} = 7.6 Hz), 122.8 (t, J_{C-F} = 243.0 Hz), 72.7, 72.0, 70.7, 58.7, 56.6, 55.9, 52.3, 42.8, 42.2, 41.7 (t, J_{C-F} = 28.9 Hz), 40.5, 40.3, 36.6, 36.0, 35.5, 35.4, 34.7, 32.8 (t, J_{C-F} = 23.9 Hz), 30.7, 28.3, 28.2 (t, J_{C-F} = 4.1 Hz), 27.3, 26.5 (t, J_{C-F} = 1.7 Hz), 24.3, 23.5, 20.9, 18.6, 12.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –93.7 (app. h, *J* = 16.0 Hz, 2F); HRMS-ESI m/z calcd for $C_{27}H_{43}F_2O_2$ $[(M+H)-(H_2O)]^+$ 437.3226, found 437.3226.



25

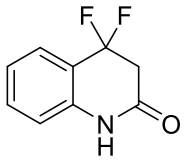
Ethyl 3,3-difluoro-5-phenylpentanoate (25). Prepared according to the general procedure I on 30 mg scale of **1a**, the desired product (24.7 mg, 0.102 mmol, 73%) was isolated as a pale-yellow oil after purification by flash chromatography (10% EtOAc/hexanes).

Ethyl 3,3-difluoro-5-phenylpentanoate (25). Prepared according to the general procedure I on 30 mg scale of **1b**, the desired product (21.6 mg, 0.090 mmol, 77%) was isolated as a pale-yellow oil after purification by flash chromatography (10% EtOAc/hexanes).

Ethyl 3,3-difluoro-5-phenylpentanoate (25). Prepared according to the general procedure I on 30 mg scale of **1c**, the desired product (30 mg, 0.098 mmol, 43%) was isolated as a pale-yellow oil after purification by flash chromatography (10% EtOAc/hexanes). The

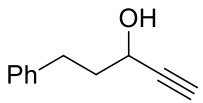
product was slightly contaminated with residual CH_2Cl_2. IR (ATR, Diamond) ν (cm^{-1}) = 3030, 2937, 1740, 1456, 1375, 1229, 1149, 1097, 1028, 905; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.32-7.29 (m, 2H), 7.23-7.20 (m, 3H), 4.19 (q, *J* = 7.1, 2H), 2.94 (t, *J* = 14.6 Hz, 2H), 2.86-2.82 (m, 2H), 2.40-2.30 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 167.1 (t, J_{C-F} = 8.0 Hz), 140.4, 128.7, 128.5, 126.4, 121.9 (t, J_{C-F} = 242.9 Hz), 61.4, 42.2 (t, J_{C-F} = 28.6 Hz), 38.0 (t, J_{C-F} = 24.2 Hz), 28.5 (t, J_{C-F} = 5.0 Hz), 14.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –94.4 (p, *J* = 15.7, 115.0 Hz, 2F); HRMS-ESI m/z calcd for $C_{13}H_{17}F_2O_2$ $[M+H]^+$ 243.1171, found 243.1191.

4. Subsequent transformation



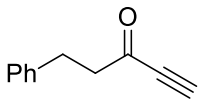
4-4-Difluoro-3,4-dihydroquinolin-2(1*H*)-one (26). A mixture of **20** (30 mg, 0.122 mmol, 1 equiv.) and Pd/C (10 wt% Pd on C, 13.0 mg, 0.012 mmol, 0.1 equiv.) was suspended in MeOH (1.2 mL, 0.1 M) and treated with AcOH (7 µL, 0.122 mmol, 1 equiv.). The flask was evacuated and purged with H_2 (1 atm) and the reaction was vigorously stirred for 2 hours. The H_2 balloon was removed and the reaction was stirred for 18 hours, filtered though Celite and concentrated *in vacuo*. The desired compound (20.0 mg, 0.109 mmol, 89%) was isolated as a white thick oil after flash chromatography (50% EtOAc/hexanes). IR (ATR, Diamond) ν (cm^{-1}) = 2953, 2926, 2857, 1666, 1613, 1440, 1093, 909, 794, 709. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 11.88 (s, 1H), 7.81 (ddd, *J* = 8.1, 1.4, 0.6 Hz, 1H), 7.61 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.43 (ddt, *J* = 8.3, 1.7, 0.8 Hz, 1H), 7.29 (ddd, *J* = 8.2, 8.2, 1.0 Hz, 1H), 1.29 (t, *J* = 13.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm)= 166.4, 138.8 (d, J_{C-F} = 9.3 Hz), 132.4, 123.1, 122.0 (d, J_{C-F} = 3.9 Hz), 116.2 (d, J_{C-F} = 3.4 Hz), 113.5 (d, J_{C-F} = 21.0 Hz), 103.1 (d, J_{C-F} = 15.8 Hz), 29.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) = –90.3 (t, *J* = 14.2 Hz, 2F); HRMS-ESI m/z calcd $C_9H_8F_2NO$ $[M+H]^+$ 184.0568, found 184.0560.

5. Spectra



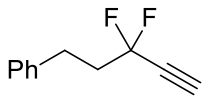
ESI-1

^{1}H NMR (500 MHz, $CDCl_3$)



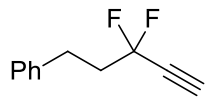
ESI-2

^{1}H NMR (500 MHz, $CDCl_3$)



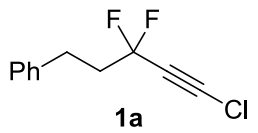
ESI-3

^{1}H NMR (500 MHz, $CDCl_3$)



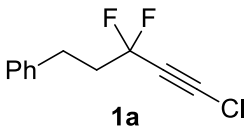
ESI-3

^{19}F NMR (470 MHz. $CDCl_3$)



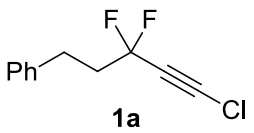
1a

^{1}H NMR (500 MHz, $CDCl_3$)



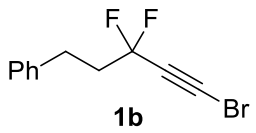
1a

^{13}C NMR (126 MHz, $CDCl_3$)



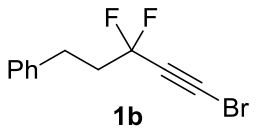
1a

^{19}F NMR (470 MHz, $CDCl_3$)



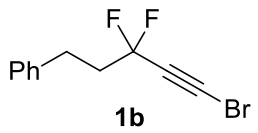
1b

^{1}H NMR (500 MHz, $CDCl_3$)



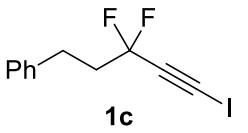
1b

^{13}C NMR (126 MHz, $CDCl_3$)



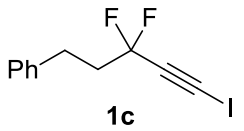
1b

^{19}F NMR (470 MHz, $CDCl_3$)



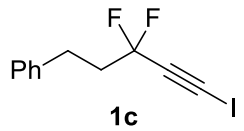
1c

^{1}H NMR (500 MHz, $CDCl_3$)



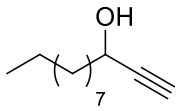
1c

^{13}C NMR (126 MHz, $CDCl_3$)



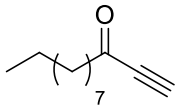
1c

^{19}F NMR (470 MHz, $CDCl_3$)



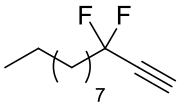
ESI-4

^{1}H NMR (500 MHz, $CDCl_3$)



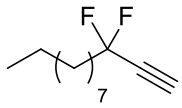
ESI-5

^{1}H NMR (500 MHz, $CDCl_3$)



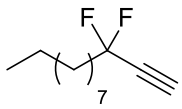
ESI-6

^{1}H NMR (500 MHz, $CDCl_3$)



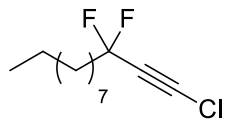
ESI-6

^{13}C NMR (126 MHz, $CDCl_3$)



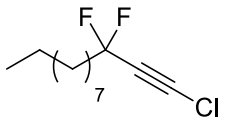
ESI-6

^{19}F NMR (470 MHz, $CDCl_3$)



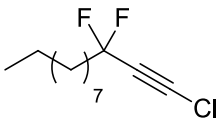
2a

^{1}H NMR (500 MHz, $CDCl_3$)



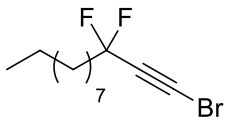
2a

^{13}C NMR (126 MHz, $CDCl_3$)



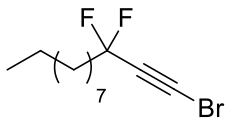
2a

^{19}F NMR (470 MHz, $CDCl_3$)



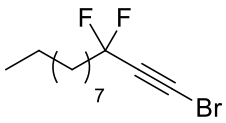
2b

^{1}H NMR (500 MHz, $CDCl_3$)



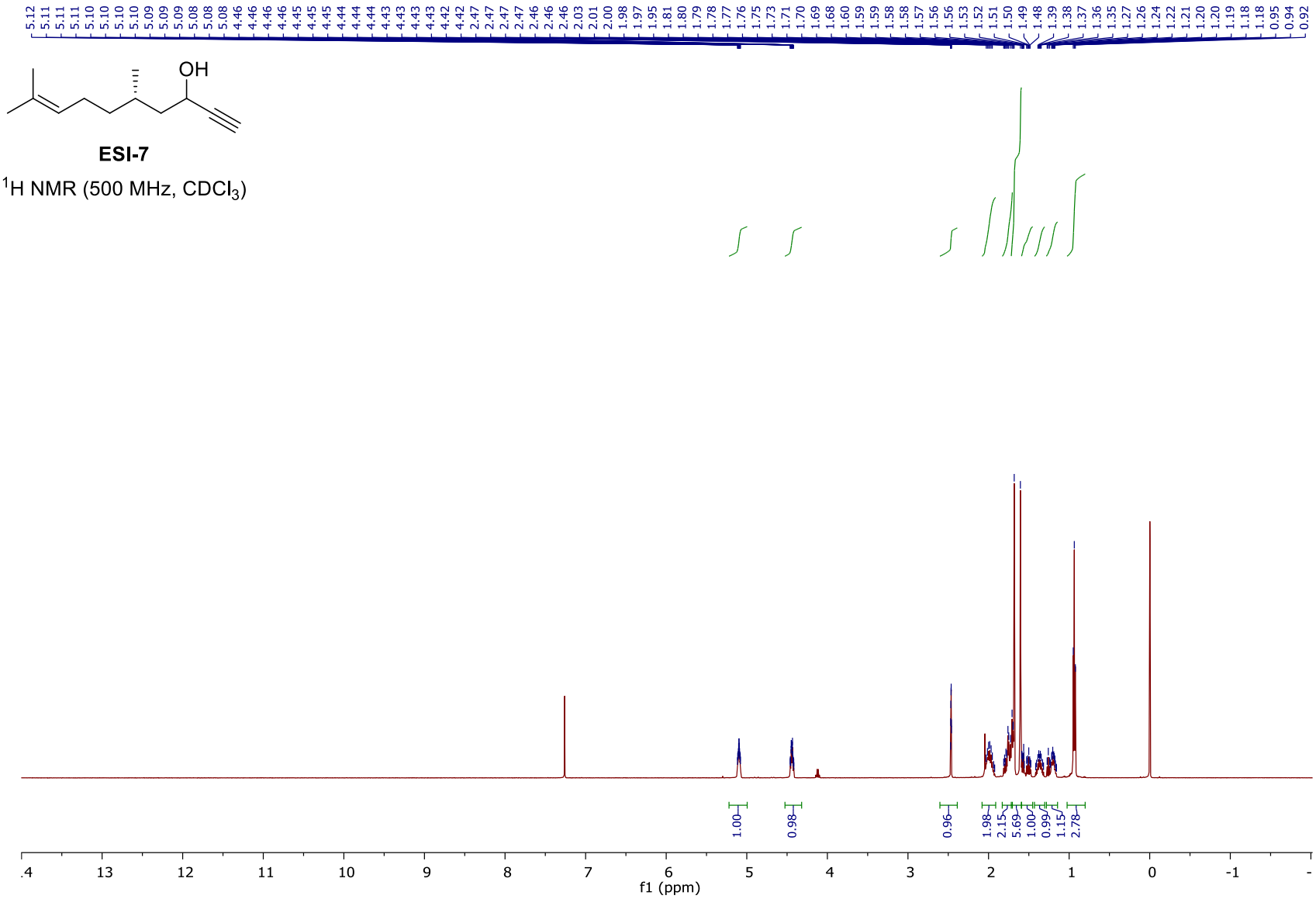
2b

^{13}C NMR (126 MHz, $CDCl_3$)



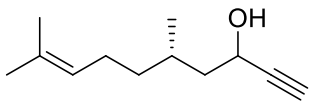
2b

^{19}F NMR (470 MHz, $CDCl_3$)



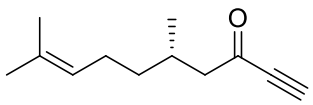
ESI-7

^{1}H NMR (500 MHz, $CDCl_3$)



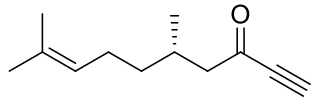
ESI-7

^{13}C NMR (126 MHz, $CDCl_3$)



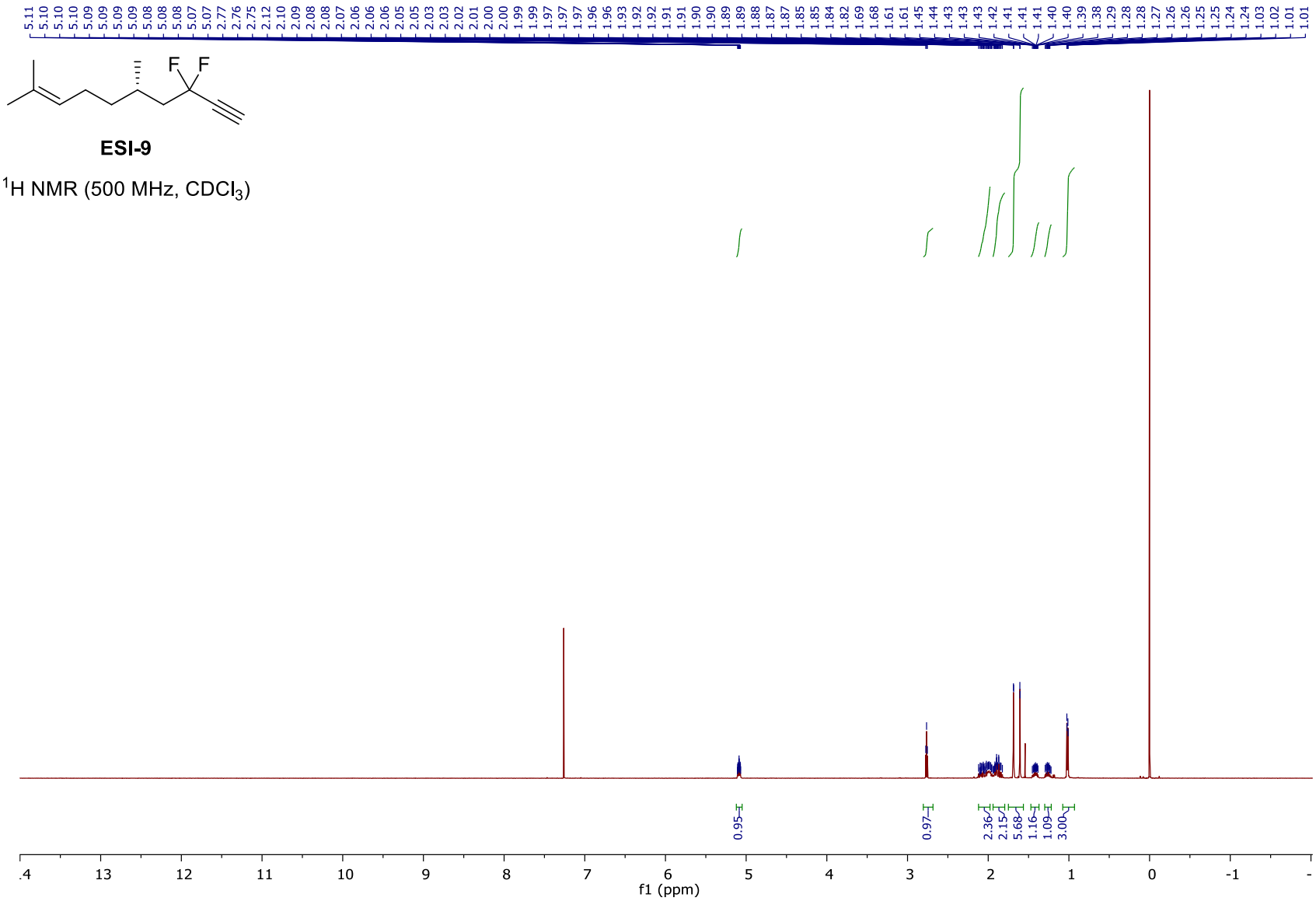
ESI-8

^{1}H NMR (500 MHz, $CDCl_3$)



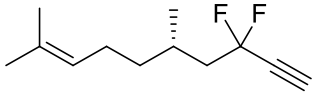
ESI-8

^{13}C NMR (126 MHz, $CDCl_3$)



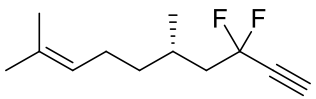
ESI-9

^{1}H NMR (500 MHz, $CDCl_3$)



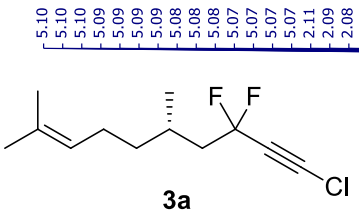
ESI-9

^{13}C NMR (126 MHz, $CDCl_3$)



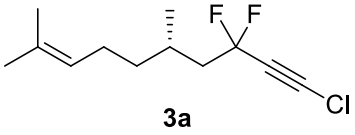
ESI-9

^{19}F NMR (470 MHz, $CDCl_3$)



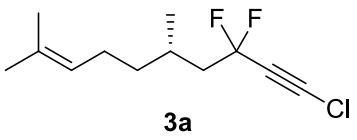
3a

^{1}H NMR (500 MHz, $CDCl_3$)



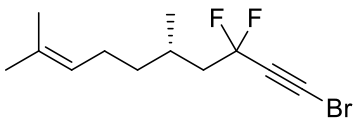
3a

^{13}C NMR (126 MHz, $CDCl_3$)



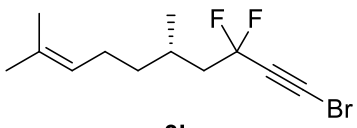
3a

^{19}F NMR (470 MHz, $CDCl_3$)



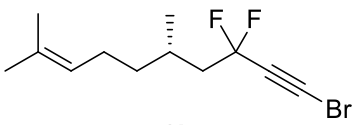
3b

^{1}H NMR (500 MHz, $CDCl_3$)



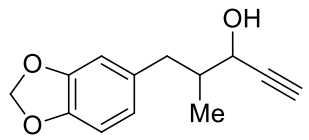
3b

^{13}C NMR (126 MHz, $CDCl_3$)



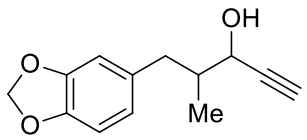
3b

^{19}F NMR (470 MHz, $CDCl_3$)



ESI-10

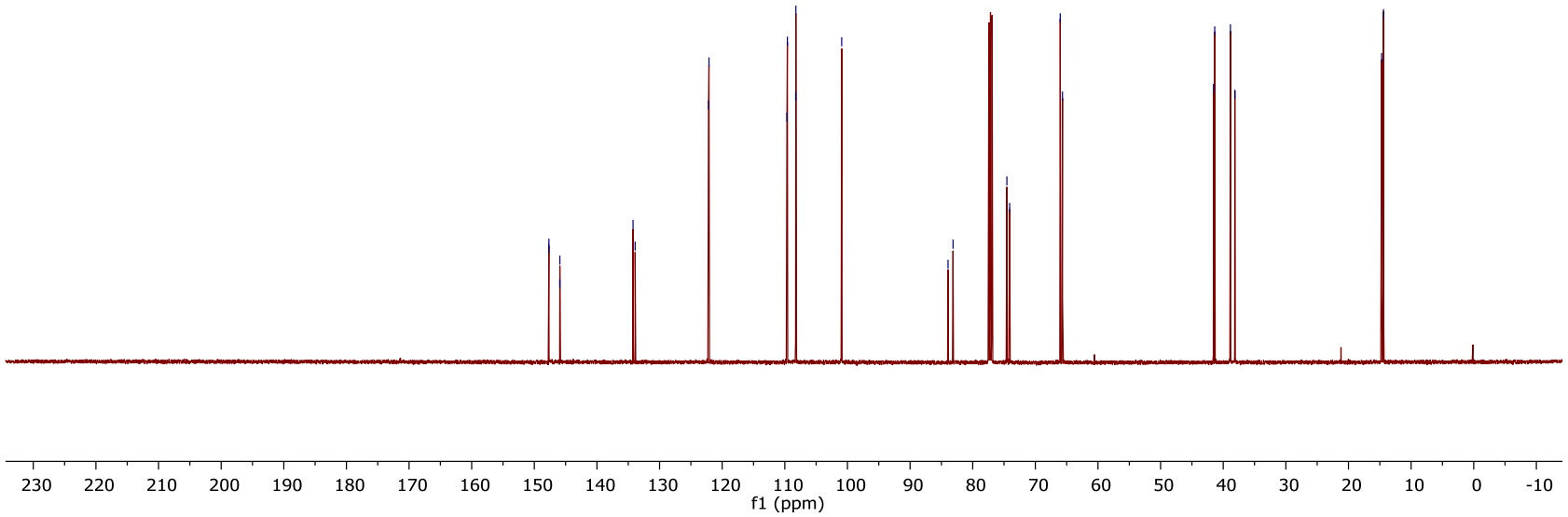
^{1}H NMR (500 MHz, $CDCl_3$)

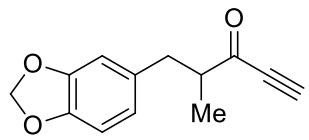


ESI-10

^{13}C NMR (126 MHz, $CDCl_3$)

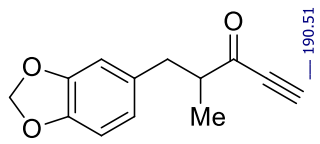
147.70
147.67
145.93
145.92
134.24
133.90
122.18
122.11
109.67
109.60
108.27
108.24
100.92
83.94
83.14
74.54
74.10
66.03
65.66
41.55
41.35
38.85
38.15
14.71
14.41





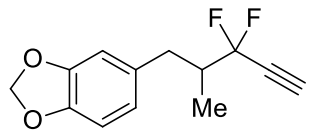
ESI-11

^{1}H NMR (500 MHz, $CDCl_3$)



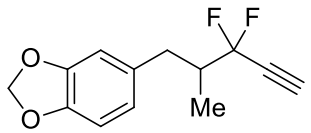
ESI-11

^{13}C NMR (126 MHz, $CDCl_3$)



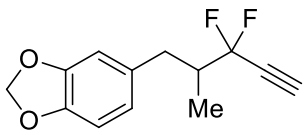
ESI-12

^{1}H NMR (500 MHz, $CDCl_3$)



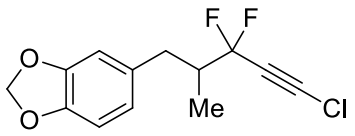
ESI-12

^{13}C NMR (126 MHz, $CDCl_3$)



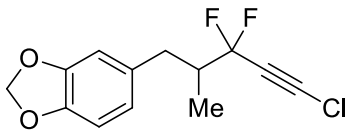
ESI-12

^{19}F NMR (470 MHz, $CDCl_3$)



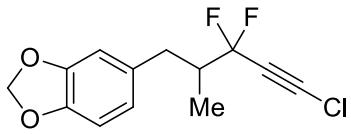
4a

^{1}H NMR (500 MHz, $CDCl_3$)



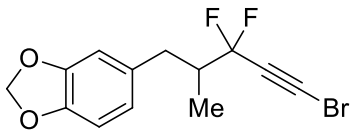
4a

^{13}C NMR (126 MHz, $CDCl_3$)



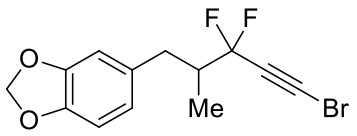
4a

^{19}F NMR (470 MHz, $CDCl_3$)



4b

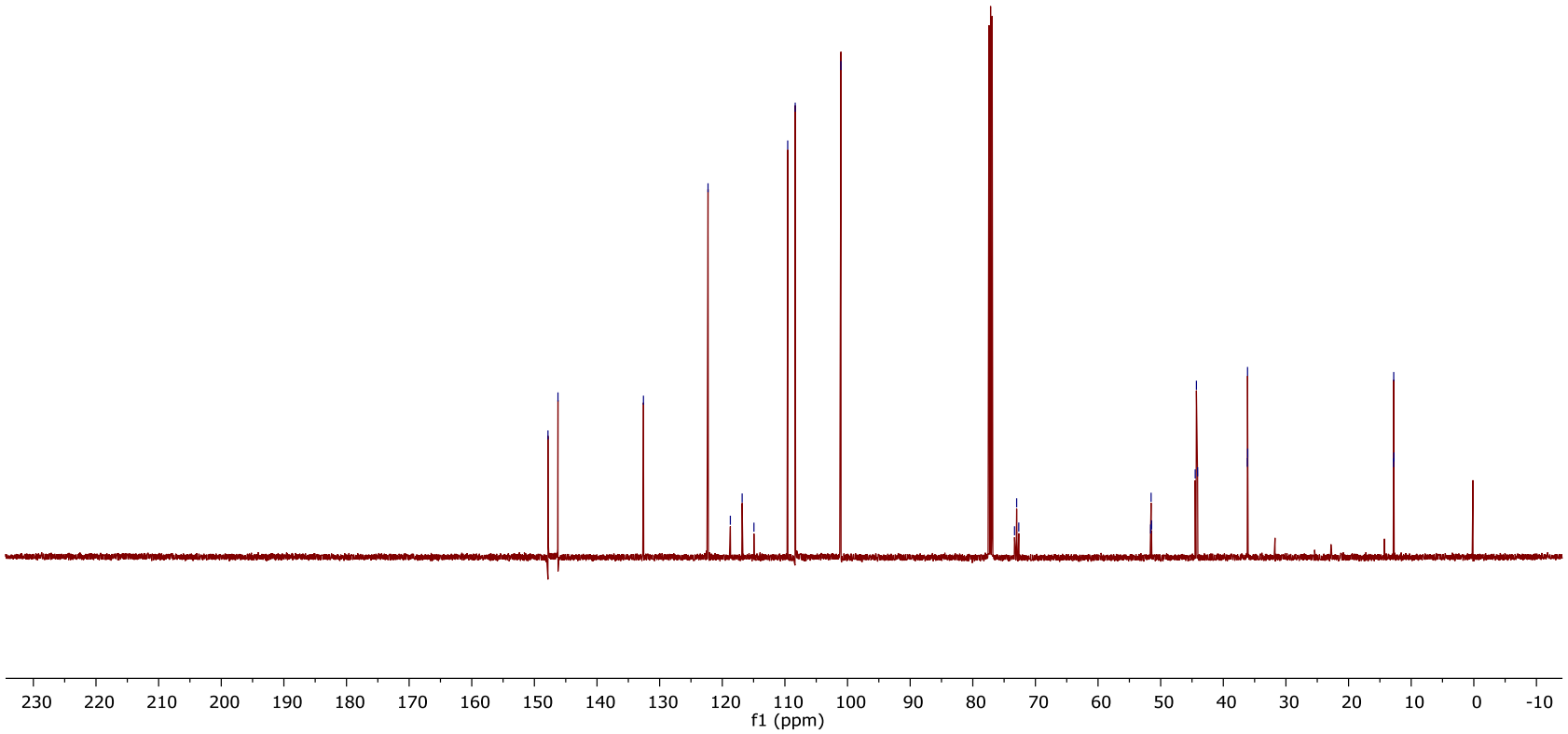
^{1}H NMR (500 MHz, $CDCl_3$)

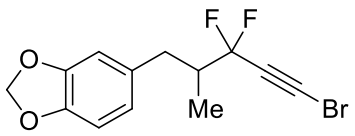


4b

^{13}C NMR (126 MHz, $CDCl_3$)

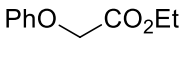
147.83
146.23
132.59
122.27
118.71
116.83
114.94
109.55
108.35
101.06
73.33
73.00
72.66
51.60
51.53
51.46
44.48
44.29
44.10
36.16
36.13
36.10
12.81
12.79
12.76





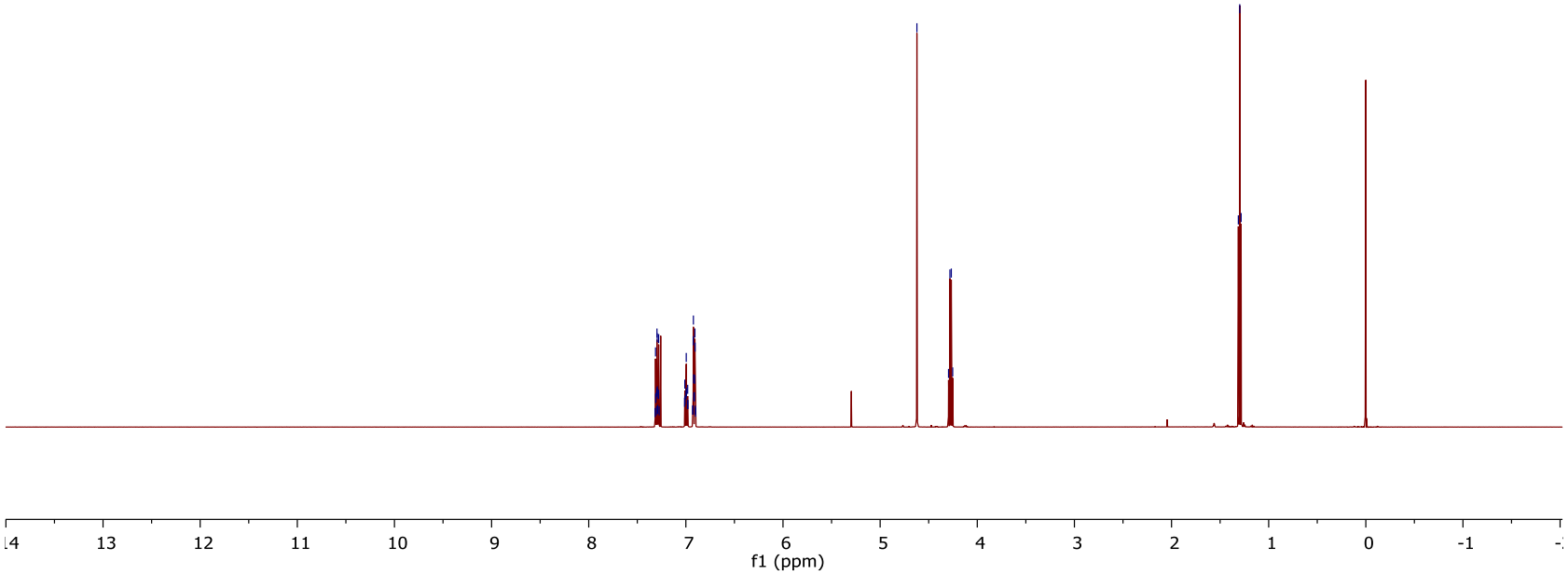
4b

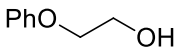
^{19}F NMR (470 MHz, $CDCl_3$)



ESI-13

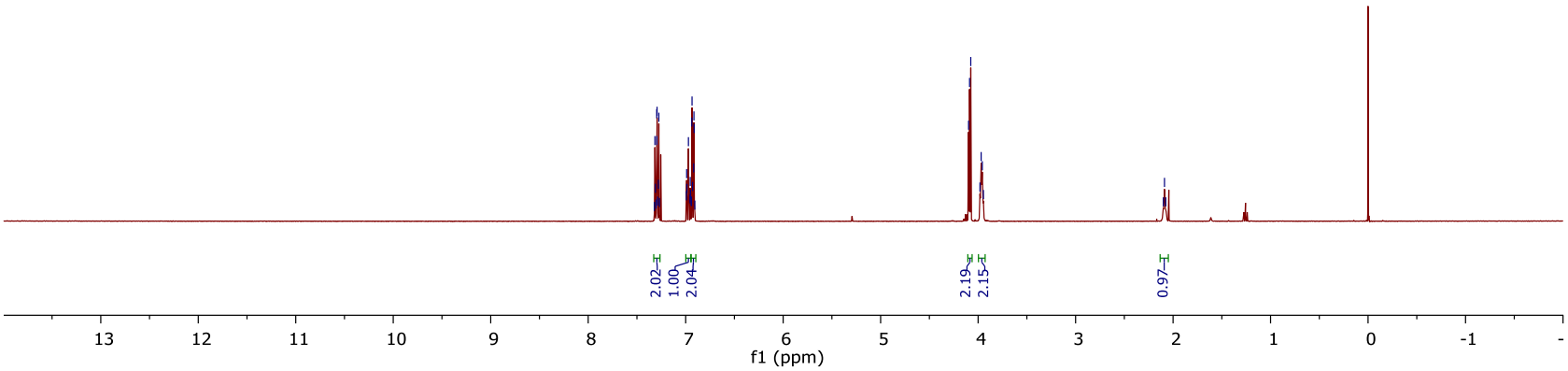
^{1}H NMR (500 MHz, $CDCl_3$)

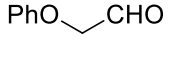




ESI-14

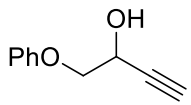
^{1}H NMR (500 MHz, $CDCl_3$)





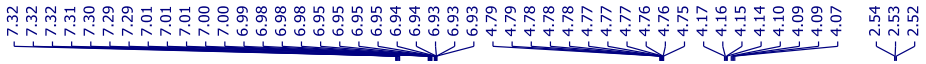
ESI-15

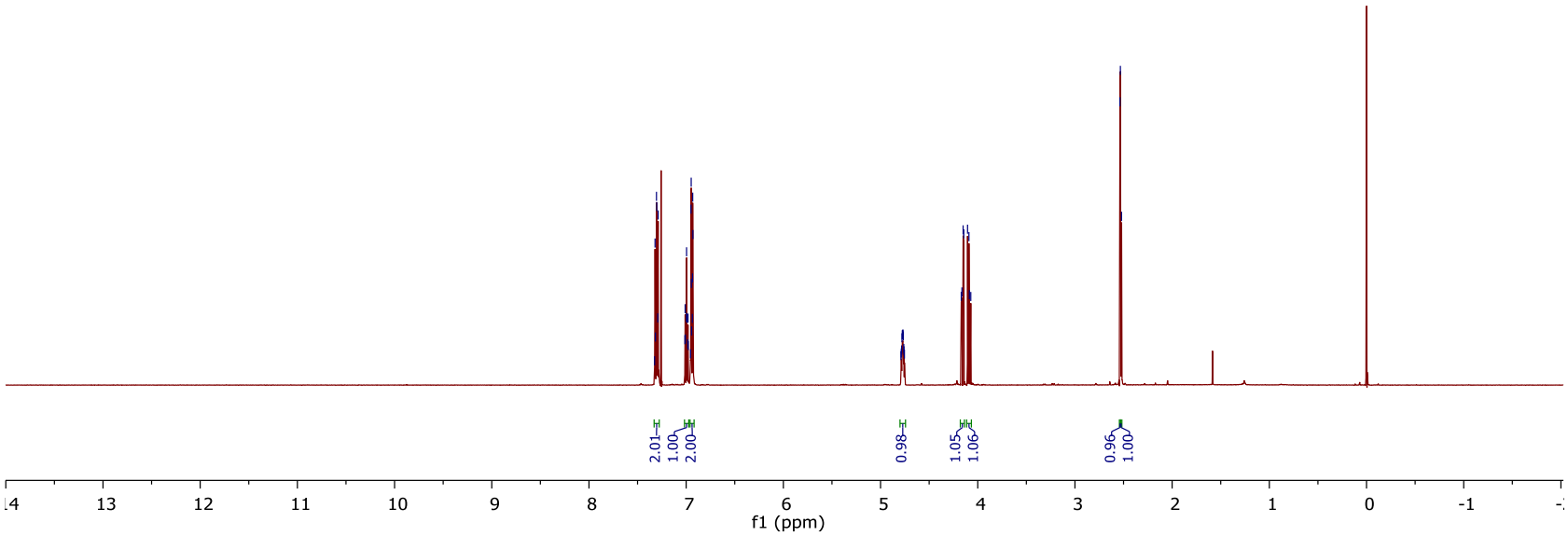
^{1}H NMR (500 MHz, $CDCl_3$)

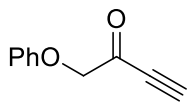


ESI-16

^{1}H NMR (500 MHz, $CDCl_3$)

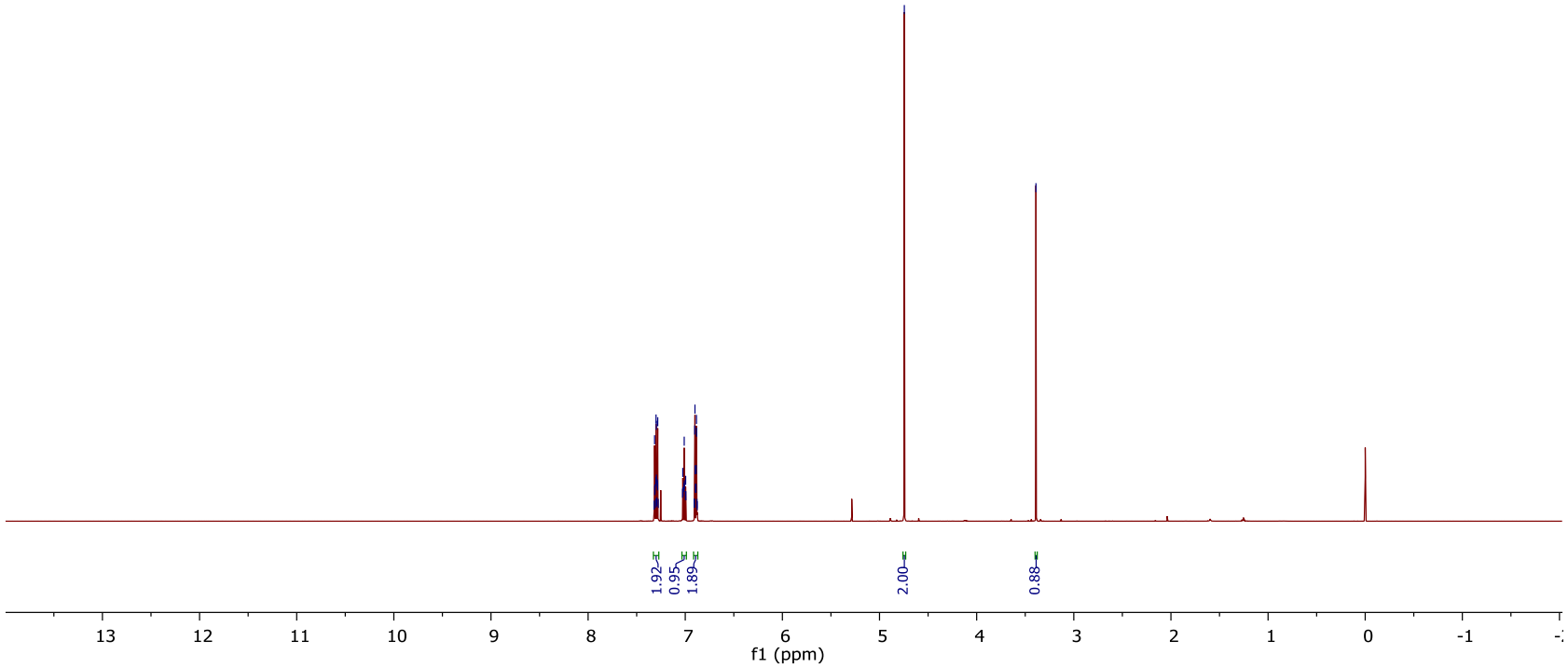


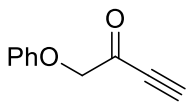




ESI-17

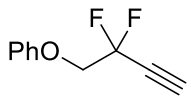
^{1}H NMR (500 MHz, $CDCl_3$)





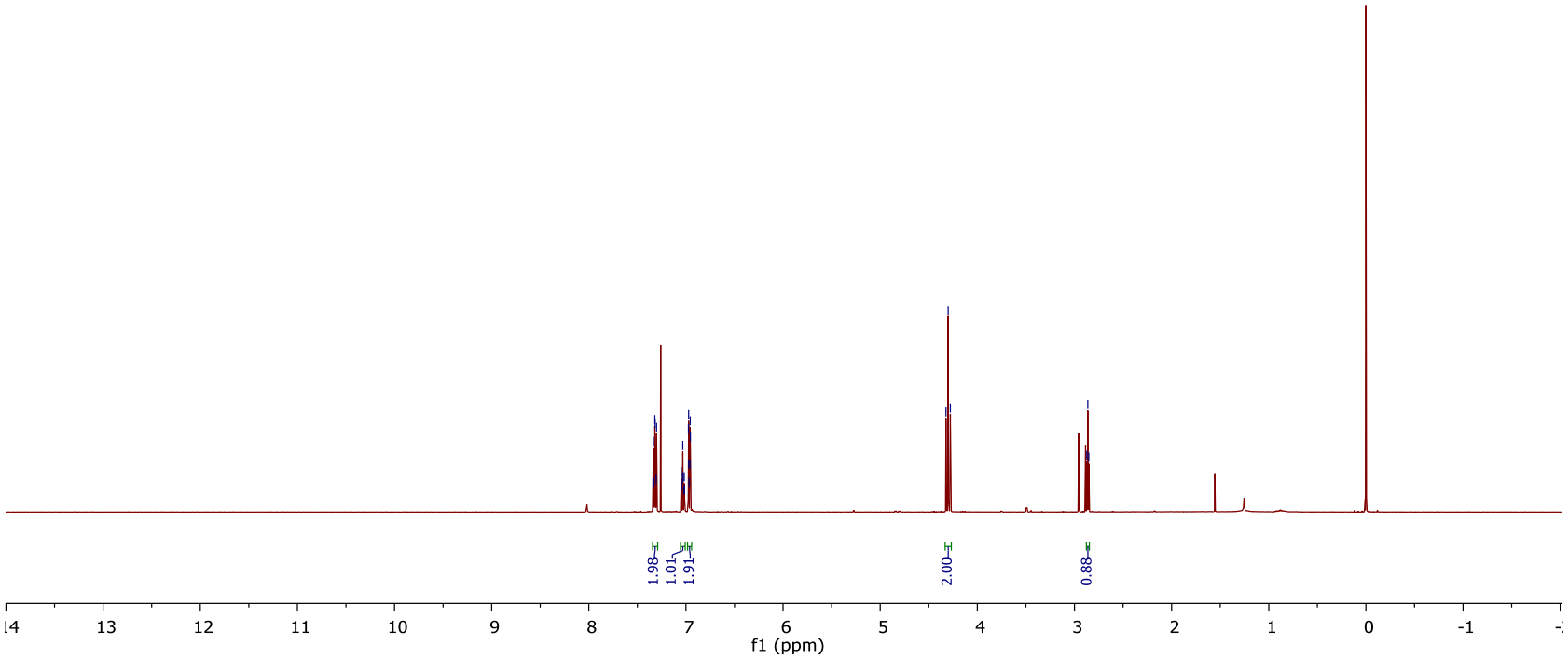
ESI-17

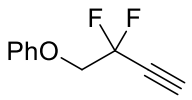
^{13}C NMR (126 MHz, $CDCl_3$)



ESI-18

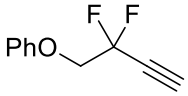
^{1}H NMR (500 MHz, $CDCl_3$)





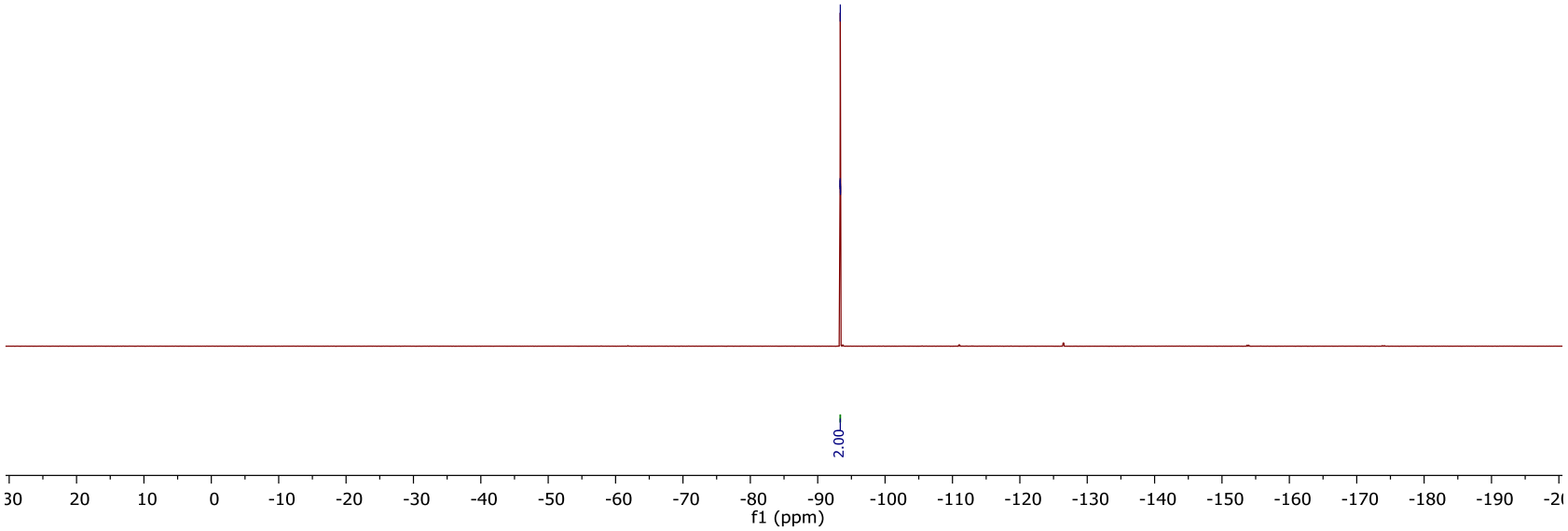
ESI-18

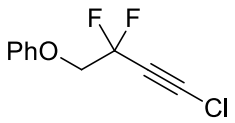
^{13}C NMR (126 MHz, $CDCl_3$)



ESI-18

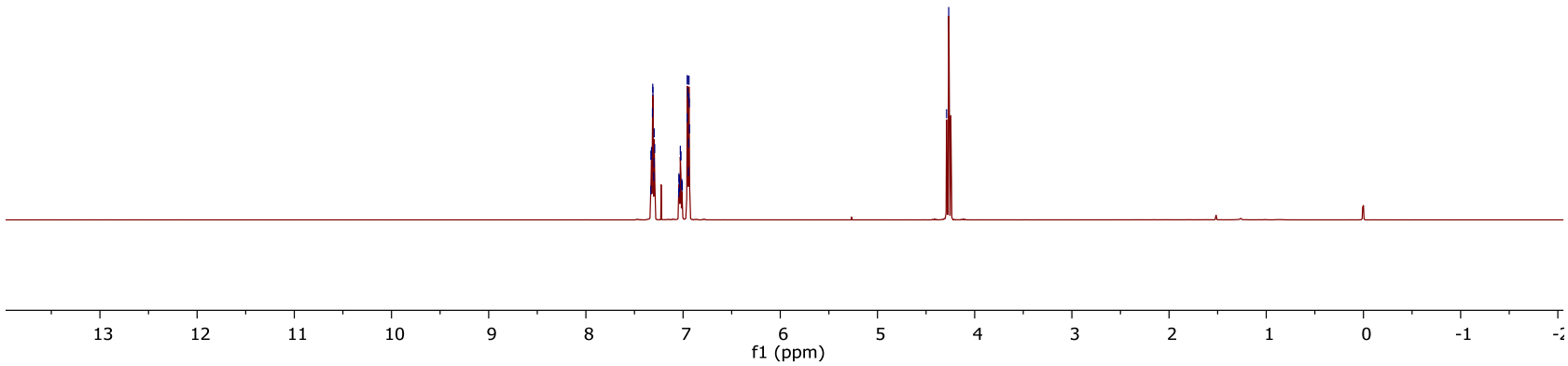
^{19}F NMR (470 MHz, $CDCl_3$)

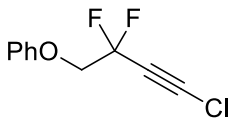




5a

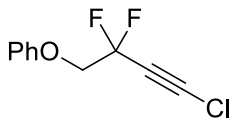
^{1}H NMR (500 MHz, $CDCl_3$)





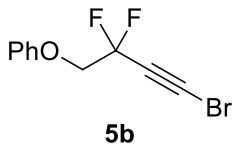
5a

^{13}C NMR (126 MHz, $CDCl_3$)



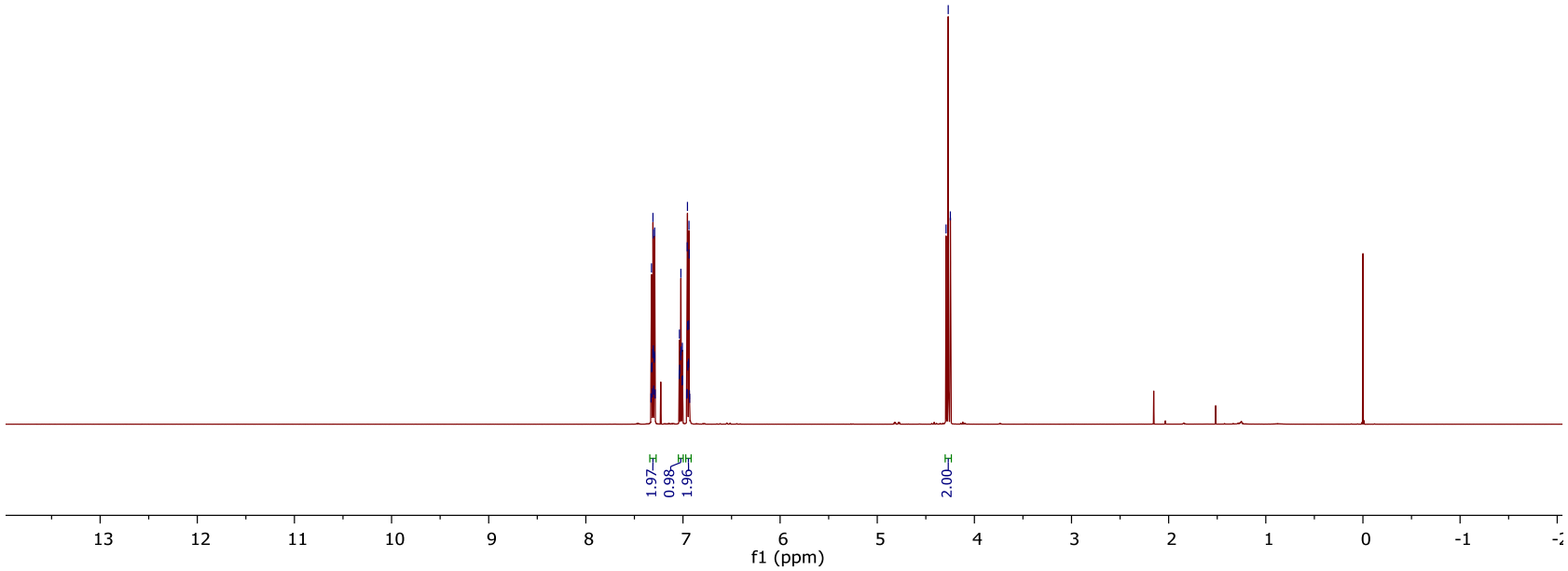
5a

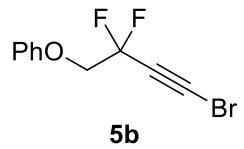
^{19}F NMR (470 MHz, $CDCl_3$)



5b

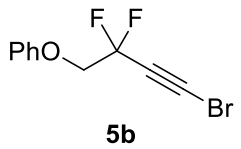
^{1}H NMR (500 MHz, $CDCl_3$)





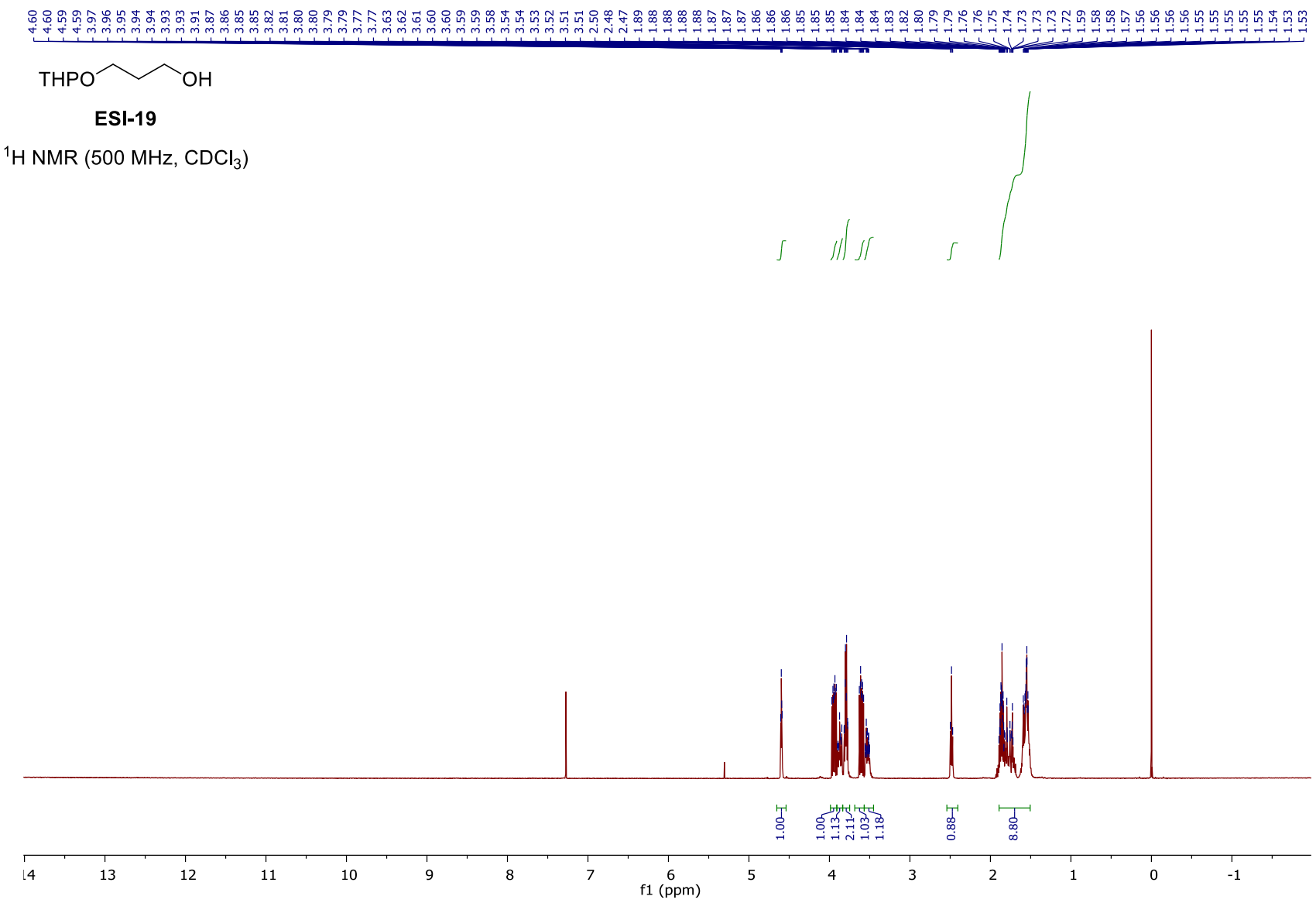
5b

^{13}C NMR (126 MHz, $CDCl_3$)



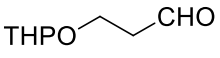
5b

^{19}F NMR (470 MHz, $CDCl_3$)



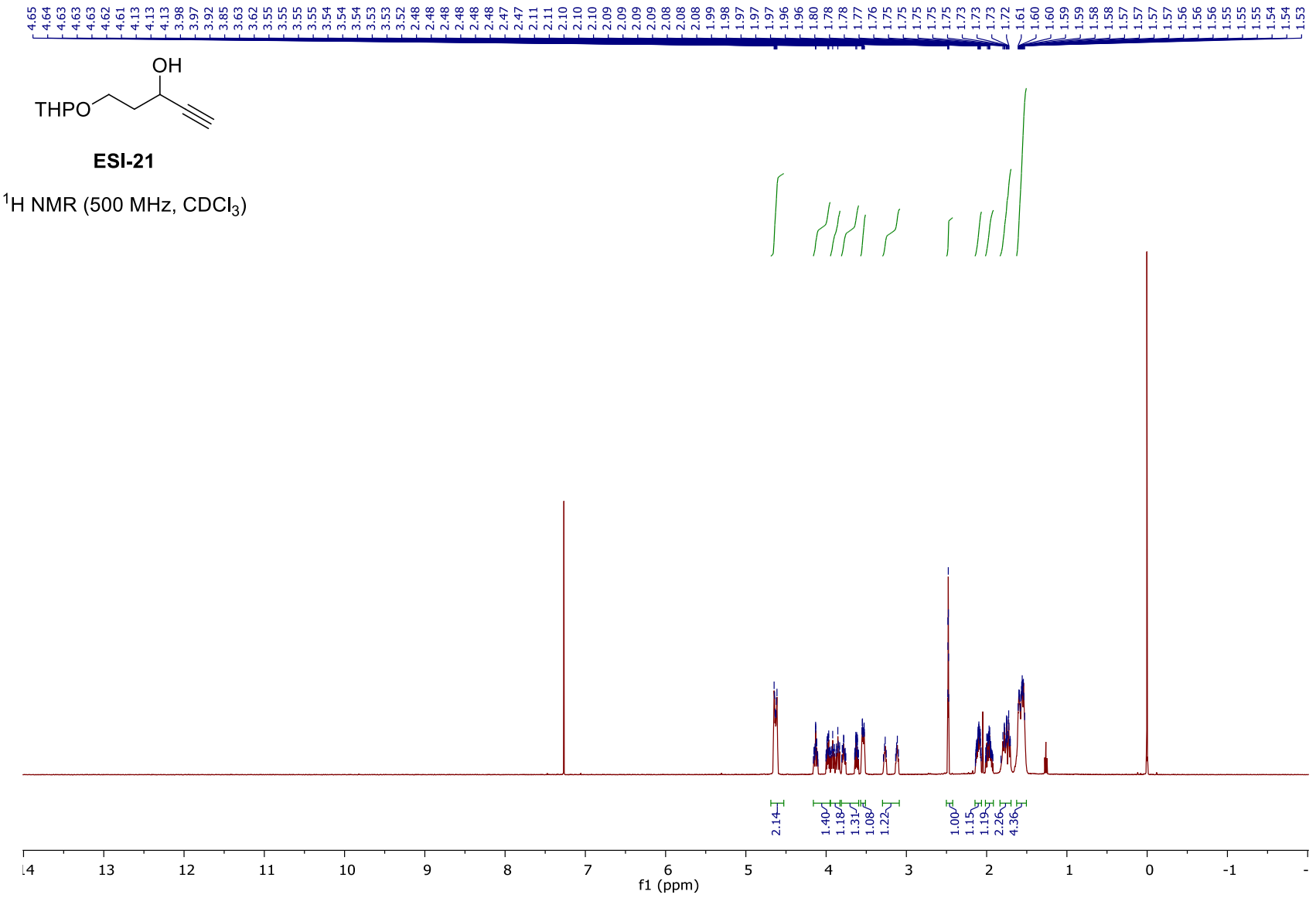
ESI-19

^{1}H NMR (500 MHz, $CDCl_3$)



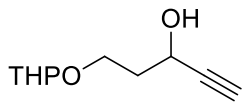
ESI-20

^{1}H NMR (500 MHz, $CDCl_3$)



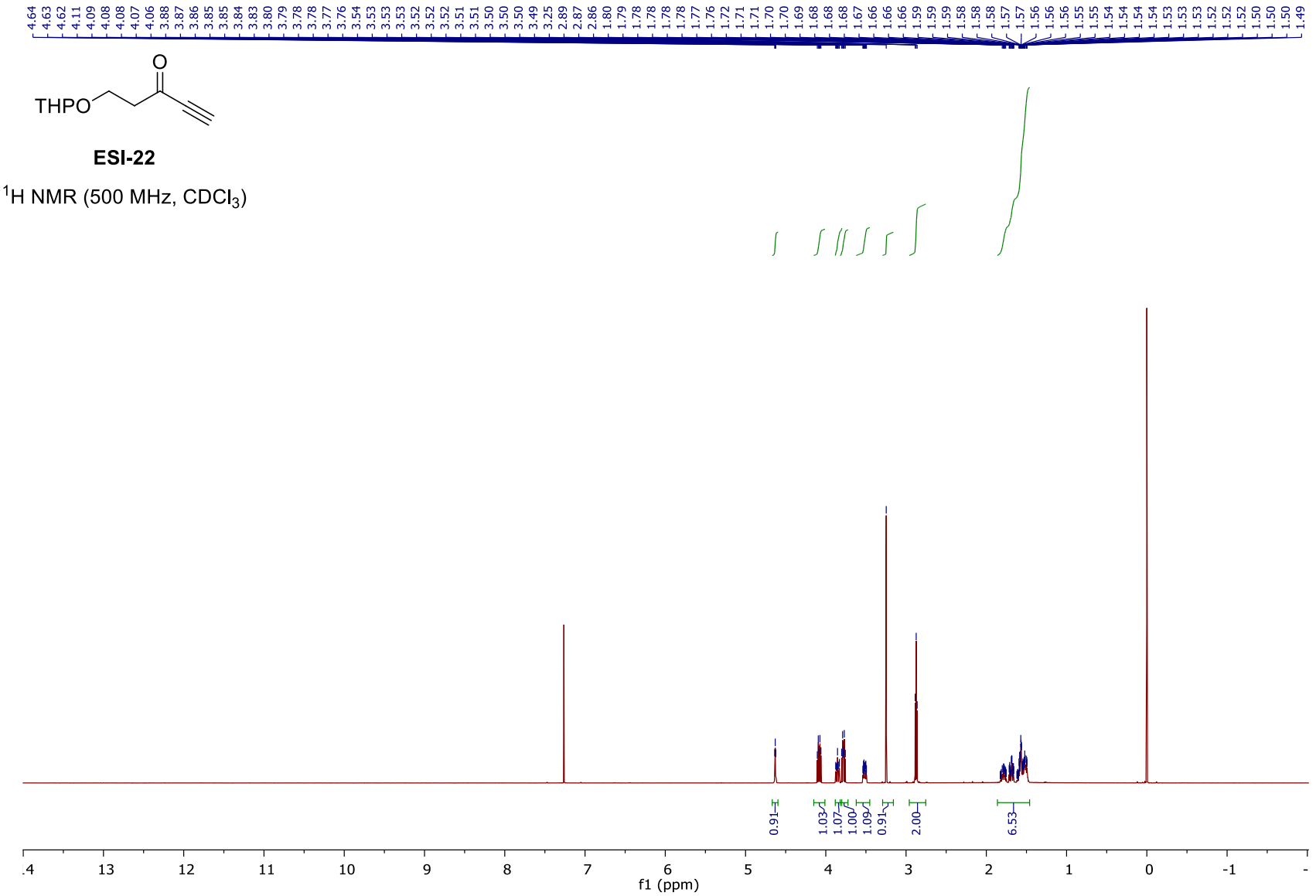
ESI-21

^{1}H NMR (500 MHz, $CDCl_3$)



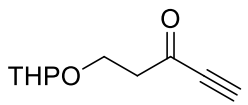
ESI-21

^{13}C NMR (126 MHz, $CDCl_3$)



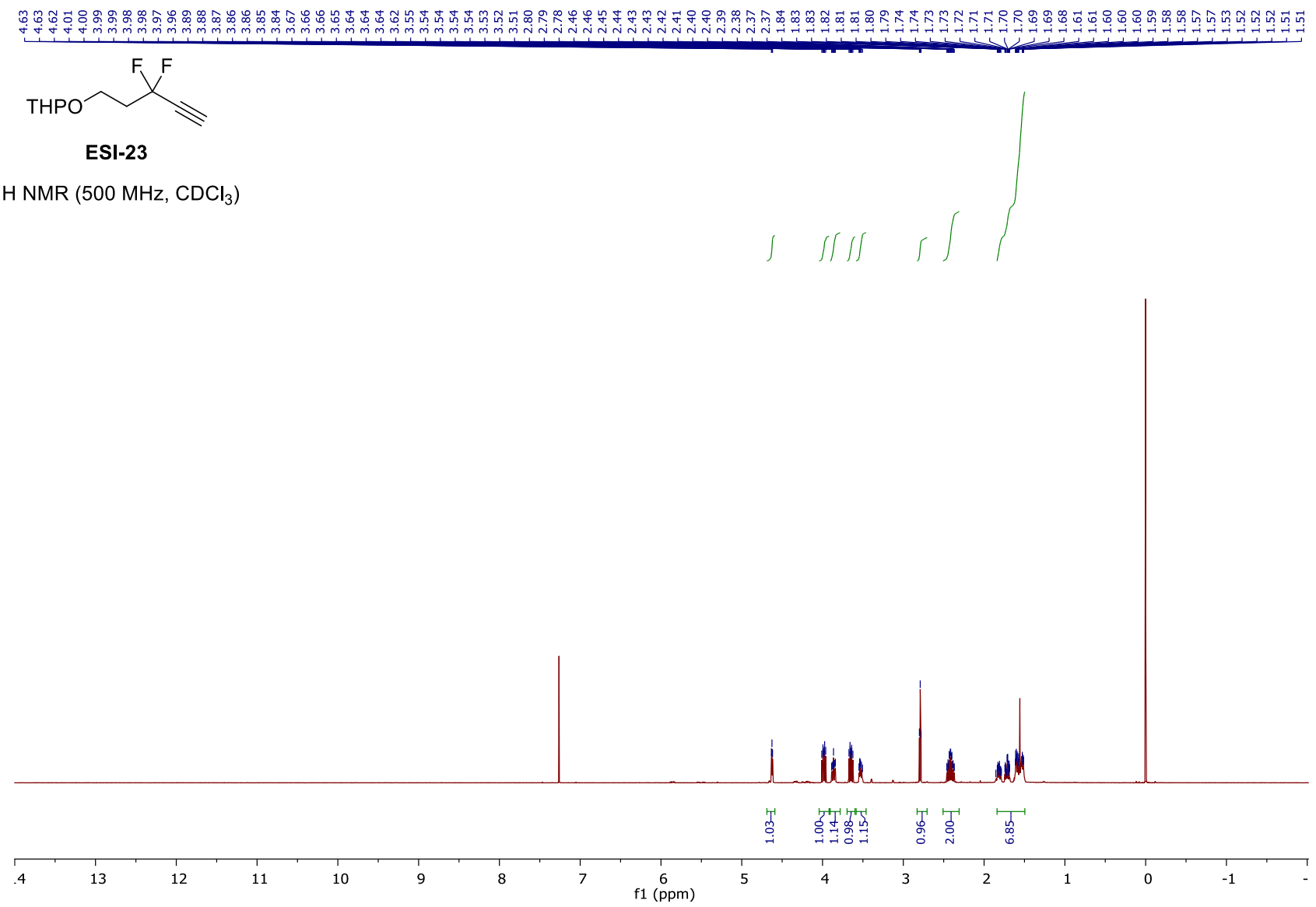
ESI-22

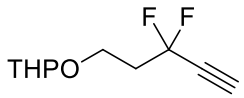
^{1}H NMR (500 MHz, $CDCl_3$)



ESI-22

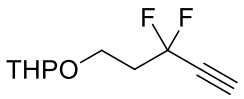
^{13}C NMR (126 MHz, $CDCl_3$)


F F
THPO
ESI-23
1H NMR (500 MHz, CDCl3)
1.03
1.00
1.14
0.98
1.15
0.96
2.00
6.85
f1 (ppm)



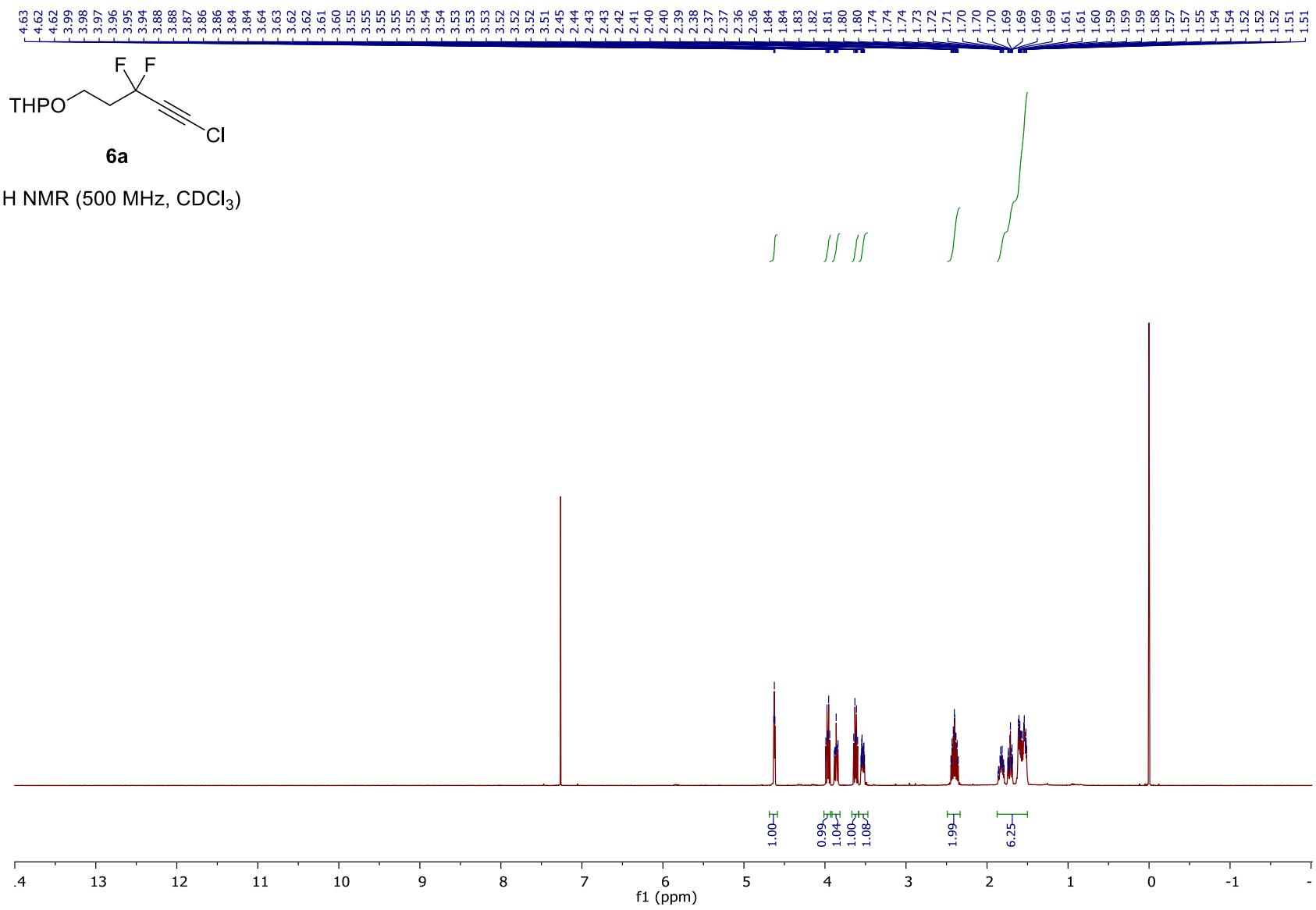
ESI-23

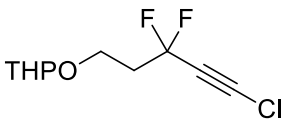
^{13}C NMR (126 MHz, $CDCl_3$)



ESI-23

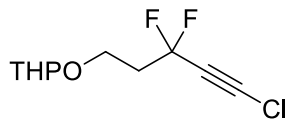
^{19}F NMR (470 MHz, $CDCl_3$)


F F
THPO
Cl
6a
1H NMR (500 MHz, CDCl3)
1.00
0.99
1.04
1.00
1.08
1.99
6.25
f1 (ppm)



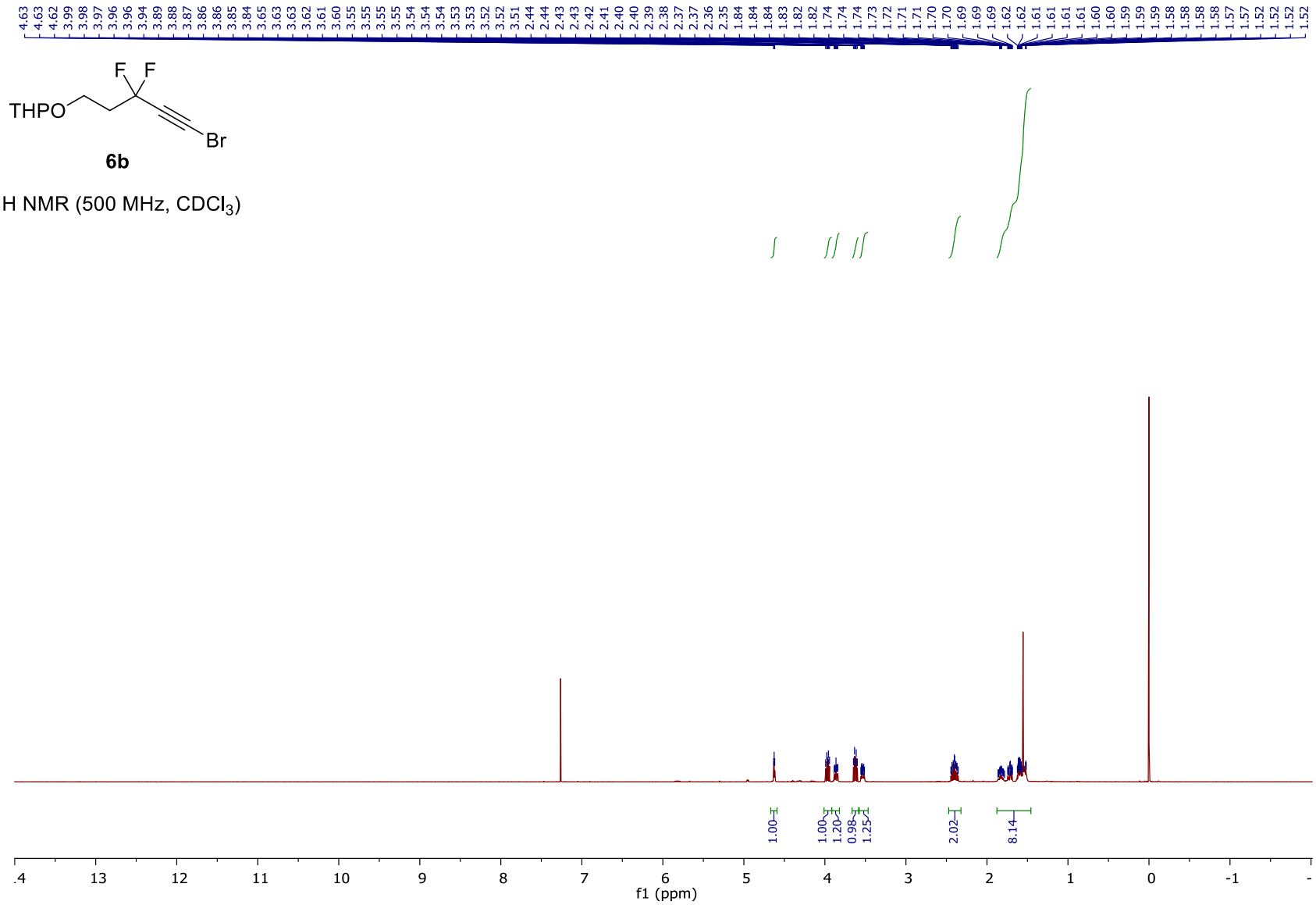
6a

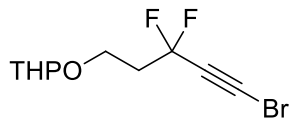
^{13}C NMR (126 MHz, $CDCl_3$)



6a

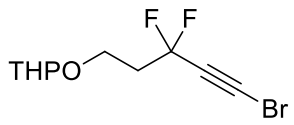
^{19}F NMR (470 MHz, $CDCl_3$)


F F
THPO
Br
6b
1H NMR (500 MHz, CDCl3)
1.00
1.00
1.20
0.98
1.25
2.02
8.14
f1 (ppm)



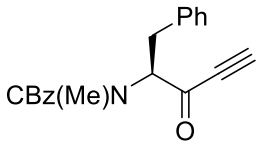
6b

^{13}C NMR (126 MHz, $CDCl_3$)



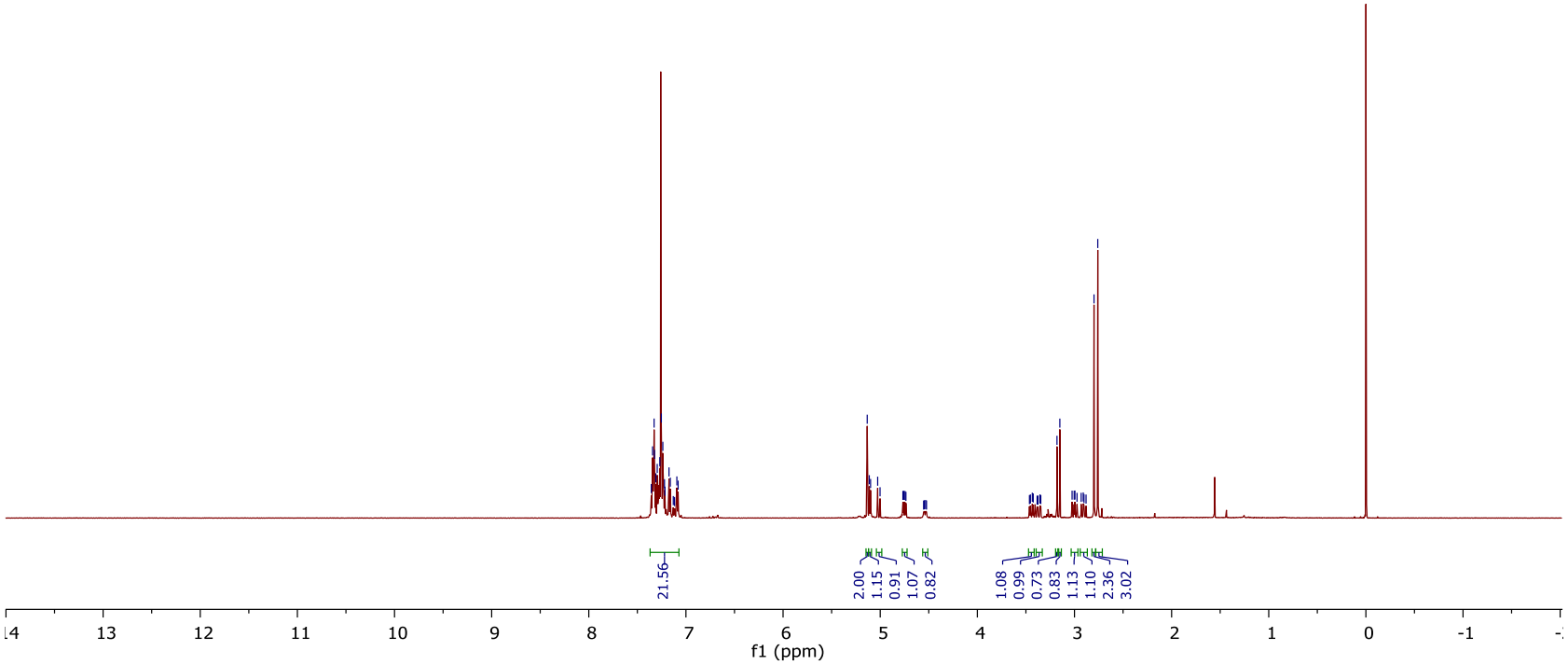
6b

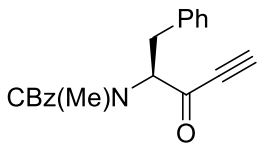
^{19}F NMR (470 MHz, $CDCl_3$)



ESI-24

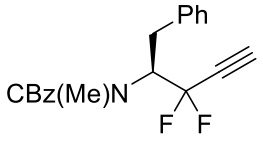
^{1}H NMR (500 MHz, $CDCl_3$)





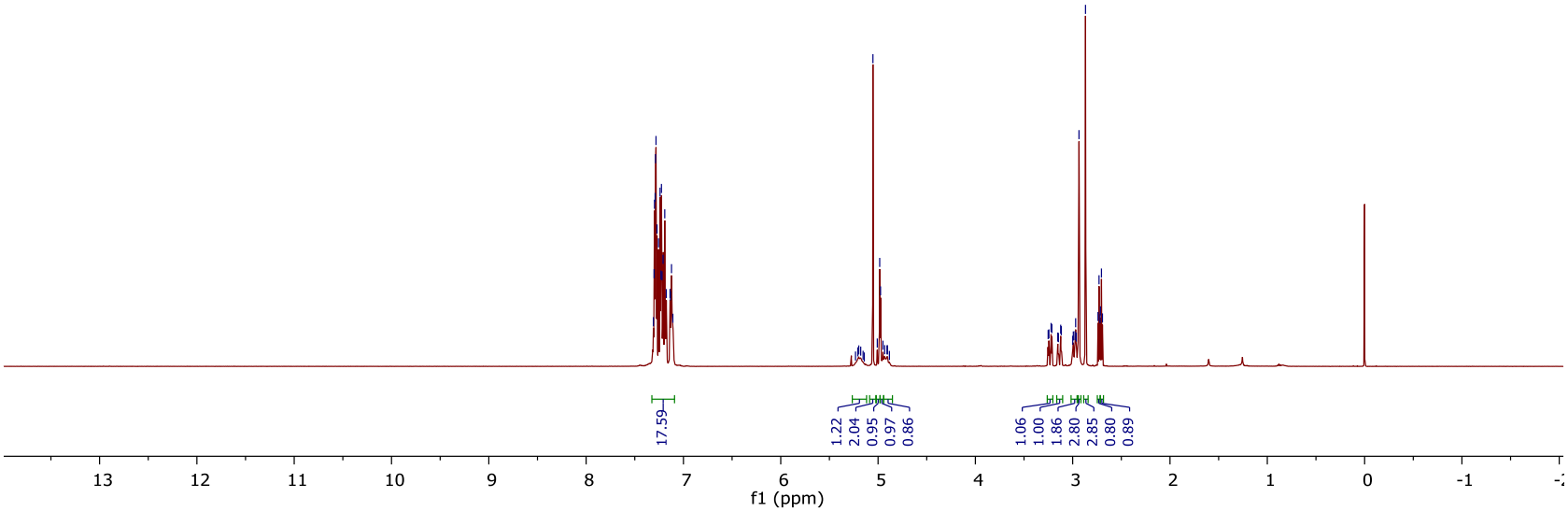
ESI-24

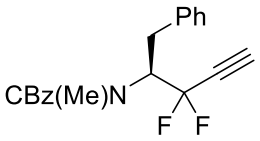
^{13}C NMR (126 MHz, $CDCl_3$)



ESI-25

^{1}H NMR (500 MHz, $CDCl_3$)

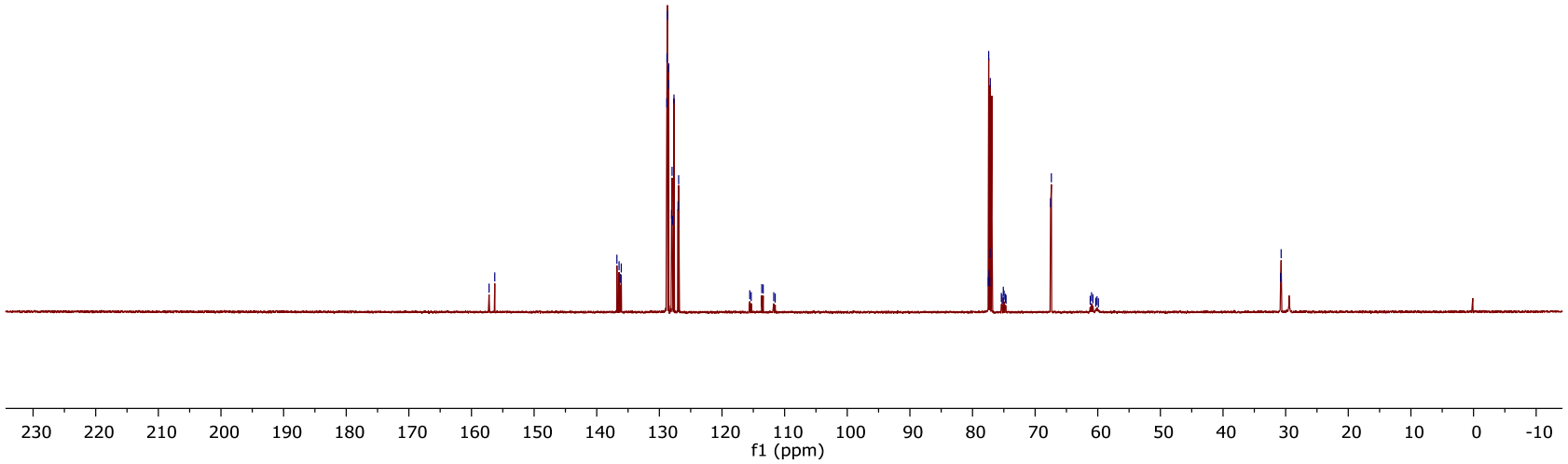


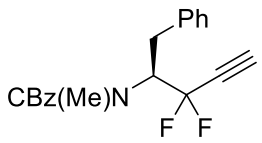


ESI-25

^{13}C NMR (126 MHz, $CDCl_3$)

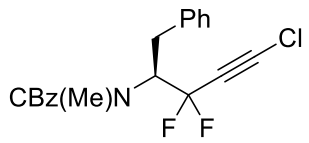
157.19
156.28
136.78
136.43
136.25
136.08
128.80
128.78
128.73
128.51
128.50
128.05
127.97
127.90
127.67
127.02
126.92
115.56
115.34
113.65
113.42
111.74
111.51
77.47
77.41
77.36
77.25
77.20
77.16
75.40
75.28
75.08
74.96
74.77
74.65
67.53
67.41
61.20
60.99
60.77
60.33
60.11
59.90
30.82
30.72





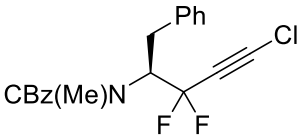
ESI-25

^{19}F NMR (470 MHz, $CDCl_3$)



7a

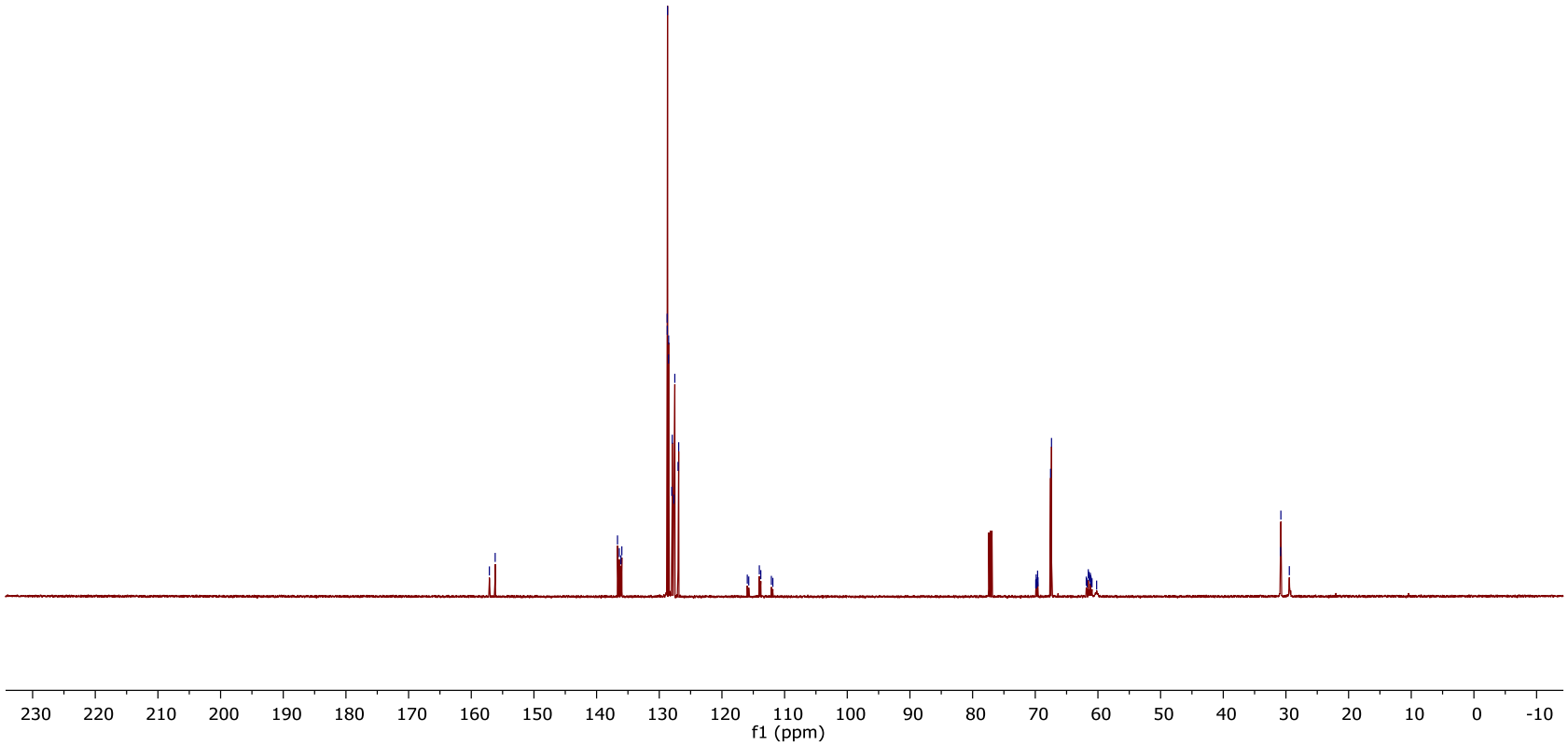
^{1}H NMR (500 MHz, $CDCl_3$)

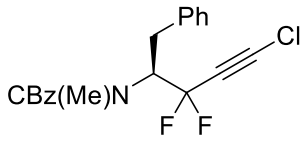


7a

^{13}C NMR (126 MHz, $CDCl_3$)

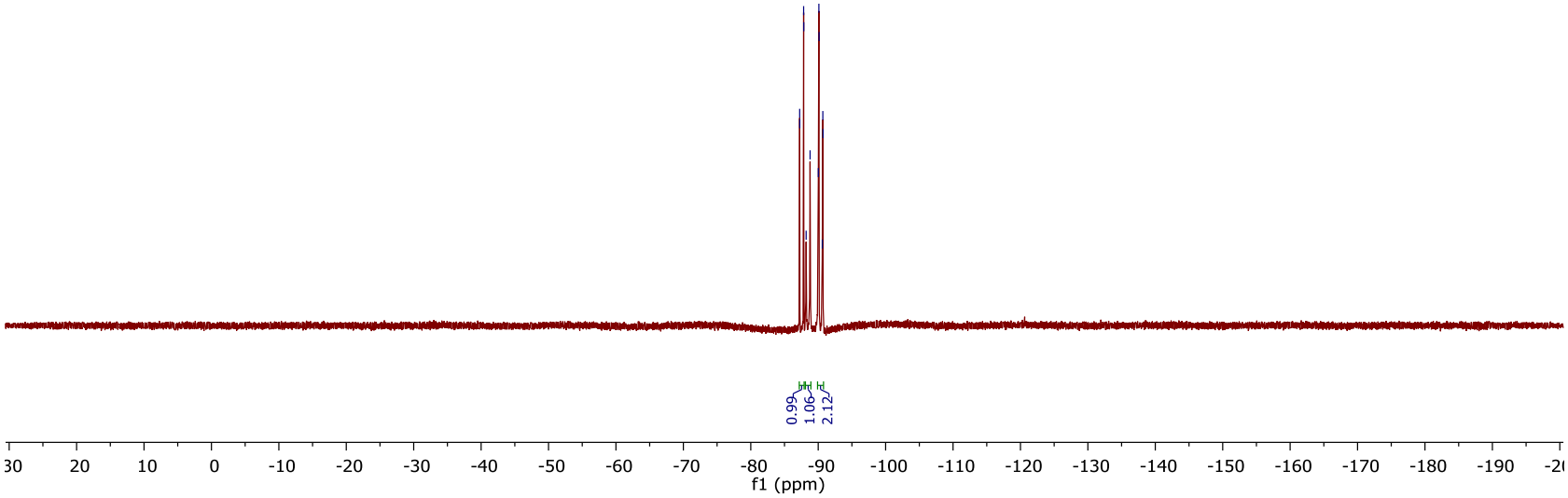
157.11
156.19
136.66
136.38
136.12
135.97
128.74
128.72
128.68
128.53
128.50
128.01
127.93
127.67
127.52
127.00
126.90
115.95
115.72
114.03
113.80
112.11
111.87
69.92
69.85
69.79
69.69
69.62
69.56
67.56
67.41
61.86
61.74
61.54
61.41
61.21
61.17
61.15
61.08
60.94
60.21
30.86
30.81
29.46

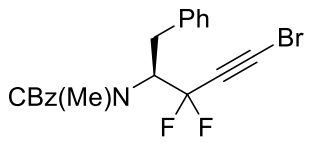




7a

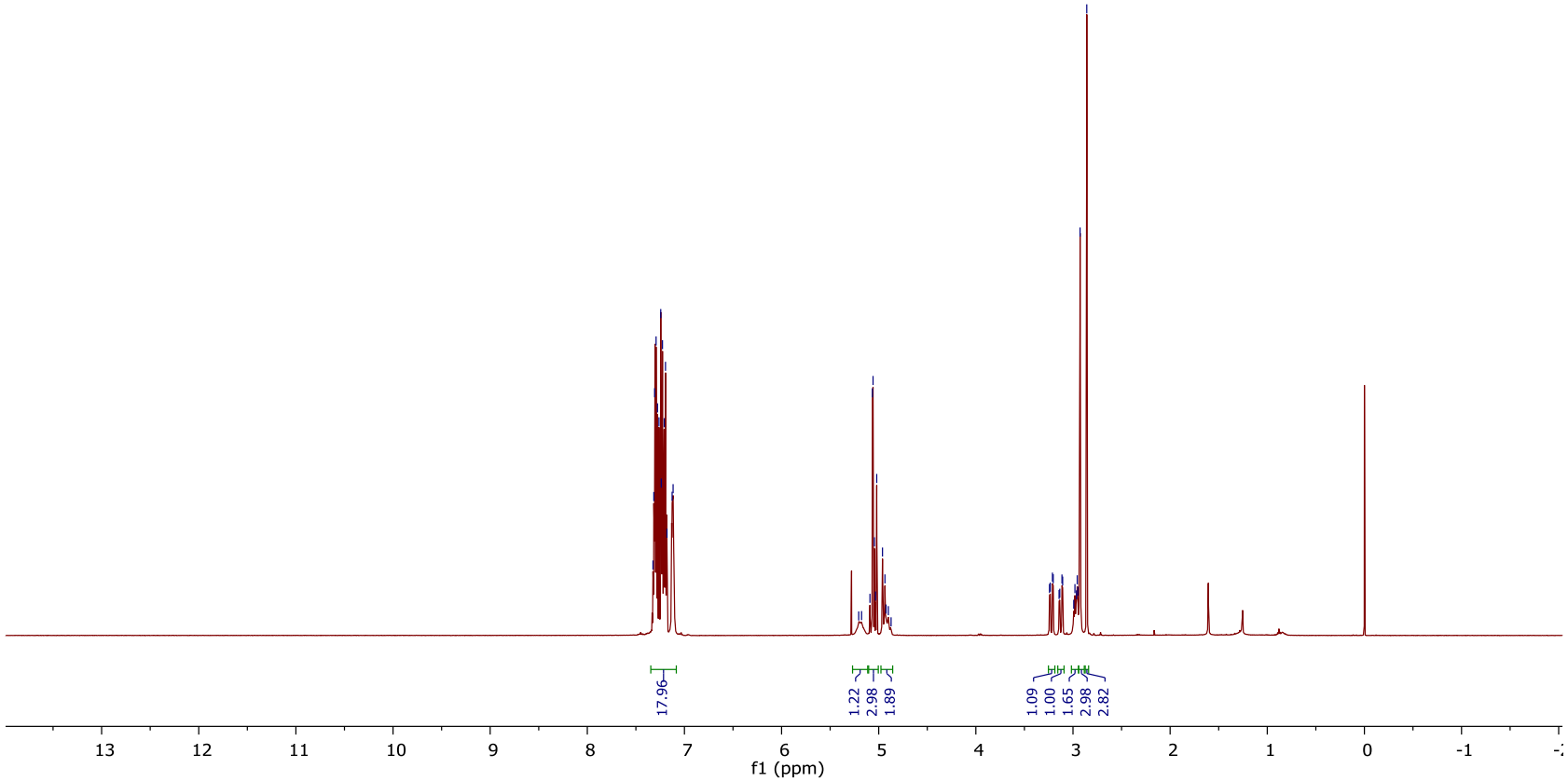
^{19}F NMR (470 MHz, $CDCl_3$)

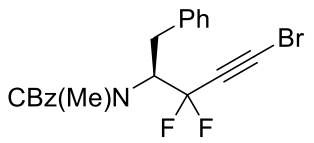




7b

^{1}H NMR (500 MHz, $CDCl_3$)

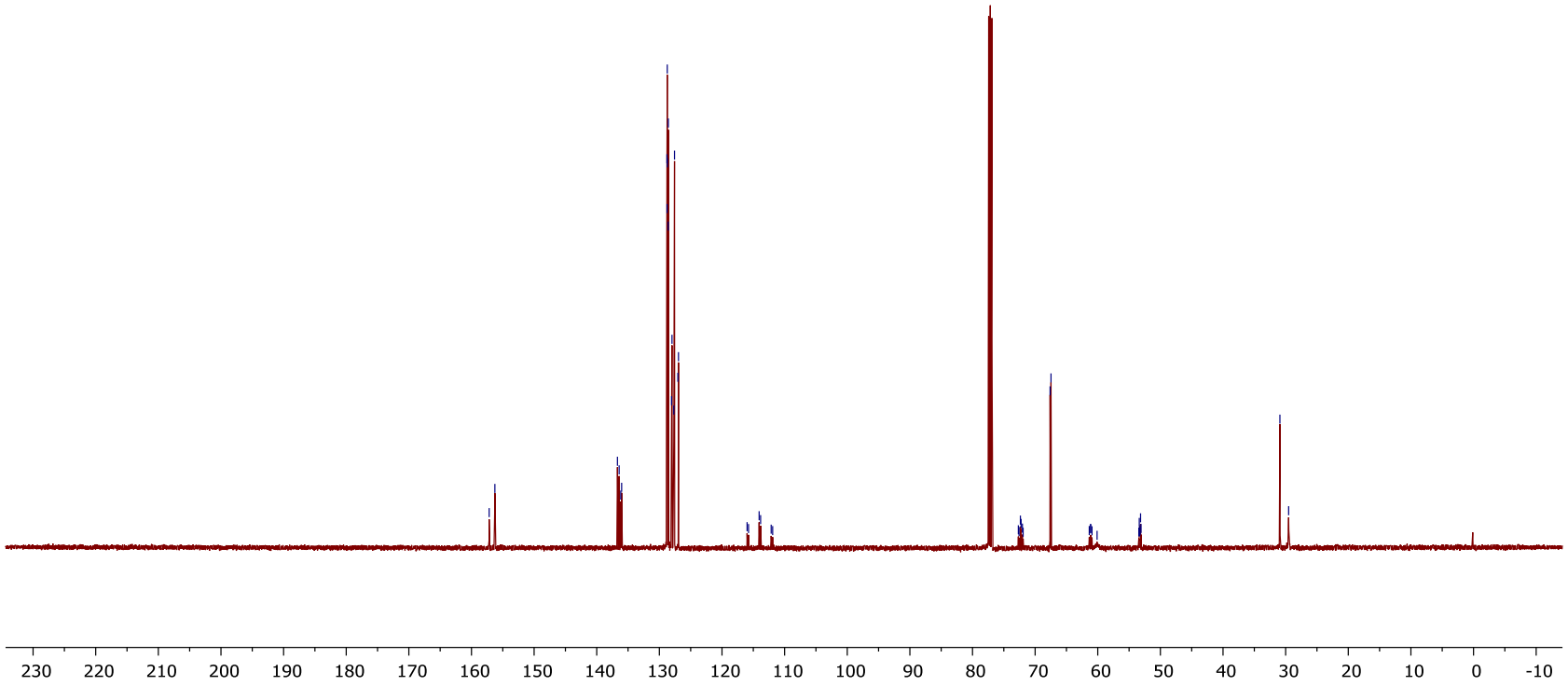


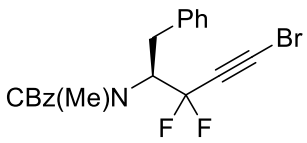


7b

^{13}C NMR (126 MHz, $CDCl_3$)

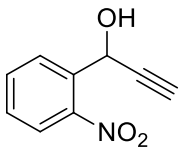
157.17
156.26
136.69
136.42
136.17
136.02
128.79
128.77
128.74
128.73
128.59
128.57
128.04
127.98
127.70
127.58
127.05
126.95
115.99
115.76
114.07
113.84
112.15
111.91
72.68
72.57
72.35
72.24
72.03
71.92
67.61
67.47
61.36
61.15
61.13
60.92
60.11
53.44
53.37
53.30
53.24
53.17
53.09
30.92
29.52





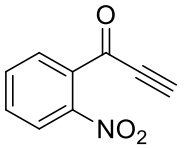
7b

^{19}F NMR (470 MHz, $CDCl_3$)



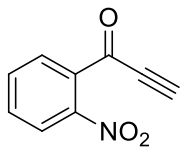
ESI-26

^{1}H NMR (500 MHz, $CDCl_3$)



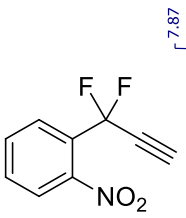
ESI-27

^{1}H NMR (500 MHz, $CDCl_3$)



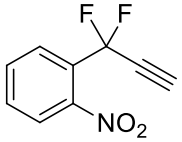
ESI-27

^{13}C NMR (126 MHz, $CDCl_3$)



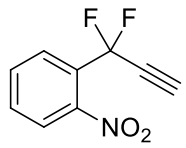
ESI-28

^{1}H NMR (500 MHz, $CDCl_3$)



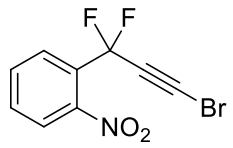
ESI-28

^{13}C NMR (126 MHz, $CDCl_3$)



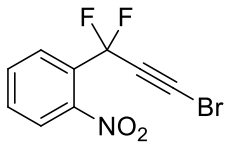
ESI-28

^{19}F NMR (470 MHz, $CDCl_3$)



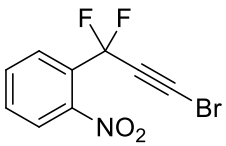
8b

^{1}H NMR (500 MHz, $CDCl_3$)



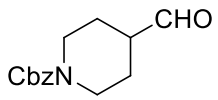
8b

^{13}C NMR (126 MHz, $CDCl_3$)



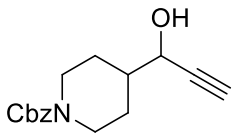
8b

^{19}F NMR (470 MHz, $CDCl_3$)



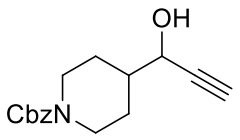
ESI-29

^{1}H NMR (500 MHz, $CDCl_3$)



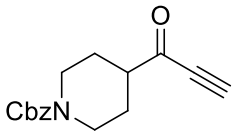
ESI-30

^{1}H NMR (500 MHz, $CDCl_3$)



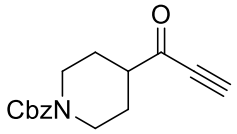
ESI-30

^{13}C NMR (126 MHz, $CDCl_3$)



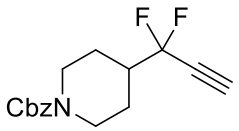
ESI-31

^{1}H NMR (500 MHz, $CDCl_3$)



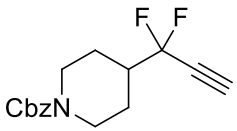
ESI-31

^{13}C NMR (126 MHz, $CDCl_3$)



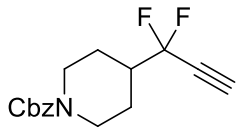
ESI-32

^{1}H NMR (500 MHz, $CDCl_3$)



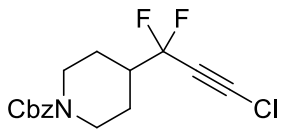
ESI-32

^{13}C NMR (126 MHz, $CDCl_3$)



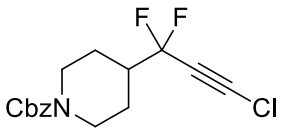
ESI-32

^{19}F NMR (470 MHz, $CDCl_3$)



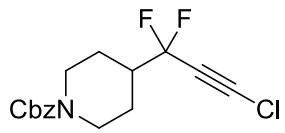
9a

^{1}H NMR (500 MHz, $CDCl_3$)



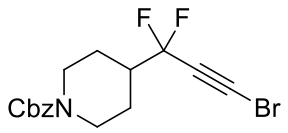
9a

^{13}C NMR (126 MHz, $CDCl_3$)



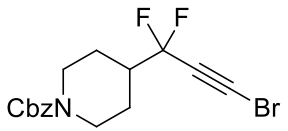
9a

^{19}F NMR (470 MHz, $CDCl_3$)



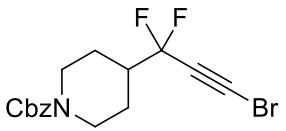
9b

^{1}H NMR (500 MHz, $CDCl_3$)



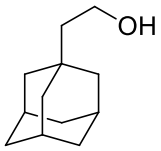
9b

^{13}C NMR (126 MHz, $CDCl_3$)



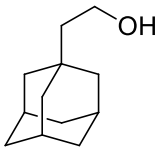
9b

^{19}F NMR (470 MHz, $CDCl_3$)



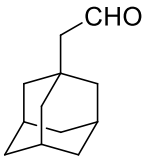
ESI-33

^{1}H NMR (500 MHz, $CDCl_3$)



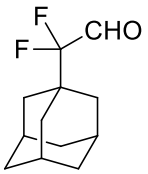
ESI-33

^{13}C NMR (126 MHz, $CDCl_3$)



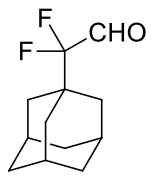
ESI-34

^{1}H NMR (500 MHz, $CDCl_3$)



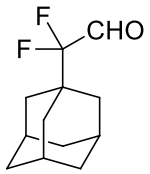
ESI-35

^{1}H NMR (500 MHz, $CDCl_3$)



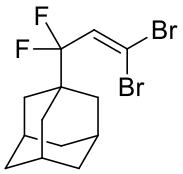
ESI-35

^{13}C NMR (126 MHz, $CDCl_3$)



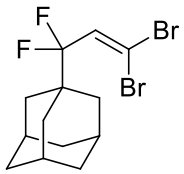
ESI-35

^{19}F NMR (470 MHz, $CDCl_3$)



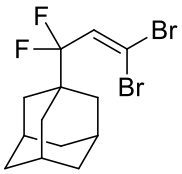
ESI-36

^{1}H NMR (500 MHz, $CDCl_3$)



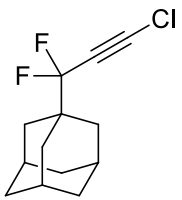
ESI-36

^{13}C NMR (126 MHz, $CDCl_3$)



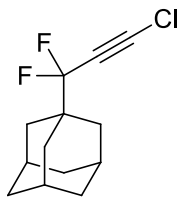
ESI-36

^{19}F NMR (470 MHz, $CDCl_3$)



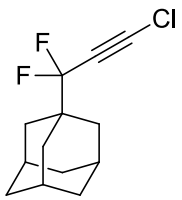
10a

^{1}H NMR (500 MHz, $CDCl_3$)



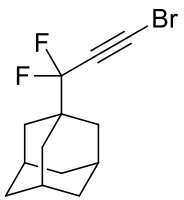
10a

^{13}C NMR (126 MHz, $CDCl_3$)



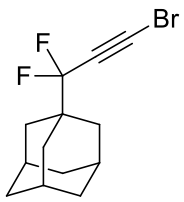
10a

^{19}F NMR (470 MHz, $CDCl_3$)



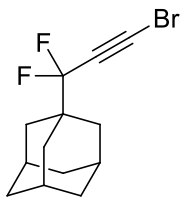
10b

^{1}H NMR (500 MHz, $CDCl_3$)



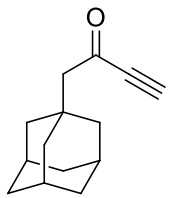
10b

^{13}C NMR (126 MHz, $CDCl_3$)



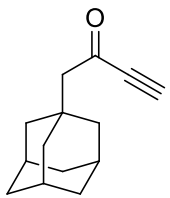
10b

^{19}F NMR (470 MHz, $CDCl_3$)



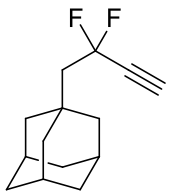
ESI-37

^{1}H NMR (500 MHz, $CDCl_3$)



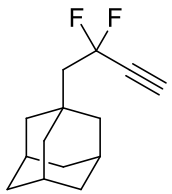
ESI-37

^{13}C NMR (126 MHz, $CDCl_3$)



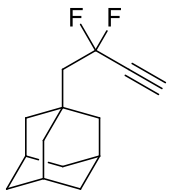
ESI-38

^{1}H NMR (500 MHz, $CDCl_3$)



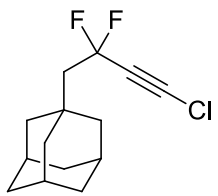
ESI-38

^{13}C NMR (126 MHz, $CDCl_3$)



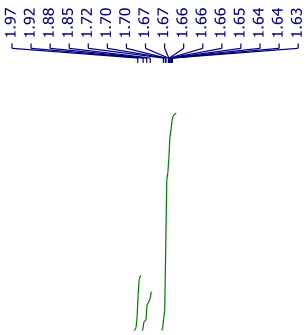
ESI-38

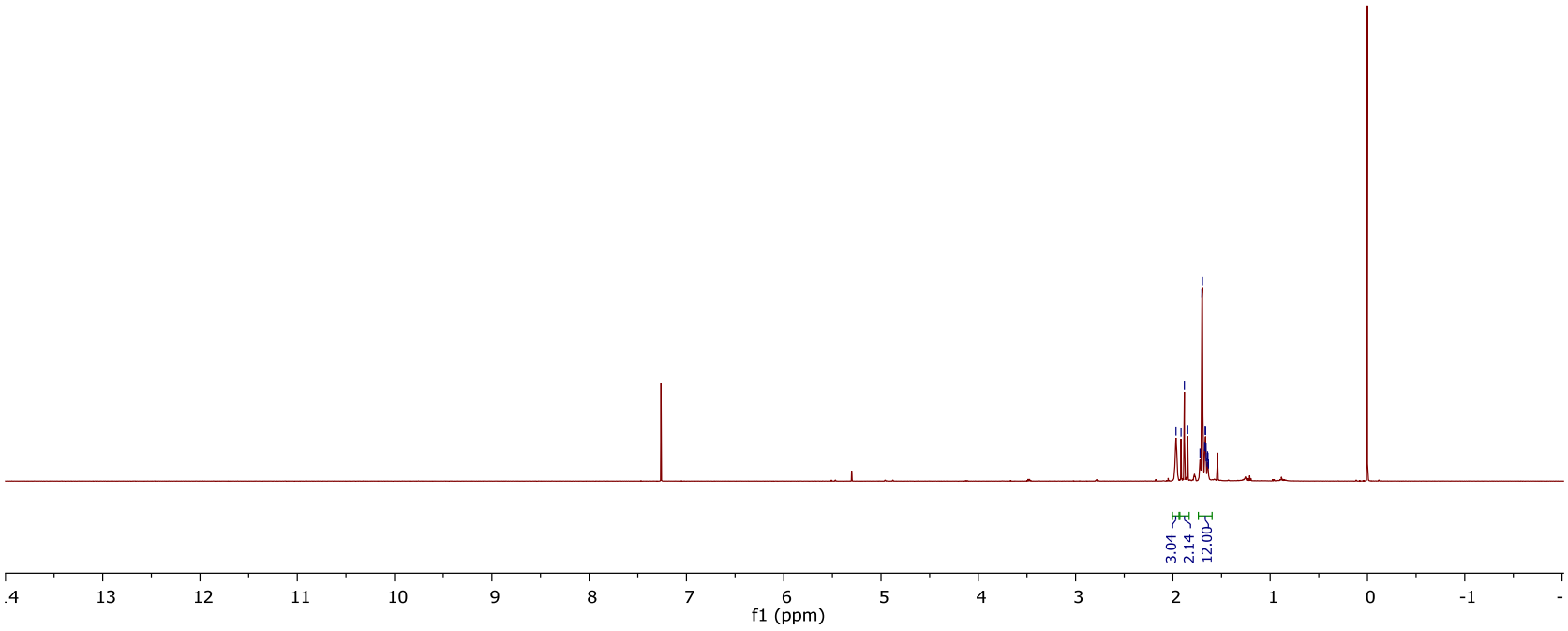
^{19}F NMR (470 MHz, $CDCl_3$)

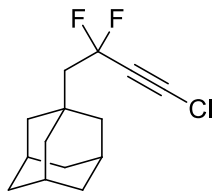


11a

^{1}H NMR (500 MHz, $CDCl_3$)

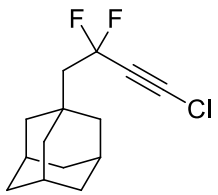






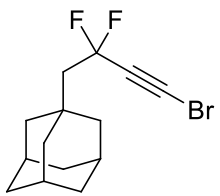
11a

^{13}C NMR (126 MHz, $CDCl_3$)



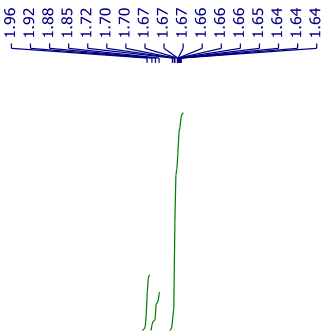
11a

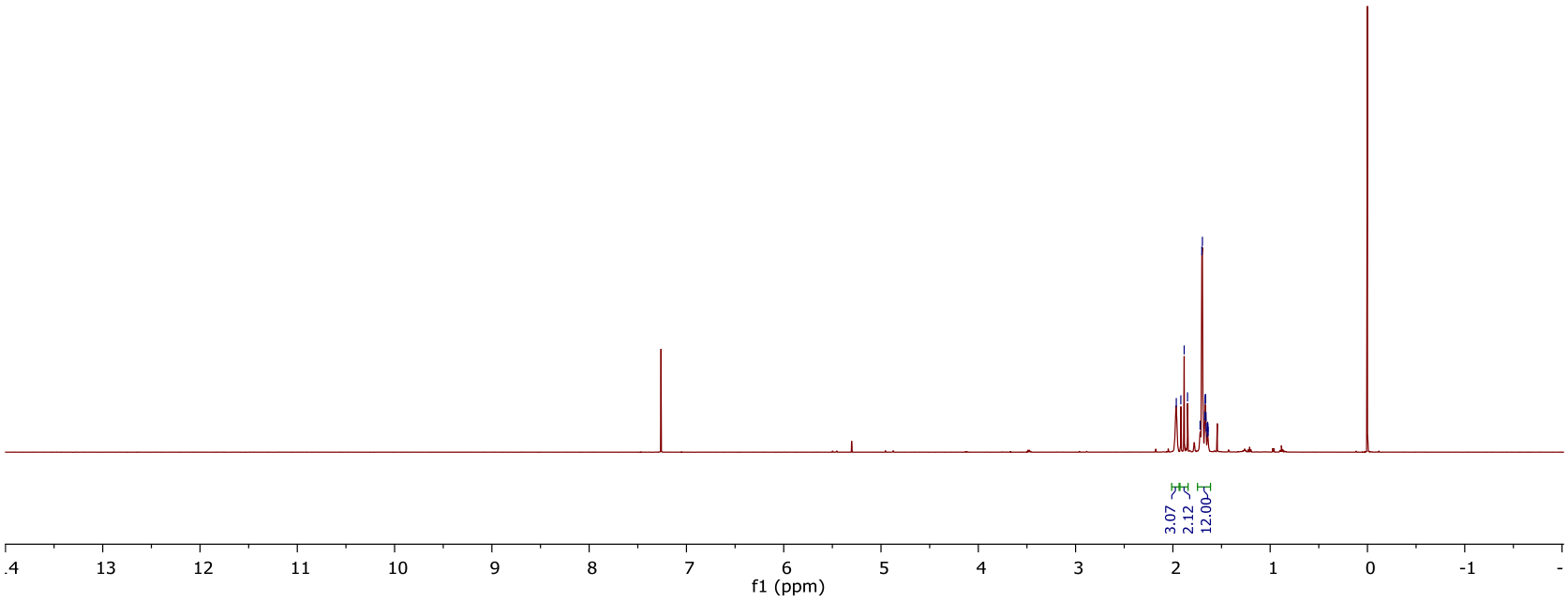
^{19}F NMR (470 MHz, $CDCl_3$)

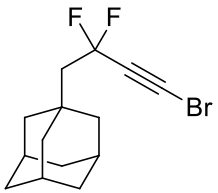


11b

^{1}H NMR (500 MHz, $CDCl_3$)

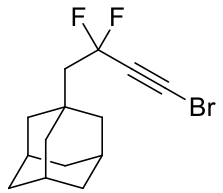






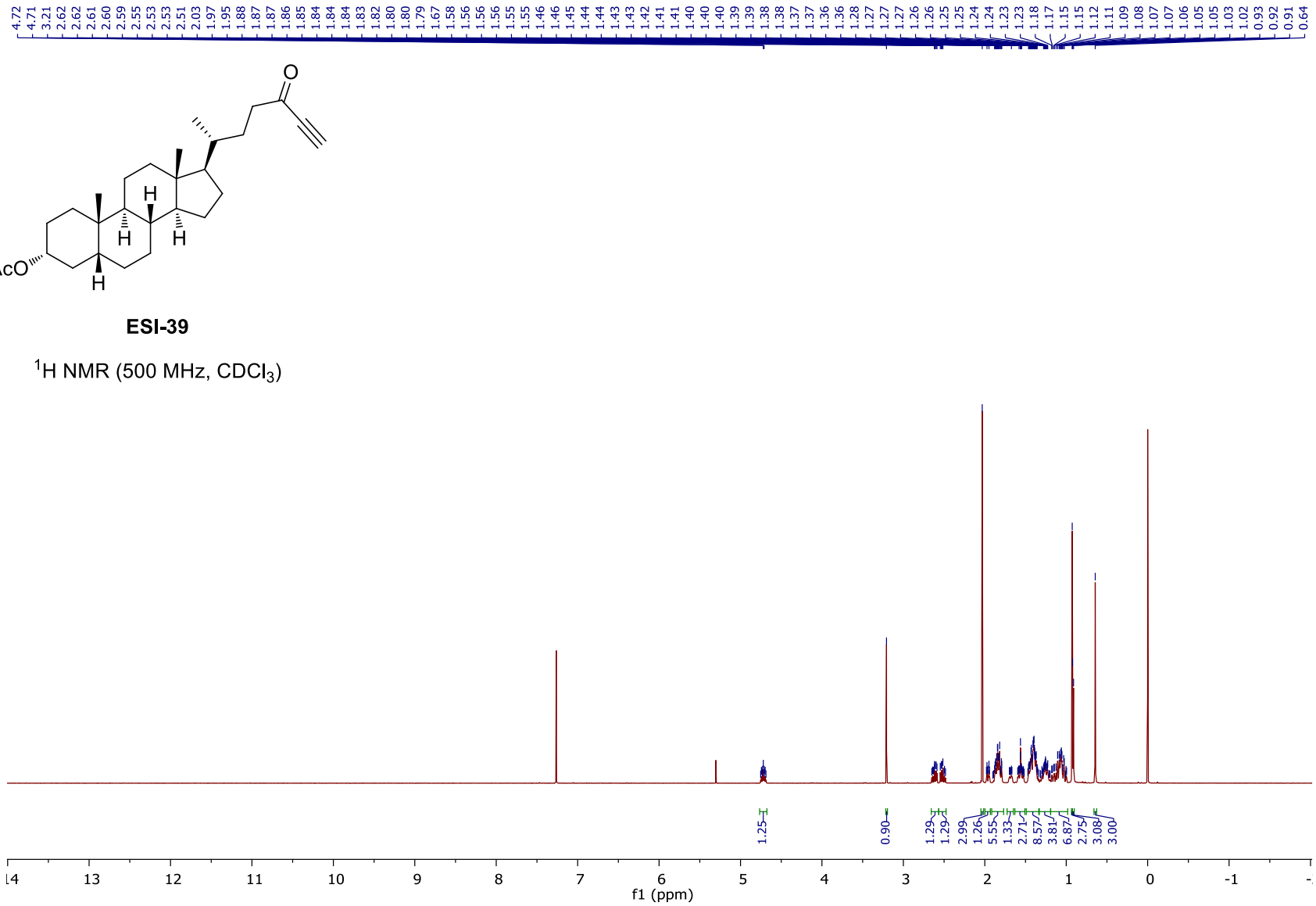
11b

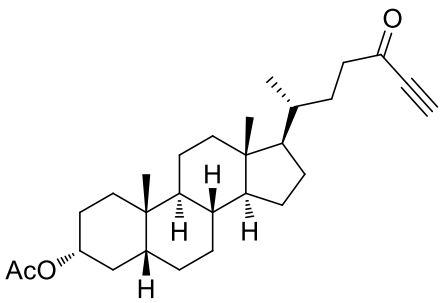
^{13}C NMR (126 MHz, $CDCl_3$)



11b

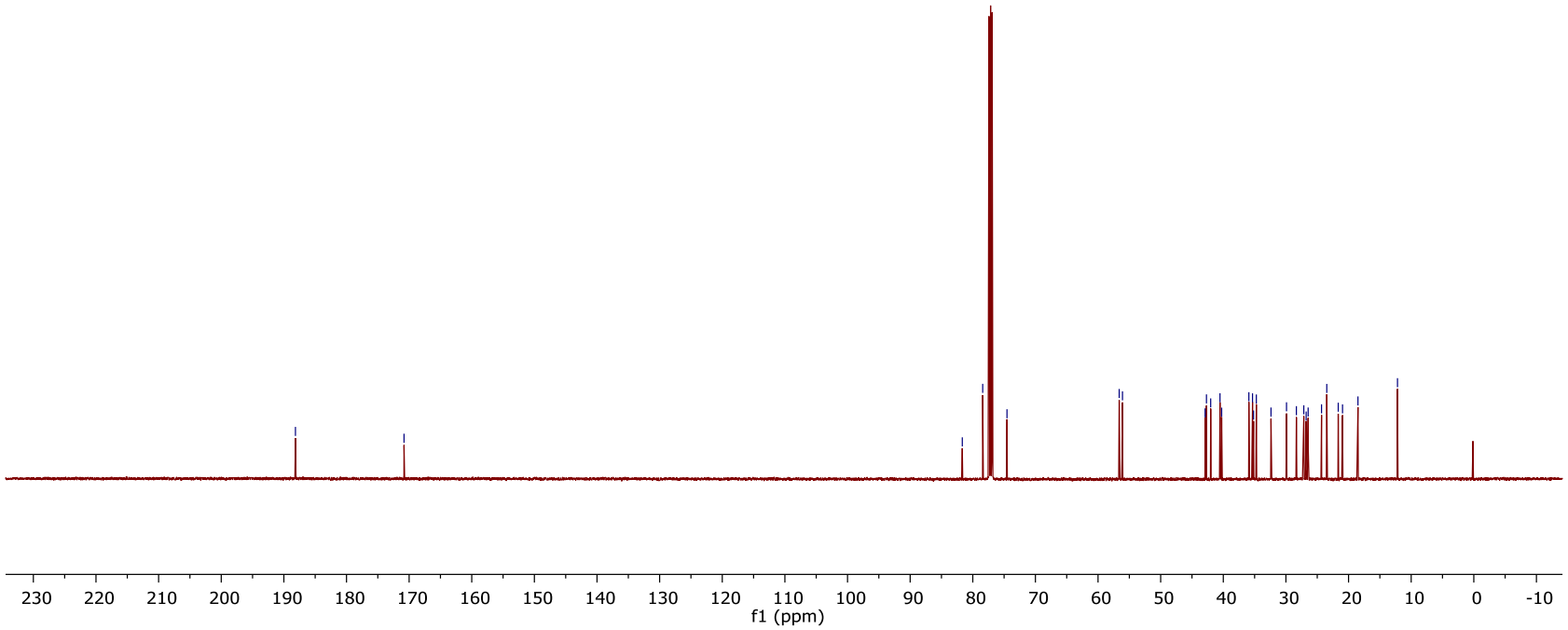
^{19}F NMR (470 MHz, $CDCl_3$)

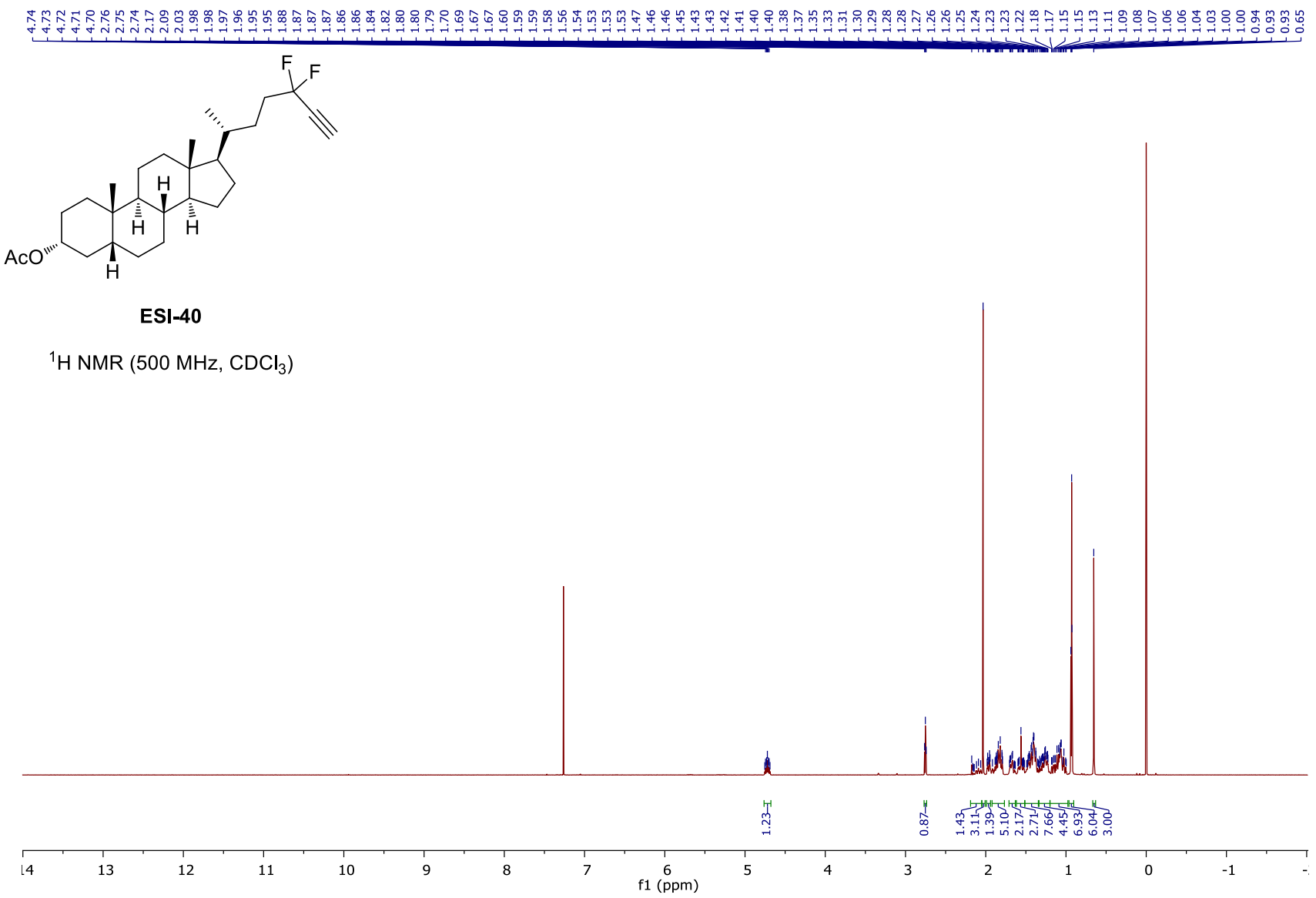

4.72 4.71 3.21 2.62 2.62 2.61 2.60 2.59 2.55 2.53 2.53 2.51 2.03 1.97 1.95 1.88 1.87 1.87 1.86 1.85 1.84 1.84 1.84 1.83 1.82 1.80 1.80 1.79 1.67 1.58 1.56 1.56 1.56 1.55 1.55 1.46 1.46 1.45 1.44 1.44 1.43 1.43 1.42 1.41 1.41 1.40 1.40 1.40 1.39 1.39 1.38 1.38 1.37 1.37 1.36 1.36 1.28 1.27 1.27 1.27 1.26 1.26 1.25 1.25 1.24 1.24 1.23 1.23 1.18 1.17 1.15 1.15 1.12 1.11 1.09 1.08 1.07 1.07 1.06 1.05 1.05 1.03 1.02 0.93 0.92 0.91 0.64
O
H
H
H
AcO
H
ESI-39
1H NMR (500 MHz, CDCl3)
1.25
0.90
1.29
1.29
2.99
1.26
5.55
1.33
2.71
8.57
3.81
6.87
2.75
3.08
3.00
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)



ESI-39

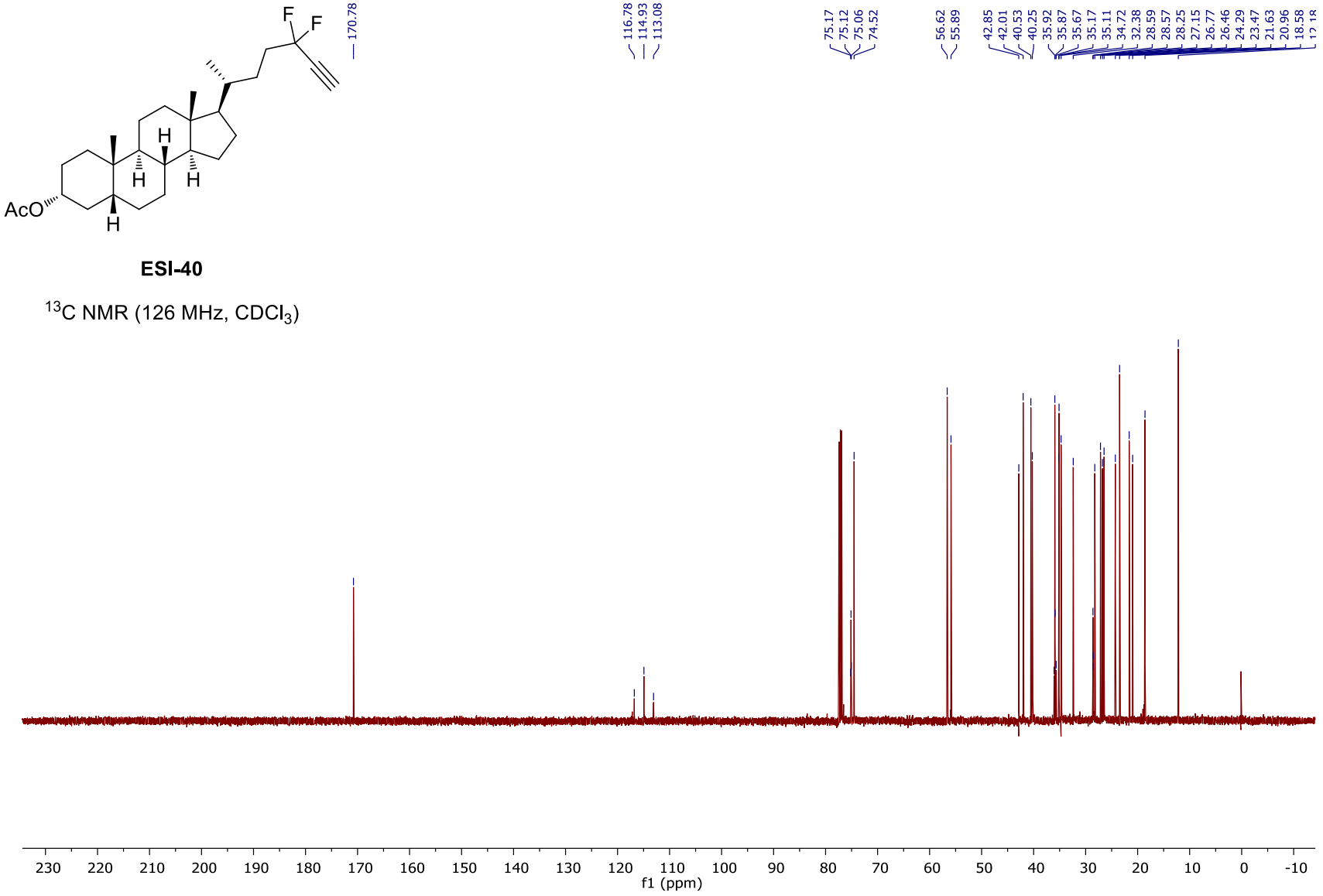
^{13}C NMR (126 MHz, $CDCl_3$)





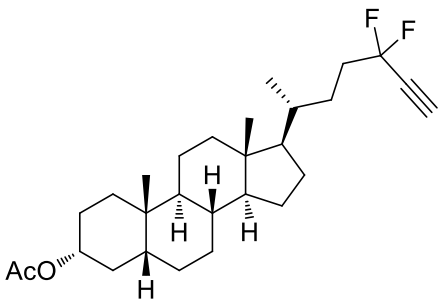
ESI-40

^{1}H NMR (500 MHz, $CDCl_3$)



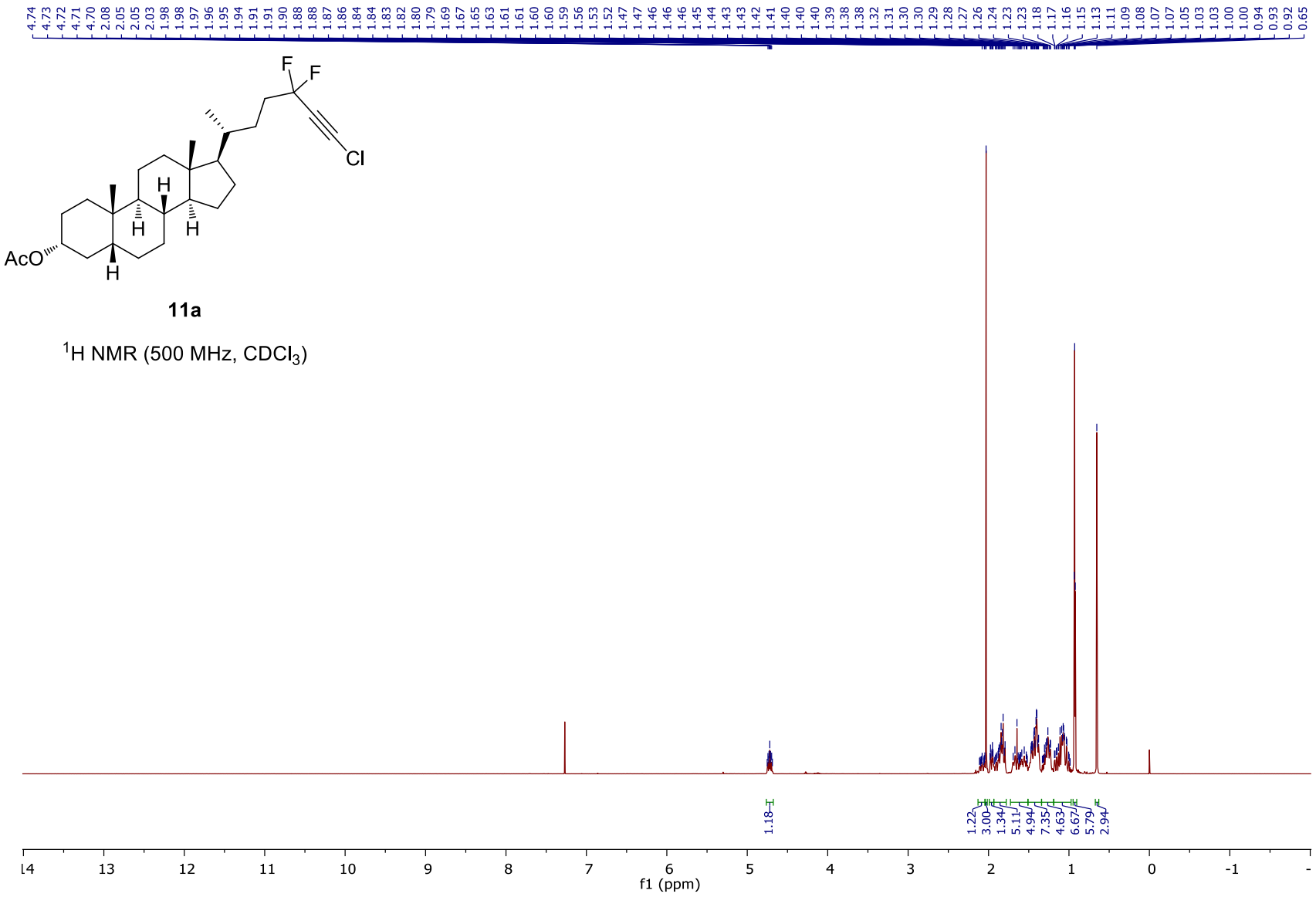
ESI-40

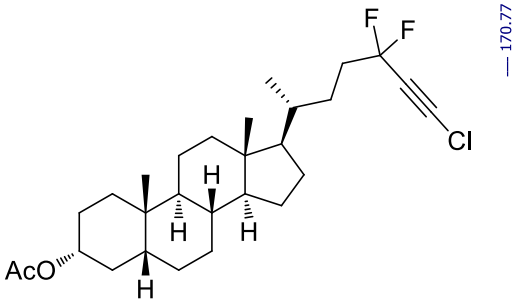
^{13}C NMR (126 MHz, $CDCl_3$)



ESI-40

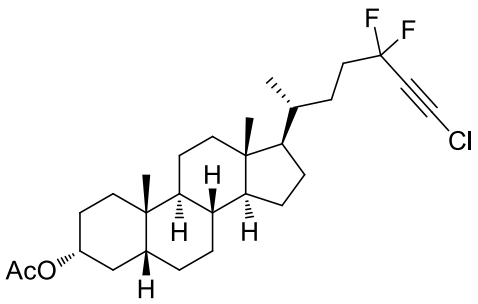
^{19}F NMR (470 MHz, $CDCl_3$)


F
F
Cl
H
H
H
H
AcO
11a
1H NMR (500 MHz, CDCl3)
f1 (ppm)



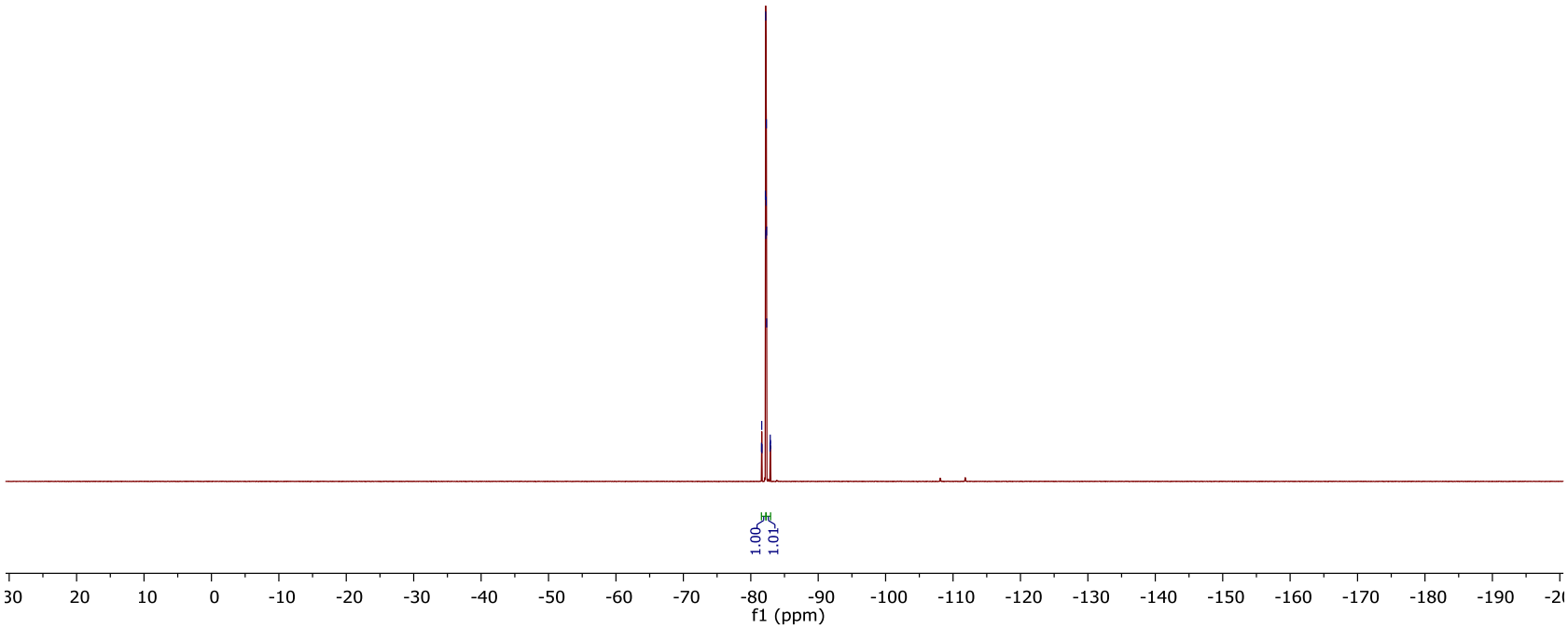
11a

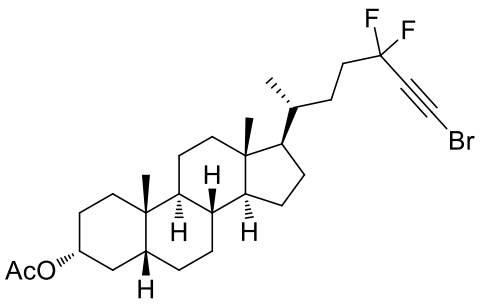
^{13}C NMR (126 MHz, $CDCl_3$)



11a

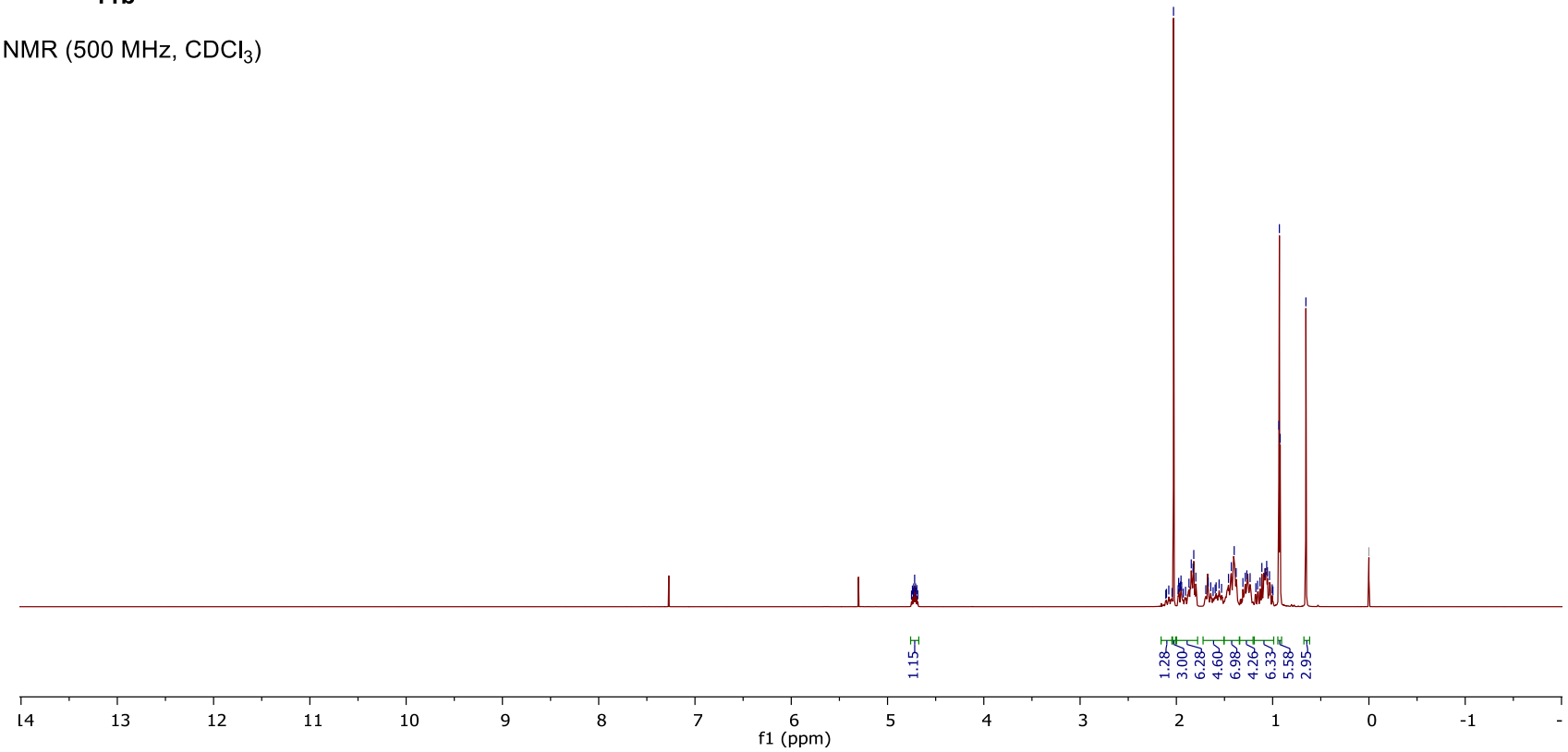
^{19}F NMR (470 MHz, $CDCl_3$)

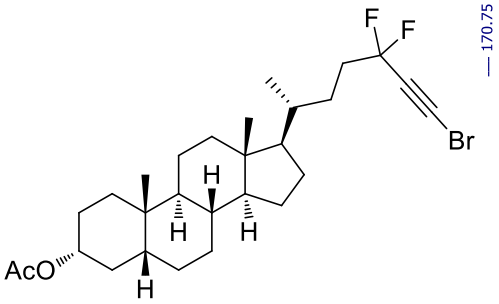




11b

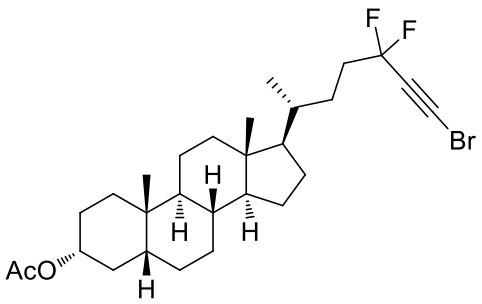
^{1}H NMR (500 MHz, $CDCl_3$)





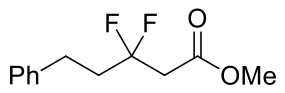
11b

^{13}C NMR (126 MHz, $CDCl_3$)



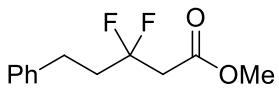
11b

^{19}F NMR (500 MHz, $CDCl_3$)



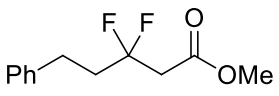
13

^{1}H NMR (500 MHz, $CDCl_3$)



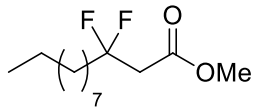
13

^{13}C NMR (126 MHz, $CDCl_3$)



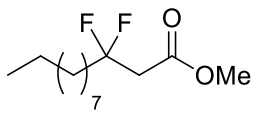
13

^{19}F NMR (470 MHz, $CDCl_3$)



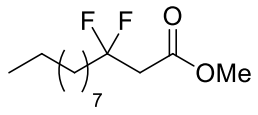
14

^{1}H NMR (500 MHz, $CDCl_3$)



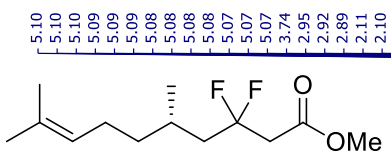
14

^{13}C NMR (126MHz, $CDCl_3$)



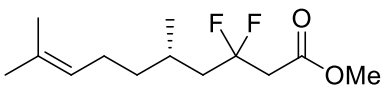
14

^{19}F NMR (470 MHz, $CDCl_3$)



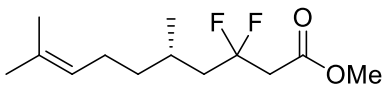
15

^{1}H NMR (500 MHz, $CDCl_3$)



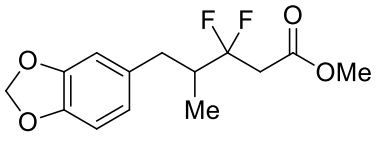
15

^{13}C NMR (126 MHz, $CDCl_3$)



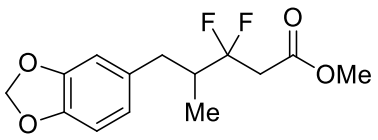
15

^{19}F NMR (470 MHz, $CDCl_3$)



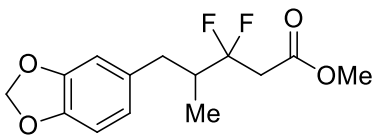
16

^{1}H NMR (500 MHz, $CDCl_3$)



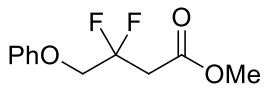
16

^{13}C NMR (126 MHz, $CDCl_3$)



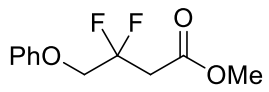
16

^{19}F NMR (470 MHz, $CDCl_3$)



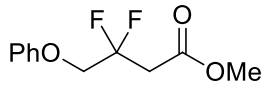
17

^{1}H NMR (500 MHz, $CDCl_3$)



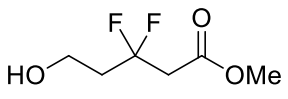
17

^{13}C NMR (126 MHz, $CDCl_3$)



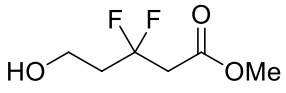
17

^{19}F NMR (470 MHz, $CDCl_3$)



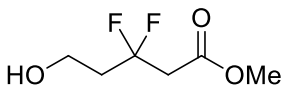
18

^{1}H NMR (500 MHz, $CDCl_3$)



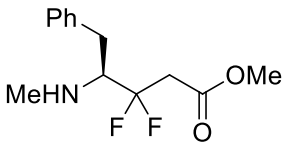
18

^{13}C NMR (126 MHz, $CDCl_3$)



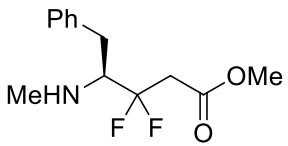
18

^{19}F NMR (470 MHz, $CDCl_3$)



19

^{1}H NMR (500 MHz, $CDCl_3$)

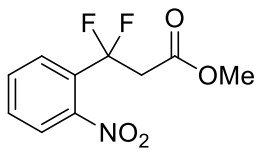


19

^{13}C NMR (126 MHz, $CDCl_3$)

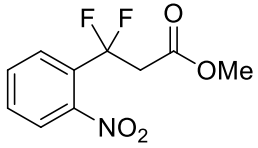
19

^{19}F NMR (470 MHz, $CDCl_3$)



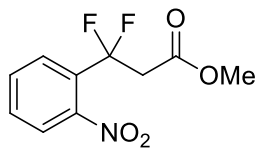
20

^{1}H NMR (500 MHz, $CDCl_3$)



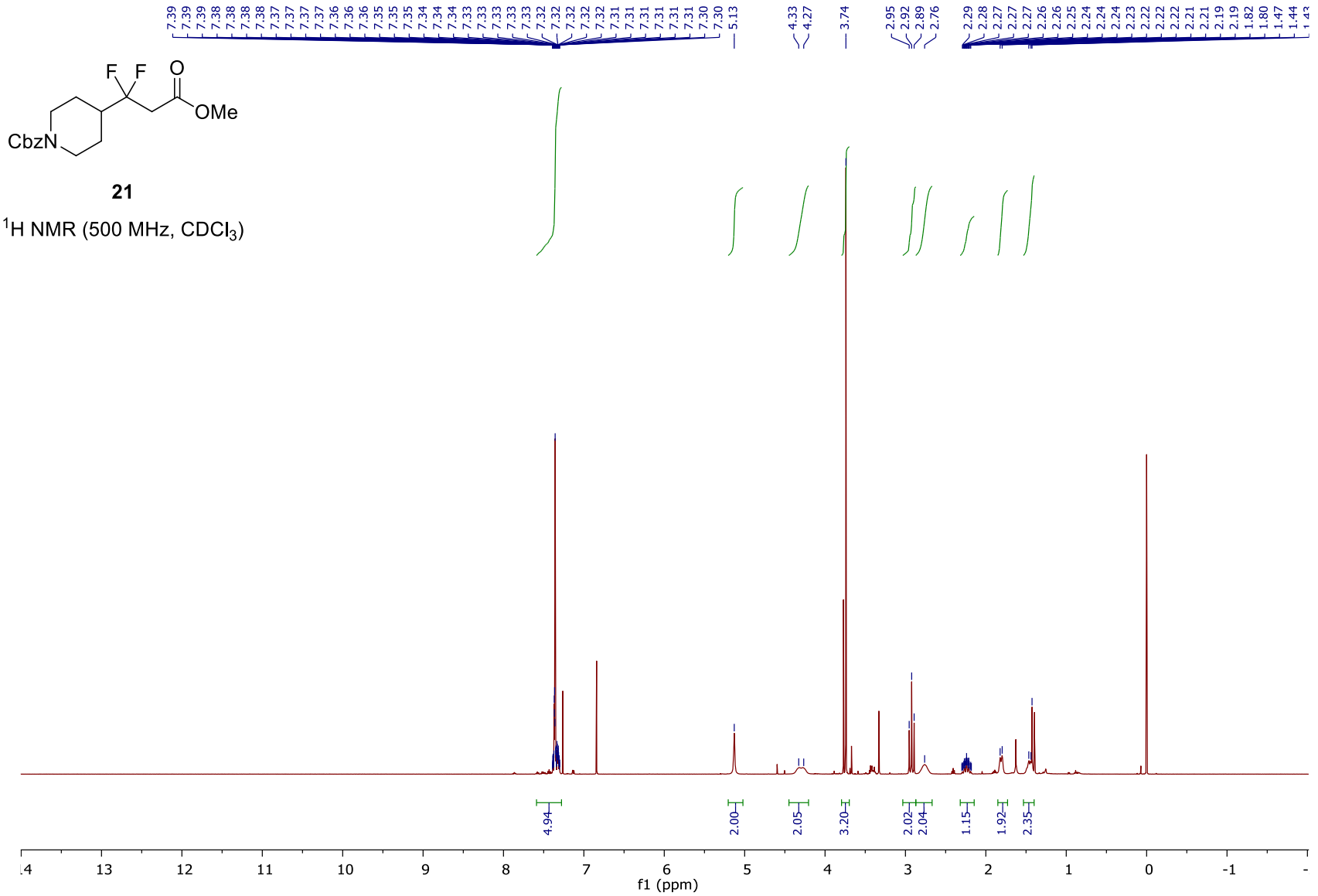
20

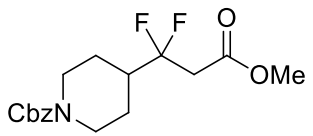
^{13}C NMR (126 MHz, $CDCl_3$)



20

^{19}F NMR (470 MHz, $CDCl_3$)

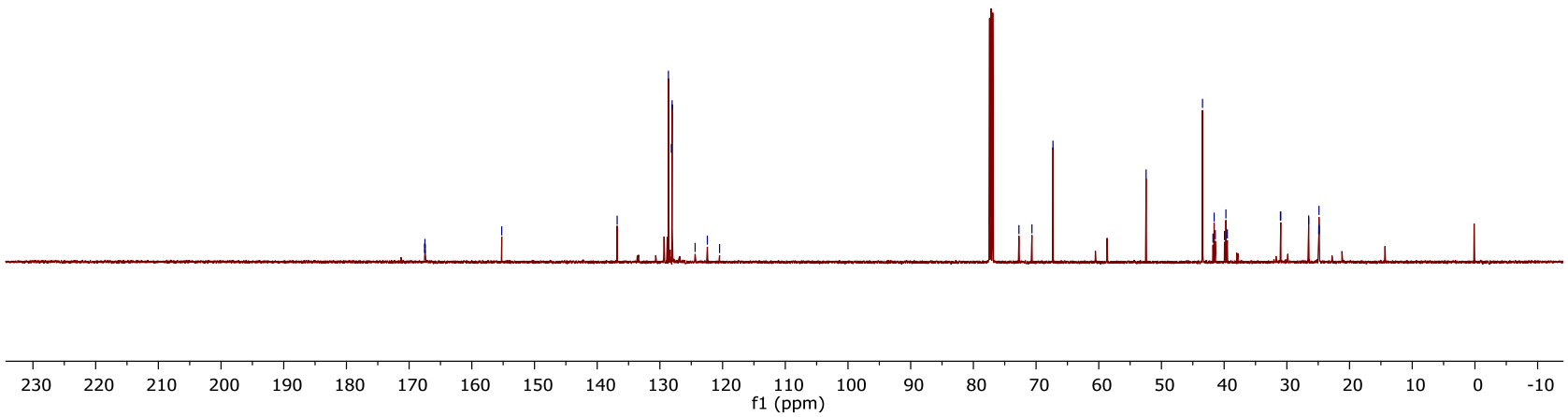

F F O
OMe
CbzN
21
1H NMR (500 MHz, CDCl3)
f1 (ppm)

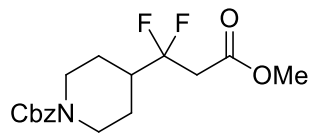


21

^{13}C NMR (126 MHz, $CDCl_3$)

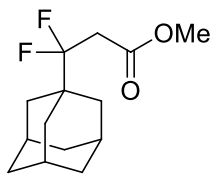
167.54
167.48
167.42
155.23
136.82
128.64
128.18
128.05
124.38
122.43
120.48
72.73
70.66
67.30
52.45
43.45
41.78
41.60
41.41
39.95
39.72
39.49
31.02
30.97
26.52
26.51
24.91
24.87
24.84





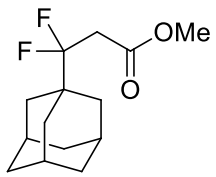
21

^{19}F NMR (470 MHz, $CDCl_3$)



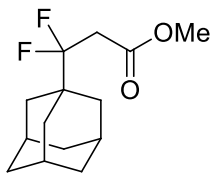
22

^{1}H NMR (500 MHz, $CDCl_3$)



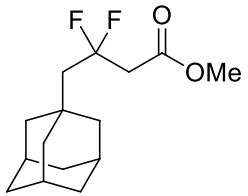
22

^{13}C NMR (126 MHz, $CDCl_3$)



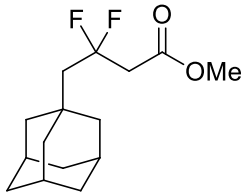
22

^{19}F NMR (470 MHz, $CDCl_3$)



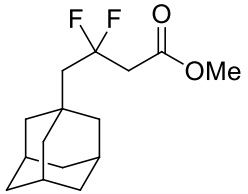
23

^{1}H NMR (500 MHz, $CDCl_3$)



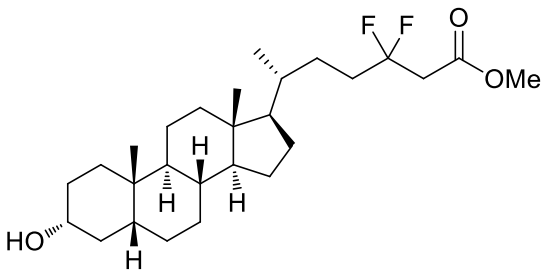
23

^{13}C NMR (126 MHz, $CDCl_3$)



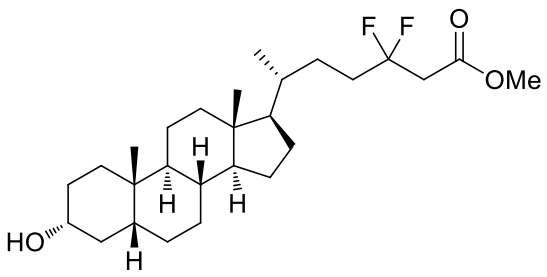
23

^{19}F NMR (470 MHz, $CDCl_3$)



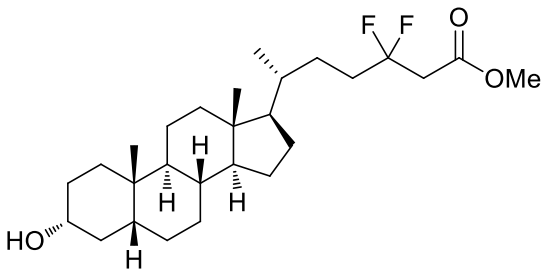
24

^{1}H NMR (500 MHz, $CDCl_3$)



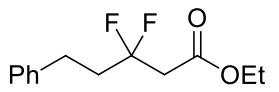
24

^{13}C NMR (126 MHz, $CDCl_3$)



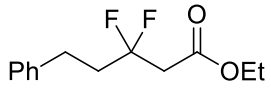
24

^{19}F NMR (470 MHz, $CDCl_3$)



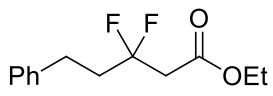
25

^{1}H NMR (500 MHz, $CDCl_3$)



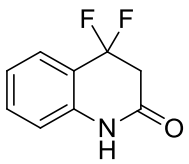
25

^{13}C NMR (126 MHz, $CDCl_3$)



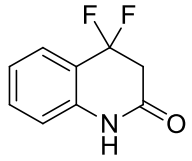
25

^{19}F NMR (470 MHz, $CDCl_3$)



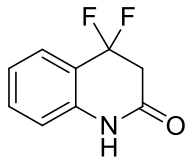
26

^{1}H NMR (500 MHz, $CDCl_3$)



26

^{13}C NMR (126 MHz, $CDCl_3$)



26

^{19}F NMR (470 MHz, $CDCl_3$)